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## Postanesthesia Apnea in Former Preterm Infants for Inguinal Herniorrhaphy: An Update of Risk Factors from an Individual Participant Data Meta-analysis

Priti G. Dalal, M.D., Charles J. Coté, M.D., Shobha Malviya, M.D., Tian Qiu, M.B.B.S., M.P.H., Mary Ellen McCann, M.D., Andrew Davidson, M.B.B.S., M.D., Steven Sale, M.B.Ch.B., Choon Looi Bong, M.B.Ch.B., Karen Brown, M.D., Vernon M. Chinchilli, Ph.D., for the Society for Pediatric Anesthesia Quality and Safety Committee–Apnea Task Force Collaborative Group\*

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### ABSTRACT

Postmenstrual age (PMA) is the major risk factor for postanesthesia apnea. The authors hypothesized that modern anesthesia may reduce the at-risk PMA cutoff threshold. The aim of this individual participant data meta-analysis was to identify the PMA above which postanesthesia apnea risk is less than 1%. Individual participant data from 12 prospective studies undergoing open inguinal herniorrhaphy were analyzed. A total of 132 of 751 (17.6%) former preterm infants experienced postanesthesia apnea. The data indicate that the PMA cutoff at which the risk of postanesthesia apnea was approximately 10%, approximately 5%, and less than 1% was 53 weeks, 57 weeks, and 65 weeks, respectively, after general anesthesia and approximately 38 weeks, 40 weeks, and 45 weeks, respectively, after neuraxial anesthesia. Anemia was a risk factor only for infants more than 48 weeks PMA. Postanesthesia apnea onset was earlier and odds for occurrence were higher for general anesthesia without (odds ratio, 6;  $P = 0.008$ ) and with caudal block (odds ratio, 2.94;  $P = 0.012$ ) compared to neuraxial anesthesia. Anesthetic technique has important implications; neuraxial anesthesia appears to reduce the at-risk PMA for postanesthesia apnea compared with general anesthesia.

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The most prudent care plan regarding the postanesthesia disposition of former preterm infants who are at risk for postanesthesia apnea remains a conundrum for pediatric anesthesiologists. The postmenstrual age (PMA) cutoff that should trigger admission for postanesthesia monitoring, the safe duration of postanesthesia monitoring, and optimal monitors remain unclear. Thirty years ago, Coté *et al.*<sup>1</sup>

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Priti G. Dalal, M.D.: Department of Anesthesiology and Perioperative Medicine, Pennsylvania State College of Medicine, Pennsylvania State Health Children's Hospital, Hershey, Pennsylvania.

Charles J. Coté, M.D.: Harvard Medical School, Division of Pediatric Anesthesia, Department of Anesthesia, Critical Care and Pain Management, Massachusetts General Hospital, Boston, Massachusetts.

Shobha Malviya, M.D.: Anesthesiology, University of Michigan, Ann Arbor, Michigan.

Tian Qiu, M.B.B.S., M.P.H.: Department of Public Health Sciences, Pennsylvania State University, Hershey, Pennsylvania.

Mary Ellen McCann, M.D.: Harvard Medical School, Department of Anesthesia, Critical Care and Pain, Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts.

Andrew Davidson, M.B.B.S., M.D.: Melbourne Children's Trials Centre, Murdoch Children's Research Institute, Department of Anaesthesia, Royal Children's Hospital, Parkville, Australia.

Steven Sale, M.B.Ch.B.: Bristol Royal Hospital for Children, Bristol, United Kingdom.

Choon Looi Bong, M.B.Ch.B.: Kandang Kerbau Women's and Children's Hospital, Duke-NUS Medical School, Singapore.

Karen Brown, M.D.: Department of Anesthesia, McGill University Health Center, Montreal, Canada.

Vernon M. Chinchilli, Ph.D.: Department of Public Health Sciences, Pennsylvania State College of Medicine, Hershey, Pennsylvania.

\*Members of the Society for Pediatric Anesthesia Quality and Safety Committee–Apnea Task Force Collaborative Group are listed in the appendix.

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**Abbreviations:** ASA, American Society of Anesthesiologists; CPAP, continuous positive airway pressure; IPD, individual participant data; PACU, postanesthesia care unit; PCA, postconceptual age; PMA, postmenstrual age; SGA, small for gestational age

performed a combined analysis of original data from eight prospective studies and concluded that infants with PMA less than 46 weeks were at greatest risk of experiencing postanesthesia apnea, and that risk did not decrease to less than 1% until approximately 57 weeks PMA. The limitations of that analysis were that the types of postanesthesia monitors used, duration of monitoring, times of first and last postanesthesia apnea events, number of events experienced by each infant, and rescue interventions to address apneic events were unavailable, and all patients were managed with general anesthesia using legacy inhalation agents (halothane/isoflurane); none were managed with neuraxial anesthesia or with more modern inhalation agents (sevoflurane/desflurane).

Currently, institutions across the world use heterogeneous criteria for admission, monitoring, and discharge of former preterm infants after anesthesia. The purpose of this analysis is to provide an updated resource for future evidence-based recommendations regarding the at-risk PMA for postanesthesia apnea, duration of monitoring, types of monitoring, and optimal anesthetic technique. The rationale for our study was that the introduction of newer inhalation agents, expanded use of neuraxial anesthesia, *e.g.*, the General Anesthesia Compared to Spinal Anesthesia (GAS) study,<sup>2</sup> and longer duration of monitoring might impact guidance regarding the PMA triggering admission for postanesthesia monitoring, *i.e.*, postanesthesia apnea risk less than 1%. Our hypothesis was that modern anesthesia (newer drugs and anesthetic practices) may reduce the PMA below which infants are at risk.

We previously performed a systematic review and aggregate data meta-analysis of more than 6,000 English language published manuscripts retrieved from multiple databases (1966 to 2025).<sup>3</sup> This analysis revealed a number of risk factors (metaregressors) that may contribute to an increased risk for postanesthesia apnea in former preterm infants. We confirmed that the previously recognized PMA<sup>4</sup> at the time of procedure was the major risk factor but also found several new risk factors. Our aggregate data meta-analysis enabled us to identify prospective studies with the potential for sharing original data to allow an individual participant data (IPD) meta-analysis.<sup>5,6</sup> Thus, the primary aim of this study, with a much larger database than the analysis by Coté *et al.*, was to more precisely identify the PMA above which the postanesthesia apnea risk was less than 1%. Our secondary aims were to identify associated risk factors and optimal monitoring methods for this cohort, as well as to shed light on the management of full-term infants after anesthesia.

## Materials and Methods

Our systematic review and aggregate data meta-analysis<sup>3</sup> identified 19 studies with appropriate data for an IPD meta-analysis.<sup>2,7–24</sup> The corresponding/senior authors of these studies were contacted to obtain their data. We made up to five attempts to contact the authors by email.

