

Perioperative anaphylaxis in children: aetiology, time sequence and patterns of clinical reactivity

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Running title: Perioperative anaphylaxis in children

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Word count: 2510

Number of tables and figures: 3 tables and 3 figures

Material in the electronic repository, if applicable: no

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/pai.13124](#)

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Article type : Original

i. A statement with potential conflict of interests related to the manuscript content

None of the authors report any potential conflicts of interest.

ii. Financial support

This study was supported by the European Academy of Allergy and Clinical Immunology as part of the long-term research fellowship awarded to Dr. Ekaterina Khaleva, supervised by Prof. George du Toit. The funding sponsor had no role in the study design; collection, analyses, or interpretation of data; writing of the manuscript; or the decision to publish.

iii. Abstract and keywords

Background. Perioperative anaphylaxis (PA) in children is an uncommon but potentially life-threatening complication associated with anaesthesia. Early identification and management of PA is essential to optimize clinical outcomes.

Methods. We performed a retrospective study of anaesthesia records from paediatric patients with PA from centres in the United Kingdom, France, and the United States over a period of ten years. Time-sequence of clinical signs and physiological variables during PA were collected, along with results of allergy testing.

Results. Twenty-nine children with PA were included. Median age was 11 years. Based on the modified Ring and Messmer Grading Scale, severe reactions were seen in 25 (86%) members of this cohort, with 4 (14%) experiencing cardiac arrest. Cardiovascular collapse was the first clinical sign of PA in 59% of cases, followed by tachycardia and bronchospasm. In 16 (55%) cases, the initial signs of PA involved multiple organ systems. When the initial signs of PA were cardiovascular and/or respiratory, more epinephrine doses were administered. Average time from initial sign of PA to treatment with epinephrine was 6 min (SD 6, range 1-25). The causative allergen was identified in 15 patients.

Conclusion. Severe hypotension is the most common presenting sign of PA in children. Initial cardiovascular and/or respiratory signs are associated with the need for increased epinephrine doses. Further studies should optimise the prediction, identification, and early management of PA in children.

Key words: anaesthesia, anaphylaxis, epinephrine, children, drug allergy, hypersensitivity, hypotension, perioperative, skin tests, tryptase

iv. Main text

1. INTRODUCTION

There is little published data on perioperative anaphylaxis (PA) in children. Paediatric data consist of case studies¹⁻⁶, a protocol review^{7,8}, and surveys⁹⁻¹². Recent data from the Sixth National Audit Project (NAP6) in the United Kingdom describes PA in 11 children, giving an incidence of 2.7 per 100,000¹³. Earlier reports show that PA in children is rare, ranging from 1 in 7,741¹⁴ to 1 in 10,000 cases¹¹. The most commonly reported culprits in children are beta-lactam antibiotics and neuromuscular blocking agents (NMBAs)^{9,13,14}.

Hypersensitivity reactions in the perioperative setting may be difficult to diagnose as signs often mimic adverse effects of anaesthesia such as

hypotension immediately after induction or bronchospasm in patients with reactive airways^{15,16}. Moreover, anaphylaxis can be caused by immunological and non-immunological mechanisms¹⁷, which are difficult to differentiate during the event.

Perioperative allergic reactions typically occur in a well-monitored theatre environment, providing an excellent opportunity to better understand the pathophysiological changes that occur during PA. This study aimed to characterize the clinical presentation, time-dependent vital signs (VS), and subsequent allergy investigations in children with PA in order to facilitate more timely recognition and treatment.

2. METHODS

2.1 Study subjects

This is a retrospective study of paediatric patients with suspected PA from 6 centres during 2006-2016. Patients aged 1 to 18 years who experienced suspected PA and had anaesthetic charts documenting the event were reviewed. Cases with grade 3 or 4 anaphylaxis based on the modified classification system proposed by J. Ring and K. Messmer who required epinephrine were included¹⁸. Grade 3 was defined as life-threatening with signs of significant cardiovascular and/or respiratory compromise; and grade 4 was defined as cardiac or respiratory arrest¹⁸. Reactions included cases of IgE-mediated and non-allergic PA. The following factors were used to assess severity: amount of epinephrine and fluid administered by weight, total number of epinephrine doses administered, lowest recorded systolic blood pressure (sBP), and cancellation of surgery.

Cases were collected from 5 tertiary hospitals (3 in the UK, 1 in France and 1 in the USA) as described in the Supplementary Materials. Audit approval for the study was obtained from the Quality and Standard Department and/or Internal Review Board at each collaborating site. The

project was reviewed by the Research and Development Department in Guy's and St Thomas NHS Foundation Trust (GSTT).

Paediatric patients were divided into three groups: 1) cases with confirmed PA, 2) probable PA defined as patients experiencing grade 3-4 clinical manifestations of anaphylaxis with no trigger identified and with the exclusion of mastocytosis, and 3) control cases without PA. Criteria for confirmed PA included clinical signs of anaphylaxis grade 3-4 and elevated tryptase levels during the acute reaction ($>1.2 \times$ basal tryptase level $+2$ mcg/L) and/or positive skin prick test (SPT)/intradermal test (IDT) /specific IgE (sIgE). Probable cases had clinical signs of anaphylaxis grade 3-4 without an identifiable non-allergic cause, and lacked or had negative tryptase results¹⁶. The control group included children from 1 to 18 years old who had elective surgery without developing signs of PA, randomly identified through the GSTT electronic system.

2.2 Data collection

Patient data were extracted from medical notes, referral forms, and anaesthetic charts.

2.3 Statistical analyses

This study included all available paediatric patients who experienced PA at the collaborating centers. Probable and confirmed PA cases were combined into a single cohort for the analyses due to their low count and similarity between groups with respect to the parameters measured. To ensure that differences in VS between PA cases and controls were not solely due to differences in age, a comparison of mean group differences in vitals was done between an age-adjusted multivariable linear model and an unadjusted model.

Wilcoxon rank-sum tests were used to compare PA cases to controls. Reaction severity was analyzed by logistic regression, with initial cardiovascular signs (CVS) and respiratory signs (RS) as covariates. The

association of epinephrine administration with initial CVS or RS was assessed by ordinal logistic regression. One-way ANOVA was used to compare drug types, classified as antibiotics, NMBA, or other.

All analyses were performed using JMP Pro 14 and SAS 9.4.

3. RESULTS

3.1 Demographics

Demographic data are presented in **Table 1**. A total of 29 PA patients were included. Patients in the control group (n=62) were randomly selected from patients who had undergone elective surgeries (predominantly otolaryngology interventions) and were significantly younger than the PA group (median age 4 versus 11 years, $p<0.01$).

3.2. Clinical manifestations of PA

Clinical features of PA in children are summarised in **Figure 1**. Twenty-five (86%) children had grade 3 reactions; four (14%) had grade 4 reactions with cardiac arrest. Cardiovascular collapse was the first clinical feature of anaphylaxis in 59% of all cases, followed by tachycardia, bronchospasm, and difficulty ventilating. CVS were present in 97% (28) of patients. In 16 (55%) cases, initial signs of PA involved multiple organ systems.

