2015

Diagnosis and management of respiratory adverse events in the operating room

Adrian Regli
The University of Notre Dame Australia, Adrian.Regli@nd.edu.au

Britta S. von Ungern-Sternberg

This non-refereed article was originally published as:
Regli, A., & von Ungern-Sternberg, B. S. (2015). Diagnosis and management of respiratory adverse events in the operating room. *Current Anesthesiology Reports, 5* (2), 156-167.

Original non-refereed article available here:
10.1007/s40140-015-0103-z

Diagnosis and management of respiratory adverse events in the operating room

Adrian Regli,[1, 2, 3, 4] Britta S von Ungern-Sternberg[5, 6]

[1] Consultant, Intensive Care Unit, Fiona Stanley Hospital, 102-118 Murdoch Drive, Murdoch WA 6150 Perth, Australia
[2] Consultant, Intensive Care Unit, Fremantle Hospital, Alma Street, Fremantle WA 6959 Perth, Australia
[3] Clinical Associate Professor, School of Medicine and Pharmacology, The University of Western Australia, 35 Sterling Highway, Crawley WA 6009 Perth, Australia
[4] Associate Professor, School of Medicine, The Notre Dame University, 38 Henry Street, Fremantle WA 6959, Australia
[5] Consultant, Department of Anaesthesia and Pain Management, Princess Margaret Hospital for Children, Perth, Australia
[6] Chair of Paediatric Anaesthesia, School of Medicine and Pharmacology, The University of Western Australia, 35 Sterling Highway, Crawley WA 6009 Perth, Australia

Corresponding author
Prof. Britta S von Ungern-Sternberg
Chair of Paediatric Anaesthesia
Princess Margaret Hospital for Children, Perth, Australia
Britta.regli-vonungern@health.wa.gov.au

Keywords
Respiratory adverse events, respiratory complications, laryngospasm, bronchospasm, pediatric anesthesia, stridor, desaturation, apnea, obstructive

sleep apnea, asthma, outcome, perioperative, anesthesia, treatment, premedication, critical incident, treatment, prevention, child, upper airway obstruction, expiration reflex, coughing, cardiac arrest

Abstract

Perioperative respiratory adverse events cause more than three quarters of all perioperative critical incidents in pediatric anesthesia and approximately half of anesthesia-related cardiac arrests. We can define seven main clinical types of perioperative respiratory adverse events: upper airway obstruction, laryngospasm, bronchospasm, severe persistent cough, apnea, stridor, and oxygen desaturation. Depending on the definitions used for preoperative respiratory adverse events and the cohort of children examined, the incidence varies between 8% and 21%.

This review discusses the recognition and treatment of perioperative respiratory adverse events. Furthermore, it provides guidance on how to identify children who are at increased risk for developing perioperative respiratory adverse events and how to tailor the perioperative anesthetic management for the individual child in order to minimize the risk of perioperative respiratory adverse events.

Introduction

PRAE

Perioperative respiratory adverse events (PRAE) cause not only more than three-quarters of all perioperative critical incidents in pediatric anesthesia [1, 2], they also cause 30-70% of all anesthesia related cardiac arrests [3-5], three quarter of all unplanned postoperative admissions to the pediatric intensive care unit [6] as well as approximately half of all pediatric anesthesia-related malpractice claims [7].

Aim and scope of review

This review discusses the recognition and treatment of PRAE. Furthermore, it provides guidance on how to identify children who are at increased risk for developing PRAE and how to tailor the perioperative anesthetic management for the individual child in order to minimize the risk of PRAE.

Since PRAE are a major cause of morbidity and mortality in pediatric anesthesia, a better understanding of the perioperative prevention and management of PRAE are important to improve the safety of children undergoing anesthesia. This article does not discuss PRAE related to difficult airway management.

In the perioperative period, we can define seven main clinical types of PRAE [8, 9]:

1. **Partial and complete upper airway obstruction** is a mechanical obstruction to airflow that can be defined clinically as erratic respiratory efforts in combination with an inspiratory stridor, a snoring noise or paradoxical movement of the abdomen [10, 11]. Partial or complete upper airway obstruction is generally reversed by the use of airway maneuvers (e.g. chin lift, jaw thrust).
2. **Laryngospasm** is a partial or complete airway obstruction at the level of the larynx. A clinical definition of a laryngospasm is either absent airflow or

inspiratory stridor coupled with muscle rigidity of the abdominal and chest walls during increased inspiratory effort. Associated clinical signs may include cough, expiration reflex, breathholding and straining during inspiration and expiration as part of the laryngeal reflex responses to laryngeal stimulation.

3. **Bronchospasm** is a severe narrowing of the distal airways and can be defined as an increased respiratory effort, particularly during expiration, and wheeze on auscultation or silent chest with minimal chest movement in severe cases. Associated clinical signs may include cough, straining during inspiration and expiration, use of accessory muscle, as well as tracheal and chest wall tugging.
4. **A severe persistent cough** is defined as a series of pronounced, persistent severe coughs lasting for > 10 seconds in duration. A severe cough might be associated with a laryngospasm (see above).
5. **Apnea** is defined as complete cessation of gas flow for > 10 seconds irrespective of the presence or absence of inspiratory efforts (varying definitions) or less if the apnea is associated with bradycardia, cyanosis or pallor.
6. **Stridor** is defined as an abnormal, high-pitched breathing sound mainly on inspiration that is produced by increased turbulent airflow through a partially obstructed airway.
7. **Oxygen desaturation** has a range of definitions in the perioperative period that span from < 90-95%. In many institutions, 95% is the cut-off value for discharge to the patient ward and is thus the most commonly used definition of perioperative oxygen desaturation in an otherwise healthy child. Oxygen desaturation is often caused by the occurrence of other PRAE (e.g. laryngospasm), with the latter the goal of the intervention to restore the oxygen saturation.

Epidemiology

Depending on the definitions used for PRAE and the cohort of children examined, the incidence of PRAE varies between 8% and 21% [8, 12, 13]. In the largest observational trial reported to date, the incidence of PRAE in children was approximately 15% [8], with oxygen desaturation reported in 10%, coughing in 7%, upper airway obstruction in 4%, laryngospasm in 4%, bronchospasm in 2%, and stridor in 1% [8]. The patient-related risk factors associated with PRAE are summarized in Table 1 [1, 2, 8, 13-22].

Upper airway obstruction

Epidemiology

For the purpose of this review, upper airway obstruction (supra-glottic airway obstruction) is defined as mechanical non–reflex mediated airway obstruction. Most anesthetic agents cause a dose-dependent reduction in pharyngeal muscles tone thereby increasing the degree of upper airway obstruction. As a result of the relative benign nature of upper airway obstruction in the hands of skilled anesthetists, their occurrence is often underreported or not reported at all [1, 12, 15, 17]. The incidence of mechanical upper airway obstruction has been reported between 3.6 and 9.1% [8, 13]. However, failure to maintain a patent airway due to the lack of skill in the operator or in observation may rapidly result in hypoxemia, bradycardia or even cardiac arrest [4, 5, 23]. Therefore, airway maneuvers that restore airway patency belong to the core clinical skills of every anesthetist.

