The pediatric patient and upper respiratory infections

Tom Elwood MD, Assistant Professor and Katherine Bailey MD, Clinical Fellow

Department of Anesthesiology and Pain Medicine, Mailstop 4D-1, Children's Hospital and Regional Medical Center, 4800 Sand Point Way NE, Seattle, WA 98105-0317, USA

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Children frequently present for elective surgery in the setting of an active or recent upper respiratory infection. Respiratory adverse events are increased in this setting, but the threshold for cancelling a case varies widely between clinicians. A decision to cancel surgery should take into consideration the amount of respiratory secretions during the acute illness, coexisting pulmonary disease, the requirement for intubation, and the surgical site (airway, thorax, upper abdomen—each with their potential for complications). More data are needed on the risks of proceeding with surgery in the presence of these factors and on the impact of potential therapies to decrease the incidence of adverse events. Lidocaine and other therapies that reduce laryngospasm in well patients need to be evaluated in children with upper respiratory infection.

**Key words:** respiratory tract infections; viral disease; postoperative complications; pediatric anesthesia; bronchospasm; laryngospasm; oxygenation; risk factors; decision-making

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‘Good judgment comes from experience; and often experience comes from bad judgment.’ Rita Mae Brown (1944)

Every clinician learns sooner or later that a recent upper respiratory tract infection (URI) leads infrequently and capriciously to an emergence from anesthesia fraught with difficulty. Parents are often surprised to learn that their child remains at increased risk for weeks beyond clinical resolution of the illness. Scientific study has been hampered by the rarity of the outcomes that matter—laryngospasm and unexpected hospital admission.

Clinicians vary widely in their threshold for cancelling elective surgery due to URI. A recent study demonstrated the breadth of this issue. In a practice survey with 212 (54%) respondents in both academic and private practice settings, one third stated that they seldom cancelled cases due to URI, one in five stated that they usually cancelled cases due to URI, one in 30 stated that they always cancelled cases, and one in 100 reported never cancelling cases due to URI. The study found that anesthesiologists practising for more than 10 years were more likely to cancel elective patients with URIs than those who had been in practice for less than 10 years ($P<0.05$). This is more likely to reflect the seasoned anesthesiologists' experience with infrequent severe outcomes in this setting rather than unfamiliarity with recent literature. Among those surveyed, factors that influenced the decision included the urgency of surgery, the presence of reactive airways disease, fear of complications, and previous experience of anesthetizing patients with URIs. Factors that did not contribute to the decision to cancel were economic factors (distance travelled, cost of cancellation, fear of litigation, pressure to expedite cases) and parental attitude.

Economic factors are an imposition on parents, however. The consequences of their child's...
cancelled surgery were surveyed in 127 parents (64% response rate). URI was noted as the cause of cancellation in 35% of these cases. Of those not cancelled until after arrival at the hospital, 39% of mothers and 50% of fathers missed a day of work. The mean round trip distance travelled was 160 miles. Beyond these factors, there is the considerable cost of staffing an operating room that goes unused because of a cancellation. While economic factors do not appear to affect the anesthesiologist's decision to cancel patients, the impact of cancellation upon the family is substantial.

Several studies have been undertaken to identify patient, anesthetic and surgical risk factors that can guide the anesthesiologist in deciding which patients are appropriate to submit to anesthesia.

**Definition**

The definition of active or recent upper (versus lower) respiratory tract infection varies between studies. One early study defined an active URI as having two or more of the following symptoms: rhinorrhea, sore or scratchy throat, sneezing, nasal congestion, malaise, cough or fever. Since signs of chronic rhinitis can be indistinguishable from URI to the clinician evaluating a patient for the first time, parents may be a better resource as they can identify a change from baseline symptoms. After one study found that parental assessment was a better predictor of outcome than the above symptom-based score, subsequent studies have included parental confirmation in the definition of URI.

**Natural history of disease**

The prevalence of URI ranges between 3 and 70% in pediatric studies (Table 1)—but note that researchers often pick procedures or times of year for enrollment that favor a high incidence of URI. Rescheduling surgery does not guarantee evasion of URI-mediated sequelae, since preschool-age children have an average of six URIs per year; a second URI may develop in the interim.

