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Opioid-Induced Respiratory Depression—Pediatric Considerations

by Tricia Vecchione, MD, MPH, and Constance L. Monitto, MD

Following surgery, respiratory depression can occur for a variety of reasons and results in potentially catastrophic complications.[1] One of the recurring causes of respiratory depression in the postoperative period is the perioperative use of opioids.[2] In light of this, institutions and professional societies, including the Anesthesia Patient Safety Foundation (APSF), have developed recommendations regarding patient monitoring[3,4] and published articles advocating that decisions regarding the appropriate level of postoperative monitoring be guided by preoperative assessment of patient-specific risk factors.[5] As with adults, perioperative respiratory complications occur in pediatric patients and constitute a common cause of postoperative adverse events.[6] However, children are not "little adults." Hence, extrapolating previously published guidelines and studies must be undertaken with caution.

PEDIATRIC RISK FACTORS FOR OPIOID-INDUCED RESPIRATORY DEPRESSION

There is limited literature available addressing risk factors for opioid-induced respiratory depression (OIRD) in children. While comorbidities including diabetes mellitus and cardiac disease are significant risk factors for critical respiratory events in adults after parenteral opioid therapy,[7,8] given their low incidence in children, they are unlikely to be primary drivers in the pediatric setting. Instead, evidence from patient audits and data tracking administration of naloxone, a surrogate indicator of OIRD, has helped identify risk factors (Figure 1). For example, underlying respiratory disease and developmental delay have been identified as comorbidities that may play a role in increasing risk for pediatric OIRD.[9-11]

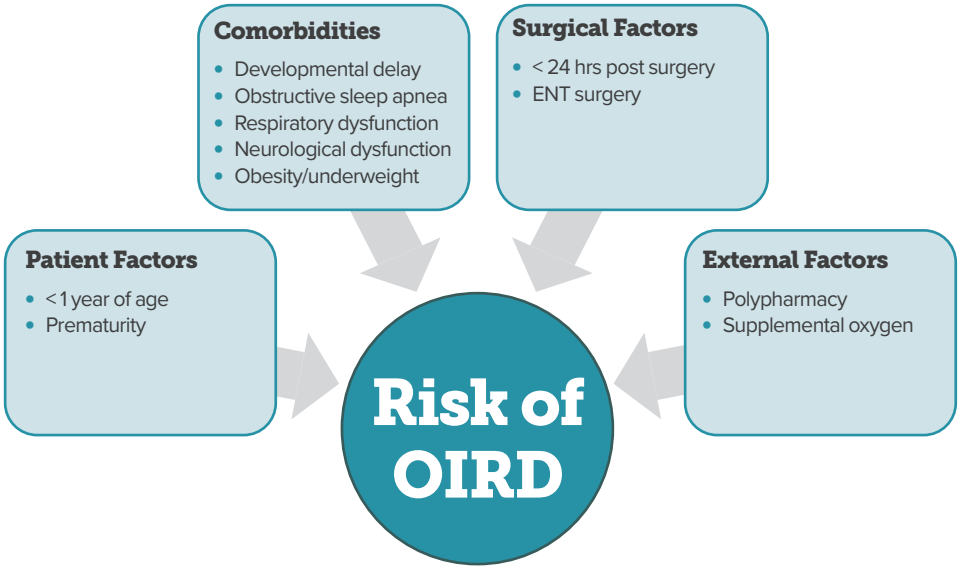

Figure 1. Summary of risk factors associated with increased risk of Opioid Induced Respiratory Depression {*OIRD) in children.*[4,10]

Another risk factor for OIRD in the pediatric population is young age. In a retrospective review of pediatric patients who required naloxone for critical respiratory events, increased incidence was associated with younger age as well as prematurity.[10] Increased risk may be attributed to physiologic differences regarding metabolism and excretion of opioids between young infants and older children and adults. For example, the half-life of morphine is prolonged and clearance is lower in newborns. Thus, depending on dosing, infants younger than one month of age may achieve higher serum levels that decline more slowly as compared to levels in older children and adults, putting them at elevated risk.[12]

