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Journal
Pediatric Anesthesia, 28(6)

ISSN
1155-5645

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Publication Date
2018-06-01

DOI
10.1111/pan.13391

Peer reviewed

HHS Public Access

Author manuscript

Paediatr Anaesth. Author manuscript; available in PMC 2018 December 12.

Published in final edited form as:

Paediatr Anaesth. 2018 June ; 28(6): 520–527. doi:10.1111/pan.13391.

Estimating Pediatric General Anesthesia Exposure: Quantifying Duration and Risk

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Abstract

Introduction: Understanding the duration of pediatric general anesthesia exposure in contemporary practice is important for identifying groups at risk for long general anesthesia exposures and designing trials examining associations between general anesthesia exposure and neurodevelopmental outcomes.

Methods: We performed a retrospective cohort analysis to estimate pediatric general anesthesia exposure duration during 2010–2015 using the National Anesthesia Clinical Outcomes Registry.

Results: A total of 1,548,021 pediatric general anesthetics were included. Median general anesthesia duration was 57 minutes (IQR 28–86) with 90th percentile 145 minutes. Children aged <1 year had the longest median exposure duration (79 minutes, IQR 39–119) with 90th percentile 210 minutes, and 13.7% of this very young cohort was exposed for greater than 3 hours. High ASA physical status and care at a university hospital were associated with longer exposure times.

Conclusion: While the vast majority (94%) of children undergoing general anesthesia are exposed for less than 3 hours, certain groups may be at increased risk for longer exposures. These

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Disclosures:

Ethics: No IRB approvals were needed for this project

findings may help guide the design of future trials aimed at understanding neurodevelopmental impact of prolonged exposure in these high-risk groups.

Keywords

adolescent; child; infant; neonate; general anesthesia; neurodevelopment

Introduction:

The neurodevelopmental impact of early exposure to general anesthesia (GA) in the pediatric population is still poorly understood. Data from young animal models suggest that exposure to commonly used anesthetic agents for extended durations or for multiple episodes may result in neurodegenerative histologic changes[1–4] and downstream effects on social-behavioral and cognitive functioning.[5–9] Cohort studies in human children have shown mixed results.[10–14] Notably, the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study found that anesthesia exposure before 36 weeks of age did not result in statistically significant differences in IQ and other neuropsychiatric test scores between exposed and unexposed siblings measured at age 8 to 15 years.[15] However, two large, recently published cohort studies found modest increased risk for neurodevelopmental deficits in young children exposed to general anesthesia at age 2 to 4 years[16] and after age 2 years[17] compared to children exposed earlier in life. Given the ongoing concerns about this age-specific neurologic vulnerability of young children, the U.S. Food and Drug Administration recently released a warning about the neurodevelopmental effects of early childhood exposure to drugs used for general anesthesia and sedation, “especially for procedures that may last longer than 3 hours or if multiple procedures are required in children under 3 years.”[18]

To date, the only randomized controlled trial in human children is the General Anesthesia compared to Spinal anesthesia (GAS) trial. Preliminary results showed no measurable difference in neurodevelopmental outcomes after 2 years in young infants undergoing inguinal hernia repair under general versus spinal anesthesia.[19] In the GAS trial, the median sevoflurane exposure duration was 54 minutes (IQR 41–70).[19]

Although data from this trial suggest that short, single GA exposures may be safe, it is unknown what proportion of pediatric general anesthetics involves longer exposure durations. Currently, large-scale studies across broad heterogeneous populations that quantify pediatric GA exposure duration or seek to estimate factors associated with longer exposures are lacking.

Methods:

We estimated pediatric GA exposure duration by performing a retrospective cohort analysis of pediatric general anesthetics in the National Anesthesia Clinical Outcomes Registry (NACOR). The NACOR is a national data repository, which includes observational, de-identified, validated anesthetic cases for surgeries and for diagnostic, therapeutic, and imaging procedures submitted from partnering healthcare entities in the United States and represents a broad array of facility types from diverse geographic regions.[20] NACOR is a

project of the American Society of Anesthesiologists' Anesthesia Quality Institute and is registered as a Qualified Registry and Qualified Clinical Data Registry by the Center for Medicare and Medicaid Services and as such, does not require patient consent or IRB approval. Participating healthcare entities are classified in NACOR as University Hospitals, Community Hospitals including large (over 500 beds) facilities, medium (100–500 bed) facilities, and small (fewer than 100 bed) facilities, Specialty Hospitals, Surgery centers (both attached and freestanding), and various office and clinic-based settings including Pain Clinics, Surgeon Offices, and Dental Offices. For the purposes of this analysis, we combined the three categories of community hospital into a single "Community Hospital" category, we combined the 2 categories of surgery centers into a single "Surgery Center" category, and we also combined "Pain Clinic," "Surgeon Office," and "Dental Office" categories into a single "Other" category. The condensing of these categories was done because the level of granularity provided was above that required for this analysis. Participation is voluntary and each participating entity and provider is de-identified. The NACOR employs a multi-staged process of case validation to ensure the accuracy of each case in its database.[21] The NACOR database and similar methodologies have been used successfully in the past with other patient subgroups. [22, 23]

Pediatric patients aged 0 days up to 18 years undergoing procedures under general anesthesia (GA) between January 2010 and March 2015 were included. Exclusion criteria included patients classified as ASA physical status VI (including cases imputed in the NACOR as ASA VI) and patients missing data on age, anesthetic type, and case duration. Sedation and MAC cases were also excluded from the analysis. Patients receiving multiple anesthetics over the study period were unlinked. As NACOR does not collect induction and emergence times, exposure duration was defined as the interval between recorded anesthesia start and anesthesia stop. When multiple anesthetic types were listed along with GA, the principal anesthetic technique was assumed to be GA. Given concerns about age-specific neuronal vulnerability of infants and young children[16–18], additional analyses were performed focused on children aged <4 years. Summary statistics were used to estimate GA exposure duration.