<p>| Prevalence of URI history in pediatric anesthesia. |</p>
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<th>Study size (n)</th>
<th>Active URI (%)</th>
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NA, not available; URI, upper respiratory infection.

Studies in adult patients revealed that both the upper and lower airways are affected by URI. Viral infections damage respiratory epithelium and mucosa, sensitizing the airway to the irritant effects of anesthetic gases and secretions, resulting in airway smooth muscle activation. Viral infections increase ventilation-perfusion mismatch, increase closing volumes and compromise diffusion capacity. This has been demonstrated clinically as persistent increases in airway reactivity for 6–8 weeks after onset of URI—well beyond resolution of clinical symptoms.

Cancelled surgery should be delayed until pulmonary changes resolve. It is the duration of persistent subclinical changes that drives clinical decision-making. Accordingly, it is essential to scrutinize the timeline of return-to-baseline pulmonary function in these studies. In a histamine challenge study in 12 adults, the majority of subjects returned to normal after 4 weeks, and only four of 12 subjects had changes that persisted longer. In 39 adult subjects, airway hyperreactivity to carbachol made a steep decline toward normal during the initial 2 weeks after presentation with URI. Lung conductance in 18 adults decreased with a cold air exercise challenge at 1 and 3 weeks, but had normalized by 6 weeks.
The length of delay necessary until rescheduled surgery is not clear. Children cannot cooperate with tests providing the above data on return-to-baseline function, so the course in children has to be extrapolated. A study to determine the minimum delay seems formidable—a logistical nightmare of randomizing the delay until rescheduled surgery. One must be guided by the duration of pulmonary changes in the above studies. It is common to advise patients to reschedule at least 2 weeks after peak symptoms.

**Risks augmented by URI**

The respiratory adverse events during general anesthesia in the setting of URI are bronchospasm, laryngospasm, breath-holding, arterial desaturation, need for re-intubation, bacterial pneumonia, and unanticipated hospital admission. As detailed below, the adverse events encountered are those common to pediatric anesthesia, and rarely cause long-term sequelae.

In a prospective study with 1078 patients comprising roughly equal thirds having active URI symptoms, recent URI symptoms within the previous 4 weeks, or no URI symptoms, respiratory adverse events were most prevalent in the active URI group. There was a significantly higher incidence of both breath-holding and severe coughing in the active URI symptom group (30.5 and 9.8%) compared to both the recent URI group (23.3 and 5.7%) and the asymptomatic controls (17.9 and 4.2%). There was also a significantly higher incidence of desaturation in both the active (15.7%) and recent (14.7%) URI groups versus the non-URI group. There was no statistically significant difference in the incidence of bronchospasm or laryngospasm between groups—not surprising for an outcome of low occurrence. In this study only nine of 407 patients (2.2%) with an active URI confirmed by the parent required succinylcholine for management of laryngospasm, and only three children—one with a recent URI and two with active URIs—required unanticipated admission to hospital.

Cancellation of cardiac surgery carries special import because of the extensive time and materials committed to a planned case. Outcomes were chronicled prospectively in 713 patients with congenital cardiac disease having open heart surgery, of which 96 proceeded despite active URI symptoms. Patients with URI had a significantly higher incidence of respiratory adverse events (29.2 versus 17.3%, \( P<0.01 \)), multiple postoperative complications (25 versus 10.3%, \( P<0.01 \)) and bacterial infection (5.2 versus 1.0%, \( P=0.01 \)). Logistical regression analysis identified presence of URI as an independent risk factor for both postoperative infections and multiple postoperative complications in children presenting for open heart surgery. While this study found that intensive care unit stays were longer for children with URIs (80±90 versus 60±60 hours, \( P<0.01 \)), length of hospital stay was not significantly different between groups (8.4 versus 7.8 days, \( P>0.05 \)).