The increased risk of postoperative respiratory depression with obstructive sleep apnea (OSA)[13] is also reported in children. Following tonsillectomy, children with severe OSA are more sensitive to morphine-induced respiratory depression and require less morphine than those with mild sleep apnea.[14] OSA is relatively common in pediatrics, occurring in 1–5% of children.[15] However, preoperative screening can be somewhat challenging. Polysomnography is the gold standard in diagnosis, but it is not available for most pediatric patients. There is no validated risk assessment questionnaire applicable to children of all ages; however, pediatric-specific risk factors and symptoms of OSA have been reported.[16]

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Experts Suggest Continuous Monitoring of Oxygenation and Ventilation for at Least 24 Hours Postoperatively in Pediatric Patients Who Receive Opioids

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Childhood obesity is also a risk factor for naloxone administration.[10] This may be attributed to the strong association between obesity and OSA or may reflect inaccurate dosing related to obesity. In contrast to adults, weight-based dosing is a common practice for many pediatric medications, but opiate dosing based on total body weight can cause dangerous respiratory depression. Therefore, dosing should be based on ideal or lean body mass.[17] Interestingly, in children, being underweight is a risk factor for respiratory events as well.[10]

Excessive sedation has been observed prior to opioid-related morbidity in a majority of children.[4] While the sedating effects of opioids in opioid-naive patients are well known, central nervous system (CNS) depression can be compounded by co-administration of anxiolytics, muscle relaxants, anticonvulsants, and other sedating medications. Such combinations can lead to life-threatening respiratory events and increased risk for naloxone interventions.[10] This is particularly important as co-administration of opioids and other CNS depressants has been reported to be common in pediatric practice with more than 40% of respondents allowing co-administration of these medications in a 2010 survey of pediatric pain management practice.[18] While practice may have changed in the intervening decade, given the recent focus on opioid sparing with multimodal analgesic regimens, this polypharmacy is unlikely to have decreased dramatically.

Following surgery, the highest risk for respiratory depression occurs within the first postoperative day. In fact, 75% of episodes in children who received naloxone for critical respiratory events were seen within the first 24 hours after surgery. Events occurred in patients who received opioids via the intravenous, oral, and neuraxial routes, suggesting no method of administration is intrinsically without risk.[10]

CURRENT RECOMMENDATIONS FOR MONITORING OF PEDIATRIC PATIENTS

To minimize the risk of respiratory depression, the APSF has long advocated that continuous electronic monitoring of oxygenation and ventilation, when supplemental oxygen is provided, be used to preemptively identify and potentially prevent OIRD.[3] While no studies specifically differentiate the monitoring requirements for pediatric patients, a consensus statement endorsed by the Society for Pediatric Anesthesia supports extra vigilance in the care of select patients, including neonates, children with OSA, and those with underlying neuromuscular diseases or cognitive impairment, which can impact respiratory muscle function and/or impede assessment of the patient's level of pain or consciousness. Furthermore, pediatric patients initiating opioid therapy, especially in the initial postoperative period, those who are receiving escalating doses of parenteral opioid, and those receiving opioids in conjunction with other CNS depressants are deemed worthy of increased vigilance.[4]

Expert opinion supports monitoring of pediatric patients receiving initial doses of parenteral opioids or opioids by patient-controlled analgesia (PCA), PCA by proxy, and/or constant infusion, specifically recommending continuous respiratory rate and pulse oximetry monitoring for the first 24 hours unless the patient is awake and actively being observed.[4,12] Previous research supports the utilization of more frequent continuous monitoring in children. In a 2010 survey study of pediatric pain management practice, respondents reported that continuous pulse oximetry monitoring was commonplace when PCA opioid was provided.[18] However, continuous monitoring of respiratory rate was less consistently utilized (Figure 2).

