Risk factors for adverse events in children with colds emerging from anesthesia: a logistic regression

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Summary

Background: Recent upper respiratory infection (URI) in children increases respiratory adverse events following anesthesia for elective surgery. The increased risk continues weeks after resolution of acute URI symptoms. Few systematic analyses have explored specific risk factors. This logistic regression explores the relationship between preoperative URI symptoms and adverse events during emergence from anesthesia.

Methods: Data were combined from control groups of several prospective observational and interventional studies in elective pediatric anesthesia in a tertiary care pediatric hospital. In each study, a blinded observer, distinct from the anesthesia care team, prospectively recorded the presence of stridor, oxygen desaturations (and their duration), coughing and laryngospasm. Parents were subsequently asked about the presence of 10 cold symptoms during the 6 weeks prior to operation.

Results: Our model, based on a dataset of 335 patients, did not demonstrate an association between any particular symptoms and the rate of respiratory adverse events during emergence from anesthesia, with the exception of low-grade fever which appeared to be mildly protective. Respiratory adverse events were affected by the airway management technique (device used and timing of extubation), and adverse events were increased if peak URI symptoms had occurred within the preceding 4 weeks.

Conclusions: Specific preoperative symptoms were not useful in predicting respiratory adverse events during emergence from anesthesia.

Keywords: recent upper respiratory infection; adverse events; respiratory; anesthesia; logistic regression; anesthesia emergence

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Introduction

Since children suffer an average of six colds per year (1), it is not surprising that in prospective studies about half of unselected children presenting for elective surgery have a history of upper respiratory tract infection (URI) within 6 weeks prior to surgery [61% (2), 70% (3), 68% (4), 68% (5), 30% (6)]. The association between a recent URI and respiratory adverse events during emergence from anesthesia, such as bronchospasm, laryngospasm and oxygen desaturation, has been documented both retrospectively (7,8) and prospectively (5,9,10). Evaluation of children for this risk is complicated by the fact that the potential for problematic emergence from anesthesia persists long after clinical resolution of the acute upper respiratory illness (11,12).

Few systematic analyses have been published concerning risk factors associated with adverse events during emergence from anesthesia in children with recent URI (4,5,13,14). There are strongly held opinions, and clinical practice varies widely between clinicians (15,16). A systematic analysis of risk factors for adverse events could allow a more directed preoperative history in patients with recent URI, and a more scientific approach to determining the risk of proceeding with anesthesia.

Methods

Data were amalgamated from several prospective interventional and observational clinical studies detailed below, employing similar standardized anesthetics. For the current analysis, patients were grouped by presence or absence of URI within the preceding 6 weeks. Where data from interventional studies are concerned, only the control patients were used. Following written informed parental consent and patient assent or consent as age-appropriate, a total of 335 patients were included in the analysis used to build the logistic regression model. The Institutional Review Board at Children’s Hospital and Regional Medical Center, Seattle, USA (IRB) approved the current study. TE was principal investigator for all component studies.

Endpoint observations

Data were collected by blinded observers for each study. There were four or fewer observers for each study. The observers were anesthesia department research associates, medical students, anesthesia residents, or anesthesia fellows, all of whom were trained by the principal investigator for the component studies (TE) to observe and record endpoints consistently, to recognize high-pitched monophonic inspiratory stridor as distinguished from expiratory vocalizations and to judge adequacy of a pulse oximetry signal. In all cases, the observer was separate from and additional to the anesthesia care team. Interrater reliability has been assessed with these simultaneous observers, where in 44 cases in a component study, a second blinded and independent observer recorded endpoints simultaneously, achieving a high interrater reliability of endpoints (Intra-class Correlation Coefficient (ICC) 0.93–0.96) (3), and in 22 patients in another study from our institution the ICC was >0.91 for all endpoints (3).

The observation period was 20 min, timed from the removal of the airway device (tracheal tube, laryngeal mask or face mask) by a member of the anesthesia care team. Endpoints recorded were presence, and duration in seconds, of oxygen desaturation (<94%, <90%, <85% in room air); number of coughs; and presence and severity (graded by treatment required) of laryngospasm. Occurrence of one or more of oxygen desaturation below 90%, 10 or more coughs, or any degree of laryngospasm, was classed as a respiratory adverse event.