**Patient risk factors**

Several factors emerge as independent risk factors for adverse respiratory events in children with URIs, as identified by logistic regression analysis. While specific predictors differ, the common thread in these analyses is URI characterized by secretions (rhinorrhea and congestion) and the presence of underlying pulmonary disease.
By employing logistic regression in 1078 children with active, recent or no URI symptoms, patient risk factors associated with adverse outcomes included copious secretions \( (P=0.0001) \), ex-premature infants \( (P=0.007) \), nasal congestion \( (P=0.014) \), parental smoking \( (P=0.018) \), and reactive airway disease \( (P=0.028) \). ASA status did not correlate with adverse outcomes.

Another study\(^5\) looked prospectively at 2051 children, again divided into active URI symptoms (22.3%), recent URI symptoms within 6 weeks (45.8%) and asymptomatic controls (30%). Significant patient predictors were parental confirmation of the child's URI symptoms, presence of nasal secretions, history of snoring, passive smoke exposure, and sputum production.

It has been shown that younger patients, especially infants, have a higher incidence of airway complications.\(^16\) and \(^17\). The specific role age plays in the presence of URI was not elaborated in all studies, but one study\(^14\) showed that infants less than 6 months old with active URIs had a higher incidence of bronchospasm (20.8 versus 4.7\%, \( P=0.08 \)) than older children. This same study also showed that children under 2 years old had a higher incidence of oxygen desaturation than older children (21.5 versus 12.5\%, \( P=0.023 \)).

During preoperative assessment of children with recent colds, it seems prudent on the basis of these studies to concentrate on symptoms and signs that quantify respiratory secretions, and to search for underlying pulmonary disease. Copious rhinorrhea, nasal congestion, or productive cough during the recent illness should be sought when deciding to cancel a case. Asking parents whether rhinorrhea or other symptoms were mild, moderate, or severe during the recent illness may be of use, though this is not yet proven. Patients with fever or abnormal lung findings (bronchitic cough, wheezing) have been excluded from most studies; these are likely additional factors that warrant cancellation, although this has not been tested prospectively.

A special situation is the child just developing URI symptoms on the day of surgery, since the severity of peak symptoms from the illness cannot be assessed at that stage. In the absence of objective evidence, the clinician may best be guided by the presence of fever, decreased appetite and other constitutional symptoms, and abnormal lung findings.

**Anesthetic risk factors**

Under anesthesia, the ciliary apparatus responsible for clearing tracheal secretions is impaired.\(^18\) The impaired clearance of secretions augmented in the aftermath of a URI, coupled with the inspissating effect of inhaled anhydrous gases, likely have cumulative effects contributing to respiratory adverse events. So far, however, studies have not identified duration of surgery as an independent risk factor for complications.\(^14\), \(^15\), and \(^16\).

Intubation is associated with adverse complications in patients with URI undergoing general anesthesia. Children with URIs had an overall two- to seven-fold increased risk of perioperative respiratory adverse events in a retrospective study.\(^17\) Among those not intubated, those with URI had a ninefold increased risk of respiratory adverse events when compared to children without URI. In children who underwent endotracheal intubation, those with URI had an 11-fold greater risk of respiratory events than those without URI. Furthermore, since
children with mucopurulent nasal secretions were excluded from study participation, the relative risk could even be higher.

These findings are supported by the prospective study of 1078 patients divided into active, recent and no URI symptoms which identified endotracheal intubation in children under 5 as an independent risk factor for postoperative respiratory adverse events ($P=0.0002$). Of note, duration of anesthesia and awake versus deep extubation were not identified as risk factors.

Similarly, in the study of 2051 children with active, recent, or no URI symptoms, choice of airway management was identified as an independent risk factor for postoperative adverse events. Specifically, the risk was higher with endotracheal intubation than with laryngeal mask airway (LMA) or facemask, respectively. Additionally, this study revealed that use of reversal agents was an independent risk factor for postoperative adverse events.

The magnitude of effect seen in retrospective studies has been far greater than in prospective studies, so it is important to mention two biases of retrospective data that may be present. Data capture required anesthesiologists to flag a case for specific complications. When a child suffered a minor complication, the anesthesiologist may have been subconsciously more likely to flag the complication in the presence of a URI, when there was both reason to expect complications and an external cause on which to blame the complication. Also, there may have been a selection bias; airway management was up to the anesthesiologist, who may have chosen to intubate children with more severe URI to facilitate treatment of complications.