In post-hoc analysis, to further analyze whether avoidable GA exposures were occurring, surgical current procedural terminology (CPT) codes were queried for the three most common procedures being conducted in children <4 years and <1 year of age. The most frequent surgical CPT codes were crosschecked against ICD-9 codes to ensure validity. To further explore the issue of excess GA exposure in academic settings, GA duration times for the most common procedure in children <4 and <1 years old, "Procedures of the Middle Ear", and specifically tympanostomy tube placements, were compared between cases performed in university hospital settings vs. all other settings. To obtain only tympanostomy tube cases and exclude more complex middle ear procedures, cases were further restricted to those lasting <120 minutes for which only one ICD-9 diagnostic code existed and in which the reported anesthesia CPT code, which is the anesthesia billing code derived from the ASA Crosswalk, was for tympanostomy tube placement.

Nonparametric descriptive statistics were used where data were non-normally distributed, but otherwise parametric techniques were employed. Statistical analyses were completed in R (version 3.3.2).

Results

Out of 2,473,411 pediatric anesthetics in the NACOR database, 1,756,743 (71.1%) had complete data on anesthesia type and 2,338,326 (94.5%) had complete data on anesthesia duration (Figure 1). There were a total of 1,548,337 (62.6%) pediatric general anesthetics with complete data on exposure duration. After exclusion of patients with ASA physical status designation VI, this left 1,548,021 pediatric general anesthetics (Table 1) on which the remainder of the analysis was conducted. These complete data came from a total of 1,555 unique facilities and 256 practices. Cases with incomplete data on anesthesia type or anesthesia duration (see Supplementary Table S1) had similar distributions as complete cases regarding age, sex, and ASA physical status.

The median age of children in the cohort was 6 years. The majority of cases were ASA I (56%) and II (32%) physical status. General anesthesia was the principal anesthetic technique in the vast majority of anesthetics (92.7%). The overall median duration of GA exposure was 57 minutes (IQR 28–86, Table 2). GA duration varied by age, with the longest median durations among <1 year old patients and patients 13 years or older (Figure 2). Overall, younger children (aged 0–4 years) had median duration 52 minutes (IQR 23–81) whereas children >4 years were exposed for a median of 60 minutes (IQR 32–88).

The vast majority of general anesthetics (94%) were less than 3 hours (Figure 3). The GA exposure duration 10^{th} and 90^{th} percentiles were 21 and 145 minutes in all patients, 22 and 210 minutes in those aged <1 year, 14 and 143 minutes in those aged 1 year, 15 and 114 minutes in those aged 2 years, 20 and 124 minutes in those aged 3 years, and 20 and 124 minutes for children aged 4 years (Table 2). Children aged 13 years or more had median exposure time of 70 minutes (IQR 37–103) with 10^{th} and 90^{th} percentiles 30 and 170 minutes, respectively. The proportion of general anesthetics performed on ASA III, IV, and V patients was higher among <1 year olds compared to older children (Table 3). GA exposures lasting >3 hours comprised 13.7% of GA exposures among patients aged <1 year, which was the largest proportion of any age group. Additionally, ASA III, IV, and V patients comprised a larger proportion of cases lasting >3 hours. When the <1 year age group was limited to ASA I and II patients, median GA duration dropped from 79 minutes to 65 minutes (IQR 33–97).

Surgical CPT codes were 85% completely coded. The most common procedure in children <4 years of age was “Procedures of the Middle Ear” (16%, mean duration = 20.2 minutes, σ = 31.6 minutes), followed by “Excision and Destruction Procedures on the Pharynx, Adenoids, and Tonsils” (9.6%, mean duration = 42 minutes, σ = 38 minutes), followed by “Procedures on the Dentoalveolar Structures” (4.7%, mean duration = 92.5 minutes, σ = 65 minutes). The most common procedure in children <1 year of age was also “Procedures of the Middle Ear” (6.6%, mean duration = 21.8 minutes, σ = 40.8 minutes), followed by “Circumcision” (3.5%, mean duration = 66.7 minutes, σ = 55 minutes), followed by

"Incision Procedures on the Stomach" (3.3%, mean duration = 81.4 minutes, σ = 57.3 minutes).

Sicker patients (ASA III, IV, and V) and care at a university hospital setting were associated with longer GA exposure times. University hospital settings cared for a larger percentage of patients with higher ASA physical status designations; however, anesthetic exposure durations for patients from all ASA classes were higher at university hospital settings than in other facility types (Table 3). As the most common procedure in children <4 and <1 years old was "Procedures of the Middle Ear", we compared durations of this procedure, specifically tympanostomy tube placements, performed in university settings vs. all other settings. There were 71,054 cases of tympanostomy tubes; data appeared parametric with mean of 18.4 minutes and median of 17 minutes. In univariate analysis using a T-test, we found that exposure durations in university settings were 29 minutes compared to 18 minutes in non-academic settings ($t=32$, $p<0.0001$). A linear regression was performed, adjusting for ASA status and including an interaction term between university hospital setting and ASA physical status (as patients that are higher ASA and in an academic hospital setting may have more complex disease requiring expertise in an academic environment and therefore more anesthesia time). The interaction term had a coefficient of 4.9, st err=0.31, $t=15.8$, and was significant with $p<0.0001$. This regression model estimated that university settings added 3.2 minutes of anesthesia time on average (R-squared = 0.07, F-statistic=1552, $p<0.0001$) compared with non-academic settings.