3.3. Characteristics of pathophysiological changes

Confirmed and probable PA patients had similar CVS (sBP, diastolic blood pressure (dBP), heart rate (HR)) and oxygen saturation (SpO₂), which differed significantly from controls ($p<0.05$). The lowest recorded sBP in children with PA was 30 mmHg. Ten (34%) PA cases had SpO₂ less than 85%. **Figure 2A** shows lowest recorded sBP, dBP, and SpO₂ during surgery for each group.

Figure 2B compares the variability in VS recorded during the perioperative period between children with and without PA. PA cases demonstrate more variability and VS in PA cases fluctuate more dramatically compared to controls. Since PA cases and controls differed in age, with controls being younger, an age-adjusted multivariable linear model was compared to an unadjusted model (**Figure 2C**). Age and anaphylaxis are independently associated with vitals. As expected, the difference in vitals between PA cases and controls is slightly larger in the age-adjusted model (**Table S1**).

3.4. Treatment and severity of PA in children

All PA patients received epinephrine; 22 cases (76%) received only intravenous (IV) epinephrine, 3 patients received intramuscular (IM), 3 IV and IM, and 1 IV and inhaled. (**Table 2**). In addition to intermittent boluses of epinephrine, six patients (21%) received epinephrine infusions. Mean time from initial sign of PA to epinephrine administration was 7 minutes (range 1-25) for grade 3 and 1 minute (range 1-5) for grade 4 reactions; 25 (86%) patients received epinephrine within 10 minutes. Mean number of doses of epinephrine, not counting infusions, was 3 (range 1-10) for grade 3 and 7.5 (range 1-14) for grade 4 reactions. Mean administration of epinephrine was 3.8 mcg/kg (range <0.1-21.4) for grade 3 reactions (n=25) and 54.2 mcg/kg (range 0.6-137.5) for grade 4 reactions (n=4). For eleven patients with grade 3 reactions, initial treatment with ephedrine, phenylephrine, or inhaled bronchodilators (e.g. albuterol, salbutamol) was ineffective and subsequently epinephrine was administered. In these patients, average time from initial PA treatment to epinephrine administration was 7.8 (range 5-20) minutes.

Information on the fluid therapy and weight of the patient was available for 13 patients; all received i.v. crystalloid, and two also received gelofusine. The volume of crystalloid administered during the first hour was 8-70 ml kg⁻¹ (median 26 ml kg⁻¹).

In addition to epinephrine and fluids, 19 patients received antihistamines and 26 corticosteroids, 11 patients ephedrine and/or phenylephrine, 8 inhaled salbutamol, 3 magnesium sulphate for bronchospasm, 2 an infusion of noradrenaline and 1 vasopressin.

We evaluated whether initial signs of PA were associated with reaction severity. When patients presented with CVS (OR 2.1; 95% CI 0.4-11.3; $p=0.39$) or RS (OR 1.4; 95% CI 0.3-6.6; $p=0.7$), the probability of a severe reaction (defined as grade 4 or surgical cancellation) was higher. However, this association did not reach statistical significance using a multivariable logistic regression model. When patients presented with CVS (OR 2.9; 95% CI 1.3-7.1; $p=0.01$) or RS (OR 2.3; 95% CI 2.3-5.3; $p=0.03$), a statistically significant association with number of epinephrine doses administered was observed using ordinal logistic regression. Patients where initial signs were both CVS and RS received the highest number of epinephrine doses, while patients without initial signs of CVS or RS received the lowest number of epinephrine doses (**Figure 3**). Though the association did not reach statistical significance through ordinal logistic regression, when patients presented with CVS (OR 1.3; 95% CI 0.5-3.7; $p=0.65$) or RS (OR 1.1; 95% CI 0.4-2.9; $p=0.88$), a higher amount of epinephrine (mcg/kg) was administered via any route, in comparison to cases not presenting with CVS or RS.

3.5. Results of diagnostic investigations

Diagnostic testing was undertaken using local hospital allergy clinic protocols; results are shown in **Table 3**. Out of the 29 patients with confirmed or probable PA, a causative allergen was identified in 15 based on: elevated sIgE in one case, positive SPT in five cases, and positive IDT in nine cases. NMBAs were the most common drug class (11 cases) responsible for PA, with eight cases caused by atracurium. Antibiotics were the causative drug in eight cases. Twenty-one (72%) patients had serum tryptase samples taken during the reaction.

4. DISCUSSION

We present the physiological and clinical characteristics of paediatric patients who experienced life-threatening PA and required epinephrine for resuscitation. Findings are compared to the recent paediatric NAP6 data, as well as with children undergoing routine general anaesthesia for elective surgeries who did not experience PA. We demonstrate that PA in childhood is associated with a need for rapid and high dose epinephrine administration and that PA presenting with cardiovascular and/or respiratory signs as initial clinical features are associated with the administration of more doses of epinephrine.

Among clinical features that appeared at any time during an anaphylactic episode, hypotension was the most prevalent. Occurrence of other major features were similar to those seen in NAP6 in children, with the exception of cardiovascular and respiratory arrest seen in our study. In contrast with the NAP6 paediatric cohort where bronchospasm and/or high airway pressures were the first clinical features of anaphylaxis in 64% of cases¹³; our data show that hypotension was the predominant presenting feature, followed by tachycardia and bronchospasm. Despite a median age of 11 years, our findings align with data obtained in the NAP6 adult cohort, where hypotension was the presenting feature in 46% of cases, and bronchospasm/high airway pressure was the presenting feature in 18% of cases¹⁹.

NMBA- or antibiotic-induced anaphylaxis usually developed within five minutes after drug administration. This is similar to findings in adult PA^{13,20,21}. All grade 4 severity reactions commenced within five minutes of drug administration, consistent with a previous study²².

Hypotension, oxygen desaturation, and bradycardia are ominous clinical signs during allergic reactions. In both confirmed and probable PA cases, minimum sBP, dBP, and SpO2 were significantly lower than in controls. The lowest recorded sBPs in more than 50% of our cases were <50 mmHg,

similar to paediatric NAP6 values¹². Ten (34%) children in our study had SpO₂ <85%, again similar to NAP6. While tachycardia in the setting of hypotension is common in anaphylaxis¹⁷, bradycardia is also seen; the most common cause of perioperative bradycardia in paediatric patients is hypoxia, which can occur with the bronchospasm that often accompanies anaphylaxis¹⁵. Bradycardia was seen in 17% of our patients, similar to paediatric NAP6 (18%) and adult NAP6 (13%) patients¹². Similarly, maximum HR in the PA group was significantly higher than controls.

Epinephrine is first line therapy for treatment of anaphylaxis^{13,20,23,24}. However, in our study, eleven patients received alternate treatment after sign(s) of PA started, prior to epinephrine administration. For these patients, a diagnosis of PA may not have initially been apparent. Treatment with epinephrine was faster for grade 4 reactions than for grade 3. Similar to adult studies, high cumulative doses of epinephrine were administered, most often via the intravenous route²⁵. The median number of epinephrine doses given in our study (3, range 1-14) is similar to that given in the paediatric (2.5, range 0-9) NAP6 cohort^{12,13}. In addition to epinephrine, fluid administration is a critical step in management of hypotension^{20,23,26}. All patients received i.v. crystalloids with a similar medium dose as that reported in the NAP6 pediatric cohort (20 ml kg⁻¹). Although, cancellation of surgery is not always an indicator of severity, but all of our cases were elective; thus we suspect that decisions to proceed with the surgery were made based on the severity of the reaction rather than urgency to complete it.