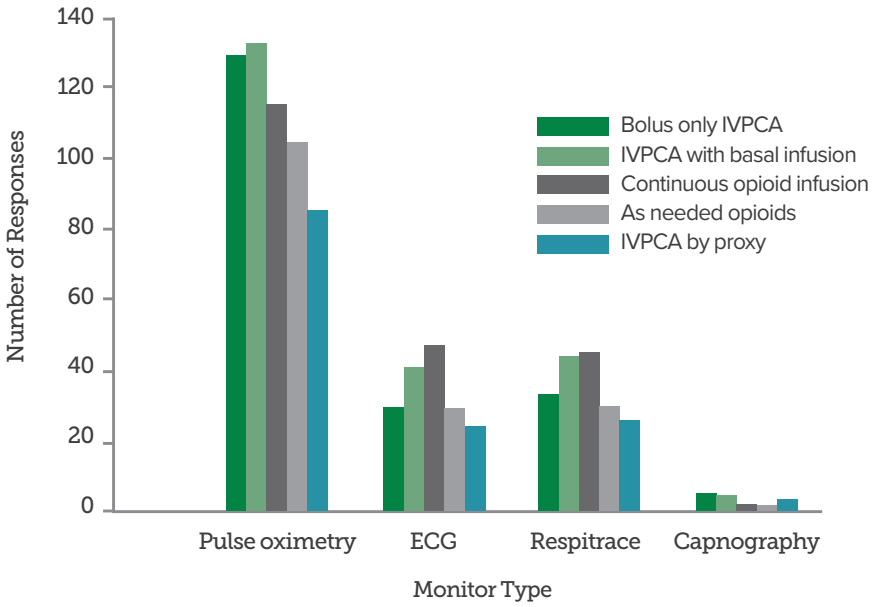

Figure 2: Type of patient monitoring used when opioids are administered to pediatric patients. (Total number of respondents who answered question, 149; total number of respondents who provided IV patient-controlled analgesia [IVPCA] by proxy, 95.) Ninety percent of respondents reported using pulse oximetry monitoring when patients were administered PCA. Electrocardiographic monitoring and capnography were always used in conjunction with pulse oximetry, whereas respiratory inductive plethysmography (Respitrace) was almost always provided in conjunction with pulse oximetry (>90%) but was occasionally used as the sole type of monitoring.[17] Reprinted with permission from Anesthesia & Analgesia *and Wolters Kluwer Health, Inc. Nelson KL, Yaster M, Kost-Byerly S, Monitto CL. A national survey of American Pediatric Anesthesiologists: patient-controlled analgesia and other intravenous opioid therapies in pediatric acute pain management.* Anesth Analg. *2010;110:754–760.[18]*

Additional recommendations from the Society for Pediatric Anesthesia for the use of perioperative opioids in children include regular assessment of level of sedation using a validated sedation score that evaluates the patient's level of alertness as opposed to a scale designed to monitor procedural sedation. The Pasero opioid sedation scale is one such option.[19] Admission to a highly monitored environment, such as a step-down unit, PACU, or ICU, is advised when initiating opioid analgesia in infants younger than three months of age. It is also recommended that continuous monitoring of respiratory rate and electrocardiogram be considered in pediatric patients on oxygen therapy, as supplemental oxygen may impair the sensitivity and response time of pulse oximetry as a monitor for apnea/hypopnea.[4]

PEDIATRIC RESPIRATORY MONITORING AND ASSOCIATED CHALLENGES

As with adults, respiratory monitoring in children should preemptively identify OIRD in time to intervene and prevent the occurrence of critical events. Ideally, respiratory monitoring should continuously and accurately measure oxygenation, respiratory rate, carbon dioxide (CO_2) tension, and airflow.

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Desaturation Can Be a Late Warning Sign of Respiratory Insufficiency When Patients Are Receiving Oxygen

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Monitors currently exist to track each parameter; however, each has limitations as a predictor of impending respiratory failure (Table 1).