We were unable to establish communication with corresponding authors from four studies. The author of another study shared data, but due to loss of contact and inability to clarify key words in the data set and its retrospective study design, that study was also excluded. Two more studies were excluded since the authors shared relevant detailed data from their subsequent studies<sup>23,24</sup>; hence data from these subsequent studies were used in our analysis. Thus, detailed individual patient information from 12 studies<sup>2,7–13,16,17,23,24</sup> regarding anesthetic technique, time of first and last apnea event, and interventions to manage postanesthesia apnea events enabled us to perform an IPD meta-analysis (Supplemental Digital Content table 1, <https://links.lww.com/ALN/E426>).

The acquired data included anesthetic technique, associated medications, types of monitoring devices in the postanesthesia care unit (PACU), continued monitoring after PACU discharge, timing of apnea events (especially first and last), and rescue interventions. Inclusion criteria were prospective, observational studies with an infant population (age less than 12 months), open inguinal hernia surgery, and postanesthesia apnea as a primary or secondary outcome variable. A postanesthesia apnea event was defined as a respiratory pause lasting 15 s or more or less than 15 s if accompanied by bradycardia (heart rate less than 80 or greater than 20% decrease from baseline) or desaturation (less than 80%). Anemia was defined as a hemoglobin less than 10 g/dL. Preterm infants were defined as those infants born at gestational age less than 37 weeks. Exclusion criteria were nonhernia surgery, age 12 months or more, infants who required preoperative noninvasive or invasive ventilation, and non-English language studies. All studies were approved by their respective institutional review boards; data user agreements with Pennsylvania State University (Hershey, Pennsylvania) were obtained as required, and all shared data were de-identified. Data from manuscripts that reported postconceptual age (PCA) were converted to PMA, in adherence to the policy statement of the American Academy of Pediatrics (Itasca, Illinois).<sup>4</sup> Accordingly, gestational age was defined as time elapsed (weeks) between the first day of the last menstrual period and the day of delivery; PMA at time of procedure was defined as the sum of gestational age and time elapsed from birth to the day of the procedure (weeks); PMA is approximately 2 weeks longer than the PCA. Assignments of small (SGA), appropriate, or large for gestational age were made using standard World Health Organization (Geneva, Switzerland) charts.<sup>25,26</sup>

## Statistical Analysis

We pursued an IPD meta-analysis<sup>5,6</sup> instead of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines<sup>27</sup> for systematic reviews. Due to the extremely low incidence of postanesthesia apnea observed in the dataset for full-term infants, this group was excluded *a priori*. Our analysis thus focused only on former

preterm infants. Descriptive statistics were computed for participant characteristics by apnea status and basic tests were applied using two-sample *t* tests for continuous variables and Fisher exact tests for categorical variables. We used mixed-effects logistic regression models with cluster-specific random effects to explore the relationship between postanesthesia apnea and various risk factors, since the outcome variable was binary, and the data were derived from 12 studies. These models estimated the log odds of a binary outcome variable as a linear combination of the risk factors, including both fixed and random effects. We conducted univariable logistic regression analyses to determine odds ratios of 14 potential risk factors (PMA, gestational age, birth weight, weight at time of surgery, anesthetic technique [neuraxial *vs.* general anesthesia], inhalational agents, intra-operative opioids and nondepolarizing muscle relaxants, American Society of Anesthesiologists [ASA; Schaumburg, Illinois] Physical Status, opioids given in PACU, anemia, history of supplemental oxygen, history of apnea, and weight for gestational age). We then conducted multivariable logistic regression analyses to investigate the association between PMA and postanesthesia apnea. In the multivariable model, we included gestational age, anesthetic technique, birth weight, and anemia as covariates, based on statistical signals identified in our aggregate data meta-analysis.<sup>3</sup> The frequency of postanesthesia apnea events per infant was categorized into three outcomes: no apnea events, a single apnea event, or multiple apnea events. Mixed-effects ordinal logistic regression was applied to investigate the association between various factors and the frequency of apnea events per infant. Similarly, a multivariable model with the same covariates was used to examine the association between PMA and the number of postanesthesia apnea events.

Since the duration of monitoring (minutes) after anesthesia varied among infants, the logarithm of monitoring duration was included as an adjustment in the models. To evaluate the association between pulse oximetry and respiratory monitoring, we restricted the dataset to infants who were monitored with pulse oximetry, and classified those with any additional type of respiratory monitoring as “yes” and those without as “no.” A mixed-effects logistic regression model was then applied to examine the association.

Kaplan–Meier plots for the time to first or last postanesthesia apnea events were constructed to compare the survival trends of infants receiving different anesthetic techniques. For statistical analysis, anesthetic techniques were classified into four types: (1) general anesthesia (with or without ilioinguinal nerve block or local infiltration), (2) general anesthesia with a caudal block, (3) failed neuraxial anesthesia converted to general anesthesia, and (4) neuraxial anesthesia (spinal or caudal anesthesia with or without sedation). To analyze the association between anesthetic technique and time to first or last postanesthesia apnea event, Cox proportional hazards models were applied.

Missing values were not imputed, and outliers were omitted from the analysis (see table 1 for missing value information; details on outliers are provided in the Results section). Statistical analyses were carried out using the R Project for Statistical Computing (version 2023.06.1 + 524; <https://www.r-project.org/>, accessed December 9, 2025). Five<sup>2,13,17,23,24</sup> of the 12 studies that shared their original records provided detailed monitoring data, timing of apnea events, number of events, and rescue interventions for at least 12h after anesthesia; these data were examined separately. Two-sided *P* values < 0.05 were considered significant. For each parameter, results are described as mean  $\pm$  SD for normally distributed data, and as median and interquartile range for data that were not normally distributed. Because infants had multiple rescue interventions per postanesthesia apnea event, these were classified based on the highest level of intervention used per apnea event in the following order: no intervention, stimulation, use of oxygen/continuous positive airway pressure (CPAP), bag-valve-mask ventilation, unplanned escalation to intensive care unit, tracheal intubation, chest compressions, and use of epinephrine for cardiopulmonary resuscitation.