Discussion

In this study, we found that roughly half of children requiring surgery with general anesthesia are exposed to general anesthetics for approximately an hour or more. Very young children (<1 year), older children (≥13 years), as well as sicker children or those treated in an academic hospital setting, tended to have longer exposures. The median GA exposure times estimated from this study in infants <1 year of age were comparable to those reported in the GAS trial (median 54 minutes with IQR 41–70)[19] suggesting that the findings of the GAS trial may be generalizable to many very young infants in current clinical practice. The longer median GA exposure times found in this very young age group are likely associated with the higher proportion of higher ASA physical status-designated patients, as median exposure time decreased substantially in this age group when general anesthetics performed on patients with ASA III, IV, and V were excluded. It should also be noted that these very young patients are (1) least likely to have an option of postponing anesthesia and surgery and (2) most likely to have chronic medical conditions that also might contribute to adverse neurodevelopmental outcomes. As the rate of perioperative severe critical events has been shown to increase in patients with higher ASA physical status and among neonates and infants,[24] our finding highlights the complex interplay of patient, surgical, and anesthetic factors when considering the effect of anesthetic duration on patient outcomes and invites further inquiry into determining the extent to which anesthetic exposure duration may be associated with additional patient morbidity and mortality.

As a group, children 1–4 years of age had lower median GA exposure times than both children <1 year and older children, which is reassuring given concerns about GA exposure

raised in this vulnerable subpopulation. Furthermore, patients exposed for >3 hours comprised approximately only 6% of the overall study cohort. This provides some reassurance that the large majority of children receiving GA may be at low risk for prolonged exposure times. Still, certain groups, especially patients aged <1 or >13 years, or with additional morbidities and complexity, as reflected by high ASA physical status designations, had longer GA exposure times.

Care at an academic center was also associated with longer GA exposure times. In a post-hoc univariate analysis, we estimated 11 minutes of additional exposure during tympanostomy tube placement while a linear regression adjusting for ASA physical status and with an interaction term between university settings and ASA status estimated approximately 3 minutes of additional exposure time. This adjusted estimate is a small absolute amount, around 10–20% additional anesthesia time, and may reflect the presence of trainees in academic settings, the culture as it pertains to case duration in academic practice, or unmeasured confounding due to case complexity. While tympanostomy tube placement was chosen because of its relatively high frequency in young children which enabled a meaningful analysis, the absolute increase in general anesthesia exposure duration is unlikely to have a meaningful effect on neurobehavioral and developmental outcomes. One may assume that similar proportional increases may exist for other operations or procedures in university hospitals compared to other settings, although extrapolating this time difference may not be accurate. In addition, while we were able to describe the most commonly performed procedures in young children, it is difficult to determine the extent to which these exposures were avoidable. Given the concern for hearing loss or recurrent ear infections, many parents will accept the risk of additional anesthesia time for tympanostomy tube placement. Overall, it is difficult to draw conclusions on the avoidability of these anesthetics.

There are several limitations inherent in this study. First, while GA duration may be an important determinant in the dose-response relationship between exposure and neurodevelopmental outcomes, the contributors of exposure are much more complex, including medication type, dose, timing, and duration. As these data were not included in the NACOR, this analysis cannot comment on other components of exposure. We also used duration of anesthetic care to estimate anesthetic exposure; however, billed anesthetic care time is reasonably representative of time between induction and postoperative care unit admission. Because the NACOR classified the primary anesthetic type as GA if multiple anesthetic types were listed along with GA, this may have resulted in overestimation of GA prevalence and duration. We did not include sedation and MAC cases in this analysis, although the animal data suggest exposure to many of these agents also are associated with the same risks as GA. This may result in a conservative estimate of the number of patients exposed. Also, while the practice of regional techniques in children has been documented as remarkably safe,[25] we were not able to examine whether performance of a regional block under general anesthesia, as is commonplace in pediatric anesthesia practice, substantially lengthened exposure durations because these data are not captured adequately in NACOR. However, the time required to perform a regional or neuraxial block under general anesthesia should be collected and examined in the future as this practice may warrant additional scrutiny, understanding that the use of a regional block administered as an adjunct

to general anesthesia may also serve to decrease depth of anesthesia and therefore total dose of systemic agents.

Because participation in NACOR is voluntary, it is unknown whether the sample included is representative of nationwide practice patterns, although the size and diversity of the sample was large. The NACOR does not use a unique identifier, so the proportion of children receiving repeat anesthetic exposures, a putative risk factor in some retrospective cohort analyses, could not be determined. Lastly, approximately 6% and 30% of cases in the sample were missing data on anesthesia duration and type, respectively. However, when compared, incomplete cases had similar distributions as complete cases regarding major covariates, so that this was unlikely a source of major bias.