Upper airway obstruction is particularly common in children with obstructive sleep apnea [24]. Obstructive sleep apnea occurs in approximately 10% of the school-age children [25]. Symptoms range from mild snoring to obstructive sleep apnea syndrome with episodic apneas and desaturations.

Causes

The upper airway, which is mainly composed of soft tissues, maintains its patency during inspiration by the outward action of the pharyngeal airway muscles. Children are particularly susceptible to upper airway obstruction because the dimensions of their airways are smaller, thus increasing the resistance to airflow.

Most anesthetic agents reduce muscle activity in a dose-dependent manner, thereby reducing the patency of the airway also in a dose-dependent manner [10, 26-29]. In contrast to common belief that general anesthesia causes a predominant reduction in genioglossus muscle activity with the tongue being the main site of obstruction, the soft palate and the epiglottis are more frequently the site of perioperative upper airway obstruction in children [30-37].

Upper airway obstruction can be caused by anatomical abnormalities (e.g. tonsillar or adenoidal hypertrophy) or a reduction in upper airway muscle tone (e.g. anesthetic agents). In children with OSAS, tonsillar and adenoidal hypertrophy reduce the volume of the upper airway [25, 38]; commonly the soft tissue is thickened due to larger retropharygneal nodes [39, 39]. There is an age related maximum increase in the bulk of the oropharyngeal soft tissue (particularly tonsils and adenoids) in relation to the bone structures with the upper airway being smallest at the age of four years [40].

Diagnosis

Clinical signs of a perioperative upper airway obstruction range from snoring and inspiratory stridor to paradoxical movements of the abdomen and absent airflow during partial and total upper airway obstruction, respectively [10, 11, 29].

Treatment

Airway maneuvers generally reverse upper airway obstruction by increasing glottic opening [10, 11]. Both chin and jaw thrust effectively increase the cross sectional area in the pharynx. Chin lift increases the antero-posterior dimensions at all pharyngeal levels with predominance at level of the epiglottis [41]. Neck flexion (chin to chest) decreases whereas neck extension in general increases the dimensions of the pharyngeal space, the latter attenuating the resistance to inspiration and therefore the severity of upper airway obstruction [26]. Turning the head to the side however has only a small influence on upper airway dimensions [26]. Positioning the child in the lateral decubitus position reduces airway obstruction and substantially enhances the effectiveness airway maneuvers [42]. A neck collar to prevent downward displacement of the mandible and maintaining slight neck extension increases cross sectional area at the level of epiglottis and tongue and can be used during MRI [43]. Alternately, upper airway patency can be preserved in most infants and children during MRI by simply placing a roll under the shoulders or cervical spine to extend the neck [44].

CPAP is defined as continuous positive airway pressure. It provides continuous positive pressure in the upper airway throughout all phases of the respiratory cycle. This positive pressure offsets in part, the negative pressure created during maximum inspirational effort, thereby increasing the cross sectional area of the pharynx [29]. Pressures as little as 5 cmH_2O can be sufficient to overcome sedation related upper airway obstruction but greater pressures may be required in children with tonsillar or adenoid hyperplasia [29]. This so called airway splinting is useful not only in children with OSAS but also in those with anesthesia-related upper airway obstruction [10, 29, 36].

Laryngospasm

Epidemiology

The incidence of perioperative laryngospasm varies widely in the literature from 0.1 to 16%, primarily due to differences in its definition [20, 45]. While perioperative laryngospasm occurs in approximately 4% of children in a general pediatric population [8, 13], smaller frequencies have been reported in retrospective studies or when only severe forms have been reported (e.g. laryngospasm triggering a “call for help”) [1, 2, 17, 45-47], whereas greater frequencies have been reported in children with associated risk factors (Table 1).

Laryngospasm occurs most frequently during emergence from anesthesia, and next most commonly during induction of anesthesia. Laryngospasm is infrequent during maintenance and in the post-anesthesia care unit (0.1 to 0.4%) [8, 13, 17-19, 45, 46, 48]. Laryngospasm is not only the most frequent respiratory cause of perioperative cardiac arrest in children [4], but it is also responsible for half of the perioperative “call for help” emergencies [47]. If left untreated, laryngospasm can rapidly lead to hypoxemia, bradycardia and cardiac arrest or in older children and adolescents, to negative pressure pulmonary edema, the need for ongoing mechanical ventilation and intensive care admission [49, 50].

Causes

There are two main causes for perioperative laryngospasm: imprimis, a lack of inhibition of glottic reflexes due to inadequate central nervous system depression and, secondly, an increased mechanical stimuli in the airway [51]. The causes of mechanical stimulation at an inappropriate depth of anesthesia include the presence of a tracheal tube, particularly at the time of intubation or extubation, secretions, gastric fluid or blood irritating the vocal cords, or stimulation of the airway by an artificial airway device, laryngoscope or suction catheter [51]. Although clinical experience suggests that laryngeal reflexes are more

pronounced during lighter levels of anesthesia, the literature describes similar incidences after direct laryngeal stimulation (except for the expiration reflex) at different levels of sevoflurane anesthesia [9, 52, 53]. However, the time to return to normal breathing during deeper levels of anesthesia is less than during lighter levels of anesthesia [9]. Therefore, the common practice to deepen anesthesia in case of a laryngospasm and other respiratory reflex responses remains warranted. Risk factors for laryngospasm are summarized in Table 1.

Pathophysiology

Simulation of the superior laryngeal nerve in response to stimulation of the supraglottic tissue and especially the vocal cords can trigger a reflex innervation of the intrinsic laryngeal muscle via the recurrent laryngeal nerve leading to laryngeal reflex responses including laryngospasm (closure of vocal cords and/or false cords), cough, expiration reflex (cough without preceding inspiration) and apnea (cessation of airflow > 10s) [9, 52, 54-56]. Apnea can occur in combination with a prolonged laryngospasm or alone. Interestingly, the incidence of laryngeal reflex responses decreases the more distal within the respiratory tract a stimulus occurs [52].

Laryngospasm has been subdivided into partial and complete airway obstruction [57]. Contraction of the adductor muscles (intrinsic laryngeal muscles) often causes incomplete vocal cord closure (“shutter mechanism”) [57] resulting in limited gas flow across the vocal cords, and possibly stridor. Contraction of the thyrohyoid muscle, sternohyoid muscle, sternothyroid muscle (extrinsic laryngeal muscles) causes an upward movement of the larynx relative to the hyoid bone. Concurrently, excessive laryngeal tissue folds including the paraglottis and false cords resulting in complete glottic closure (“ball valve mechanism”) [57]. In the latter scenario, gas flow ceases and stridor is inaudible. Video analysis of laryngeal stimulation confirms glottic closure during cough, expiration reflex and

laryngospasm occurs predominantly at the level of the false cords [9, 54, 55].

Diagnosis

Laryngospasm is a form of acquired upper airway obstruction. For the trainee anesthetist or the occasional pediatric anesthetist, classic upper (supraglottic) airway obstruction and laryngospasm are often difficult to differentiate [58]. Airway maneuvers are immediately effective in treating upper airway obstruction and in many cases can also relieve laryngospasm [9, 51, 55, 56, 59].