## Results

Original data for 1,132 infants<sup>2,7–13,16,17,23,24</sup> undergoing inguinal hernia repair were obtained from the authors; data from 29 were deleted due to incomplete records or errors in documentation. One infant with 99 postanesthesia apnea events was excluded from the frequency and timing of apnea events analysis (ordinal logistic regression and Kaplan–Meier curves) because it was deemed to be a statistical outlier. Thus, 1,102 infants (751 former preterm and 351 full-term infants; ASA Physical Status I to III) were included in the final dataset. Overall, 133 of 1,102 infants (12.1%) experienced postanesthesia apnea, 132 of whom were former preterm infants and 1 of whom was a full-term infant. This corresponds to an incidence of 17.6% (132 of 751) in former preterm infants and an incidence of 0.3% (1 of 351) in full-term infants. Due to the small sample size (*n* = 1) for apneic infants in the full-term infant group, we focused our analysis only on former preterm infants. Five studies (*n* = 560) provided data regarding the timing of apnea events; these data were available for 62 of 70 former preterm infants who experienced apnea (timing data was missing for eight infants) across the five studies.<sup>2,13,17,23,24</sup> Data regarding timing of apnea events were not available in the other seven studies that included the remaining 191 former preterm infants. Details regarding the type of airway management (*e.g.*, endotracheal intubation or laryngeal mask airway, *etc.*) for infants who received general anesthesia varied and were not available in all study subjects. Hence airway management data were not included in the analysis.

There was considerable heterogeneity with the types of monitors utilized and monitoring duration. Monitoring

**Table 1.** Distribution of the Demographic Characteristics of Former Preterm Infants (n = 751) Based on the Occurrence of Postanesthesia Apnea Events

| Characteristics*                                 | Overall<br>(n = 751)         | No Apnea<br>(n = 619)        | Apnea<br>(n = 132)           | P Value† |
|--------------------------------------------------|------------------------------|------------------------------|------------------------------|----------|
| Postmenstrual age, weeks, mean ± SD (range)      | 44.5 ± 5.1<br>(33.9 to 62.0) | 44.9 ± 5.2<br>(33.9 to 62.0) | 42.6 ± 4.2<br>(35.3 to 56.0) | < 0.001  |
| Gestational age, weeks, mean ± SD (range)        | 32.0 ± 3.2<br>(23.0 to 36.9) | 32.3 ± 3.1<br>(24.0 to 36.9) | 30.5 ± 3.2<br>(23.0 to 36.1) | < 0.001  |
| Birth weight, kg, mean ± SD (range)              | 1.7 ± 0.7<br>(0.5 to 4.2)    | 1.7 ± 0.7<br>(0.5 to 4.2)    | 1.5 ± 0.6<br>(0.7 to 3.0)    | 0.005    |
| Missing, No.                                     | 107                          | 56                           | 51                           |          |
| Weight at the time of surgery, mean ± SD (range) | 3.7 ± 1.1<br>(1.4 to 7.1)    | 3.8 ± 1.1<br>(1.7 to 6.9)    | 3.0 ± 1.0<br>(1.4 to 7.1)    | < 0.001  |
| Missing, No.                                     | 248                          | 183                          | 65                           |          |
| Anesthetic technique, No. (%)                    | 751                          |                              |                              | < 0.001  |
| General anesthesia                               | 262                          | 193 (31.2)                   | 69 (52.3)                    |          |
| General anesthesia with caudal block             |                              |                              |                              |          |
| Failed neuraxial converted to general anesthesia | 35                           | 29 (4.7)                     | 6 (4.5)                      |          |
| Neuraxial anesthesia                             | 194                          | 186 (30.0)                   | 8 (6.1)                      |          |
| Inhalational agents, No. (%)                     | 522‡                         | 404                          | 118                          | 0.004†   |
| Halothane, isoflurane                            | 248                          | 183 (46.1)                   | 65 (61.9)                    |          |
| Sevoflurane, desflurane                          | 254                          | 214 (53.9)                   | 40 (38.1)                    |          |
| Missing, No.                                     | 20                           | 7                            | 13                           |          |
| Intraoperative opioid, No. (%)                   | 748                          | 10 (1.6)                     | 8 (6.2)                      | 0.006    |
| Missing, No.                                     | 3                            | 0                            | 3                            |          |
| Nondepolarizing muscle relaxant, No. (%)         | 521‡                         | 156 (42.0)                   | 59 (62.8)                    | < 0.001  |
| Missing, No.                                     | 1                            | 0                            | 1                            |          |
| ASA Physical Status III vs. I to II, No. (%)     | 356                          | 225 (88.2)                   | 90 (89.1)                    | 1.0      |
| Missing, No.                                     | 395                          | 364                          | 31                           |          |
| Opioid given in PACU, No. (%)                    | 602                          | 6 (1.2)                      | 1 (0.9)                      | 1.0      |
| Missing, No.                                     | 149                          | 123                          | 26                           |          |
| Anemia (hemoglobin less than 10 g/dl), No. (%)   | 673                          | 203 (36.7)                   | 31 (25.8)                    | 0.026    |
| Missing, No.                                     | 78                           | 66                           | 12                           |          |
| History of supplement oxygen, No. (%)            | 490                          | 153 (35.7)                   | 24 (39.3)                    | 0.572    |
| Missing, No.                                     | 261                          | 190                          | 71                           |          |
| Apnea history, No. (%)                           | 677                          | 37 (6.6)                     | 35 (29.2)                    | < 0.001  |
| Missing, No.                                     | 74                           | 62                           | 12                           |          |
| Small for gestational age, No. (%)               | 644                          | 119 (21.1)                   | 9 (11.0)                     | 0.037    |
| Missing, No.                                     | 107                          | 56                           | 51                           |          |