In each study, after clinical data were recorded, the observer asked the parents (or caregiver) in person about the presence and severity of 10 symptoms of URI during the preceding 6 weeks. This allowed observers to be blind to URI status while recording endpoints, thus minimizing bias. The specific wording for each symptom was ‘runny nose,’ ‘congested or stuffed up,’ ‘sneezing,’ ‘coughing,’ ‘hoarse voice,’ ‘change in appetite or eating,’ ‘change in sleeping pattern,’ ‘sore throat,’ ‘fever’ and ‘malaise’ (‘could you tell she wasn’t well from across the room’). Each symptom (except fever) was graded by parents as none, mild, moderate, or severe at the peak of symptoms. The preoperative time span since peak symptoms was recorded. Parents (or care-
givers) were also asked to state whether they considered any symptoms described to represent a URI (cold), and it was this parental assessment, rather than the presence of any particular symptom complex, which determined the child’s grouping as ‘URI present’ or ‘URI absent,’ in accord with a study showing that parental report of URI is a better predictor of postoperative laryngospasm than a symptom tally (17).

Component studies

Albuterol premedication study
Completed between January 1997 and June 1998 (3), this study assessed the effect of nebulized bronchodilator premedication on adverse events during emergence from anesthesia. Control patients received a halothane inhalational induction.

Air vs nitrous oxide study
Completed between 1998 and 1999 (2), this study compared oxygenation while emerging from anesthesia after maintenance anesthesia randomized to either an air–oxygen or nitrous oxide–oxygen carrier gas mixture. [All patients in this study were included in our analysis, as both techniques fell within standard of care for these patients, and because of the inability of the intervention to make a difference as proven by mathematical modeling (18).]

Heart rate variability observational study
In this study (19), a preoperative ECG tracing was undertaken before observing patients during emergence from a standardized anesthetic after midazolam premedication.

Tonsillectomy extubation study
Patients having a standardized anesthetic for tonsillectomy with or without adenoidectomy or myringotomy had an inhalational induction, and control patients were extubated while still deeply anesthetized, during application of CPAP (Frigon, et al., unpublished data).

Prospective observational URI study
From August 2004 to May 2005, 89 healthy (American Society of Anesthesiologists I and II) patients aged between 1 month and 18 years undergoing elective surgery, with and without URI, were recruited for observation during emergence from anesthesia (additional data collected for the present analysis to attain adequate sample size). Anesthetic technique was at the discretion of the anesthesiologist. Exclusion criteria in all studies were medical conditions that have the potential to increase oxygen desaturations after surgery: chronic lung disease (i.e. asthma, cystic fibrosis, bronchopulmonary dysplasia, chronic aspiration, severe obstructive sleep apnea); congenital heart disease; neuromuscular disorders, cerebral palsy, seizures; severe craniofacial abnormalities; chromosomal abnormalities; and history of prematurity (<36 weeks gestation) in infants from 1 to 12 months of age. Patients scheduled for surgery of the trachea, thorax, upper abdomen, or for neurosurgery were also excluded, as surgical factors could influence the rate of respiratory adverse events. Table 1 shows the variables recorded for each patient in the amalgamated dataset.

Statistics
Power was calculated using one-tailed $t$-tests and Fisher’s exact test, based on the data from a similar study (20), and appeared to be sufficient (>80% at $P = 0.05$) across a range of scenarios for the group of 335 patients. A one-tailed $t$-test (rather than two-tailed) was used because of the well-documented positive association between URI and adverse events (5,7,8,9,10,21,22).

Statistical analysis of the amalgamated dataset was performed using STATA version 8.2 (Stata Corporation, College Station, TX, USA). Taking the main outcome to be any respiratory adverse event (presence of one or more of the three sub outcomes: 10 or more coughs, oximetry below 90% on room air, any grade of laryngospasm), each demographic, anesthetic and URI variable underwent bivariate analysis using Student’s $t$-test or Pearson’s chi-squared test. All variables with $P$-value <0.2 in bivariate analysis were considered using a multivariate analysis logistic regression model. In common with all logistic regression analyses, this produced a model applicable to the dataset from which it was generated. Ideally, this model would now be validated in a separate prospective dataset of equal or greater size to ensure that the associations shown are robust. To our knowledge, such
follow-up validation has not been published for any of the previous regression analyses which addressed respiratory adverse event rates in children with colds during anesthesia emergence (4,5,14).