The most common monitoring methods in pediatric practice are continuous pulse oximetry and transthoracic impedance plethysmography. Since its introduction to pediatric practice in the 1980s, pulse oximetry has provided critical information regarding adequacy of oxygenation in infants and children. Pulse oximetry monitoring is frequently available on pediatric units, and monitoring itself is well tolerated by patients of all ages. However, desaturation can be a late warning sign of respiratory insufficiency, particularly when patients are receiving supplemental oxygen.[4] Unfortunately, whether due to surgical complexity, patient comorbidities, or analgesic administration, studies report a frequent need for supplemental oxygen to maintain adequate oxygenation postoperatively.[11,18] This need puts children at increased risk of unrecognized hypoventilation by increasing the time between apnea/hypopnea and desaturation.

Transthoracic impedance plethysmography monitoring of respiratory rate, a technique that can identify apnea and hypopnea, hallmarks of opioid effects on brainstem respiratory centers, is also commonly available and well tolerated. However, care must be taken to utilize age-appropriate respiratory parameters. Unfortunately, respiratory rate monitoring using this technique may be inaccurate due to suboptimal ECG electrode placement, motion artifact, and physiological events that cause chest wall movement, such as coughing and crying. Further, it may fail to identify respiratory insufficiency in the setting of undiagnosed airway obstruction.

Measurement of arterial $PaCO_2$ provides a well-validated assessment of ventilation but requires arterial access and does not provide continuous information. Noninvasive surrogate measures of $PaCO_2$ that do provide continuous data include transcutaneous and end-tidal PCO_2 ($etCO_2$) monitoring. Transcutaneous gas monitoring fell out of favor in the 1980s in part due to technical challenges, including the risk of skin burns when used on neonates. However, as a result of technological advances, transcutaneous PCO_2 monitoring is now clinically feasible and safe. These monitors have been evaluated in pediatric populations,[20] but have not been studied in infants and children receiving opioid medications in the postoperative setting. While correlation is good with steady state $PaCO_2$, response time precludes rapid identification of acute changes in ventilation, limiting its utility as an early warning monitor.

Alternatively, End tidal CO_2 ($etCO_2$) monitoring provides early, reliable warnings of ventilatory insufficiency when used to monitor intubated, anesthetized, or deeply sedated patients. Capnography with nasal and oral sampling has been studied in non-intubated adults receiving PCA[2,7] and is a more sensitive indicator of respiratory compromise than saturation monitoring, supporting capnography's potential use as an early warning monitor of impending respiratory insufficiency. In light of these findings, the APSF has recommended that capnography be used to monitor ventilation when supplemental oxygen is provided to postoperative patients receiving opioids. However, appropriate use requires patient cooperation in wearing the specially designed capnography cannula for prolonged periods in order to detect low tidal volumes exhaled from both the mouth and the nose. These cannulas may be uncomfortable or interfere with activities such as eating or talking, impacting patient compliance. And when studied in nonintubated, nonsedated postoperative pediatric patients, capnography was, in fact, often poorly tolerated for these very reasons, limiting implementation in pediatric monitoring paradigms.[21]

A clear understanding of the information provided by capnography monitoring is essential. While capnography provides an accurate measure of respiratory rate, the meaning of $etCO_2$ values may differ substantially between patients with a natural or artificial airway. As noted in the PRODIGY trial, over 60% of patients monitored had episodes of $etCO_2 < 15$ mm Hg (>50% had low $etCO_2$ and low respiratory rate), but no patient had an $etCO_2 > 60$ mm Hg.[7] These results suggest that in many instances $etCO_2$ values did not reflect $PaCO_2$, but were instead a surrogate indicator of poor airflow due to unrecognized obstruction.