An inspiratory stridor is usually audible during partial laryngospasm [51], whereas stridor is absent during complete laryngospasm [56]. Laryngospasm might be preceded by an expiration reflex that can be coupled with an “expiratory stridor” [57]. Depending on the degree of airway obstruction, paradoxical chest movements, intercostal recessions and tracheal tug are often present [51, 56]. Some clinicians insist that the only “true” laryngospasm is complete laryngospasm [50]. However, both partial and complete laryngospasm are associated with increased morbidity. When managing a pediatric airway emergency, it is more important to actually treat laryngospasm than to engage in a discourse about the academic subtyping of the laryngospasm [51].

Treatment

Laryngospasm is a time-dependent, critical event that requires immediate treatment. It is important to minimize or eliminate the cause of the airway stimulation and to rapidly deepen anesthesia (e.g. propofol 0.5-0.8 mg/kg IV) [56, 60-62]. At the same time, airway maneuvers should be performed (e.g. jaw thrust) and the inspired oxygen concentration increased to 100% [51, 56].

Jaw thrust has the potential to convert a total into a partial or no laryngospasm by lengthening the laryngo-hyoid distance thereby reducing the “ball-valve” effect [56, 57]. In addition to subluxing the temperomandibular joint and opening the mouth, applying the jaw thrust to the coronoid process at the ascending ramus of the mandible causes intense pain [63]. This elicits a “fright and flight” response, which includes vocalization, a maneuver that opens the vocal cords. This alone may break a partial laryngospasm.

During partial laryngospasm CPAP alone may be sufficient to overcome the increased airway resistance caused by the glottis narrowing [51, 56]. However in the presence of a complete laryngospasm, CPAP may increase the pressure of the false cords onto the vocal cords (ball valve effect, see above), insufflate the stomach and cause respiratory aspiration of gastric content [56, 57]. It is therefore advisable to perform airway maneuvers before the application of CPAP. In case of severe desaturation without response to the initial steps, succinylcholine 1–2 mg/kg ± IV atropine (10-20 mcg/kg) should be given without delay. An early bail out is vital to avoid catastrophic outcomes of laryngospasm [9, 51, 56].

In the absence of IV access, intralingual (submental approach) or intramuscular succinylcholine can be applied 3-4 mg/kg [64]. Interestingly, only around 50% of children given a NMBA to treat laryngospasm will require endotracheal intubation [45].

Prevention

Education

The incidence of perioperative laryngospasm in infants and children can be reduced by education and training with regards to the prevention, recognition and treatment of a laryngospasm [51]. The introduction of an education package for staff halved the incidence of laryngospasm that resulted in “a call for help” [47].

Ensuring availability of emergency drugs such as propofol, succinylcholine and atropine at all times is strongly recommended [47].

Airway device

Despite published findings that the use of LMA was associated with a greater risk of laryngospasm than ETT [12, 15, 19, 45, 47], a large observational trial found that the incidence of laryngospasm after an ETT was associated with double the rate of laryngospasm (6%) when compared with that after using LMA (3%) in children [8, 18]. This latter finding is consistent with a recent meta-analysis that also reported a reduced incidence of laryngospasm with LMAs as compared with ETTs [65]. The explanation for these inconsistent findings might be selection bias or different techniques involved when using ETT or LMA [12, 15, 19, 45, 47]. Amongst other factors, inadequate anesthetic depth whilst inserting and removing an LMA, multiple attempts at intubation, intubation by a trainee as compared with a consultant have been identified as factors increasing the incidence of laryngospasm [8, 18].

With regards to the frequency of laryngospasm or bronchospasm, there was no difference found in an RCT when comparing deep vs awake ETT removal in children undergoing adenotonsillectomy [66]. However, the frequencies of severe coughing and postoperative hoarse voice were greater in children whose airways were extubated awake. There was also a trend towards more frequent and prolonged hemoglobin desaturations. In contrast, the frequency of airway obstruction (not associated with desaturation) was more common after deep tracheal extubation [66]. Of all airway management options, the use of a face mask was associated with the smallest frequency of laryngospasm [8, 12, 18].

Anesthetic agents

While premedication with midazolam does not appear to influence the occurrence of laryngospasm [8, 18], it is associated with a 1.8 fold increase in overall PRAE. Against common belief, the incidence of laryngeal reflex responses to direct laryngeal stimulation (except for the expiration reflex) is not influenced by the depth of anesthesia [9, 52, 53]. However, the time to return to a normal breathing pattern during a deeper level of anesthesia is less than after a lighter level of anesthesia [9], supporting the common practice to deepen anesthesia in case of laryngeal reflex responses.

To reduce the risk of laryngospasm, an IV induction is preferred instead of an inhalational induction [8, 9, 45, 67]. While NMBA can reduce the risk of laryngospasm at the time of tracheal intubation [68], a large observational cohort study demonstrated a greater incidence of laryngospasm in the postoperative period [8]. Maintenance of anesthesia with sevoflurane, propofol or isoflurane is associated with a significantly smaller incidence of laryngospasm compared with desflurane, which should be avoided in children (see also under bronchospasm) [8, 69].

The role of opioids to prevent laryngospasm remains controversial [54, 70]. However, remifentanyl is increasingly used to suppress laryngeal and bronchial reflex constriction during airway manipulations [71].

Lignocaine

IV lignocaine reduces the frequency of laryngospasm [55, 72]. Whether it is applied topically by spraying the vocal cords either blindly or under direct vision before placing the ETT, this role of lignocaine remains controversial since some studies reported the frequency of laryngospasm actually increased when lignocaine was used for intubation without muscle relaxants [8, 73].

Other agents

Magnesium (15 mg/kg magnesium IV in 30 ml NaCL 0.9% over 20 min) may be used to prevent laryngospasm after adeno-tonsillectomy [74, 75]. Preoperative salbutamol either via metered dose inhaler or via nebulizer (2.5 mg if weight <20 kg, 5 mg if weight >20 kg) 10–30 min prior to surgery may reduce the risk of laryngospasm and bronchospasm in patients with recent upper respiratory tract infection [20].

Bronchospasm

Epidemiology

While the incidence of perioperative bronchospasm in the general pediatric population is 0.2-4.1% [1, 8, 13, 46, 76], it is 2.2-5.7% in children with asthma. Generally, perioperative bronchospasm has a benign outcome although some episodes may warrant admission to PICU (3.8% of children with bronchospasm) or cardiac arrest (in 1-2.4%) [4, 5, 8, 76].

Causes

There are three major triggers for perioperative bronchospasm [77]:

1) Mechanical: Airway manipulation (e.g. tracheal intubation) can stimulate tracheal and laryngeal sensory nerves with efferent activation of the vagus nerve (para-sympathetic acetylcholine binding the M3 muscarinic receptors) leading to a bronchoconstriction.

2) Anaphylactoid reaction (non-immunological): Medications (e.g. morphine) can directly degranulate mast cell and basophils with subsequent histamine release and binding to histamine receptors leading to bronchoconstriction.