Results

Adverse respiratory event data were available for 316 patients, 83 of whom were recruited as part of the ‘prospective observational URI’ study to attain adequate sample size for the present analysis. Of these 316 patients, 176 (55.7%) had a recent URI [defined as URI within the preceding 6 weeks, consistent with other studies (4,5,14)]. The mean (± standard error) age was 53.8 (±2.1) months, and 67.4% were male.

Table 2 lists the variables considered in the multivariate analysis, while Table 3 shows the final logistic regression model. The ‘airway management’ variable in Table 3 is a composite of the ‘airway management device’ and ‘deep vs awake extubation’ variables. This is because these two variables shared the ‘mask only’ category, and thus could not be assessed in the model as separate variables.

The only URI symptom which displayed association with occurrence of postoperative respiratory complications (P < 0.2) on bivariate analysis and was therefore retained for the regression modeling was low-grade fever. This appeared to be weakly protective in the overall model [odds ratio (OR) = 0.46, P = 0.20].

Use of midazolam premedication seemed to increase postoperative respiratory complications (OR = 3.05, P = 0.018). Inclusion of regional anesthesia as part of a multimodal anesthesia technique tended toward a protective effect but did not reach statistical significance in this model (OR = 0.32, P = 0.195).

Airway management device was associated with respiratory adverse events (P = 0.003). Compared with laryngeal mask airway (LMA) removed at a deep level of anesthesia (deep), use of tracheal tube (TT) with deep extubation tended to increase the respiratory adverse event rate (OR = 2.39), while use of a facemask alone decreased respiratory adverse events (OR = 0.15). The difference between LMA and TT was less noticeable when awake extubation was used (OR = 0.65 and 1.26, respectively).

Time since URI was strongly associated with respiratory adverse events (P < 0.001). Adverse events were highest in patients with a URI currently or within the previous 4 weeks. Among these patients, the highest rate was in those with peak symptoms 2–4 weeks prior (OR = 5.25, P = 0.007 vs OR = 3.83, P = 0.028 for URI < 2 weeks prior). Those with a URI 4–6 weeks prior to anesthesia had a lower rate of adverse events than those with
no preceding URI (OR = 0.24, P = 0.150). There was no evidence that duration of anesthetic was associated with the occurrence of respiratory adverse events (OR = 1.01, P = 0.107).

### Table 2
Variables considered in the multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subcategories</th>
<th>Yes (n = 128)</th>
<th>No (n = 188)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months (mean)</td>
<td></td>
<td>52.1</td>
<td>54.9</td>
<td>0.735</td>
</tr>
<tr>
<td>Length of anesthesia (min; mean)</td>
<td></td>
<td>76.4</td>
<td>61.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Premedication (%)</td>
<td>Yes</td>
<td>44.8</td>
<td>64.6</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>55.2</td>
<td>35.5</td>
<td></td>
</tr>
<tr>
<td>Airway management device (%)</td>
<td>LMA/deep</td>
<td>36.8</td>
<td>32.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>TT/deep</td>
<td>33.3</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LMA/awake</td>
<td>6.1</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT/awake</td>
<td>19.3</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mask only</td>
<td>4.4</td>
<td>22.4</td>
<td></td>
</tr>
<tr>
<td>Recent URI (%)</td>
<td>Yes</td>
<td>60.9</td>
<td>52.1</td>
<td>0.122</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>39.1</td>
<td>47.9</td>
<td></td>
</tr>
<tr>
<td>Time since URI (%)</td>
<td>No URI</td>
<td>38.3</td>
<td>47.3</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>4-6 weeks</td>
<td>9.4</td>
<td>19.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 &lt;4 weeks</td>
<td>28.9</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;2 weeks</td>
<td>23.4</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>Low-grade fever (%)</td>
<td>Present</td>
<td>17.3</td>
<td>26.6</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>82.7</td>
<td>73.4</td>
<td></td>
</tr>
<tr>
<td>Use of regional technique (%)</td>
<td>Used or not possible</td>
<td>93.8</td>
<td>87.6</td>
<td>0.074</td>
</tr>
<tr>
<td></td>
<td>Not used</td>
<td>6.3</td>
<td>12.4</td>
<td></td>
</tr>
<tr>
<td>Use of opioid (%)</td>
<td>Used</td>
<td>67.5</td>
<td>51.0</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>Not used</td>
<td>32.5</td>
<td>49.0</td>
<td></td>
</tr>
<tr>
<td>Airway management personnel (%)</td>
<td>New resident</td>
<td>12.6</td>
<td>7.7</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>Experienced resident</td>
<td>33.9</td>
<td>48.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fellow or CRNA</td>
<td>15.0</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Faculty</td>
<td>38.6</td>
<td>33.7</td>
<td></td>
</tr>
</tbody>
</table>