Out of 21 (72%) children with tryptase measured in our study, 15 (71%) were elevated from baseline. In the paediatric NAP6 cohort, four (50%) of eight tryptase levels "showed elevation or dynamic changes"¹². Furthermore, out of 11 children described in the NAP6 study only 3 cases had confirmed allergic anaphylaxis; one was non-allergic, two were anaphylaxis not-specified, and five were uncertain.

Similar to the paediatric NAP6 cohort, NMBAs were the predominant causative agent in our study, with atracurium accounting for the majority

of cases^{12,13}. We identified two patients with suspected teicoplanin-induced anaphylaxis, one of which was confirmed on skin testing. Teicoplanin was not identified as a cause in paediatric NAP6 cases but accounted for 23% of adult NAP6 cases¹⁹.

Strengths of our data include the rigor used to define PA cases. All guidelines on PA recommend measuring tryptase levels, with three samples required in the UK²¹. In our study, tryptase results were available in 21 out of 29 (72%) cases. In addition, with the exception of a few vitals, the detailed and frequent recording of vital signs during PA allowed us to assess in detail the time-sequence of vitals and clinical signs for the majority of cases.

Limitations include the inability to identify a causative drug in some cases of PA – this may have arisen due to insufficient testing, non-immunological reactions, or overlooking the triggering agent²⁸. Some medications may have produced false positive results; this is increasingly recognized for NMBAAs. The retrospective nature of this study precluded standardized testing regimens across centers, though contemporary guidelines now exist for the investigation of suspected PA reactions in children^{29,30}. Finally, we included cases that clinically presented as PA, which probably included non-allergic anaphylaxis.

Our study has several clinical implications. First, it suggests that severe hypotension beyond that anticipated during routine anaesthesia is frequently the first presenting sign of PA in children. Second, presenting CVS and/or RS may portend a more severe reaction, at least with regard to the number of epinephrine doses required. Nevertheless, epinephrine has a narrow therapeutic window and it is imperative that anesthetists are trained to diagnose and treat PA as early as possible for a good outcome. Third, anaesthetists should be aware that while anaphylaxis is rare in children, suspected cases should always be referred for investigation. Fourth, recent guidelines on diagnostic testing in adults also apply to children²⁹; however, sensitivity and specificity of tests in the paediatric population needs to be established. Finally, our study highlights the

importance of accurate documentation, tryptase measurement, and communication between anaesthetists and allergists in order to prevent re-exposure to the causative drug in future surgeries – in our cohort one child had multiple prior episodes of PA.

Conclusion

PA in children is often accompanied by severe hypotension which is the most common presenting feature. Initial cardiovascular and/or respiratory signs were associated with more epinephrine doses. The results highlight the importance of full allergy work up using standardized regimens and tryptase measurement. Further studies are needed in order to better understand characteristics of PA in children, facilitate rapid diagnosis and treatment, evaluate the diagnostic value of tests, and establish protocol for this age group.

Acknowledgments

I am grateful to the EAACI Scientific Committee for the opportunity to conduct this project. I would also like to acknowledge local and international collaborators: Rachel Pegg, Anca Chiriac, Robert Boyle, Antony Aston, and Aida Semic-Jusufagic.

Conflicts of interest

AF, AY, HTB, NJ, GdT and EK have no conflict of interest to report in relation to this work. LHG is an adjudication committee member for Merck, New Jersey USA and Novo Nordisk, Denmark.

Authors contributions

EK and GdT conducted the study. GdT, AF, HTB, EK and LHG were involved in the conception and design of the study. GdT, AF, NJ contributed to data acquisition and/or data collection. AY, HTB, AF, EK analyzed and

interpreted the data. EK wrote the original draft. AF, AY, EK, GdT LHG, NJ, HTB reviewed, drafted and edited the manuscript. All authors provided critical review of the manuscript and approved the final version.

vi. References

1. Malsy M, Leberle R, Ehehalt K, Sinner B, Hobbhahn J. Anaphylactic reaction 5 minutes after the start of surgery: a case report. *BMC Res Notes*. 2015;8:117.
2. Jenson RD, Latham LB, Vitalpur GV, Dierdorf SF. Immunoglobulin e-mediated anaphylaxis on the tenth exposure to cisatracurium in a 4-year-old child. *A A Case Rep*. 2013;1(3):49-51.
3. Wahl RU, Wurpts G, Merk HF. [Perioperative anaphylaxis caused by rocuronium allergy in a child]. *Hautarzt*. 2011;62(11):812-814.
4. Sampathi V, Lerman J. Case scenario: perioperative latex allergy in children. *Anesthesiology*. 2011;114(3):673-680.
5. Oligbu G, Ahmed L. Teicoplanin-Induced Anaphylactic Reaction in Children: A Case Report. *Pharmacy (Basel)*. 2018;6(4):09.
6. Choi SH, Yi JW, Rha YH. Rocuronium anaphylaxis in a 3-year-old girl with no previous exposure to neuromuscular blocking agents. *Asian Pac J Allergy Immunol*. 2013;31(2):163-166.
7. Lucas-Polomeni MM, Rochefort-Morel C, Delaval Y. [Peroperative anaphylactic shock in children: management and evaluation]. *Ann Fr Anesth Reanim*. 2012;31(1):e45-46.
8. Michavila Gomez AV, Belver Gonzalez MT, Alvarez NC, et al. Perioperative anaphylactic reactions: Review and procedure protocol in paediatrics. *Allergol Immunopathol (Madr)*. 2015;43(2):203-214.
9. Karila C, Brunet-Langot D, Labbez F, et al. Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center. *Allergy*. 2005;60(6):828-834.
10. Mertes PM, Alla F, Trechot P, Auroy Y, Jouglu E, Groupe d'Etudes des Reactions Anaphylactoides P. Anaphylaxis during anesthesia in France: an 8-year national survey. *J Allergy Clin Immunol*. 2011;128(2):366-373.

11. Habre W, Disma N, Virag K, et al. 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.
12. Thomas M, Harper N, Cook T. Paediatric anaesthesia. *From the Report and findings of the 6th National Audit Project, Royal College of Anaesthetists*. 2018:216-221.
13. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: management and outcomes in the 6th National Audit Project (NAP6). *Br J Anaesth*. 2018;121(1):172-188.
14. Murat I. Anaphylactic reactions during paediatric anaesthesia ; results of the survey of the French Society of Paediatric Anaesthetists (ADARPEF) 1991–1992 . *Pediatric Anesthesia*. 1993;3(6):339-343.
15. Ramgolam A, Hall GL, Zhang G, Hegarty M, von Ungern-Sternberg BS. Inhalational versus Intravenous Induction of Anesthesia in Children with a High Risk of Perioperative Respiratory Adverse Events: A Randomized Controlled Trial. *Anesthesiology*. 2018;128(6):1065-1074.
16. Garvey LH. Perioperative hypersensitivity reactions: diagnosis, treatment and evaluation. *Current Treatment Options in Allergy*. 2016;3(2):113-128.
17. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med*. 2006;47(4):373-380.
18. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet*. 1977;1(8009):466-469.
19. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). *Br J Anaesth*. 2018;121(1):159-171.
20. Kolawole H, Marshall SD, Crilly H, Kerridge R, Roessler P. Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists Perioperative Anaphylaxis Management Guidelines. *Anaesth Intensive Care*. 2017;45(2):151-158.