3) Immunological-anaphylaxis: Medications or other external stimuli can cause an immune mediated (immunoglobulin E) degranulation of mast cells and basophils with subsequent bronchoconstriction as described above.

The airway response to any of the above triggers can vary between subclinical mildly increased bronchial smooth muscle tone and a severe life threating bronchospasm and anaphylactic shock if immune mediated. However, the most common trigger for perioperative bronchospasm appears to be mechanical [76]. Indeed, perioperative bronchospasm occurs mainly during induction and emergence when mechanical stimulation of the airway is greatest [12].

Risk factors

Numerous risk factors for perioperative bronchospasm have been identified (Table 1). In general, airway inflammation causes airway susceptibility thereby increasing the risk of bronchospasm or laryngospasm following airway manipulation. Importantly, acute and chronic airway inflammation and can persist beyond the presence of respiratory symptoms. Of note: While an acute asthma exacerbation increases the risk for perioperative bronchospasm, a perioperative bronchospasm is unlikely to progress to an asthma exacerbation.

Diagnosis

Bronchospasm can be described as a sudden increase in bronchial smooth muscle tone associated with increased airflow obstruction often of short duration. Clinical signs include increased respiratory effort, particularly during expiration, and wheeze on auscultation. In severe cases the patient may have minimal chest movement with silent chest on auscultation. Additionally slow or incomplete expiration on inspection, oxygen desaturation, a prolonged phase 2 as well as an increased slope of phase 3 on the capnogram, high airway pressures and delayed expiratory flow on the flow-time curve may be noticed. If the bronchospasm is secondary to an anaphylactic or anaphylactoid reaction then rash, urticarial, angioedema, hypotension and tachycardia can be present [78].

Endobronchial intubation, pneumothorax, pulmonary edema, kinked or obstructed endotracheal tube can mimic a bronchospasm and need to be excluded.

Treatment of bronchospasm

As in the case of laryngospasm, treating an episode of perioperative bronchospasm should aim primarily to reduce any further stimuli and if possible, deepen the level of anesthesia followed by the administration of 100% oxygen. IV propofol or preferably volatile anesthetic agents are excellent bronchodilators that have been used to treat severe exacerbations of asthma (see below).

Beta-2 agonists should be considered. Importantly, compared with the doses used in awake children, the doses required to achieve a clinical response in children with intubated airways are more than 10 fold greater as less than 3% of the dose reaches the bronchial site of action [79, 80]. Recent evidence suggests that variability in the response to beta-2 agonists in some children may be explained by four single nucleotide polymorphisms within the glutathione-dependent S-nitrosoglutathione reductase, adrenergic receptor beta-2 and

carbamoyl phosphate synthetase-1 [81]. Future treatments may be adjusted based on these polymorphisms, to ensure successful goal-directed therapies.

If severe airflow obstruction persists, beta-2 agonists may also be given as a continuous infusion e.g. salbutamol 15 mcg/kg bolus over 10 min followed by 1 to 5 mcg/kg/min [82, 83]. In addition, anticholinergics including atropine 20 mcg/kg, glycopyrolate 20-40 mcg/kg and/or IV magnesium sulfate [84] may provide further bronchodilation.

Glucocorticosteriods should be considered if the bronchospasm is severe and persistent, especially when the bronchospasm may be the result of bronchial hyperreactivity or asthma. Inhaled or oral steroids are the main pillar of asthma treatment as they can reliably reduce airway inflammation and therefore reduce bronchial edema, bronchial mucus production and reduce the bronchial smooth muscle tone.

Ventilation of the lungs in children with a bronchospasm should follow the principles of protective lung ventilation for patients with severe airflow limitation (e.g. asthma exacerbation). The main principle is to minimize the risk of hyperinflation and barotrauma. A small respiratory rate, with a greater expiratory time and a decreased inspiratory to expiratory ratio (I:E ratio) should be applied whilst accepting “permissive hypercapnia”. At physiological lung conditions, plateau pressure should be limited since they are similar to alveolar pressures and are closely associated with the incidence of barotrauma. However, in the presence of airflow obstruction (e.g. in asthmatic children), plateau pressures and even more so peak inspiratory pressures do not reliably reflect alveolar pressures and higher airway pressures can be accepted without the risk of barotrauma. Flow-time curves can aid to monitor whether expiratory flows return to baseline [85, 86].

In children who develop a perioperative bronchospasm, a trial of high flow humidified oxygen or noninvasive ventilation might be beneficial in the post anesthetic care unit, not only to improve oxygenation but also to reduce the work of breathing. Noninvasive ventilation is feasible in children with asthma exacerbations and may have a role in children with prolonged perioperative bronchospasm. When using noninvasive ventilation, PEEP is ideally set below auto-PEEP (around 5 cmH_2O), whilst for inspiratory pressures, 10 and 15 cmH_2O are typically required [87].

Bronchospasm prevention

Premedication

Premedication with beta-2 agonists is recommended for all children with moderate or severe asthma or in those who are actively wheezing due to reactive airway disease (e.g. upper respiratory tract infection) in order to reduce the risk of PRAE [20, 88, 89].

Even though benzodiazepines might be useful to reduce preoperative anxiety, benzodiazepines do not reduce the incidence of perioperative laryngospasm or bronchospasm but instead may increase desaturations and upper airway obstructions particularly in children with an increased risk for PRAE [8]. Despite reflex bronchoconstriction blunting properties the role alpha-agonists as a premedication remains unclear [77, 90-93].

Lignocaine

In adult asthmatic volunteers, inhaled and IV lignocaine blunts broncho-constrictive effects of histamine and acetylcholine (but not metacholine) as well as of airway manipulation [94-98]. However, caution should be used since IV lignocaine can decrease airway diameter [99] and cause bronchospasm [100].

Airway manipulation

In general, less invasive airway devices and less airway manipulation reduce the risk of PRAE (see also under laryngospasm) [8]. If a child needs an ETT, we recommend the use of a cuffed as opposed to an uncuffed ETT in children with airway susceptibility especially to allow the application of greater peak airway pressures during mechanical ventilation [101]. A further advantage irrespective of the presence of airflow obstruction is that cuffed ETTs are associated with less postoperative sore throat [102].

Anesthetic agents

All volatile and most IV anesthetic agents are direct bronchodilators under physiological conditions [77]. In general, volatile anesthetic agents only have a limited ability to blunt reflex bronchoconstriction but exhibit good bronchodilatory effects, whereas propofol IV has particularly good ability to blunt reflex bronchoconstriction but a reduced bronchodilatatory effect [8, 103, 104], making propofol IV the induction agent of choice in children with increased risk of developing PRAE.

Compared with other volatile anesthetic agents, desflurane is associated with an increased bronchial smooth muscle tone and airway resistance, especially in children with increased airway susceptibility and should therefore be avoided [8, 69, 77, 105, 106].

In comparison with thiopental and etomidate, propofol is associated with least airway resistance after tracheal intubation [107]. Thiopental is better avoided in children with asthma due to its increased risk of causing bronchospasm on induction (probably via non-immunological anaphylaxis) [108, 109].