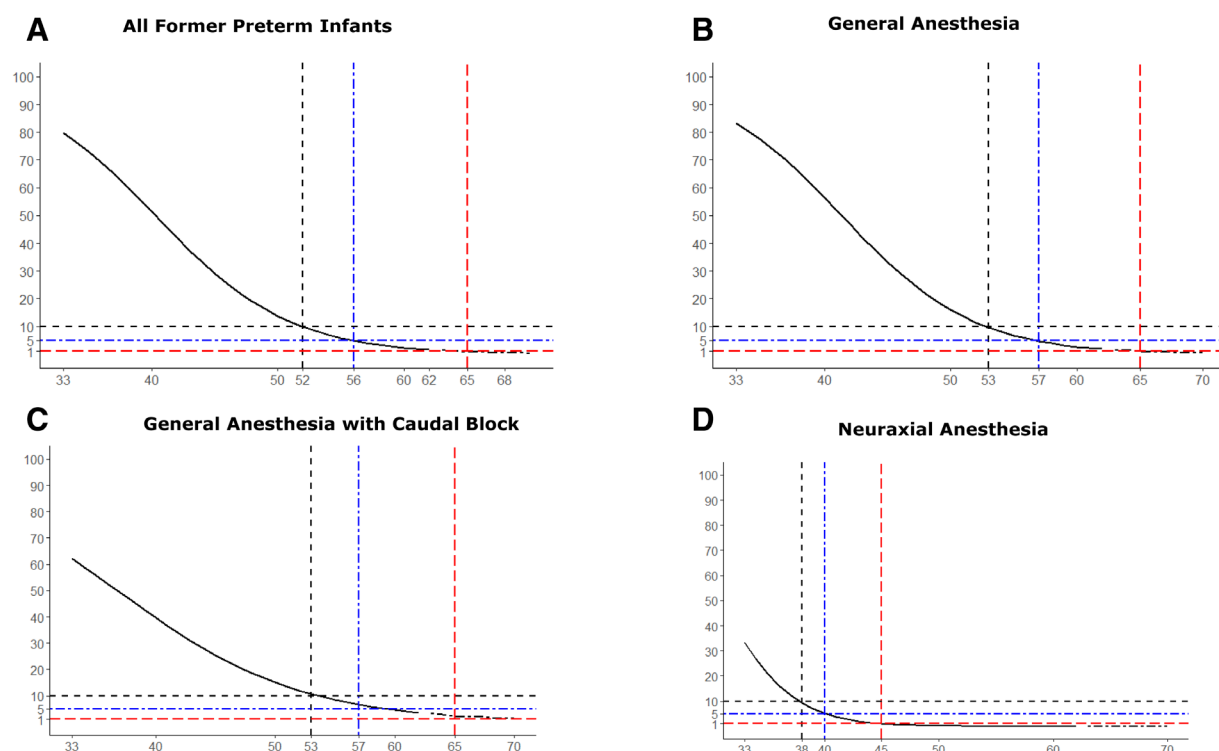
\*Mean ± SD (range) for continuous variables, and No. (%) for categorical variables. †P values for the differences of each characteristic between postanesthesia apnea and no postanesthesia apnea cohorts. For continuous variables, the two-sample *t* test was used; for categorical variables, the Fisher exact  $\chi^2$  test was used. ‡Totals less than total number of patients reviewed due to missing data.

ASA, American Society of Anesthesiologists.

devices included capnography, nasal thermistors, motion detectors, actigraphy, respiratory induction plethysmography, impedance pneumography, and pulse oximetry; some infants had more than one type of monitor. Infants managed with general anesthesia received a variety of inhalation agents, nondepolarizing neuromuscular blocking agents, and opioids; 35 infants with failed neuraxial anesthesia were converted to general anesthesia with sevoflurane. Some infants were managed with neuraxial anesthesia and sedation based on individual study protocol. All infants who received nondepolarizing muscle relaxants received reversal agents. Some infants received caffeine.

Figure 1 presents the analysis for predictive probability of apnea based on the PMA. Since the oldest infant in

our dataset was 62 weeks PMA, we extrapolated the curves to obtain the predictive probability at a 1% threshold. Figure 1A includes data for all 751 former preterm infants with any anesthetic technique. Figure 1B plots data for those who had general anesthesia only; figure 1C plots data for infants receiving general anesthesia with a caudal block; figure 1D plots data for those receiving neuraxial anesthesia. For those receiving general anesthesia, our data suggest that the risk for postanesthesia apnea was approximately 10% at 53 weeks PMA, was approximately 5% at 57 weeks PMA, and did not fall to less than 1% until approximately 65 weeks PMA. For those receiving neuraxial anesthesia, our data suggest that the risk for postanesthesia apnea was approximately 10% at 38 weeks PMA, was approximately



**Fig. 1.** (A) Data from all 751 former preterm infants regardless of anesthetic technique. (B) Data for those who had general anesthesia. (C) Data for infants receiving general anesthesia and a caudal block. (D) Data from those receiving neuraxial anesthesia. Note that for those receiving general anesthesia (B), the risk for postanesthesia apnea is approximately 10% at approximately 52 weeks postmenstrual age (PMA), is approximately 5% at approximately 57 weeks PMA, and does not fall to less than 1% until approximately 65 weeks PMA. For those receiving neuraxial anesthesia (D), the risk for postanesthesia apnea is approximately 10% at approximately 38 weeks PMA, is approximately 5% at approximately 40 weeks PMA, and does not fall to less than 1% until approximately 45 weeks PMA. (A) Probability plots for predictive at-risk PMA in all former preterm infants ( $n = 751$ ) regardless of anesthetic technique. (B) All infants managed with general anesthesia only. (C) Infants managed with general anesthesia with a caudal block. (D) All infants managed with neuraxial anesthesia. PMA, postmenstrual age.

5% at 40 weeks PMA, and did not fall to less than 1% until approximately 45 weeks PMA. Of note, the predictive probability of postoperative apnea rapidly declined with increasing PMA: approximately 34 per 1,000 (3.4%) at 58 weeks, approximately 23 per 1,000 (2.3%) at 60 weeks, approximately 9 per 1,000 (0.9%) at 65 weeks, approximately 3 per 1,000 (0.3%) at 70 weeks, and approximately 1 per 1,000 (0.01%) at 75 weeks, respectively.

Table 1 presents the distribution of demographic data, rates, and proportion characteristics of the former preterm infants based on the primary outcome variable, *i.e.*, postanesthesia apnea *versus* no postanesthesia apnea. The mean PMA, gestational age, birth weight, and weight at the time of surgery were significantly lower in the postanesthesia apnea group. A significantly higher proportion of infants in the postanesthesia apnea group had a history of apnea, received intraoperative opioids, received nondepolarizing muscle relaxants, received legacy inhalational agents (halothane/isoflurane *vs.* sevoflurane/desflurane), and received any form of general anesthesia (with or without caudal or failed neuraxial block converted to general anesthesia)

compared with neuraxial anesthesia as the sole anesthetic. Eight of 194 former preterm infants (PMA range, 37.43 to 41.14; median, 38.93 weeks) managed with neuraxial anesthesia (two of whom also received sedation) experienced at least one postanesthesia apnea event (apnea incidence, 4.1%) *versus* 124 of 557 (PMA range, 35.29 to 56; median, 42 weeks) who received any form of general anesthesia (apnea incidence, 22.3%;  $P < 0.001$ ). There was no difference between the two groups (apnea *vs.* no apnea) with regard to a history of receiving supplemental oxygen or opioids in the PACU. A higher proportion of infants in the no postanesthesia apnea cohort were anemic and SGA.