Conclusion

In this cohort of over 1.5 million children, the duration of general anesthetic exposure is under 1 hour for most pediatric patients, and patients aged 1–12 years typically have the shortest exposure durations. This large cross-sectional sample suggests that more than 90% of children who receive GA fall outside the parameters stipulated in the FDA warning about anesthetic exposure and neurotoxicity. However, <1 year olds, ≥13 year olds, patients with high ASA physical status designations, and patients receiving care in academic settings were at increased risk for prolonged GA exposure. These risk factors for prolonged exposure should be considered when elective operations are indicated for children who fall into the FDA-defined vulnerable category, and employing mitigating strategies, including increased use of adjunctive agents and techniques that have not been associated with neurotoxicity such as ultrashort-acting opioids, alpha agonists, and regional blockade, or postponement of non-urgent procedures, should be entertained when clinically appropriate. These findings may guide future studies of neurodevelopmental outcomes in children undergoing anesthesia. Further controlled trials are needed to address neurotoxicity risks in infants and young children at highest risk due to prolonged exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We would like to thank the Anesthesia Quality Institute for use of the National Anesthesia Clinical Outcomes Registry (NACOR) data.

Funding: There was no funding source for this project.

Disclosures: On a separate project, co-author ELW was supported by a National Institute of General Medical Sciences training grant (4T32GM008440, PI: Judith Hellman). Co-author DMP receives book royalties from Wolters Kluwer. DP and AD are editors of Pediatric Anesthesia.

References:

1. Brambrink AM; Evers AS; Avidan MS; Farber NB; Smith DJ; Zhang X; Dissen GA; Creeley CE; Olney JW, Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. Anesthesiology 2010, 112 (4), 834–41. [PubMed: 20234312]

2. Stratmann G; Sall JW; May LD; Bell JS; Magnusson KR; Rau V; Visrodia KH; Alvi RS; Ku B; Lee MT; Dai R, Isoflurane differentially affects neurogenesis and long-term neurocognitive function in 60-day-old and 7-day-old rats. Anesthesiology 2009, 110 (4), 834–48. [PubMed: 19293705]

3. Slikker W; Zou X; Hotchkiss CE; Divine RL; Sadovova N; Twaddle NC; Doerge DR; Scallet AC; Patterson TA; Hanig JP; Paule MG; Wang C, Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci 2007, 98 (1), 145–58. [PubMed: 17426105]

4. Brambrink AM; Back SA; Riddle A; Gong X; Moravec MD; Dissen GA; Creeley CE; Dikranian KT; Olney JW, Isoflurane-induced apoptosis of oligodendrocytes in the neonatal primate brain. Ann Neurol 2012, 72 (4), 525–35. [PubMed: 23109147]

5. Lee BH; Chan JT; Hazarika O; Vutskits L; Sall JW, Early exposure to volatile anesthetics impairs long-term associative learning and recognition memory. PLoS One 2014, 9 (8), e105340. [PubMed: 25165850]

6. Lee JH; Zhang J; Wei L; Yu SP, Neurodevelopmental implications of the general anesthesia in neonate and infants. Exp Neurol 2015, 272, 50–60. [PubMed: 25862287]

7. Kong FJ; Ma LL; Hu WW; Wang WN; Lu HS; Chen SP, Fetal exposure to high isoflurane concentration induces postnatal memory and learning deficits in rats. Biochem Pharmacol 2012, 84 (4), 558–63. [PubMed: 22705347]

8. Fredriksson A; Ponten E; Gordh T; Eriksson P, Neonatal exposure to a combination of N-methyl-D-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology 2007, 107 (3), 427–36. [PubMed: 17721245]

9. Paule MG; Li M; Allen RR; Liu F; Zou X; Hotchkiss C; Hanig JP; Patterson TA; Slikker W; Wang C, Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. Neurotoxicol Teratol 2011, 33 (2), 220–30. [PubMed: 21241795]

10. Wilder RT; Flick RP; Sprung J; Katusic SK; Barbaresi WJ; Mickelson C; Gleich SJ; Schroeder DR; Weaver AL; Warner DO, Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 2009, 110 (4), 796–804. [PubMed: 19293700]

11. Kalkman CJ; Peelen L; Moons KG; Veenhuizen M; Bruens M; Sinnema G; de Jong TP, Behavior and development in children and age at the time of first anesthetic exposure. Anesthesiology 2009, 110 (4), 805–12. [PubMed: 19293699]

12. Flick RP; Katusic SK; Colligan RC; Wilder RT; Voigt RG; Olson MD; Sprung J; Weaver AL; Schroeder DR; Warner DO, Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics 2011, 128 (5), e1053–61. [PubMed: 21969289]

13. Hansen TG; Pedersen JK; Henneberg SW; Pedersen DA; Murray JC; Morton NS; Christensen K, Academic performance in adolescence after inguinal hernia repair in infancy: a nationwide cohort study. Anesthesiology 2011, 114 (5), 1076–85. [PubMed: 21368654]

14. Bartels M; Althoff RR; Boomsma DI, Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet 2009, 12 (3), 246–53. [PubMed: 19456216]

15. Sun LS; Li G; Miller TL; Salorio C; Byrne MW; Bellinger DC; Ing C; Park R; Radcliffe J; Hays SR; DiMaggio CJ; Cooper TJ; Rauh V; Maxwell LG; Youn A; McGowan FX, Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood. JAMA 2016, 315 (21), 2312–20. [PubMed: 27272582]

16. Graham MR; Brownell M; Chateau DG; Dragan RD; Burchill C; Fransoo RR, Neurodevelopmental Assessment in Kindergarten in Children Exposed to General Anesthesia before the Age of 4 Years: A Retrospective Matched Cohort Study. Anesthesiology 2016, 125 (4), 667–677. [PubMed: 27655179]

17. O'Leary JD; Janus M; Duku E; Wijeysundera DN; To T; Li P; Maynes JT; Crawford MW, A Population-based Study Evaluating the Association between Surgery in Early Life and Child Development at Primary School Entry. Anesthesiology 2016, 125 (2), 272–9. [PubMed: 27433745]

18. FDA. FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women 2016 http://www.fda.gov/downloads/Drugs/DrugSafety/UCM533197.pdf.