Although ketamine can blunt airway reflexes and has direct bronchodilatory properties [108], it has an inferior bronchodilatory effect in comparison to volatile anesthetic agents. Additionally, there is no outcome benefit in addition to standard treatment in children with asthma exacerbation giving ketamine only a

limited role in treating perioperative bronchospasm [110, 111]. Additionally, ketamine has not been shown to be superior to propofol as an induction agent and is associated with other adverse events in the postoperative period, e.g. a greater frequency of PONV, greater recovery times and hallucinations.

Neuromuscular blocking agents

If bronchospasm is persistent and severe, NMBA are recommended in the initial phase in order to improve mechanical ventilation [85, 112]. However, caution must be taken as NMBA can aggravate airflow obstruction via histamine liberation [77]. The risk of causing a bronchospasm through histamine liberation is greatest with mivacurium followed by suxamethonium, rocuronium, vecuronium and atracurium [77, 108]. In children, vecuronium, suxamethonium, and rocuronium have been shown to cause immunological (IgE mediated) anaphylaxis [77]. Pancuronium however does not liberate histamine and is least associated with immunological anaphylaxis.

Postoperative analgesia

Non-steroidal anti-inflammatory drugs (NSAIDs) increase leukotriene production by inhibiting the cyclooxygenase. NSAIDs have been associated with causing bronchospasm, laryngospasm, rhinorrhea, and periorbital edema especially in children with a history of asthma and chronic rhinosinusitis and nasal polyposis. Aspirin should be avoided in children with asthma to avoid aspirin asthma syndrome.

However, the frequency of NSAID-induced postoperative bronchospasm is small even in patients with asthma [113, 114]. Clinical studies in children with asthma who are receiving NSAIDs have shown no or only minimal temporary changes in respiratory function [115, 116]. Therefore, a short-term course of NSAIDs has a small risk of precipitating bronchospasm in children with asthma unless they have a history of nasal polyposis or known respiratory intolerance to NSAIDs.

Furthermore, one should also exercise caution in children with asthma when prescribing acetaminophen (paracetamol) for postoperative pain as there is emerging evidence of acetaminophen (paracetamol) being a causative agent of asthma [113].

Children with asthma

In all children with asthma, preexisting oral and /or inhaled steroids should be continued and if necessary given IV. In children with poorly controlled asthma, surgery should ideally be delayed in order to initiate or intensify medical asthma treatment and allow time for respiratory improvement. A short-term course of systemic steroids is warranted should asthma symptoms be severe and persistent or where inhaled steroid cannot be provided. When surgery cannot be delayed, initiating or intensifying asthma treatment is recommended with inhaled beta 2 agonists and IV steroids. Additionally, specialist referral for further ongoing management including PICU admission for children with severe asthma exacerbation should be considered. Children with poorly controlled asthma should immediately be given bronchodilator therapy either via nebulizer or a pMDI. If necessary, ipratropium bromide has an additional bronchodilatory effect and can be given together with the beta-2-agonsist.

Oxygen Desaturation

Oxygen desaturation is more a symptom than a diagnosis as hypoxemia is the common final result of most respiratory and some non-respiratory pathologies. Accordingly, the differential diagnosis of perioperative hypoxemia is large. The more frequent causes of hypoxemia include upper airway obstruction, bronchospasm, laryngospasm, tension pneumothorax, atelectasis, aspiration or pulmonary edema.

Apart from chest trauma or iatrogenic causes (e.g. insertion of central venous line) tension pneumothorax can be the result of injurious bag valve mask or

mechanical ventilation in the presence of a bronchospasm or asthma exacerbation. Asymmetrical chest movement, percussion and auscultation or chest XR can confirm the diagnosis prior the insertion of a chest drain. Atelectasis is frequent in children with asthma due to mucus plugging in relatively small airway calibers. If atelectasis and hypoxia is severe the patient might benefit of endobronchial suctioning. However, care must be taken as this process itself can irritate airways and itself can worsen airflow obstruction.

Conclusions

In conclusion, respiratory adverse events are common in pediatric anesthesia. A careful medical history can help to identify children at increased risk and allow the anesthesiologist to tailor the anesthestic for the individual child. In case of perioperative PRAE, treatment without delay is essential to avoid hypoxemia.

References

1. Tay, CL, Tan, GM, Ng, SB: Critical incidents in paediatric anaesthesia: an audit of 10 000 anaesthetics in Singapore. Paediatr Anaesth. 2001; 11:711-718.
2. Wan, S, Siow, YN, Lee, SM et al.: Audits and critical incident reporting in paediatric anaesthesia: lessons from 75,331 anaesthetics. Singapore Med J. 2013; 54:69-74.

* To date this is the largest retrospective analysis of perioperative critical incidences in children covering a 10 year period in a single center

3. Gobbo Braz, L, Braz, JR, Modolo, NS et al.: Perioperative cardiac arrest and its mortality in children. A 9-year survey in a Brazilian tertiary teaching hospital. Paediatr Anaesth. 2006; 16:860-866.
4. Bhananker, SM, Ramamoorthy, C, Geiduschek, JM et al.: Anesthesia-related cardiac arrest in children: update from the Pediatric Perioperative Cardiac Arrest Registry. Anesth Analg. 2007; 105:344-350.
5. Bharti, N, Batra, YK, Kaur, H: Paediatric perioperative cardiac arrest and its mortality: database of a 60-month period from a tertiary care paediatric centre. Eur J Anaesthesiol. 2009; 26:490-495.
6. Kurowski, I, Sims, C: Unplanned anesthesia-related admissions to pediatric intensive care - a 6-year audit. Paediatr Anaesth. 2007; 17:575-580.
7. Morray, JP, Geiduschek, JM, Caplan, RA et al.: A comparison of pediatric and adult anesthesia closed malpractice claims. Anesthesiology. 1993; 78:461-467.
8. von Ungern-Sternberg, BS, Boda, K, Chambers, NA et al.: Risk assessment for respiratory complications in paediatric anaesthesia: a prospective cohort study. Lancet. 2010; 376:773-783.
9. Oberer, C, von Ungern-Sternberg, BS, Frei, FJ et al.: Respiratory reflex responses of the larynx differ between sevoflurane and propofol in pediatric patients. Anesthesiology. 2005; 103:1142-1148.
10. von Ungern-Sternberg, BS, Erb, TO, Reber, A et al.: Opening the upper airway--airway maneuvers in pediatric anesthesia. Paediatr Anaesth. 2005; 15:181-189.
11. von Ungern-Sternberg, BS, Erb, TO, Frei, FJ: [Management of the upper airway in spontaneously breathing children. A challenge for the anaesthetist]. Anaesthesist. 2006; 55:164-170.
12. Bordet, F, Allaouchiche, B, Lansiaux, S et al.: Risk factors for airway complications during general anaesthesia in paediatric patients. Paediatr Anaesth. 2002; 12:762-769.
13. Mamie, C, Habre, W, Delhumeau, C et al.: Incidence and risk factors of perioperative respiratory adverse events in children undergoing elective surgery. Paediatr Anaesth. 2004; 14:218-224.
14. Schreiner, MS, O'Hara, I, Markakis, DA et al.: Do children who experience laryngospasm have an increased risk of upper respiratory tract infection? Anesthesiology. 1996; 85:475-480.
15. Tait, AR, Malviya, S, Voepel-Lewis, T et al.: Risk factors for perioperative adverse