Univariable logistic regression analysis for potential risk factors confirmed that PMA at the date of surgery, gestational age, birth weight, weight at the time of surgery, any form of general anesthesia (general anesthesia with or without ilioinguinal block or local anesthetic infiltration, general anesthesia with caudal block, failed neuraxial block converted to general anesthesia *vs.* neuraxial anesthesia), a history of the use of supplemental oxygen, and a history of apnea were all significant risk factors (table 2). There was

**Table 2.** Univariable Regression Analysis of Risk Factors Associated With Postanesthesia Apnea in Former Preterm Infants

| Variable                                         | OR (95% CI)       | P Value |
|--------------------------------------------------|-------------------|---------|
| Postmenstrual age, weeks                         | 0.83 (0.78–0.88)  | < 0.001 |
| Gestational age, weeks                           | 0.85 (0.79–0.91)  | < 0.001 |
| Birth weight                                     | 0.62 (0.41–0.93)  | 0.020   |
| Weight at the time of surgery, kg                | 0.59 (0.43–0.81)  | 0.001   |
| Anesthetic technique                             |                   |         |
| General anesthesia                               | 6.01 (1.59–22.7)  | 0.008   |
| General anesthesia with caudal block             | 2.94 (1.28–6.78)  | 0.012   |
| Failed neuraxial converted to general anesthesia | 6.70 (2.09–21.48) | 0.001   |
| Neuraxial anesthesia                             | Ref               |         |
| Inhalational agents                              |                   |         |
| Halothane, isoflurane                            | 1.31 (0.23–7.36)  | 0.756   |
| Sevoflurane, desflurane                          | Ref               |         |
| Intraoperative opioids                           | 1.34 (0.31–5.81)  | 0.698   |
| Nondepolarizing muscle relaxant use              | 0.95 (0.40–2.25)  | 0.904   |
| ASA Physical Status III vs. I and II             | 1.46 (0.59–3.54)  | 0.400   |
| Opioid given in PACU                             | 0.39 (0.02–6.36)  | 0.510   |
| Anemia (hemoglobin less than 10 g/dl)*           | 1.2 (0.68–2.04)   | 0.564   |
| History of supplemental oxygen                   | 2.40 (1.14–5.05)  | 0.021   |
| Apnea history                                    | 2.88 (1.49–5.58)  | 0.002   |
| Small for gestational age                        | 0.57 (0.27–1.21)  | 0.144   |

\*For infants > 48 weeks PMA, anemic infants have a higher risk of experiencing postanesthesia apnea (OR, 5.2; 95% CI, 1.12–23.2;  $P = 0.0296$ ).

ASA, American Society of Anesthesiologists; OR, odds ratio; PACU, postanesthesia care unit; PMA, postmenstrual age; Ref, reference group.

no association between the occurrence of postanesthesia apnea events and the type of inhalation agent (legacy agents [halothane/isoflurane] *vs.* newer agents [sevoflurane/desflurane]), use of nondepolarizing muscle relaxants, opioids administered intraoperatively or in the PACU, anemia, or ASA Physical Status (III *vs.* I or II). Those administered general anesthesia without a caudal block had an approximately 6.8-fold greater odds ratio for a postanesthesia apnea event, while infants administered general anesthesia with caudal block had an approximately 2.5-fold greater odds ratio for a postanesthesia apnea event compared with neuraxial anesthesia as the sole anesthetic (table 2).

Multivariable regression analysis using PMA, gestational age, birth weight, weight at time of surgery, anesthetic technique (general *vs.* neuraxial), and anemia as covariates revealed PMA, gestational age, and anesthetic technique as the most significant risk factors. Since the cause-and-effect relationships of these covariates with postanesthesia apnea events and the frequency of these events are less certain, we present these results as forest plots (Supplemental Digital Content fig. 1, <https://links.lww.com/ALN/E426>). Both univariable and multivariable analyses indicate significant association of PMA with occurrence and frequency of postanesthesia apnea events.

Figure 2 illustrates the relationship between anemia (hemoglobin less than 10 g/dl) and postanesthesia apnea.

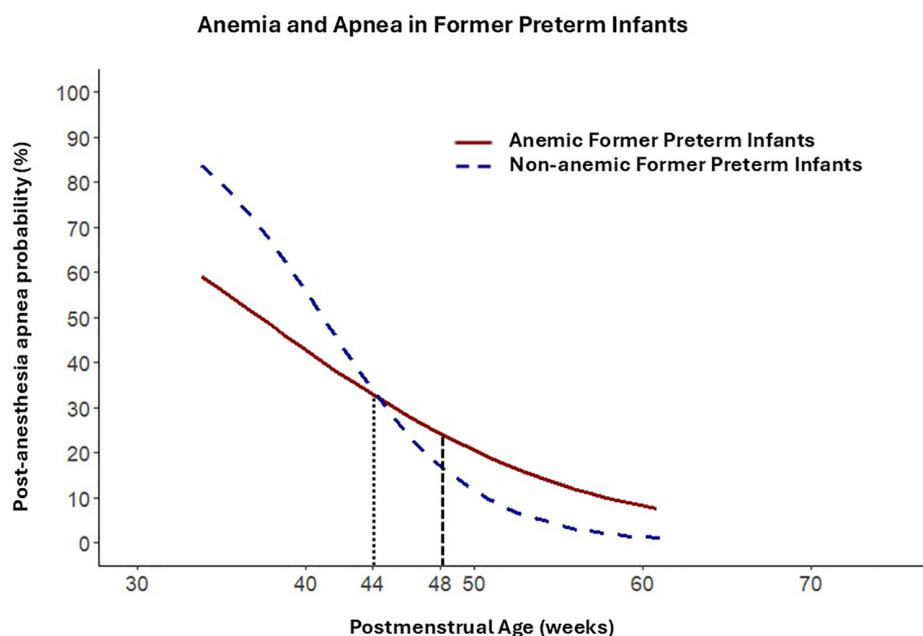
The risk for postanesthesia apnea decreases with each week increase in PMA at the time of surgery for both anemic and nonanemic former preterm infants. This risk is higher for nonanemic infants until the crossover point of 44 weeks PMA, after which the risk is higher in anemic infants, achieving statistical significance at 48 weeks PMA (odds ratio, 5.2; 95% CI, 1.12 to 23.2;  $P = 0.0296$ ).

Analysis for risk factors associated with the frequency of postanesthesia apnea events per infant (0 *vs.* 1 *vs.* greater than 1) using univariable ordinal logistic regression revealed that PMA, gestational age, birth weight, weight at time of surgery, use of general anesthesia with or without a caudal block, failed neuraxial block converted to general anesthesia compared with those managed with neuraxial anesthesia, and a history of supplemental oxygen were associated with a greater frequency of postanesthesia apnea events per infant (table 3). The type of inhalational agent (legacy *vs.* newer), use of intraoperative opioids, use of nondepolarizing muscle relaxant, opioids given in PACU, history of apnea, and SGA were not associated with an increased frequency of postanesthesia apnea events per infant (table 3). The odds ratio for frequency of postanesthesia apnea after general anesthesia without caudal block was approximately 13-fold and for general anesthesia with caudal block was approximately 5.8-fold higher in comparison to neuraxial anesthesia (table 3). Since only 6 of 752 premature infants were administered postoperative caffeine, 3 of whom experienced apnea, we are unable to provide meaningful analysis. Additionally, since only two infants managed with neuraxial anesthesia also received sedation, the data are inadequate to determine any relationship.