19. Davidson AJ; Disma N; de Graaff JC; Withington DE; Dorris L; Bell G; Stargatt R; Bellinger DC; Schuster T; Arnup SJ; Hardy P; Hunt RW; Takagi MJ; Giribaldi G; Hartmann PL; Salvo I; Morton NS; von Ungern Sternberg BS; Locatelli BG; Wilton N; Lynn A; Thomas JJ; Polaner D; Bagshaw O; Szmuk P; Absalom AR; Frawley G; Berde C; Ormond GD; Marmor J; McCann ME; consortium G, Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 2016, 387 (10015), 239–50. [PubMed: 26507180]

20. Liau A; Havidich JE; Onega T; Dutton RP, The National Anesthesia Clinical Outcomes Registry. Anesth Analg 2015, 121 (6), 1604–10. [PubMed: 26579661]

21. Institute, A. Q. AQI Data Validation and Standards. https://www.aqihq.org/data-standards-and-validation.aspx (accessed December 2016).

22. Brovman EY; Gabriel RA; Lekowski RW; Dutton RP; Urman RD, Rate of Major Anesthetic-Related Outcomes in the Intraoperative and Immediate Postoperative Period After Cardiac Surgery. J Cardiothorac Vasc Anesth 2016, 30 (2), 338–44. [PubMed: 26708695]

23. Tillquist MN; Gabriel RA; Dutton RP; Urman RD, Incidence and risk factors for early postoperative reintubations. J Clin Anesth 2016, 31, 80–9. [PubMed: 27185683]

24. Habre W; Disma N; Virag K; Becke K; Hansen TG; Jöhr M; Leva B; Morton NS; Vermeulen PM; Zielinska M; Boda K; Veyckemans F; Network, A. G. o. t. E. S. o. A. C. T., Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. Lancet Respir Med 2017, 5 (5), 412–425. [PubMed: 28363725]

25. Polaner DM; Taenzer AH; Walker BJ; Bosenberg A; Krane EJ; Suresh S; Wolf C; Martin LD, Pediatric Regional Anesthesia Network (PRAN): a multi-institutional study of the use and incidence of complications of pediatric regional anesthesia. Anesth Analg 2012, 115 (6), 1353–64. [PubMed: 22696610]

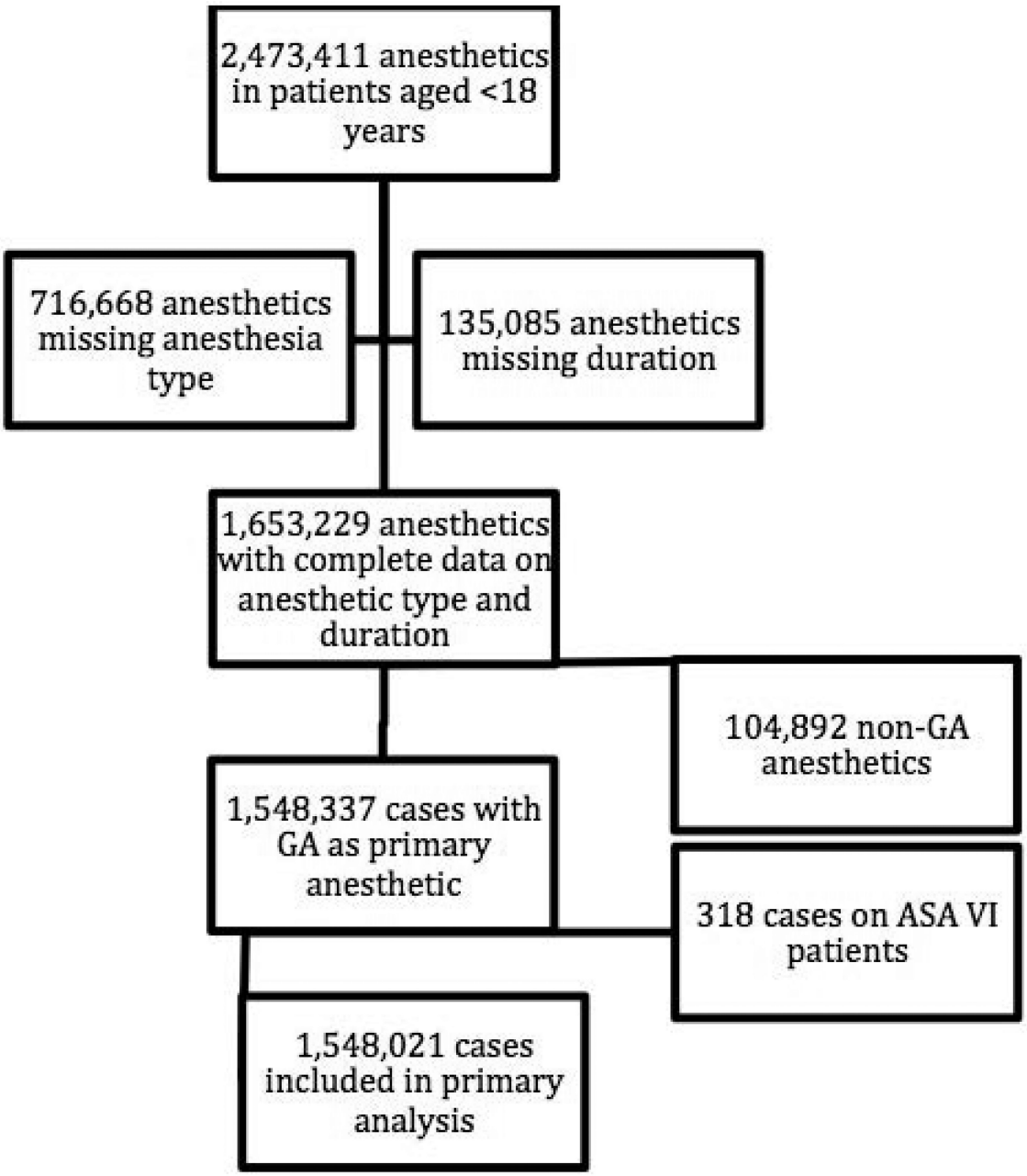
Clinical Implications:

What is already known:

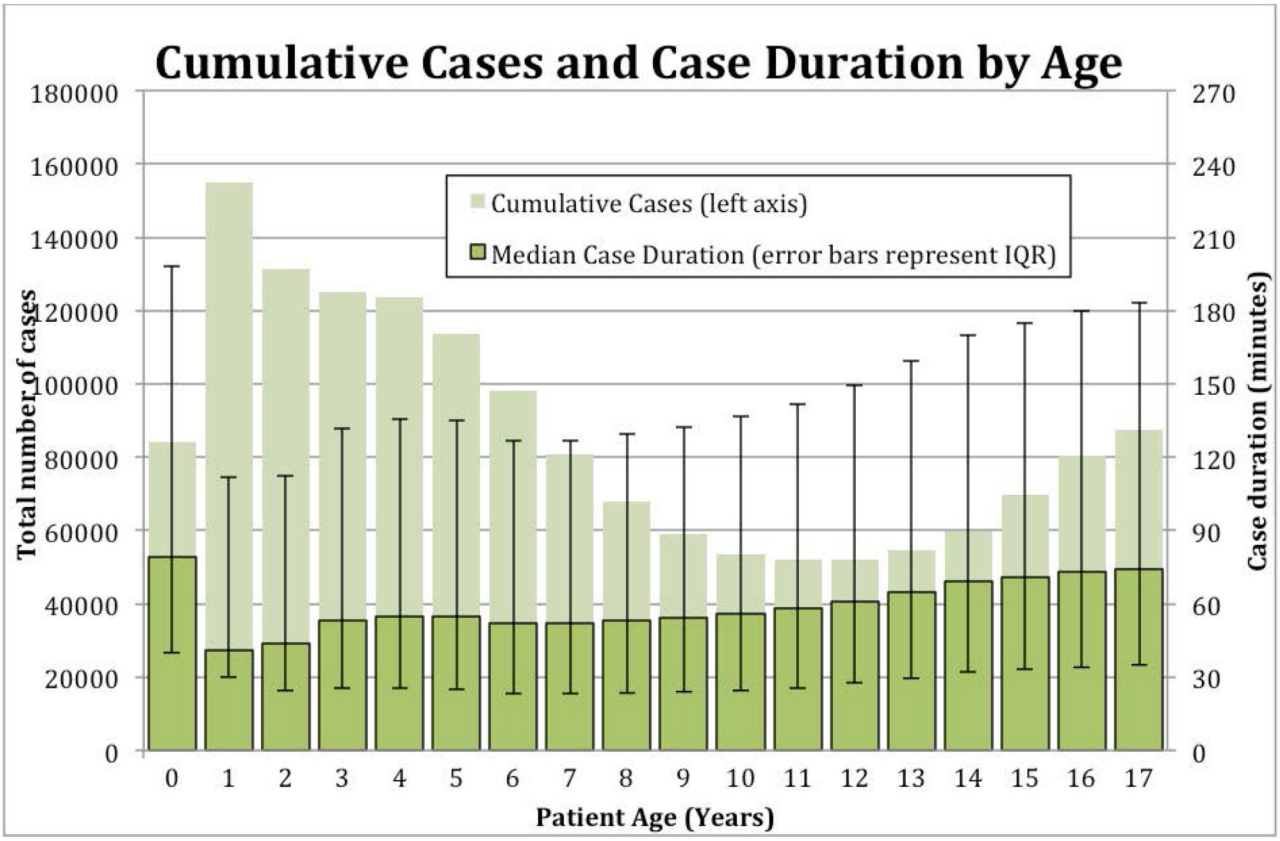
- General anesthesia exposure duration may be an important determinant of cognitive and neurodevelopmental outcomes in children.
- The United States Food and Drug Administration issued a Drug Safety Communication in December 2016 warning about the potentially detrimental neurodevelopmental effects of lengthy or repeated anesthesia exposures especially in children under 3 years of age.
- No study to date has quantified general anesthesia exposure durations or risk factors for lengthy exposures in children

What this article adds:

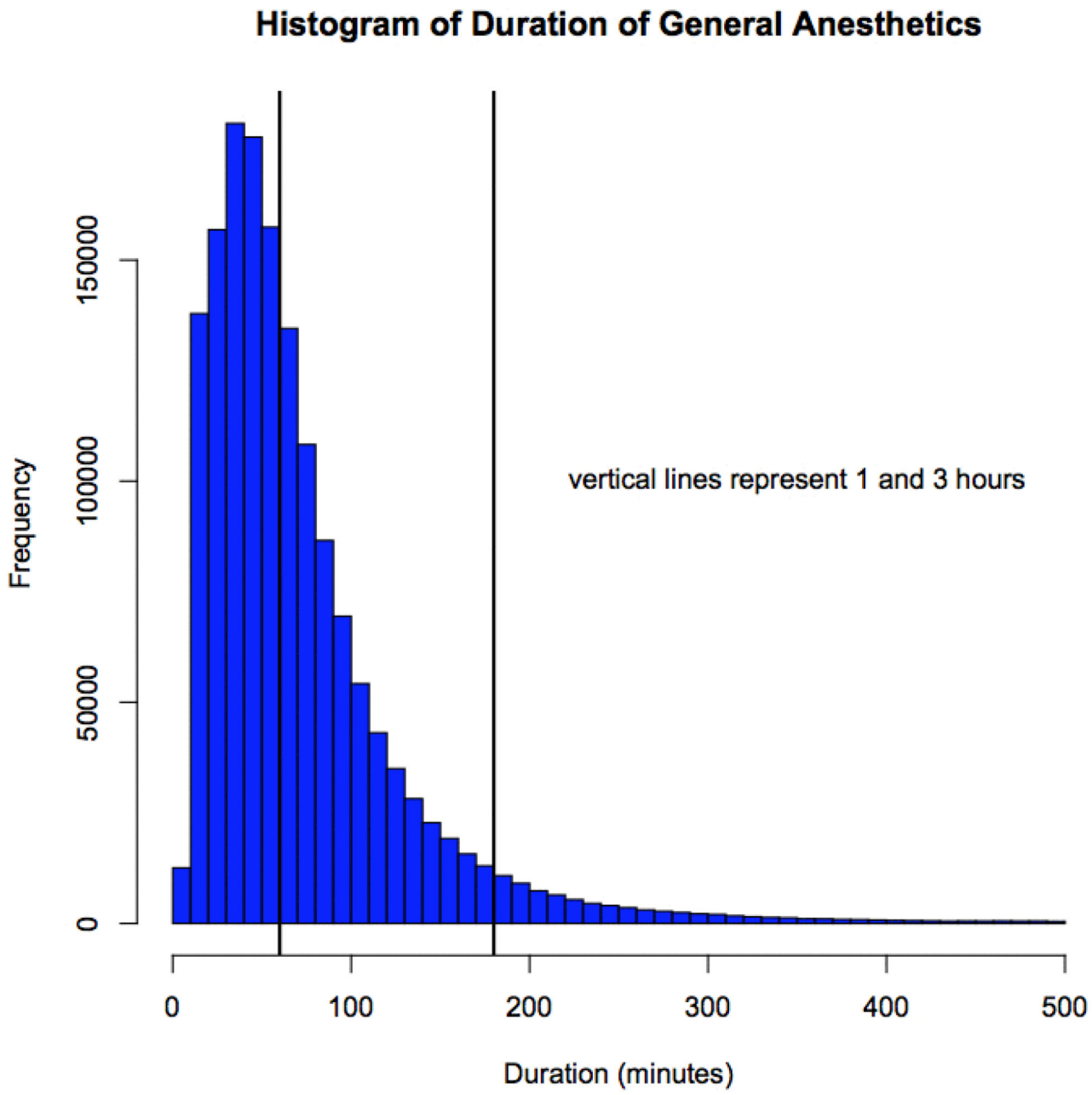
- Roughly half of children requiring surgery with general anesthesia are exposed to general anesthetics for approximately an hour or more
- The vast majority of children undergoing general anesthesia are exposed for less than 3 hours, but certain groups such as very young children (<1 year), older children (older than 12 years), or children receiving care at a university hospital setting or with additional morbidities and complexity may be at increased risk for longer exposures.



1).
STROBE diagram outlining excluding and included cohorts



2).
Cumulative case frequency and general anesthetic duration by age



3).

Histogram of pediatric general anesthesia frequency by general anesthetic duration. Note, data truncated to case duration <500 minutes to better illustrate data distribution

Table 1:

Characteristics of children undergoing anesthetics included in the National Anesthesia Clinical Outcomes Registry, 2010 to 2015 *

All Anesthetics (n=2,473,411)	
Median age in years (IQR)	6 (1-11)
Median anesthetic duration in minutes (IQR)	57 (28-86)
ASA status (n=2,038,353)	
I	1,162,244 (57.0)
II	611,566 (30.0)
III	224,108 (10.9)
IV	38,375 (1.9)
V	1,592 (0.07)
VI	468 (0.02)
Principle Anesthetic Technique (n=1,756,743)	
General	1,628,984 (92.7)
Spinal or epidural	20,866 (1.2)
Regional	5,800 (0.3)
Monitored Anesthesia Care or sedation	57,366 (3.3)
Local	280 (0.1)
Other	43,447 (2.4)
Anesthetics with complete anesthesia data, ASA<VI (n=1,548,021)	
Median age in years (IQR)	6 (1.5-10.5)
Median anesthetic duration in minutes (IQR)	57 (28-86)
ASA status (n=1,433,057)	
I	798,820 (55.7)
II	461,695 (32.2)
III	147,346 (10.3)
IV	24,160 (1.7)
V	1,036 (<0.1)
Male Sex (n=1,495,630)	853,188 (57.0)
Age Group	
<1 year	84,228 (5.4)
1 year	154,906 (10.0)
2 years	131,275 (8.5)
3 years	124,896 (8.1)
4 years	123,613 (8.0)
5-8 years	292,359 (18.9)
9-12 years	232,517 (15.0)
13-18 years	404,227 (26.1)
Region (n= 1,512,748)	