respiratory events in children with upper respiratory tract infections. Anesthesiology. 2001; 95:299-306.
16. Green, SM, Klooster, M, Harris, T et al.: Ketamine sedation for pediatric gastroenterology procedures. J Pediatr Gastroenterol Nutr. 2001; 32:26-33.
17. Murat, I, Constant, I, Maud'huy, H: Perioperative anaesthetic morbidity in children: a database of 24,165 anaesthetics over a 30-month period. Paediatr Anaesth. 2004; 14:158-166.
18. von Ungern-Sternberg, BS, Boda, K, Schwab, C et al.: Laryngeal mask airway is associated with an increased incidence of adverse respiratory events in children with recent upper respiratory tract infections. Anesthesiology. 2007; 107:714-719.
19. Flick, RP, Wilder, RT, Pieper, SF et al.: Risk factors for laryngospasm in children during general anesthesia. Paediatr Anaesth. 2008; 18:289-296.
20. von Ungern-Sternberg, BS, Habre, W, Erb, TO et al.: Salbutamol premedication in children with a recent respiratory tract infection. Paediatr Anaesth. 2009; 19:1064-1069.
21. van der Griend, BF, Lister, NA, McKenzie, IM et al.: Postoperative mortality in children after 101,885 anesthetics at a tertiary pediatric hospital. Anesth Analg. 2011; 112:1440-1447.
22. Nafiu, OO, Prasad, Y, Chimbira, WT: Association of childhood high body mass index and sleep disordered breathing with perioperative laryngospasm. Int J Pediatr Otorhinolaryngol. 2013; 77:2044-2048.
23. Tiret, L, Nivoche, Y, Hatton, F et al.: Complications related to anaesthesia in infants and children. A prospective survey of 40240 anaesthetics. Br J Anaesth. 1988; 61:263-269.
24. Lumeng, JC, Chervin, RD: Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc. 2008; 5:242-252.
25. Tait, AR, Voepel-Lewis, T, O'Brien, LM: Postsurgical behaviors in children with and without symptoms of sleep-disordered breathing. Perioper Med (Lond). 2014; 3:8.
26. Wilson, SL, Thach, BT, Brouillette, RT et al.: Upper airway patency in the human infant: influence of airway pressure and posture. J Appl Physiol Respir Environ Exerc Physiol. 1980; 48:500-504.
27. Montravers, P, Dureuil, B, Desmonts, JM: Effects of i.v. midazolam on upper airway resistance. Br J Anaesth. 1992; 68:27-31.
28. Keidan, I, Fine, GF, Kagawa, T et al.: Work of breathing during spontaneous ventilation in anesthetized children: a comparative study among the face mask, laryngeal mask airway and endotracheal tube. Anesth Analg. 2000; 91:1381-1388.
29. Meier, S, Geiduschek, J, Paganoni, R et al.: The effect of chin lift, jaw thrust, and continuous positive airway pressure on the size of the glottic opening and on stridor score in anesthetized, spontaneously breathing children. Anesth Analg. 2002; 94:494-499.
30. Crawford, MW, Arrica, M, Macgowan, CK et al.: Extent and localization of changes in upper airway caliber with varying concentrations of sevoflurane in children. Anesthesiology. 2006; 105:1147-1152.
31. Abernethy, LJ, Allan, PL, Drummond, GB: Ultrasound assessment of the position of the tongue during induction of anaesthesia. Br J Anaesth. 1990; 65:744-748.

32. Nandi, PR, Charlesworth, CH, Taylor, SJ et al.: Effect of general anaesthesia on the pharynx. Br J Anaesth. 1991; 66:157-162.
33. Mathru, M, Esch, O, Lang, J et al.: Magnetic resonance imaging of the upper airway. Effects of propofol anesthesia and nasal continuous positive airway pressure in humans. Anesthesiology. 1996; 84:273-279.
34. Litman, RS, Weissend, EE, Shrier, DA et al.: Morphologic changes in the upper airway of children during awakening from propofol administration. Anesthesiology. 2002; 96:607-611.
35. Evans, RG, Crawford, MW, Noseworthy, MD et al.: Effect of increasing depth of propofol anesthesia on upper airway configuration in children. Anesthesiology. 2003; 99:596-602.
36. Crawford, MW, Rohan, D, Macgowan, CK et al.: Effect of propofol anesthesia and continuous positive airway pressure on upper airway size and configuration in infants. Anesthesiology. 2006; 105:45-50.
37. Machata, AM, Kabon, B, Willschke, H et al.: Upper airway size and configuration during propofol-based sedation for magnetic resonance imaging: an analysis of 138 infants and children. Paediatr Anaesth. 2010; 20:994-1000.
38. Arens, R, McDonough, JM, Corbin, AM et al.: Upper airway size analysis by magnetic resonance imaging of children with obstructive sleep apnea syndrome. Am J Respir Crit Care Med. 2003; 167:65-70.
39. Arens, R, Sin, S, Nandalike, K et al.: Upper airway structure and body fat composition in obese children with obstructive sleep apnea syndrome. Am J Respir Crit Care Med. 2011; 183:782-787.
40. Jeans, WD, Fernando, DC, Maw, AR et al.: A longitudinal study of the growth of the nasopharynx and its contents in normal children. Br J Radiol. 1981; 54:117-121.
41. Reber, A, Wetzel, SG, Schnabel, K et al.: Effect of combined mouth closure and chin lift on upper airway dimensions during routine magnetic resonance imaging in pediatric patients sedated with propofol. Anesthesiology. 1999; 90:1617-1623.
42. Arai, YC, Fukunaga, K, Hirota, S et al.: The effects of chin lift and jaw thrust while in the lateral position on stridor score in anesthetized children with adenotonsillar hypertrophy. Anesth Analg. 2004; 99:1638-1641.
43. Moustafa, MA, Emara, DM, Nouh, MR: Effect of a neck collar on upper airway size in children sedated with propofol-midazolam combination during magnetic resonance imaging. Paediatr Anaesth. 2015; 25:421-427.

* Neck collar can be easily applied and reduces sedation induced upper airway obstruction in children undergoing MRI

44. Heard, C, Harutunians, M, Houck, J et al.: Propofol anesthesia for children undergoing magnetic resonance imaging: a comparison with isoflurane, nitrous oxide, and a laryngeal mask airway. Anesth Analg. 2015; 120:157-164.