The frequency of recorded apnea events was higher with the combination of pulse oximetry and any form of respiratory monitoring for postanesthesia apnea detection (capnography, nasal thermistors, motion detectors, actigraphy, plethysmography, impedance pneumography) *versus* use of pulse oximetry alone ( $P = 0.032$ ).

Figure 3, A and B, presents Kaplan–Meier survival curves for first and last postanesthesia apnea events based on the anesthetic technique. Overall, the first postoperative apnea event occurred from 0 to 593 min; the onset of apnea occurred up to approximately 10 h regardless of anesthetic technique. The last postanesthesia apnea event occurred later in infants receiving any general anesthesia technique (1 to 1,566 min) compared with those who received neuraxial anesthesia (64 to 720 min).

Figure 4 illustrates the types of interventions and their timing after arrival in PACU. Of the 560 infants with the data on timing of apnea, 62 had at least 1 event, with the number of events per infant ranging from 1 to 36. A total of 228 apnea events were reported among these 62 infants; intervention data were missing for 3 events. A total of 137 events resolved without intervention and 28 with stimulation alone, but 33 required additional oxygen or initiation of



**Fig. 2.** Risk for postanesthesia apnea in anemic (hemoglobin less than 10 g/dl) and nonanemic former preterm infants. The risk for postanesthesia apnea decreases with each week increase in postmenstrual age (PMA) at the time of surgery for both anemic and nonanemic former preterm infants. However, this risk is higher for nonanemic infants until the crossover point of 44 weeks or less PMA (predicted probability, 34%) after which the risk is higher in anemic infants achieving statistical significance at 48 weeks PMA (odds ratio, 5.2; CI 1.12 to 23.2;  $P = 0.0296$ ).

CPAP, 21 required bag-valve-mask ventilation, 2 were escalated to intensive care unit admission, 3 required tracheal intubation, and 1 needed epinephrine, chest compressions, and tracheal intubation. Supplemental Digital Content tables 1 and 2 (<https://links.lww.com/ALN/E426>) provide the breakdown of postanesthesia apnea incidence, type of monitoring, and interventions documented by each investigator. There were inadequate data to establish an association between highest level of intervention and the frequency of apnea (single *vs.* multiple).

## Discussion

Our IPD meta-analysis of former preterm infants undergoing a single procedure (inguinal herniorrhaphy) confirms many observations made by the combined analysis by Coté *et al.* performed 30 yr ago.<sup>1</sup> We chose the same probability of apnea risk threshold (less than 1%) for easy comparison.<sup>1</sup> Our analysis revealed that the risk for postanesthesia apnea extends well beyond the approximately 57 weeks PMA (approximately 55 weeks PCA) reported by Coté *et al.*, *i.e.*, this risk does not decrease to less than 1% until approximately 65 weeks PMA (approximately 63 weeks PCA), thus increasing the at-risk period by approximately 8 weeks.<sup>1</sup>

Our analysis revealed that risk of occurrence, the frequency of postanesthesia apnea events, and PMA threshold

whereby infants are at risk are significantly lower after neuraxial anesthesia *versus* general anesthesia. Additionally, the risk for apnea for those who received general anesthesia combined with a caudal block is intermediate between neuraxial anesthesia *versus* general anesthesia alone (fig. 3, A and B). General anesthesia alone was associated with an approximately 6-fold increase in risk of postanesthesia apnea, but when combined with a caudal block, only an approximately 2.9-fold increase (table 2) in risk compared with infants managed with neuraxial anesthesia, perhaps because of reduced inhalational agents. Due to the sparsity of data, we are unable to analyze the impact of neuraxial anesthesia on postanesthesia apnea occurrence in anemic infants compared with nonanemic infants. We were also unable to find a relation of increased apnea in patients managed with neuraxial anesthesia who received sedation. This observation is different from a report<sup>9</sup> that eight of nine infants managed with spinal anesthesia with ketamine sedation experienced apnea events within the first 12 h after surgery, suggesting that the impact of sedating infants during neuraxial anesthesia requires further investigation.

Rescue interventions were more frequent after general than neuraxial anesthesia; however, rescue with bag-valve-mask was required up to approximately 10 h after either neuraxial or general anesthesia, and rescue with supplemental oxygen or CPAP up to approximately 12 h after

**Table 3.** Ordinal Regression Analysis for the Frequency of Postanesthesia Apneas Adjusted for the Variable Monitoring Intervals

| Variables                                               | OR (95% CI)        | P Value |
|---------------------------------------------------------|--------------------|---------|
| Postmenstrual age, weeks                                | 0.90 (0.84–0.97)   | 0.006   |
| Gestational age, weeks                                  | 0.84 (0.76–0.92)   | < 0.001 |
| Birth weight                                            | 0.52 (0.29–0.90)   | 0.023   |
| Weight at the time of surgery                           | 0.61 (0.45–0.81)   | < 0.001 |
| Anesthetic technique (reference: neuraxial anesthesia)  |                    |         |
| General anesthesia without caudal block                 | 13.01 (3.52–48.97) | < 0.001 |
| General anesthesia with caudal block                    | 5.83 (2.55–15.82)  | < 0.001 |
| Failed neuraxial converted to general anesthesia        | 7.96 (2.11–29.21)  | 0.002   |
| Any general anesthesia vs. neuraxial anesthesia         | 6.45 (2.89–17.27)  | < 0.001 |
| Inhalational agents (reference: sevoflurane/desflurane) |                    |         |
| Halothane/isoflurane                                    | 1.36 (0.08–15.66)  | 0.818   |
| Intraoperative opioids                                  | 2.05 (0.58–6.59)   | 0.245   |
| Nondepolarizing muscle relaxant                         | 1.57 (0.756–3.29)  | 0.227   |
| Opioid given in PACU                                    | 0.51 (0.02–3.80)   | 0.574   |
| Anemia (hemoglobin less than 10 g/dl)                   | 0.75 (0.40–1.86)   | 0.369   |
| History of supplemental oxygen                          | 2.18 (1.16–4.14)   | 0.016   |
| Apnea history                                           | 3.08 (0.58–12.78)  | 0.144   |
| Small for gestational age                               | 0.58 (0.21–1.32)   | 0.229   |

Note that the patient with 99 apnea events is not included in this table.  
OR, odds ratio; PACU, postanesthesia care unit.

neuraxial and 26 h after general anesthesia (fig. 4). In our aggregate data meta-analysis,<sup>3</sup> we found a last postanesthesia apnea event as late as 56 h after general anesthesia.<sup>18</sup> Endotracheal intubation was required in three and epinephrine, endotracheal intubation, and chest compressions in one infant within 60 min after general anesthesia; the limited number of these higher interventions precludes a detailed analysis.