21. Ewan PW, Dugue P, Mirakian R, et al. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. *Clin Exp Allergy*. 2010;40(1):15-31.
22. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144-1150.
23. Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand*. 2007;51(6):655-670.
24. Mirakian R, Ewan PW, Durham SR, et al. BSACI guidelines for the management of drug allergy. *Clin Exp Allergy*. 2009;39(1):43-61.
25. Garvey LH, Belhage B, Kroigaard M, Husum B, Malling HJ, Mosbech H. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. *Anesthesiology*. 2011;115(1):111-116.
26. Laguna JJ, Archilla J, Dona I, et al. Practical Guidelines for Perioperative Hypersensitivity Reactions. *J Investig Allergol Clin Immunol*. 2018;28(4):216-232.
27. Garvey LH, Mertes PM. Perioperative anaphylaxis-management and outcomes in NAP6. *Br J Anaesth*. 2018;121(1):120-123.
28. Garvey LH. Old, New and Hidden Causes of Perioperative Hypersensitivity. *Curr Pharm Des*. 2016;22(45):6814-6824.
29. Garvey LH, Ebo DG, Mertes PM, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy*. 2019.
30. Atanaskovic-Markovic M, Gomes E, Cernadas JR, et al. Diagnosis and management of drug-induced anaphylaxis in children: An EAACI position paper. *Pediatr Allergy Immunol*. 2019;30(3):269-276.

vii. Tables

Table 1. Demographic characteristics of children with confirmed or probable perioperative anaphylaxis compared to a control group of children without anaphylaxis during surgery.

Characteristic	Confirmed	Probable	Control
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	Anaphylaxis n=22	Anaphylaxis n=7	n=62
Age (y), median (range)	11 (1-16)	11 (2-14)	4 (0-16)
Sex, n (%)			
Boys	10 (45)	3 (43)	30 (48)
Girls	12 (55)	4 (57)	32 (52)
Atopy, n (%)			
Yes	11 (61)	3 (75)	
No	7 (39)	1 (25)	
Not available	4	3	62 (100)
History of acute reactions, n (%)	1 (7)	0	NA
Drug allergy (non index), n (%)	1 (6)	1 (25)	NA
Perioperative anaphylaxis in the past, n (%)	2 (13)	1 (25)	NA
Surgery, n (%)			
Renal	2 (13)	1 (17)	0
Otolaryngology	1 (6)	0	56 (90)
Orthopedics	7 (44)	0	0
Oncology	1 (6)	1 (17)	0
Diagnostic procedure	0	3 (50)	6 (10)
Dental	1 (6)	0	0
Gastrointestinal	1 (6)	0	0
Cardiac (elective)	2 (13)	1 (17)	0
Ophthalmology	1 (6)	0	0
Not available	6	1	0
Reaction class†, n (%)			
3	18 (82)	7 (100)	NA
4	4 (18)	0	
Surgery completed, n (%)			
Yes	6 (38)	2 (33)	62 (100)
No	10 (63)	4 (67)	0
Not available	6	1	0
Location of post-operative observation, n (%)			
ICU	12 (86)	4 (80)	0
Ward	2 (14)	1 (20)	62 (100)
Not available	8	2	0

†Ring and Messmer Grading Scale¹⁸ with modifications: Grade 3 reactions were defined as life-threatening with mono- or multi-visceral signs such as cardiovascular collapse, cardiac dysrhythmias, bronchospasm, and/or mucocutaneous or gastrointestinal symptoms only in patients who required administration of epinephrine and other acute treatment. Grade 4 reactions were defined as anaphylaxis cases were cardiac and/or respiratory arrest occurred. NA-Not available; ICU-Intensive care unit.

Table 2. Lowest recorded systolic blood pressure and amount of epinephrine administered in children with perioperative anaphylaxis.

ID	Pharmacology Group/Drug	Sex	Age, yrs.	Reaction class	Case completed	Lowest recorded sBP, mmHg	N doses of epinephrine†	Infusion started	Total amount, mcg	Total amount mcg/kg
1.	Anti-fibrinolytic agent	F	6	3	N	58	2	Y	517.8	21.4
2.		M	15	3	N	30	4	N	40	0.7
3.	Benzodiazepines	M	16	4	N	30 [¶]	4	Y	464.6	5.2
4.	Antibiotics	F	11	3	N	40	5	N	60	0.9
5.		F	11	3	Y	30	3	N	100	2.1
6.		F	13	4	NA	45 [¶]	14	Y	5746.3	137.5
7.		F	13	3	N	40	4	N	95	NA
8.		M	7	3	N	45	1	N	0.25	0.01
9.		M	11	3	NA	44	1	N	40	NA
10.		M	13	3	N	50	4	N	300	NA
11.		M	14	3	N	39	10	N	100	1.6
12.	Contrast agent	F	2	3	N	70	1	N	30	2.0
13.		M	1	3	NA	55	1	N	20	1.7
14.		M	5	3	Y	30	2	N	25	1.2
15.	Bovine gelatin	M	15	3	Y	40	5	N	40	1.0
16.	Latex	F	13	3	NA	55	NA	NA	NA	NA
17.	Laxative	F	13	3	NA	40	3	N	400	NA
18.	Neuromuscular blocking agents	F	5	3	N	56	1	N	150	7
19.		F	6	3	N	70	3	N	500	NA
20.		F	8	3	N	35	5	N	220	6.1
21.		F	8	3	Y	40	1	N	130	NA
22.		F	11	3	Y	69	2	N	800	NA
23.		F	11	4	N	80 [¶]	11	Y	4682.13	73.7
24.		F	13	3	N	58	7	Y	3656	§
25.		F	15	3	N	87	2	N	1000	NA
26.		M	1	3	Y	54	3	Y	NA	‡
27.		M	11	3	Y	65	1	N	500	6.8
28.		M	15	4	NA	80 [¶]	1	N	50	0.6
29.	NSAID	M	14	3	Y	85	2	N	100	0.8

N - no; NA - not available; NSAID - non-steroidal anti-inflammatory drug; sBP - systolic blood pressure; Y- yes; Yrs - years.

†not counting infusions of epinephrine.

‡12.5 ml of epinephrine was given by infusion but no dilution was reported.

§1000mcg of epinephrine given via endotracheal route.

¶Cardiac arrest with non-recordable systolic blood pressure.

Table 3. Data from the diagnostic work up of children with perioperative anaphylaxis.