** Propofol sedation with nasal oxygen causes less respiratory adverse events compared to volatile anesthesia via laryngeal mask airway

45. Burgoyne, LL, Anghelescu, DL: Intervention steps for treating laryngospasm in pediatric patients. Paediatr Anaesth. 2008; 18:297-302.
46. Orestes, MI, Lander, L, Verghese, S et al.: Incidence of laryngospasm and bronchospasm in pediatric adenotonsillectomy. Laryngoscope. 2012; 122:425-428.
47. Mc Donnell, C: Interventions guided by analysis of quality indicators decrease the

frequency of laryngospasm during pediatric anesthesia. Paediatr Anaesth. 2013; 23:579-587.
** Departmental education together with ensuring availability to emergency drugs can significantly reduce the incidence of laryngospasms requiring “a call for help”
48. von Ungern-Sternberg, BS: Respiratory complications in the pediatric postanesthesia care unit. Anesthesiol Clin. 2014; 32:45-61.
* This review summarizes the respiratory complications and their management in the post anesthetic care unit
49. Visvanathan, T, Kluger, MT, Webb, RK et al.: Crisis management during anaesthesia: laryngospasm. Qual Saf Health Care. 2005; 14:e3.
50. Al-alami, AA, Zestos, MM, Baraka, AS: Pediatric laryngospasm: prevention and treatment. Curr Opin Anaesthesiol. 2009; 22:388-395.
51. Hampson-Evans, D, Morgan, P, Farrar, M: Pediatric laryngospasm. Paediatr Anaesth. 2008; 18:303-307.
52. Nishino, T, Kochi, T, Ishii, M: Differences in respiratory reflex responses from the larynx, trachea, and bronchi in anesthetized female subjects. Anesthesiology. 1996; 84:70-74.
53. Davidson, A: The correlation between bispectral index and airway reflexes with sevoflurane and halothane anaesthesia. Paediatr Anaesth. 2004; 14:241-246.
54. Tagaito, Y, Isono, S, Nishino, T: Upper airway reflexes during a combination of propofol and fentanyl anesthesia. Anesthesiology. 1998; 88:1459-1466.
55. Erb, TO, von Ungern-Sternberg, BS, Keller, K et al.: The effect of intravenous lidocaine on laryngeal and respiratory reflex responses in anaesthetised children*. Anaesthesia. 2013; 68:13-20.
** This interventional study demonstrates the time dependent effect of lignocaine on reducing reflexes due to airway manipulation
56. Roy, WL, Lerman, J: Laryngospasm in paediatric anaesthesia. Can J Anaesth. 1988; 35:93-98.
57. FINK, BR: The etiology and treatment of laryngeal spasm. Anesthesiology. 1956; 17:569-577.
58. Rajan, GR: Supraglottic obstruction versus true laryngospasm: the best treatment. Anesthesiology. 1999; 91:581.
59. Hammer, J, Reber, A, Trachsel, D et al.: Effect of jaw-thrust and continuous positive airway pressure on tidal breathing in deeply sedated infants. J Pediatr. 2001; 138:826-830.
60. Nawfal, M, Baraka, A: Propofol for relief of extubation laryngospasm. Anaesthesia. 2002; 57:1036.
61. Afshan, G, Chohan, U, Qamar-Ul-Hoda, M et al.: Is there a role of a small dose of propofol in the treatment of laryngeal spasm? Paediatr Anaesth. 2002; 12:625-628.
62. Batra, YK, Ivanova, M, Ali, SS et al.: The efficacy of a subhypnotic dose of propofol in preventing laryngospasm following tonsillectomy and adenoidectomy in children. Paediatr Anaesth. 2005; 15:1094-1097.
63. Larson, CPJ: Laryngospasm--the best treatment. Anesthesiology. 1998; 89(5):1293-1294.
64. Redden, RJ, Miller, M, Campbell, RL: Submental administration of succinylcholine

in children. Anesth Prog. 1990; 37:296-300.
65. Luce, V, Harkouk, H, Brasher, C et al.: Supraglottic airway devices vs tracheal intubation in children: a quantitative meta-analysis of respiratory complications. Paediatr Anaesth. 2014; 24:1088-1098.
** This meta-analysis demonstrates endotracheal intubation to have a higher incidence of laryngospasm when compared with laryngeal mask airway
66. von Ungern-Sternberg, BS, Davies, K, Hegarty, M et al.: The effect of deep vs. awake extubation on respiratory complications in high-risk children undergoing adenotonsillectomy: a randomised controlled trial. Eur J Anaesthesiol. 2013; 30:529-536.
** This randomized control trial did not show any difference in regards to respiratory adverse events in high risk children who were extubated deep or awake
67. von Ungern-Sternberg, BS, Ramgolam, A, Zhang, B et al.: Is intravenous induction of anaesthesia superior to inhalational induction in children with increased airway susceptibility? ANZCA, Singapore. 2014;
68. Devys, JM, Mourissoux, G, Donnette, FX et al.: Intubating conditions and adverse events during sevoflurane induction in infants. Br J Anaesth. 2011; 106:225-229.
69. von Ungern-Sternberg, BS, Saudan, S, Petak, F et al.: Desflurane but not sevoflurane impairs airway and respiratory tissue mechanics in children with susceptible airways. Anesthesiology. 2008; 108:216-224.
70. Erb, TO, von Ungern-Sternberg, BS, Keller, K et al.: Fentanyl does not reduce the incidence of laryngospasm in children anesthetized with sevoflurane. Anesthesiology. 2010; 113:41-47.
71. Goudra, BG, Singh, PM, Manjunath, AK et al.: Effectiveness of high dose remifentanil in preventing coughing and laryngospasm in non-paralyzed patients for advanced bronchoscopic procedures. Ann Thorac Med. 2014; 9:23-28.
* High dose remifentanyl reduced the incidence of coughing and laryngospasm during bronchoscopy
72. Mihara, T, Uchimoto, K, Morita, S et al.: The efficacy of lidocaine to prevent laryngospasm in children: a systematic review and meta-analysis. Anaesthesia. 2014; 69:1388-1396.
* Intravenous lignocaine is superior to topical lignocaine in preventing laryngospasm due to airway manipulation
73. Hamilton, ND, Hegarty, M, Calder, A et al.: Does topical lidocaine before tracheal intubation attenuate airway responses in children? An observational audit. Paediatr Anaesth. 2012; 22:345-350.
* This observational study questions the role of topical lignocaine in preventing laryngospasm due to airway manipulation
74. Gulhas, N, Durmus, M, Demirbilek, S et al.: The use of magnesium to prevent laryngospasm after tonsillectomy and adenoidectomy: a preliminary study. Paediatr Anaesth. 2003; 13:43-47.
75. Marzban, S, Haddadi, S, Naghipour, MR et al.: The effect of intravenous magnesium sulfate on laryngospasm after elective adenotonsillectomy surgery in children. Anesth Pain Med. 2014; 4:e15960.
* Intravenous magnesium might be beneficial in reducing the incidence of