Northeast	220,651 (14.6)
Midwest	414,217 (27.4)
South	577,110 (38.1)
West	300,770 (19.9)
Facility Type (n= 1,260,505)	
University Hospital	111,988 (8.9)
Community Hospital	721,198 (57.2)
Specialty Hospital	143,454 (11.4)
Surgery Center	277,187 (22.0)
Other (pain clinic, surgeon/dentist office)	6,678 (0.5)
Case Type (n= 1,295,593)	
General OR Procedure	1,022,929 (78.9)
Non-OR Procedure	263,991 (20.4)
Mixed (OR and non-OR)	8,356 (0.6)
Obstetric	317 (<0.1)

*All data as frequency (percentages) unless otherwise specified

Table 2:

Duration of General Anesthesia Overall and by Categorical Variables

General anesthesia duration (minutes)	Median (IQR)	10th Percentile	90th Percentile
Overall	**57 (28-86)**	**21**	**145**
Age Group			
<1 year	79 (39-119)	22	210
1 year	41 (11-71)	14	143
2 year	44 (19-69)	15	114
3 year	53 (27-79)	20	124
4 year	55 (29-81)	22	128
5-8 years	53 (29-77)	23	124
9-12 years	55 (31-79)	25	133
13-18 years	70 (37-103)	30	170
ASA Status			
I	54 (28-80)	19	127
II	56 (29-83)	22	140
III	81 (38-124)	31	224
IV	125 (57-193)	51	346
V	131 (73-189)	54	340
Region			
Northeast	64 (32-96)	23	157
Midwest	57 (28-86)	20	146
South	52 (25-79)	20	135
West	62 (32-92)	25	150
Facility Type			
University Hospital	79 (40-118)	30	200
Community Hospital	62 (35-89)	24	145
Specialty Hospital	50 (24-76)	20	135
Surgery Center	39 (19-59)	15	99
Other (pain clinic, surgeon/dentist office)	55 (29-81)	20	130
Case Type			
General OR Procedure	57 (28-86)	20	146
Non-OR Procedure	50 (25-75)	21	129
Mixed (OR and non-OR)	73 (45-101)	23	165
Obstetric	74 (36-112)	40	398

Table 3:

ASA physical status by key variables and anesthetic exposure duration frequency distribution by age group*

Age Category	**ASA I**	**ASA II**	**ASA III**	**ASA IV**	**ASA V**
<1 year	30,704 (37.8)	20,796 (25.6)	18,798 (23.2)	10,371 (12.8)	485 (0.6)
1 year	81,450 (56.3)	43,784 (30.2)	16,016 (11.1)	3,424 (2.4)	112 (0.1)
2 years	71,163 (58.6)	37,969 (31.3)	10,895 (9.0)	1,343 (1.1)	34 (<0.1)
3 years	68,291 (59.3)	35,772 (31.1)	10,118 (8.8)	967 (0.8)	29 (<0.1)
4 years	68,199 (59.8)	35,590 (31.2)	9,450 (8.3)	793 (0.7)	22 (<0.1)
5-8 years	155,471 (57.7)	89,458 (33.2)	22,736 (8.4)	1,838 (0.7)	55 (<0.1)
9-12 years	113,175 (52.7)	76,732 (35.7)	23,033 (10.7)	1,795 (0.8)	71 (<0.1)
13-18 years	210,367 (56.5)	121,594 (32.7)	36,300 (9.8)	3,629 (1.0)	228 (0.1)
GA Duration					
<1 hour	445,733 (59.8)	247,541 (33.2)	49,031 (6.6)	3,408 (0.5)	132 (<0.1)
1-2 hours	259,537 (55.1)	149,629 (31.8)	53,233 (11.3)	8,102 (1.7)	332 (0.1)
2-3 hours	60,679 (48.0)	38,152 (30.2)	22,491 (17.8)	4,905 (3.9)	250 (0.2)
>3 hours	32,871 (36.6)	26,373 (29.3)	22,591 (25.1)	7,745 (8.6)	322 (0.4)
Facility Type					
University Hospital	43,190 (39.8)	38,902 (35.9)	21,320 (19.7)	4,805 (4.4)	255 (0.2)
Community Hospital	362,331 (54.0)	214,658 (32.0)	80,588 (12.0)	12,879 (1.9)	567 (0.1)
Surgery Center	171,301 (72.9)	57,483 (24.5)	6,065 (2.6)	150 (0.1)	7 (<0.1)
Specialty Hospital	59,676 (41.6)	65,187 (45.5)	16,812 (11.7)	1,703 (1.2)	47 (<0.1)
Other	4,247 (64.4)	1,620 (24.6)	571 (8.7)	150 (2.3)	10 (0.2)
GA Duration	**<1 hour**	**1-2 hours**	**2-3 hours**	**>3 hours**	
Age Group					
<1 year	28,628 (34.0)	31,914 (37.9)	12,162 (14.4)	11,524 (13.7)	
1 year	97,895 (63.2)	36,134 (23.3)	10,215 (6.6)	10,662 (6.9)	
2 years	85,212 (64.9)	34,170 (26.0)	7,007 (5.3)	4,886 (3.7)	
3 years	71,079 (56.9)	40,196 (32.2)	8,727 (7.0)	4,894 (3.9)	
4 years	67,389 (54.5)	41,485 (33.6)	9,911 (8.0)	4,828 (3.9)	
5-8 years	166,741 (57.0)	93,654 (32.0)	20,756 (7.1)	11,208 (3.8)	
9-12 years	127,090 (54.7)	76,050 (32.7)	17,189 (7.4)	12,188 (5.2)	
13-18 years	162,296 (40.1)	154,960 (38.3)	51,181 (12.7)	35,790 (8.9)	

*All data as frequency (percentage by row) unless otherwise specified