Univariable and ordinal regression analysis revealed that the risk of occurrence and frequency of apnea was no different in former preterm infants anesthetized with legacy (halothane/isoflurane) *versus* newer inhalational agents (sevoflurane/desflurane); modern inhalational agents do not appear to offer advantage.

The relationship between anemia with postanesthesia apnea is complex. Overall, regression analysis did not establish a relationship with anemia, which appears to contradict the neonatal literature.<sup>10,28</sup> However, detailed analysis in relation to PMA confirmed the observation that anemia (hemoglobin less than 10 g/dl) is an important risk factor,<sup>1</sup> but this risk is not statistically significant until after 48 weeks PMA (fig. 2). This observation differed from the report by Coté *et al.* because this association showed a decreasing effect with greater PMA.<sup>1</sup> As in the analysis by Coté *et al.*,<sup>1</sup> SGA seemed to be protective of postanesthesia apnea events compared with appropriate for gestational age and large for gestational age infants; the reason for this is unclear.

Pulse oximetry, combined with any form of respiratory monitoring, identified more postanesthesia apnea events compared to pulse oximetry alone, but due to the wide variability of respiratory monitors, our results do not support a specific type of monitor.

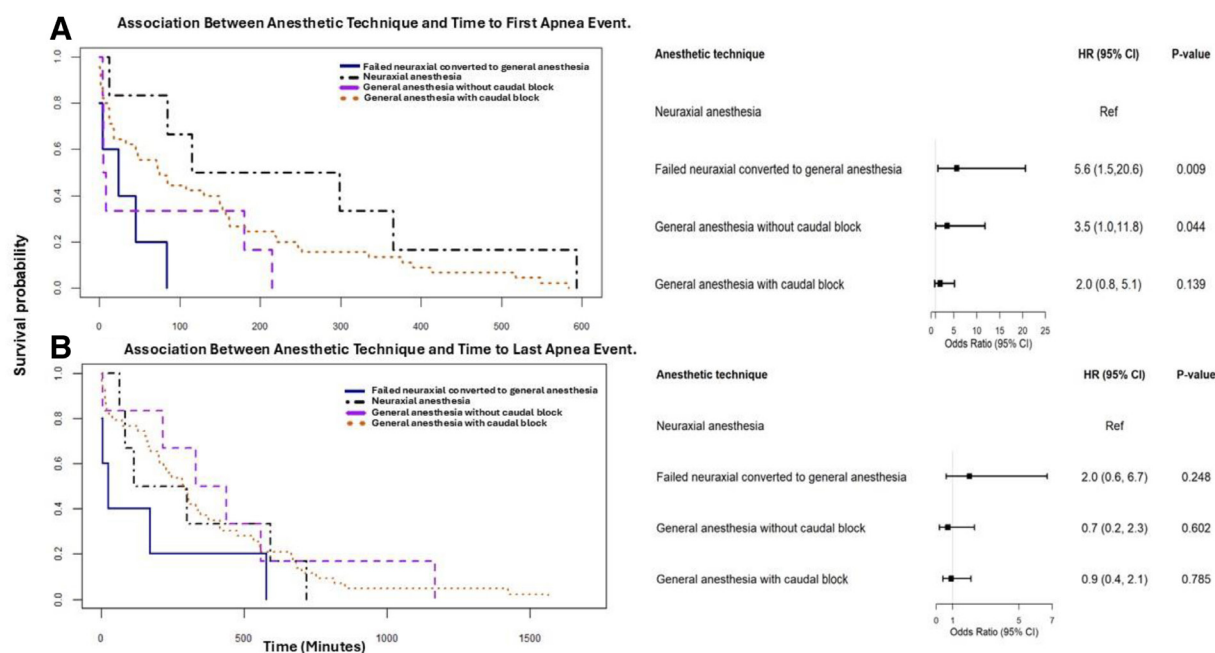
The majority of first apnea events occurred within 60 min of entering the PACU after general anesthesia, but infants managed with neuraxial anesthesia tended to have their onset of apnea after PACU discharge (fig. 4). Apnea onset occurred as late as approximately 10 h after either general or neuraxial anesthesia, supporting the previous literature suggesting that all former preterm infants should be monitored for at least 12 apnea-free hours, albeit extended as indicated, regardless of anesthetic technique.<sup>9,11,13</sup> Our analysis shifts the less than 1% at-risk PMA and provides supportive evidence for postoperative monitoring in all former preterm infants less than 65 weeks PMA receiving general anesthesia. While the number of infants who had neuraxial anesthesia at a later PMA was insufficient to derive a less than 1% threshold for apnea risk, we did find that in infants with a younger PMA (at approximately 53 weeks PMA, the probability of postanesthesia apnea with general anesthesia is 10%, whereas it is reduced to 1% with neuraxial anesthesia), neuraxial anesthesia may emerge as the preferred technique in this at-risk cohort. Further exploration of this question is warranted.

We are unable to shed additional light upon the management of full-term infants since only 1 of 350 experienced apneas. He experienced two apnea events in the PACU, which responded to stimulation. He was 44.9 weeks PMA, was 37 weeks gestational age, weighed 3.1 kg at birth, weighed 5.5 kg at the time of surgery, had a hemoglobin value 10.2 g/dl, and received sevoflurane anesthesia with a caudal block. It is possible that he was an anemic former preterm infant with an inaccurately estimated gestational age.

We focused only on former preterm infants undergoing one specific surgical procedure, *i.e.*, inguinal herniorrhaphy, to standardize the surgical stress. The timing of elective inguinal herniorrhaphy is important since the risk of incarceration and bowel strangulation with necrosis<sup>29</sup> results in an emergent rather than an elective anesthetic. Outcomes data comparing early *versus* late herniorrhaphy indicate that fewer infants had adverse events in the late repair group<sup>30</sup>; there is a dearth of data for infants with PMA beyond 57 weeks. A clinical report from the American Academy of Pediatrics confirms the conflicting and inadequate data regarding the optimal timing for surgical repair, but anesthesia risks are not addressed.<sup>31</sup>

## Strengths and Limitations

**Strengths.** An IPD meta-analysis combines raw data from individual participants across multiple studies compared to a traditional aggregate data meta-analysis that uses summary data from published studies. The advantages of an IPD meta-analysis include improved data quality and the ability



**Fig. 3.** (A) Kaplan–Meier plot of time to the first apnea event. Note that those receiving general anesthesia and those with a failed neuraxial converted to general anesthesia tended to have their first postanesthesia apnea event the earliest, those receiving general anesthesia with a caudal block at an intermediate time, and those receiving neuraxial anesthesia tended to have their first postanesthesia apnea event the latest. (B) Kaplan–Meier plot of time to the last postanesthesia apnea event. Note that those receiving general anesthesia and those receiving general anesthesia with a caudal block tended to have their last postanesthesia apnea much later than those receiving general anesthesia after failed neuraxial anesthesia or neuraxial anesthesia.

to investigate research questions in greater detail and with increased precision.<sup>5,6</sup>

We clarified that neuraxial compared with general anesthesia results in reduced occurrence and frequency of postanesthesia apnea and that the at-risk PMA is lower for infants after neuraxial anesthesia compared to those managed with general anesthesia. There appears to be no advantage with using modern compared with legacy inhalation agents. Although anemia was confirmed as a risk factor in infants more than 48 weeks PMA, further studies are needed to evaluate its impact on clinical decisions and outcomes. Pulse oximetry with any form of respiratory monitoring appears to increase apnea detection; perhaps this combination may be the best practice for monitoring until we obtain conclusive data from prospective randomized studies.