postoperative laryngospasm
76. Olsson, GL: Bronchospasm during anaesthesia. A computer-aided incidence study of 136,929 patients. Acta Anaesthesiol Scand. 1987; 31:244-252.
77. Habre, W, Petak, F: Anaesthesia management of patients with airway susceptibilities: what have we learnt from animal models? Eur J Anaesthesiol. 2013; 30:519-528.
** This excellent review provides an overview of the animal experimental evidence in the causes of anesthesia bronchospasm
78. Sheikh, A, Shehata, YA, Brown, SG et al.: Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. Cochrane Database Syst Rev. 2008; CD006312.
79. Corbridge, TC, Hall, JB: The assessment and management of adults with status asthmaticus. Am J Respir Crit Care Med. 1995; 151:1296-1316.
80. Taylor, RH, Lerman, J: High-efficiency delivery of salbutamol with a metered-dose inhaler in narrow tracheal tubes and catheters. Anesthesiology. 1991; 74:360-363.
81. Moore, PE, Ryckman, KK, Williams, SM et al.: Genetic variants of GSNOR and ADRB2 influence response to albuterol in African-American children with severe asthma. Pediatr Pulmonol. 2009; 44:649-654.
82. Travers, AH, Jones, AP, Camargo, CAJ et al.: Intravenous beta(2)-agonists versus intravenous aminophylline for acute asthma. Cochrane Database Syst Rev. 2012; 12:CD010256.
83. British Guideline on the Management of Asthma. Thorax. 2008; 63 Suppl 4:iv1-121.
84. Rowe, BH, Bretzlaff, JA, Bourdon, C et al.: Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database Syst Rev. 2000; CD001490.
85. Sabato, K, Hanson, JH: Mechanical ventilation for children with status asthmaticus. Respir Care Clin N Am. 2000; 6:171-188.
86. Sarnaik, AP, Daphtary, KM, Meert, KL et al.: Pressure-controlled ventilation in children with severe status asthmaticus. Pediatr Crit Care Med. 2004; 5:133-138.
87. Mayordomo-Colunga, J, Medina, A, Rey, C et al.: Non-invasive ventilation in pediatric status asthmaticus: a prospective observational study. Pediatr Pulmonol. 2011; 46:949-955.
88. Scalfaro, P, Sly, PD, Sims, C et al.: Salbutamol prevents the increase of respiratory resistance caused by tracheal intubation during sevoflurane anesthesia in asthmatic children. Anesth Analg. 2001; 93:898-902.
89. Lauer, R, Vadi, M, Mason, L: Anaesthetic management of the child with co-existing pulmonary disease. Br J Anaesth. 2012; 109 Suppl 1:i47-i59.
90. Yamakage, M, Iwasaki, S, Satoh, JI et al.: Inhibitory effects of the alpha-2 adrenergic agonists clonidine and dexmedetomidine on enhanced airway tone in ovalbumin-sensitized guinea pigs. Eur J Anaesthesiol. 2008; 25:67-71.
91. Groeben, H, Mitzner, W, Brown, RH: Effects of the alpha2-adrenoceptor agonist dexmedetomidine on bronchoconstriction in dogs. Anesthesiology. 2004; 100:359-363.
92. Dinh Xuan, AT, Matran, R, Regnard, J et al.: Comparative effects of rilmenidine and clonidine on bronchial responses to histamine in asthmatic subjects. Br J Clin

Pharmacol. 1988; 26:703-708.
93. Dinh Xuan, AT, Regnard, J, Matran, R et al.: Effects of clonidine on bronchial responses to histamine in normal and asthmatic subjects. Eur Respir J. 1988; 1:345-350.
94. Groeben, H, Schwalen, A, Irsfeld, S et al.: Intravenous lidocaine and bupivacaine dose-dependently attenuate bronchial hyperreactivity in awake volunteers. Anesthesiology. 1996; 84:533-539.
95. Groeben, H, Silvanus, MT, Beste, M et al.: Both intravenous and inhaled lidocaine attenuate reflex bronchoconstriction but at different plasma concentrations. Am J Respir Crit Care Med. 1999; 159:530-535.
96. Groeben, H, Silvanus, MT, Beste, M et al.: Combined lidocaine and salbutamol inhalation for airway anesthesia markedly protects against reflex bronchoconstriction. Chest. 2000; 118:509-515.
97. Adamzik, M, Groeben, H, Farahani, R et al.: Intravenous lidocaine after tracheal intubation mitigates bronchoconstriction in patients with asthma. Anesth Analg. 2007; 104:168-172.
98. Groeben, H, Peters, J: Lidocaine exerts its effect on induced bronchospasm by mitigating reflexes, rather than by attenuation of smooth muscle contraction. Acta Anaesthesiol Scand. 2007; 51:359-364.
99. Chang, HY, Togias, A, Brown, RH: The effects of systemic lidocaine on airway tone and pulmonary function in asthmatic subjects. Anesth Analg. 2007; 104:1109-1115.
100. Burches, BRJ, Warner, DO: Bronchospasm after intravenous lidocaine. Anesth Analg. 2008; 107:1260-1262.
101. Cox, RG, Barker, GA, Bohn, DJ: Efficacy, results, and complications of mechanical ventilation in children with status asthmaticus. Pediatr Pulmonol. 1991; 11:120-126.
102. Calder, A, Hegarty, M, Erb, TO et al.: Predictors of postoperative sore throat in intubated children. Paediatr Anaesth. 2012; 22:239-243.
103. Habre, W, Scalfaro, P, Sims, C et al.: Respiratory mechanics during sevoflurane anesthesia in children with and without asthma. Anesth Analg. 1999; 89:1177-1181.
104. Lele, E, Petak, F, Carnesecchi, S et al.: The protective effects of volatile anesthestics against the bronchoconstriction induced by an allergic reaction in sensitized rabbit pups. Anesth Analg. 2013; 116:1257-1264.
105. Dikmen, Y, Eminoglu, E, Salihoglu, Z et al.: Pulmonary mechanics during isoflurane, sevoflurane and desflurane anaesthesia. Anaesthesia. 2003; 58:745-748.
106. Nyktari, V, Papaioannou, A, Volakakis, N et al.: Respiratory resistance during anaesthesia with isoflurane, sevoflurane, and desflurane: a randomized clinical trial. Br J Anaesth. 2011; 107:454-461.
107. Eames, WO, Rooke, GA, Wu, RS et al.: Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. Anesthesiology. 1996; 84:1307-1311.
108. Hirshman, CA, Bergman, NA: Factors influencing intrapulmonary airway calibre during anaesthesia. Br J Anaesth. 1990; 65:30-42.
109. Rooke, GA, Choi, JH, Bishop, MJ: The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. Anesthesiology. 1997; 86:1294-1299.

110. Allen, JY, Macias, CG: The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. Ann Emerg Med. 2005; 46:43-50.
111. Jat, KR, Chawla, D: Ketamine for management of acute exacerbations of asthma in children. Cochrane Database Syst Rev. 2012; 11:CD009293.
112. Tuxen, DV, Lane, S: The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. Am Rev Respir Dis. 1987; 136:872-879.
113. McBride, JT: The association of acetaminophen and asthma prevalence and severity. Pediatrics. 2011; 128:1181-1185.
114. Lesko, SM, Louik, C, Vezina, RM et al.: Asthma morbidity after the short-term use of ibuprofen in children. Pediatrics. 2002; 109:E20.
115. Debley, JS, Carter, ER, Gibson, RL et al.: The prevalence of ibuprofen-sensitive asthma in children: a randomized controlled bronchoprovocation challenge study. J Pediatr. 2005; 147:233-238.
116. Short, JA, Barr, CA, Palmer, CD et al.: Use of diclofenac in children with asthma. Anaesthesia. 2000; 55:334-337.