These biases have finally been discounted by a prospective study. Enrolling only patients with active URI symptoms, 82 children were allocated to either an endotracheal tube or an LMA. There was a significant increase in all respiratory adverse events combined (breath-holding, laryngospasm, bronchospasm, and major oxygen desaturation) in the endotracheal intubation group (35 versus 19 events, $P<0.05$), and a significantly higher incidence of bronchospasm (12.2 versus 0%, $P<0.05$).

These results were confirmed in a second study comparing the use of an LMA versus an uncuffed endotracheal tube in 400 patients with (n=84) and without URI symptoms (n=316). Here again, the incidence of postoperative respiratory complications in patients with URIs was higher in the endotracheal intubation group (74% of n=38) than in the LMA group (32% of n=46, $P<0.001$).

**Surgical risk factors**

Surgery on the airway itself has been identified as a risk factor for postoperative respiratory adverse events ($P=0.04$). Laryngospasm in pediatric patients is more likely in airway surgery, whether or not the patients had a URI.

Studies by anesthesiologists naturally focus on the immediate perioperative period rather than on postoperative convalescence. However, one surgical factor that should also influence the decision to proceed with surgery is the incision location. An upper abdominal incision has been demonstrated to impair diaphragmatic movement for 24 hours in well patients, with
resultant atelectasis. While constrained diaphragm movement might not impair oxygenation, one can surmise that the presence of URI in patients having thoracic or abdominal incisions may increase pain through frequent coughing.

The decision to proceed with surgery should bear in mind the surgical site as a potential source of adverse events, either through blood in the airway or impairment of postoperative coughing.

**Morbidity and mortality**

While the incidence of acute perioperative respiratory adverse events is elevated in patients with active URIs, there is little suggestion to date that URI causes serious long-term complications. Most events respond to simple remedies such as succinylcholine or bronchodilators, or maneuvers such as continuous positive airway pressure (CPAP), endotracheal intubation and short-term ventilation. The presence of URI in children having cardiac surgery did not increase neurologic outcomes, including seizures (4.2 versus 2.4%) or mortality rate (4.2 versus 1.6%). A comparison of children with active, recent and no URI symptoms also showed that—despite a higher overall incidence of respiratory complications in patients with URI—the severity of adverse events was low, the children had uneventful recoveries, and there were no long-term adverse sequelae or deaths in the children studied. The study comparing LMA versus endotracheal tubes in children with URI again showed that all respiratory adverse events could be easily managed without adverse sequelae. These studies suggest that adverse events associated with anesthetizing children with URI can be easily identified and treated without exposing the patient to undue risk of long-term injury.

**Future areas of research**

**Confounding factors in assessing complication rates**

An issue that confounds the results of studies examining the effects of anesthesia in children with URI is the lack of independent observation and assessment of the child's symptoms. Physicians may subconsciously deny that their patients are having a complication, and thus may report lower-than-actual complication rates. Studies employing independent observers to assess both the patient's preoperative symptoms and postoperative adverse events may eliminate this bias.

Another bias of existing studies is the exclusion of patients with severe symptoms. Such elimination may reduce the perioperative adverse events of interest. Studies could be designed to include these patients to reduce this source of bias, such as a prospective observation of outcomes in children with URI who require emergency surgery that cannot be postponed until recovery from URI.

**Predicting adverse events**

There is currently no preoperative test to predict patients at risk for perioperative respiratory adverse events when harboring a URI. Such a test would ideally need to be safe, fast, inexpensive, and require little participation from the patient.
At first thought, one might be tempted to suggest pulmonary function testing. Large epidemiological studies of pulmonary function in mild URI in teenagers found a decreased forced expiratory volume on the first day of URI, without changes in static volumes, alveolar $N_2$ slopes or closing volumes,$^{23}$ and after a URI demonstrated a slightly increased closing volume.$^{24}$ Another longitudinal study compared pulmonary function testing in children under 11 with and without URI, in which repeated testing allowed patients to serve as their own controls. Forced vital capacity, exhaled volume in 1 second, and flows decreased during URI.$^{13}$ Preoperative assessment with pulmonary function testing would be viable only in patients old enough to cooperate, which begins at about 6 years. Unfortunately, this is older than most children presenting with recent URI, which peaks in the preschool age group (Figure 1)$^2$, so other measures of pulmonary status must be used.