LMA, laryngeal mask airway; TT, tracheal tube; URI, upper respiratory infection; CRNA, certified registered nurse anesthetist.

### Table 3
Logistic regression model (multivariate analysis) for occurrence of a respiratory adverse event, defined as 10 or more coughs, hemoglobin desaturation below 90%, and any degree of laryngospasm

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months</td>
<td>0.98 (0.97–1.00)</td>
<td>0.037</td>
</tr>
<tr>
<td>Premedicated</td>
<td>3.05 (1.21–7.67)</td>
<td>0.018</td>
</tr>
<tr>
<td>Airway management device: LMA/deep as reference</td>
<td>2.39 (0.65–8.83)</td>
<td>0.192</td>
</tr>
<tr>
<td>TT/deep</td>
<td>0.65 (0.05–8.05)</td>
<td>0.739</td>
</tr>
<tr>
<td>LMA/awake</td>
<td>1.25 (0.29–5.28)</td>
<td>0.766</td>
</tr>
<tr>
<td>TT/awake</td>
<td>0.15 (0.03–0.77)</td>
<td>0.022</td>
</tr>
<tr>
<td>Time since URI: no URI as reference</td>
<td>0.23 (0.03–1.70)</td>
<td>0.150</td>
</tr>
<tr>
<td>URI 4–6 weeks prior</td>
<td>5.24 (1.59–17.31)</td>
<td>0.007</td>
</tr>
<tr>
<td>URI &lt; 2 weeks prior</td>
<td>3.83 (1.16–12.66)</td>
<td>0.028</td>
</tr>
<tr>
<td>Low-grade fever</td>
<td>0.46 (0.14–1.52)</td>
<td>0.203</td>
</tr>
<tr>
<td>Length of anesthesia (min)</td>
<td>1.01 (1.00–1.02)</td>
<td>0.107</td>
</tr>
<tr>
<td>Use of regional technique</td>
<td>0.32 (0.06–1.80)</td>
<td>0.195</td>
</tr>
</tbody>
</table>

For multiple indicator variables, one indicator is the reference against which the others in that group are compared.

LMA, laryngeal mask airway; TT, tracheal tube.

**Discussion**

We found a tendency toward increased respiratory adverse events in children with a URI by parental...
report 2–4 weeks or <2 weeks prior to anesthesia compared with no recent URI. Conversely, a URI 4–6 weeks previously appeared to have a protective effect compared with no URI. Airway management by TT with deep extubation tended to increase respiratory adverse events, while facemask alone reduced the adverse event rate compared with use of LMA. Benzodiazepine premedication tended to increase respiratory adverse events during emergence from anesthesia.

A previous logistic regression study (4) found no difference in respiratory adverse events in children with a URI in the 6 weeks preceding anesthesia (provided URI was not present on the day of surgery), compared with those without URI in the 6 weeks preceding anesthesia. Two other systematic analyses (5,14) showed an increase in respiratory adverse events in patients with active or recent URI. We have added to these previous observations by showing that URI 2–4 weeks prior to anesthesia was associated with the highest rate of respiratory adverse events in our study. Children with URI <2 weeks prior to anesthesia had an intermediate rate of respiratory adverse events. In addition, we made the new observation that URI 4–6 weeks prior to anesthesia seemed to be protective, as this was actually associated with a lower rate of adverse events in our study compared with children who had no URI in the preceding 6 weeks by parental report. Previous authors grouped all children with recent URI together, and varied in their definition of recent URI from 0 to 2 weeks (14) through 0–4 weeks (5) to 0–6 weeks (4) preceding anesthesia.