Newer technologies, such as noninvasive respiratory volume monitoring, may provide a more sensitive assessment of airflow, specifically tidal volume and minute ventilation. Monitors have been validated in both adults and intubated, mechanically ventilated infants and children under general anesthesia.[6,22] However, in spontaneously breathing adults, tidal volume and respiratory rate trending were good, but accuracy of minute ventilation measurements was limited compared with the gold standard, spirometry.[23] Nevertheless, the trend monitoring that these devices can provide may

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Table 1: Summary of Respiratory Monitoring Modalities for Detection of OIRD.[2,4,6,7,20-23]

Monitor	Parameters measured	Advantages	Disadvantages
Pulse Oximeter	• Oxygen saturation	• High availability • Well-tolerated • Critical threshold values clearly defined	• Potentially late indicator of hypopnea/apnea • Delayed response time when supplemental oxygen provided
Transthoracic Impedance Plethysmography	• Respiratory rate	• High availability • Well-tolerated • Age-appropriate critical threshold values clearly defined	• Hypoventilation due to airway obstruction can be missed • Motion artifacts with movement
Capnography	• Respiratory rate • $etCO_2$	• Good indicator of respiratory rate • Approximate indicator of $PaCO_2$ in intubated patients	• Limited availability outside of operating room and ICU • Poorly tolerated by children • Inconsistent correlation between $PaCO_2$ and $etCO_2$ in patients with natural airway
Transcutaneous CO_2 Monitor	• Skin surface partial pressure of CO_2	• Good correlation with $PaCO_2$ • Critical threshold values clearly defined	• Limited availability • Lacks breath-to-breath monitoring capability • Slow response time precludes identification of acute changes in ventilation • Requires recalibration after 12 hours or if sensor dislodged
Noninvasive Respiratory Volume Monitor	• Respiratory rate • Tidal volume • Minute ventilation	• Good trending of tidal volume and respiratory rate • Well-tolerated	• Rare availability • Limited accuracy of minute ventilation measurements in spontaneously breathing patients • Critical minute ventilation/tidal volume threshold values not defined in children

$etc0_2$=end-tidal carbon dioxide; $PaCO_2$=partial pressure of carbon dioxide; ICU=intensive care unit, CO_2=carbon dioxide.

Capnography Should Be Used When Postoperative Patients Receiving Opioids Are on Supplemental Oxygen