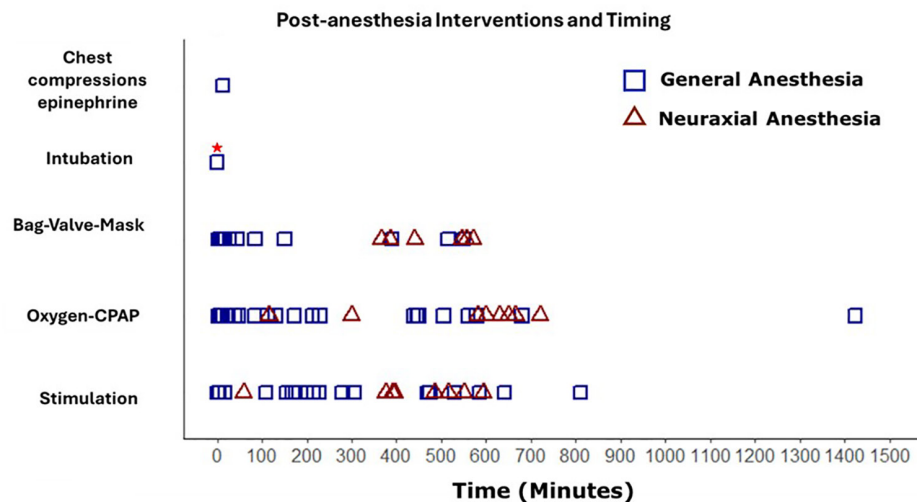
**Limitations.** We identified five covariates (PMA, gestational age, birth weight, anesthetic technique, and anemia) associated with apnea events and used multivariable regression analysis models that explored associations between risk factors. Such models serve different analytic purposes—prediction, causal inference, or descriptive association—each requiring distinct assumptions and interpretive frameworks; hence we chose to present these analyses as supplemental digital content with forest plots (Supplemental Digital Content fig. 1, <https://links.lww.com/ALN/E426>).

We chose an anemia threshold of less than 10 g/dl for ease of comparison. However, inconsistent blood transfusion thresholds,<sup>32</sup> variability in anemia definitions,<sup>33</sup> and other confounding factors<sup>34</sup> may affect this threshold.

A further limitation includes the variability of the types of monitoring to detect apnea preventing us from identifying a specific respiratory monitor that would most likely detect apnea. Another limitation is the association of apnea with intraoperative opioids or nondepolarizing muscle relaxants. Since a greater risk for apnea is associated with general anesthesia, it makes sense that *pari passu* this risk would also be associated with the medications needed to facilitate general anesthesia. The number of infants managed with caffeine or neuraxial anesthesia with sedation were inadequate for our analysis. Since our study population consisted only of preterm infants undergoing inguinal hernia surgery, we cannot comment on the generalizability of our findings to other surgical populations.

## Conclusions

Neuraxial anesthesia appears to offer advantages over general anesthesia in terms of associated risk of postanesthesia apnea in former preterm infants undergoing inguinal hernia repair. Postanesthesia apnea risk after neuraxial anesthesia extends to a much younger PMA compared with general anesthesia; however, due to the sparse data in older



**Fig. 4.** Five types of interventions and their timing after arrival in the postanesthesia care unit (PACU). Note that rescue interventions for postanesthesia apnea after neuraxial anesthesia and general anesthesia were commonly required up to 14 h after arrival in PACU and in one patient 26 h after PACU admission. One infant required epinephrine, tracheal intubation, and chest compressions; three infants had tracheal intubation at the same time after PACU arrival (*red star*).

PMA infants, we are unable to provide a precise at-risk PMA at which the probability of a postanesthesia apnea event is less than 1% after neuraxial anesthesia. Our data support monitoring former preterm infants undergoing inguinal herniorrhaphy for at least 12 apnea-free hours, even at older PMA after neuraxial anesthesia. Apnea risk rapidly decreases from approximately 34 of 1,000 at 58 weeks PMA to approximately 1 of 1,000 at 75 weeks PMA; the decision to admit these infants is thus related to what risk a practitioner is willing to accept. Since anemia is a risk factor for infants more than 48 weeks PMA, our data support preoperative screening. We understand that our study findings may have implications in resource-limited settings. Perhaps future studies of older PMA former preterm infants managed with neuraxial anesthesia may allow more statistically sound recommendations. This study sets the stage for revised professional organizations' consensus statements.

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## Competing Interests

The authors declare no competing interests.

## Correspondence

Address correspondence to Dr. Dalal: Department of Anesthesiology and Perioperative Medicine, H187, 500 University Dr, Pennsylvania State College of Medicine, Pennsylvania State Health Children's Hospital, Hershey, Pennsylvania 17033. [pdalal@pennstatehealth.psu.edu](mailto:pdalal@pennstatehealth.psu.edu)

## Supplemental Digital Content

Supplemental Digital Content file, <https://links.lww.com/ALN/E426>

Supplemental Digital Content Table 1: Apnea incidence and type of monitoring distribution

Supplemental Digital Content Table 2: Apnea incidence and frequency distribution

Supplemental Digital Content Figure 1: PMA, occurrence, frequency of apnea association

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### Appendix: Society for Pediatric Anesthesia Quality and Safety Committee–Apnea Task Force Collaborative Group

Jennifer L. Chiem, M.D.: Seattle Children's Hospital, Seattle, Washington.

Joseph P. Cravero, M.D.: Harvard Medical School, Boston Children's Hospital, Boston, Massachusetts.

Laura D. Donohue, M.D.: Mary Bridge Children's Hospital, Tacoma, Washington.

James Fehr, M.D.: Department of Anesthesiology, Stanford University, Stanford, California.

Manon Haché, M.D.: Columbia University Medical Center, New York, New York.

Eugenie Heitmiller, M.D.: Anesthesiology and Pediatrics, Children's National Hospital, George Washington School of Medicine and Health Sciences, Washington, D.C.

Tatiana Kubacki, M.D.: Columbia University Medical Center, New York, New York.