ID	Pharmacology Group/ causative drug	Age (yrs)	Reaction class	Reaction tryptase† (ng/ml)	Baseline tryptase (ng/ml)	sIgE (kUA/L)	SPT (wheal,mm)	IDT (>bleb,m
Anti-fibrinolytic agent								
1.	<i>Aprotinin</i> §	6	3	Norm	2.5	ND	NA	NA
2.	<i>Tranexamic acid</i>	15	3	28.8	4.1	ND	NA	NA
Benzodiazepines								
3.	Midazolam	16	4	31.7	4.0	ND	Neg	10
Antibiotics								
4.	<i>Vancomycin</i>	11	3	8.1	NA	ND	NA	NA
5.	<i>Cefazolin</i>	11	3	33.3	NA	ND	Neg	5
6.	<i>Teicoplanin</i>	13	4	30.2	NA	ND	NA	NA
7.	Teicoplanin	13	3	NA/NA	NA	ND	NA	17
8.	<i>Cefazolin</i>	7	3	13.7	NA	ND	NA	NA
9.	Cefuroxime	11	3	35	NA	0.03	Neg	7
10.	<i>Gentamicin</i>	13	3	18.7	NA	ND	NA	NA
11.	<i>Co-amoxiclav</i>	14	3	4.54	2.2	0.03	Neg	ND
Contrast agent								
12.	<i>Gadolinium contrast</i>	2	3	NA/ND	NA	ND	ND	ND
13.	Omnipaque	1	3	19.9	NA	ND	Neg	3
14.	<i>Contrast dye</i>	5	3	NA/ND	NA	ND	NA	NA

15.	<i>Bovine gelatin</i>	15	3	14.4	NA	0.24	ND	ND
16.	Latex	13	3	Δ 8.4	NA	28	ND	ND
Laxative								
17.	Normacol	13	3	63	NA	ND	4	ND
Neuromuscular blocking agents								
18.	Atracurium	5	3	13.9	2.7	ND	6	ND
19.	Atracurium	6	3	4	3	ND	ND	7
20.	Rocuronium	8	3	9.2[†]	3.4	ND	Neg	2
21.	<i>Atracurium</i>	8	3	NA/ND	NA	ND	Neg	flare
22.	Suxamethonium	11	3	28.2	4.3	Neg	7	ND
23.	Atracurium	11	4	41.9	NA	ND	4	ND
24.	<i>Mivacurium</i>	13	3	NA/ND	NA	ND	Neg	16 flare+ erythem
25.	Atracurium	15	3	5.1	NA	ND	Neg	3
26.	Atracurium [¶]	1	3	9.3[†]	5.9	ND	2	ND
27.	Atracurium	11	3	7.8	5.5	ND	Neg	4
28.	Atracurium [¶]	15	4	NA/ND	NA	ND	Neg	2
NSAID								
29.	<i>Ketorolac</i>	14	3	NA/ND	NA	ND	NA	NA

IDT - intradermal test; NSAID - non-steroidal anti-inflammatory drugs; NA - not available; ND - not done; Neg - negative; Norm - normal; slgE - specific immunoglobulin E to corresponding drug; SPT - skin prick test; Yrs - years; Δ tryptase (peak - baseline).

Skin testing was performed and interpreted according to BSACI protocols in the UK, and the ENDA EAACI guideline in France. Text in italics refers to suspected causative drug.

[†] Acute tryptase level measurement was defined as either the one taken after resuscitation or within 1-2 hours after the event. We took the highest measurement and compare it with the baseline level.

[‡]based on $>1.2 \times$ basal tryptase level +2 mcg/L.

[§] Aprotinin was the likely causal medication given the strong temporal relationship between administration and allergic symptoms and negative testing to other medications.

[¶] Subsequent surgeries were tolerated in absence of the suspected causative drug; in addition, in patient N° 28, IDT was performed 10 days after PA due to urgency.

viii. Figure legends

Figure 1. Clinical manifestations of children with perioperative anaphylaxis.

A. Stacked bar chart showing first signs to present (within 5 minutes of onset of anaphylaxis), signs during anaphylaxis (signs that presented at any time point after initial signs, before resolution of anaphylaxis). Signs varied by patient and were not seen in some. Numbers annotated on bars indicate percent of patients. B. Organ systems affected at PA onset. Multiple systems were affected at onset in 16 patients. Counts indicate number of patients (n=29).

Figure 2. Vital signs in children with or without perioperative anaphylaxis.

A. Lowest recorded vital signs during the perioperative period in children with or without perioperative anaphylaxis. Means (SD) are labeled, with the bar representing the mean. **B.** Variability in vitals in confirmed and probable anaphylaxis cases during the perioperative period compared to controls. Patients are shown along the x-axis, where each vertical line represents an individual patient. In the top portion, open circles represent measurements recorded during surgery for each vital sign as noted on the y-axis. In the bottom portion, points represent the range in vitals during surgery. The red lines represent the upper and lower control limits for each patient, calculated using the range as the variability estimate. The statistical control limits are calculated per-patient and represent three times the variability estimate divided by the square root of the sample size. **C.** Comparison of lowest recorded vital signs during the perioperative period by age between children with and without perioperative anaphylaxis. A multivariable linear age-adjusted model was compared to an unadjusted model to verify that difference in vitals between groups is predominantly due to anaphylaxis and not due to differences in the age distribution between the control and anaphylaxis groups. A smoothed mean response using a cubic spline is shown with confidence intervals were produced by bootstrapping the mean. dBP - diastolic blood pressure; MAP - mean arterial pressure; Min - minimum; mm Hg - millimeters of mercury; sBP - systolic blood pressure; SpO2 - peripheral oxygen saturation.

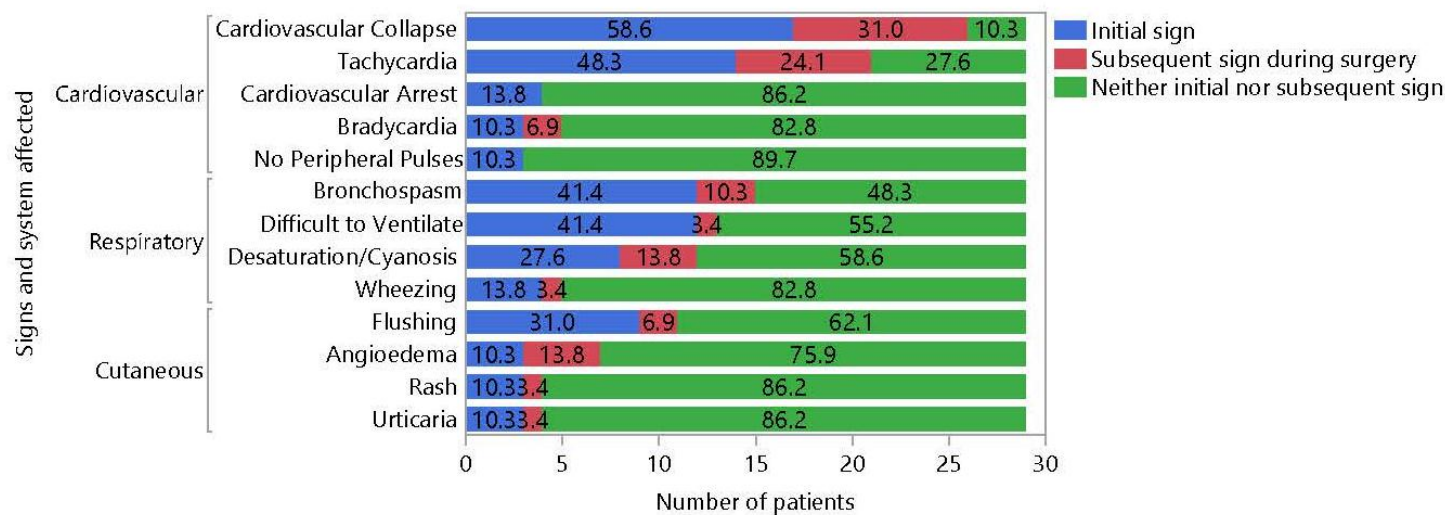
Figure 3. Probability of a severe reaction based on the initial sign(s) of anaphylaxis. Highest probability of a severe reaction (defined as grade 4 or

surgical cancellation) occurs when a patient has both cardiovascular and respiratory initial signs. Bars represent the mean predicted probability of a severe reaction in each group, where predicted probability was determined by a multivariable logistic regression model.