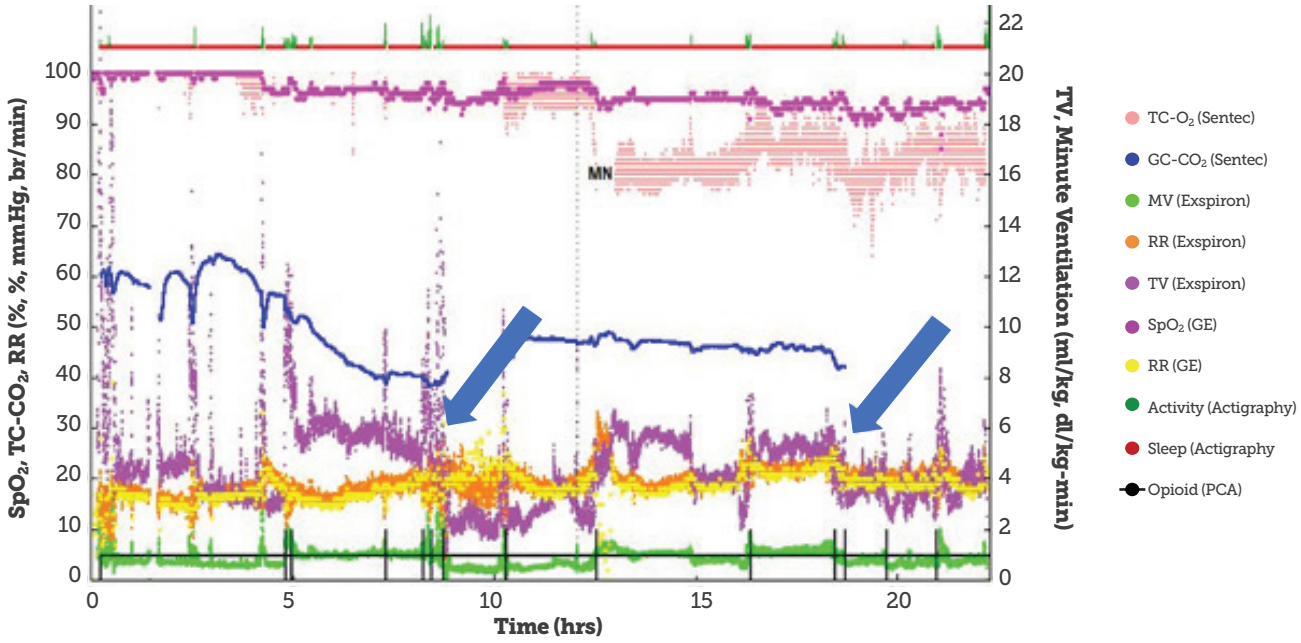

Figure 3: 24-hour data stream of oxygen saturation, respiratory rate, transcutaneous CO_2, minute ventilation, tidal volume, actigraphy and PCA opioid use in adolescent patient following posterior spinal fusion. Decreased tidal volume (TV) after PCA bolus use is demonstrated with blue arrows. MN denotes midnight. (Unpublished data from Constance Monitto).

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support their incorporation in future monitoring strategies. Preliminary data from a pilot study in adolescents receiving PCA opioid following posterior spinal fusion surgery (Figure 3) suggests the monitors are tolerated in adolescents (C. Monitto personal communication), implying that their use in pediatric monitoring paradigms is feasible. That said, critical ventilatory threshold values that could be used to predict impending, or detect present but unrecognized, respiratory compromise have yet to be clearly defined in children.

In conclusion, no models designed to predict the risk of opioid-induced respiratory decompensation in children currently exist. When stratifying risk, patient-specific factors unique to children should be included as opposed to extrapolating results from adult studies. Continuous electronic respiratory monitoring of children is reported to be more commonly utilized than in the care of adults, but no single technology provides a comprehensive solution for monitoring those with a natural airway. In the future, the use of multiple, complementary monitors in conjunction with paradigms designed to include pediatric-specific threshold alarm parameters may allow for earlier identification of episodes of respiratory insufficiency in this vulnerable population.