Other tests which could potentially assess the presence and severity of bronchospasm include exhaled carbon dioxide and nitrogen washout curves, and exhaled endogenous nitric oxide. Exhaled carbon dioxide in asthmatics correlates with severity of bronchospasm.$^{25}$ In addition, the test is non-invasive and effort-independent in adults, which suggests particular suitability for use in children. Unfortunately, exhaled carbon dioxide testing does require at least minimal patient cooperation for accuracy; adverse events could not be predicted using this method in a prospective study.$^6$ Nitric oxide is naturally excreted from the respiratory system, and levels are increased in proportion to airway reactivity$^{26}$ and $^{27}$ and during and after URI.$^{28}$ Future studies may elucidate a correlation between elevated endogenous nitric oxide levels and perioperative complications.

Respiratory adverse events have an autonomic basis, and non-invasive markers of autonomic balance such as heart-rate variability derived from several minutes of ECG recording may allow prediction of patients at risk for adverse events. Preliminary data suggest a significant relationship between heart rate variability and respiratory outcomes (Elwood, unpublished data).

**Preventing adverse events**

Studies evaluating medications to prevent respiratory adverse events (in non-URI patients) include using lidocaine to prevent laryngospasm, and using bronchodilators to prevent increases in airway resistance following intubation.

**Laryngospasm**

Most studies have shown the effectiveness of lidocaine in reducing postoperative laryngospasm in healthy patients when given prior to intubation or extubation, either intravenously$^{29}$, $^{30}$ and $^{31}$, or topically$^{31}$ and $^{32}$, as follows. A randomized, controlled, double-blind study$^{31}$ of 134 patients for elective tonsillectomy and/or adenoidectomy showed that topical and intravenous lidocaine given prior to intubation were equally effective in reducing extubation laryngospasm, though higher sedation scores were seen immediately postoperatively in the intravenous lidocaine group. A second study randomized 19 patients having tonsillectomy to lidocaine versus placebo just prior to extubation.$^{30}$ Again, lidocaine prevented coughing and laryngospasm, and no serious side-effects were noted. These studies
contrast a single earlier randomized study of 100 healthy children for tonsillectomy and adenoidectomy, where intravenous lidocaine did not decrease laryngospasm incidence versus placebo. Of note, none of these studies specifically looked at prevention of laryngospasm in patients with URIs.

Since opioids are antitussive, and laryngospasm is often accompanied by coughing, it may not be surprising that fentanyl suppressed laryngospasm. Laryngospasm induced by applying distilled water to the vocal cords was suppressed by fentanyl. Hypercarbia per se also diminishes laryngospasm, lending further support to the use of opioids in patients at risk. Prospective studies would be needed to confirm the hypothesis.

A recent intriguing study documented a beneficial effect of magnesium on laryngospasm. Magnesium may exert its effect through calcium antagonist properties that provide muscle relaxation. Forty healthy patients for tonsillectomy and/or adenoidectomy were randomized to either 15 mg/kg of intravenous magnesium or saline placebo after intubation. Magnesium lowered the incidence of laryngospasm significantly. One would need reassurance regarding deleterious effects of magnesium prophylaxis on other essential musculature before adopting this technique.

**Bronchospasm—induction agents**

Several studies have looked at the effect of various induction agents on airway resistance induced by intubation. In a simple clinical study of 59 asthmatics and 96 non-asthmatics, induction with propofol gave significantly less auscultated wheezing than barbiturates. This was followed by a more objective assessment of airway resistance when 37 patients were administered either thiopentone 4 mg/kg followed by a 15 mg/kg/h continuous infusion versus propofol 3 mg/kg followed by a 9 mg/kg/h continuous infusion and airway resistance was measured 5 minutes after intubation. Airway resistance was significantly lower in the propofol group, suggesting that in healthy patients propofol provided more protection against tracheal intubation-induced bronchospasm.