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A



B

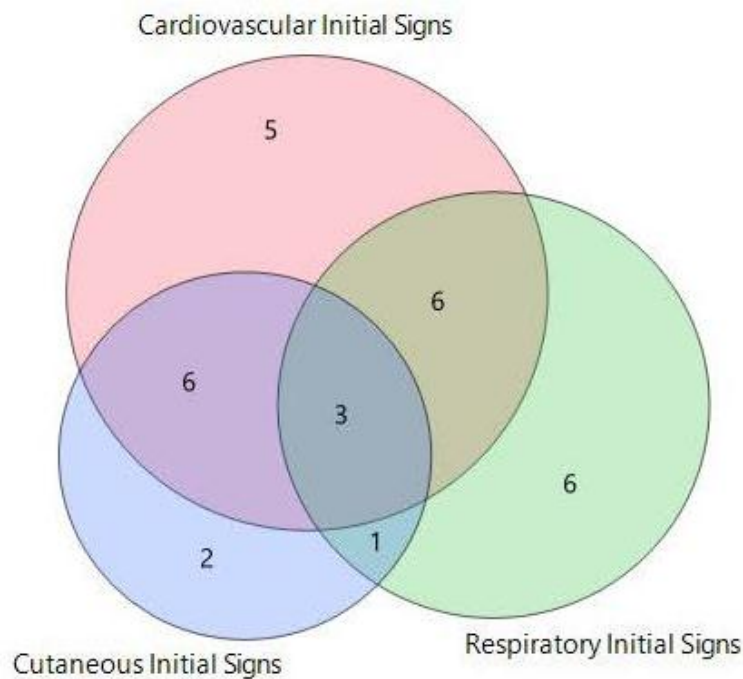