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REFERENCES

1. Lee LA, Caplan RA, Stephens LS, et al. Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology.* 2015;122:659–665. PMID: 25536092.
2. Overdyk FJ, Carter R, Maddox RR, et al. Continuous oximetry/capnometry monitoring reveals frequent desaturation and bradypnea during patient-controlled analgesia. *Anesth Analg.* 2007;105:412–418. PMID: 17646499.
3. Weinger MB, Lee LA. "No patient shall be harmed by opioid-induced respiratory depression." *APSF Newsletter.* 2011;26:21–40. https://www.apsf.org/article/no-patient-shall-be-harmed-by-opioid-induced-respiratory-depression/. Accessed February 28, 2024.
4. Cravero JP, Agarwal R, Berde C, et al. The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. *Paediatr Anaesth.* 2019;29:547–571. PMID: 30929307.
5. Weingarten TN. Opioid-induced respiratory depression–beyond sleep disordered breathing. *APSF Newsletter.* 2023;38:2,42–45. https://www.apsf.org/article/opioid-induced-respiratory-depression-beyond-sleep-disordered-breathing/. Accessed February 28, 2024.
6. Gomez-Morad AD, Cravero JP, Harvey BC, et al. The evaluation of a noninvasive respiratory volume monitor in pediatric patients undergoing general anesthesia. *Anesth Analg.* 2017;125:1913–1919. PMID: 28759491.
7. Khanna AK, Bergese SD, Jungquist CR, et al. PRediction of Opioid-induced respiratory Depression In patients monitored by capnoGraphY (PRODIGY) group collaborators. prediction of opioid-induced respiratory depression on inpatient wards using continuous capnography and oximetry: an international prospective, observational trial. *Anesth Analg.* 2020;131:1012–1024. PMID: 32925318.
8. Ramachandran SK, Haider N, Saran KA, et al. Life threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy. *J Clin Anesth.* 2011;23:207–213. PMID: 21570616.
9. Morton NS, Errera A. APA national audit of pediatric opioid infusions. *Paediatr Anaesth.* 2010;20:119–125. PMID: 19889193.
10. Chidambaran V, Olbrecht V, Hossain M, et al. Risk predictors of opioid-induced critical respiratory events in children: naloxone use as a quality measure of opioid safety. *Pain Med.* 2014;15:2139–2149. PMID: 25319840.
11. Voepel-Lewis T, Marinkovic A, Kostrzewa A, et al. The prevalence of and risk factors for adverse events in children receiving patient-controlled analgesia by proxy or patient-controlled analgesia after surgery. *Anesth Analg.* 2008; 107:70–75. PMID: 18635469.
12. Monitto CL, George JA, Yaster M: Pediatric acute pain management. In: Davis PJ, Cladis FP (eds). Smith's anesthesia for infants and children. 10th edition. Elsevier, Philadelphia, PA, 481–518, 2022.
13. Chung F, Liao P, Elsaid H, et al. Factors associated with postoperative exacerbation of sleep-disordered breathing. *Anesthesiology.* 2014;120:299–311. PMID: 24158050.
14. Brown KA, Laferriere A, Moss IR. Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirement for analgesia. *Anesthesiology.* 2004;100:806–810. PMID: 15087614.
15. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2012;130:576–584. PMID: 22926173.
16. Coté CJ, Posner KL, Domino KB. Death or neurologic injury after tonsillectomy in children with a focus on obstructive sleep apnea: Houston, we have a problem! *Anesth Analg.* 2014;118:1276–1283. PMID: 23842193.
17. Mortensen A, Lenz K, Abildstrom H, Lauritsen TL. Anesthetizing the obese child. *Paediatr Anaesth.* 2011;21:623–629. PMID: 21429056.
18. Nelson KL, Yaster M, Kost-Byerly S, Monitto CL. A national survey of American pediatric anesthesiologists: patient-controlled analgesia and other intravenous opioid therapies in pediatric acute pain management. *Anesth Analg.* 2010;110:754–760. PMID: 20185654.
19. Quinlan-Colwell A, Thear G, Miller-Baldwin E, Smith A. Use of the Pasero Opioid-induced Sedation Scale (POSS) in pediatric patients. *J Pediatr Nurs.* 2017;33:83–87. PMID: 28209260.
20. Berkenbosch JW, Tobias JD. Transcutaneous carbon dioxide monitoring during high-frequency oscillatory ventilation in infants and children. *Crit Care Med.* 2002;30:1024–1027. PMID: 12006797.
21. Miller KM, Kim AY, Yaster M, et al. Long-term tolerability of capnography and respiratory inductance plethysmography for respiratory monitoring in pediatric patients treated with patient-controlled analgesia. *Paediatr Anaesth.* 2015; 25:1054–1059. PMID: 26040512.
22. Atkinson DB, Sens BA, Bernier RS, et al. The evaluation of a noninvasive respiratory volume monitor in mechanically ventilated neonates and infants. *Anesth Analg.* 2022; 134:141–148. PMID: 33929346.
23. Gatti S, Rezoagli E, Madotto F, et al. A non-invasive continuous and real-time volumetric monitoring in spontaneous breathing subjects based on bioimpedance-ExSpiron®Xi: a validation study in healthy volunteers. *J Clin Monit Comput.* 2024;38:539–551. PMID: 38238635.