Respiratory resistance after tracheal intubation was lower after induction with propofol than with thiopental or high-dose etomidate. When 75 patients were induced with 2.5 mg/kg propofol, 0.4 mg/kg etomidate, or 5 mg/kg thiopental, and respiratory resistance measured 2 minutes after induction, resistance was significantly lower for propofol (8±3 cmH₂O/l/s) versus etomidate (11±5 cmH₂O/l/s) and thiopental (12±8 cmH₂O/l/s; P<0.05 for propofol versus either etomidate or thiopental).

**Bronchospasm—bronchodilators**

Randomized studies in asthmatics undergoing awake fiberoptic intubation demonstrate that using lidocaine for topical anesthesia significantly decreases the reduction in forced expiratory volume in 1 second (FEV₁) seen with fiberoptic endoscopy. Furthermore, this effect can be attenuated even further by salbutamol pretreatment.

A randomized controlled trial of 42 healthy adult patients administered either inhaled albuterol
Inhaled bronchodilators, such as salbutamol, ipratropium bromide, or a placebo, were compared in patients receiving intubation. The administration of either bronchodilator before intubation showed significantly lower lung resistance compared to those receiving placebo. At 2 minutes, lung resistances were 13±1 cmH₂O/l/s for placebo, 6±3 cmH₂O/l/s for the ipratropium-treated group ($P<0.05$ versus placebo), and 7±1 cmH₂O/l/s for the albuterol-treated group ($P<0.05$ versus placebo).

Three of 15 placebo-treated patients developed wheezing, whereas no patients developed wheezing in either bronchodilator-treated group ($P<0.05$ by Fisher's exact test).

Despite the above studies, a prospective study of bronchodilators in children with and without URI was not as promising. A randomized blinded study was designed to examine the incidence of postoperative respiratory events in 109 children having non-cavitary non-airway surgery who received either bronchodilator pretreatment with albuterol or ipratropium, or nebulized normal saline placebo. This study did not demonstrate a decrease in respiratory adverse events associated with albuterol or ipratropium pretreatment.

**Summary**

The management of children presenting for elective surgery with active or recent history of upper respiratory tract infection remains a challenging anesthetic dilemma. Factors which need to be taken into consideration in the management of these patients include natural history and prevalence of respiratory tract infections, presence of respiratory secretions during the acute illness, and surgical procedure site (airway, thorax, upper abdomen). Further studies are needed to delineate the relative risks of patient factors with respect to respiratory adverse events, and to improve techniques for identification of or prophylaxis for adverse events preoperatively.

**Practice points**

- During preoperative assessment of children with recent colds, concentrate on symptoms and signs that quantify respiratory secretions; be guided by parent confirmation of change from baseline symptoms.
- Patients with coexisting pulmonary disease and infants under 6 months with active URI are particularly at risk.
- The respiratory adverse events associated with URI are bronchospasm, laryngospasm, breath-holding, desaturation, reintubation, pneumonia and unanticipated admission.
- The severity of adverse events is low, the problems encountered are common to pediatric anesthesia, and long-term sequelae are rare.

**Research agenda**

- Study all patients from time of surgical booking until their eventual procedure, to capture all cancellations.
- Measure emergence outcomes in emergency surgery undertaken despite URI concerns.
• use objective third-party observers of outcomes to avoid bias

• evaluate outcomes in non-academic centers, where more experienced airway management may prevail, different pressures may exist regarding cancellation, and coexisting disease may be less prevalent

• predict adverse events using some other non-invasive marker of pulmonary disease, such as exhaled endogenous nitric oxide

• assess prevention of adverse events through medications with pulmonary actions such as opioids, glycopyrollate, cromoglycate, or inhaled steroids

• assess the effectiveness, in the recent URI setting, of measures proven to decrease laryngospasm—topical or intravenous lidocaine, opioids, or perhaps magnesium

• study operating room utilization formally to assess the economic and morbidity impact of cancellation as guidelines and practice change

• develop a multifactorial scoring system to predict complications, and test its ability to improve outcome when used prospectively

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Corresponding author. Tel.: +1 206 987 2123; Fax: +1 206 987 3935.