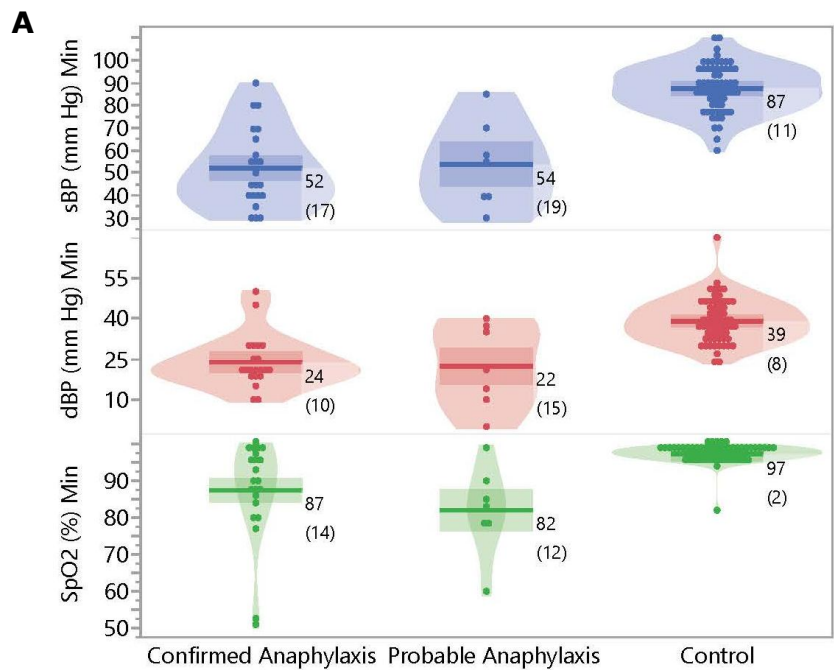
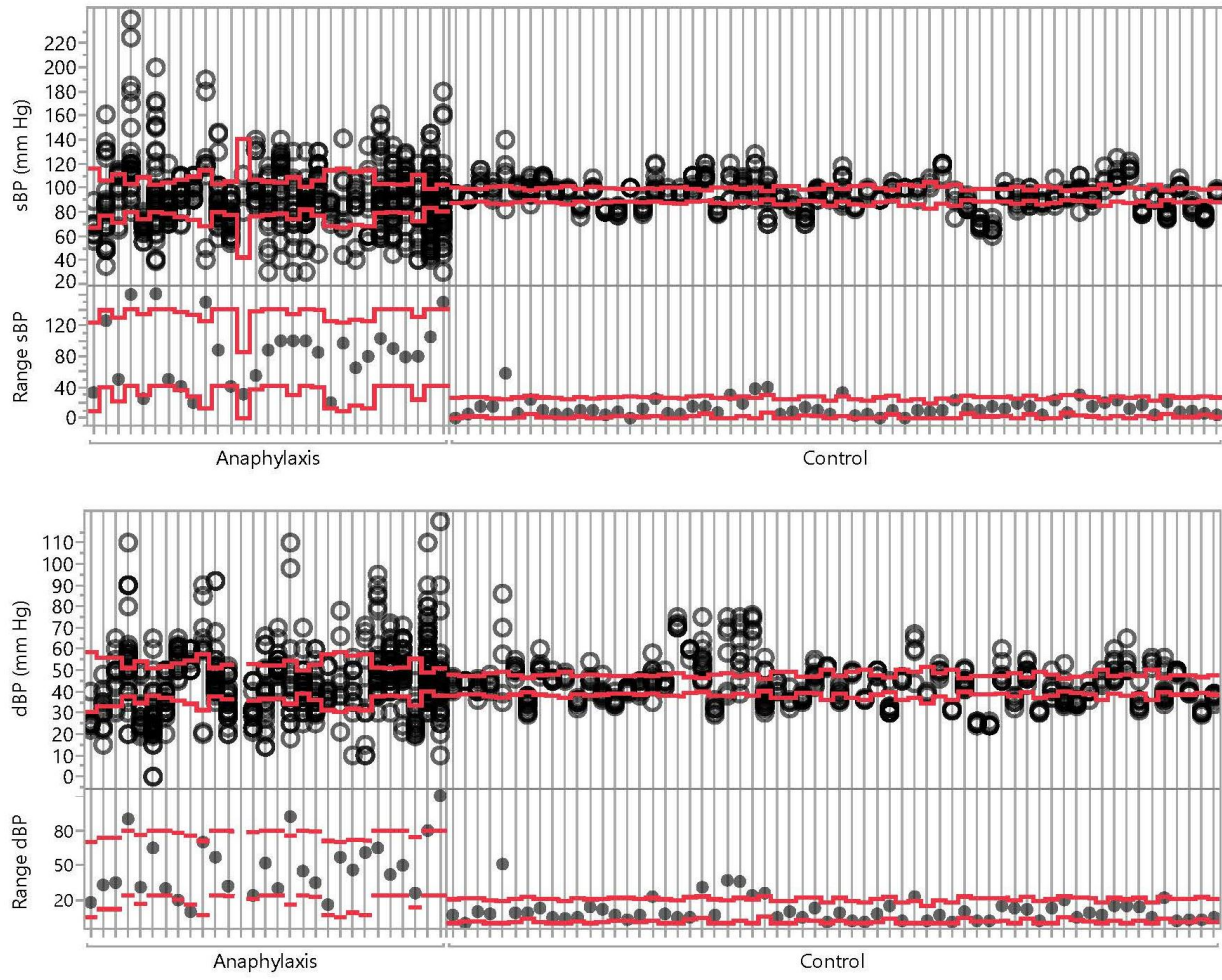
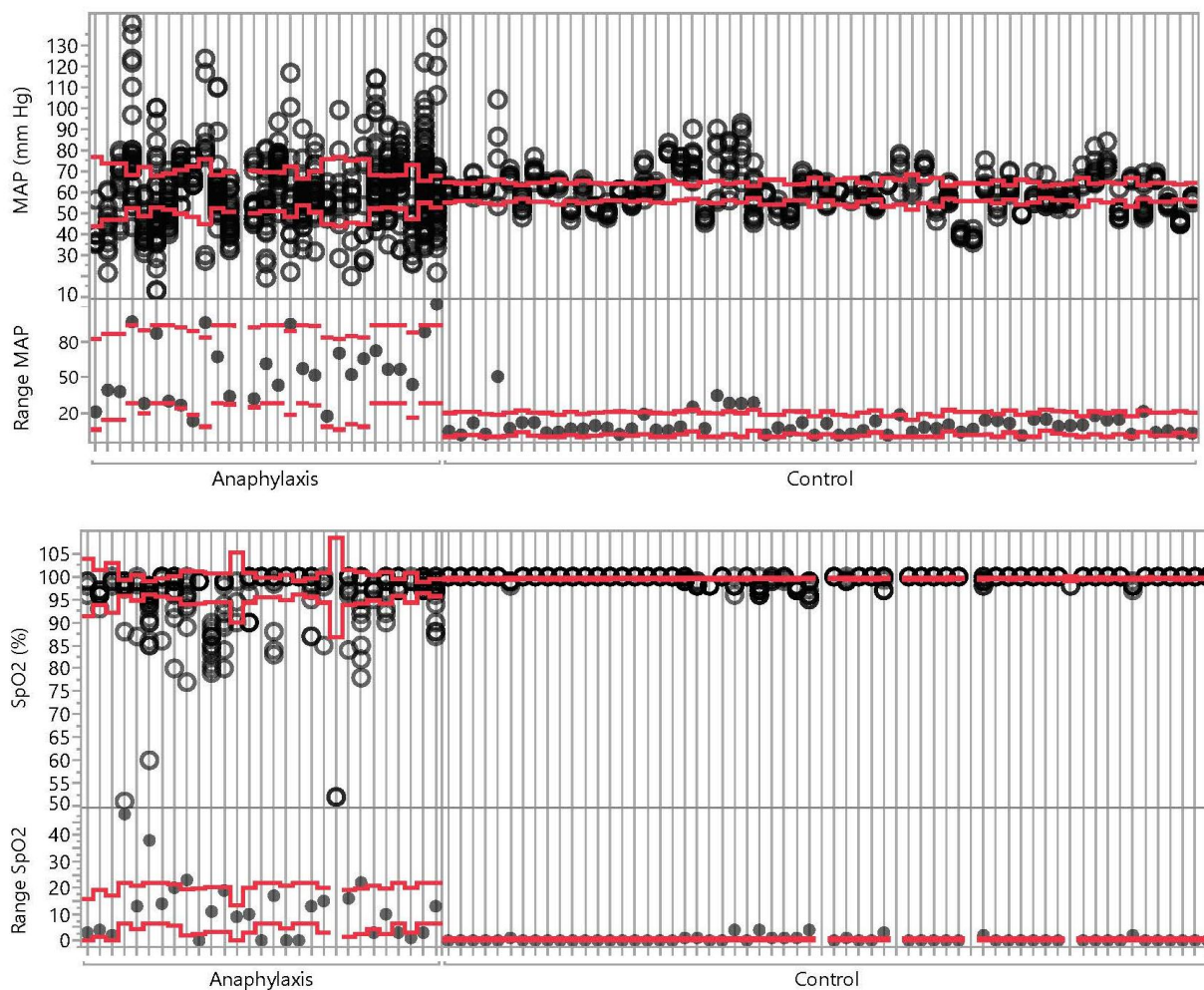