We were unable to demonstrate association between individual URI symptoms and the rate of respiratory adverse events during emergence from anesthesia. Although data on URI symptoms were collected as multiple indicator variables (mild, moderate, or severe), these were analyzed as symptom present or absent, because of the low numbers of patients having higher severity categories for each symptom. Even with reducing each symptom variable to present or absent, only low-grade fever displayed sufficient association with the outcome of postoperative respiratory adverse events to be included in the final regression model. Previous logistic regression studies have suggested that a wet and productive infection, characterized by copious secretions and nasal congestion (4,5), is associated with increased adverse events. We were unable to reproduce this association in our dataset.

We were unable to show an effect of passive smoking in our study, in contrast with previous work (4,5). This may be because our cohort of passive smokers was relatively small, only 28% of children, whereas half the children were smoke-exposed in another logistic regression study (4). We also had substantially fewer patients in total than either previous regression study [335 children vs 2051 children (4) or 1078 children (5)].

Midazolam premedication increased adverse events in our study. Perhaps residual postoperative sedation lowered minute ventilation, slowing the excretion of inhaled agents which increased propensity to oxygen desaturation while breathing room air. Use of midazolam premedication was at the discretion of the attending anesthesiologist, except for patients in the heart rate variability observational
study who all received premedication with oral midazolam.

If the protective effect of low-grade fever, or of a ‘cold’ 4–6 weeks prior to anesthesia, can be reproduced in future studies, the humoral mediators of URI may deserve investigation. Perhaps, a mediator that produces a febrile response also confers a beneficial effect on the respiratory system.

Our data improve on existing studies because of our blinded observer for adverse events, and the personal interview of parents. Our study differs from previous studies where data were also collected prospectively, because of our independent observer, avoiding any bias when adverse events are reported by the care providers themselves (4,5,14). There can be a subconscious tendency based on coping mechanisms for clinicians to minimize complications that occur in their hands (23), which would compromise data recorded by the care provider. Studies have shown that attending physicians report fewer adverse events than nurses or house staff caring for the same patients (24,25). In addition, care providers cannot be blind to the patient’s URI status, as they will require this information as part of their preanesthesia assessment. Our blinding was imperfect, as some parents inadvertently stated whether or not their child had a URI while giving consent to be in the study. Nevertheless, our observer was blind to URI status during the 20-min observation period for the vast majority of patients. ‘Cold’ symptoms were assessed by questionnaire or a preoperative admission form in other studies (5,14), rather than by personal interview immediately after anesthesia and observation period with a research associate [preoperative personal interview was used in one previous systematic analysis (4)].

We specifically excluded patients with reactive airway disease in our studies, preventing us from commenting on the known increase in risk from this common pediatric disease (5). We also excluded ex-premature children under 1 year of age, another demonstrated risk factor for adverse events (13).

There are several drawbacks to this study. By combining patients from several component studies, anesthetic techniques differ between patients, with insufficient patient numbers for each technique to allow adequate statistical analysis. However the previously published systematic analyses on which we modeled our own study (4,5,14) allowed anesthesia technique and airway management at the discretion of the attending anesthesiologist caring for the patient.

Although employing a blinded observer allows very sensitive recording of stridor and laryngospasm, it can take a trained and experienced eye to distinguish laryngospasm from vocalization during emergence from anesthesia. To minimize this effect, all observers were trained by TE.

Our observations add to the debate regarding which children with current or recent URI can safely proceed to elective surgery, and which should have their procedures postponed. In common with all logistic regression analyses, our model as given in Table 3 is applicable to the dataset from which it was generated, but should ideally be validated in a separate prospective dataset of equal or greater size to ensure that the associations shown are robust. To our knowledge such follow-up validation has not been published for any of the previous regression analyses (4,5,14).

We have expanded the observation that the time between peak URI symptoms and administration of anesthesia is important in children. Our study confirms that selection of airway management technique affects the rate of respiratory adverse events during anesthesia emergence.

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