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B



C

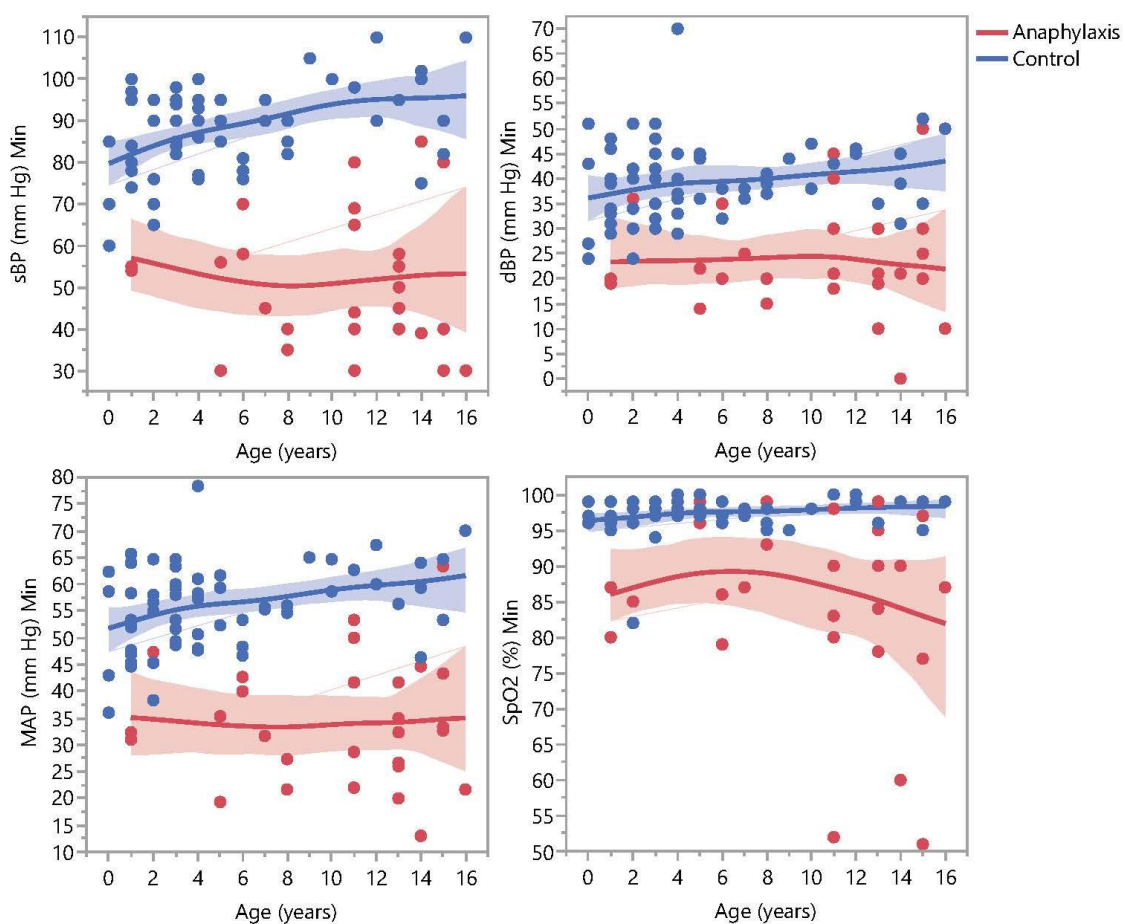
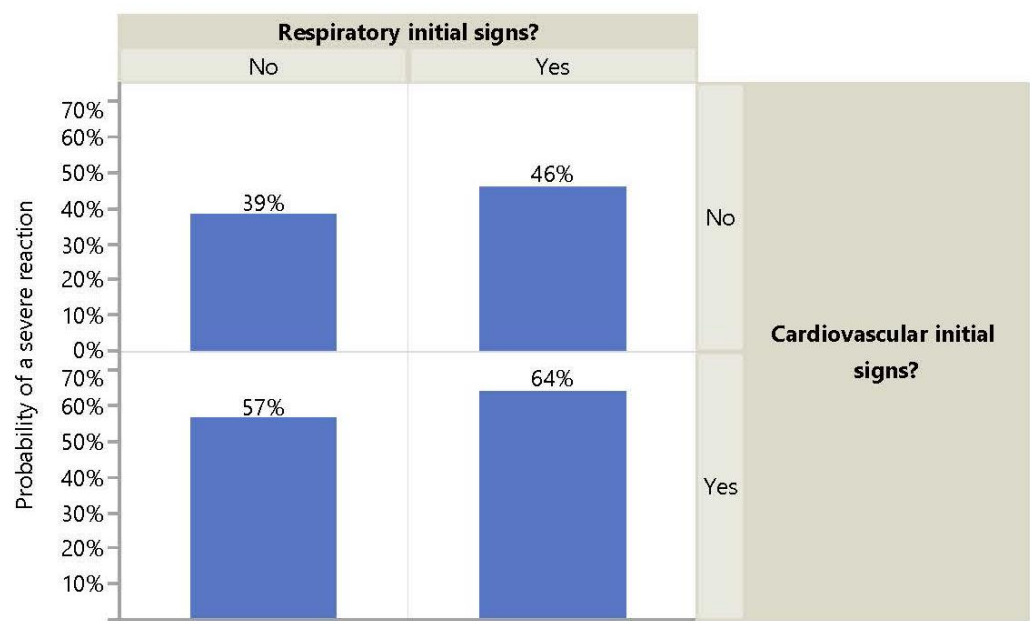


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Supplementary Online Repository Material:

Title: Perioperative anaphylaxis in children: aetiology, time sequence and patterns of clinical reactivity.

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Study centres.

Cases were collected from Guy’s and St Thomas NHS Foundation Trust (GSTT), London, UK; Sheffield Children’s NHS Foundation Trust, Sheffield, UK; St Mary’s Hospital, London, UK; Leeds Children’s Hospital, Leeds, UK; University Hospital of Montpellier, France; and Seattle Children’s Hospital, Seattle, USA.

Table S1. Comparison of mean group differences (anaphylaxis and controls) in vitals between age-adjusted and unadjusted multivariable linear models. Estimates and standard errors are with respect to controls.

	Unadjusted model		Model adjusted for age	
	Estimate +/- Std Error	P-value	Estimate +/- Std Error	P-value
Min sBP (mm Hg)	-17.5 +/- 1.5	<.0001	-19.2 +/- 1.6	<.0001
Min dBP (mm Hg)	-7.8 +/- 1.0	<.0001	-8.4 +/- 1.2	<.0001
Min SpO2 (%)	-5.6 +/- 0.9	<.0001	-5.5 +/- 1.0	<.0001
Min MAP (mm Hg)	-10.9 +/- 1.0	<.0001	-11.9 +/- 1.2	<.0001
Min Heart Rate (bpm)	-7.6 +/- 1.9	0.0001	-1.7 +/- 1.7	0.3

MAP - mean arterial pressure; Min - minimum; bpm - beats per minute; dBP - diastolic blood pressure; sBP - systolic blood pressure; SpO2 - peripheral oxygen saturation; mm Hg - millimeters of mercury.

ID	Pharmacology Group/ causative drug	Reaction class	IDT (>bleb,mm)	IDT (dilution; concentration (mg/ml))	Amount of iv. crystalloids [†] (ml ⁻¹ ; ml/kg ⁻¹)	Time between administration of the drug and first symptoms [^]
Anti-fibrinolytic agent						
1.	<i>Aprotinin</i> [§]	3	NA	NA	1000;41	5
2.	<i>Tranexamic acid</i>	3	NA	NA	NA	60
Benzodiazepines						
3.	Midazolam	4	10+20 erythema	1:1; 1	NA	4
Antibiotics						
4.	<i>Vancomycin</i>	3	NA	NA	2000;29	30
5.	<i>Cefazolin</i>	3	5	NA;2	NA	5
6.	<i>Teicoplanin</i>	4	NA	NA	NA	3
7.	<i>Teicoplanin</i>	3	17 +15 flare	1:2; NA	NA	5
8.	<i>Cefazolin</i>	3	NA	NA	NA	4
9.	<i>Cefuroxime</i>	3	7	NA;2	NA	4
10.	<i>Gentamicin</i>	3	NA	NA	NA	5
11.	<i>Co-amoxiclav</i>	3	ND	ND	3000;47	3
Contrast agent						
12.	<i>Gadolinium contrast</i>	3	ND	ND	NA	5

13.	Omnipaque	3	3	1:1;NA	150;13	5
14.	<i>Contrast dye</i>	3	NA	NA	500;25	5
15.	<i>Bovine gelatin</i>	3	ND	ND	2900;70	3
16.	Latex	3	ND	ND	NA	5
Laxative						
17.	Normacol	3	ND	ND	NA	15
Neuromuscular blocking agents						
18.	Atracurium	3	ND	ND	500;23	4
19.	Atracurium	3	7+ flare 10*12	1:1000; 0.1	NA	15
20.	Rocuronium	3	2	1:10; NA	1250;35	3
21.	<i>Atracurium</i>	3	flare	1:1000; NA	NA	5
22.	Suxamethonium	3	ND	ND	NA	5
23.	Atracurium	4	ND	ND	1500;24	4
24.	<i>Mivacurium</i>	3	16 flare+35 erythema	1:10000;NA	NA	5
25.	Atracurium	3	3 +flare 20	1:10;NA	NA	15
26.	Atracurium [§]	3	ND	ND	NA	4
27.	Atracurium	3	4	1:200;0.002	1000;14	5
28.	Atracurium [§]	4	2	1:10; NA	1500;18	5
NSAID						
29.	<i>Ketorolac</i>	3	NA	NA	1000;8	5

Table S2. Intradermal test results, concentrations, amount of fluid and timing between administration of drug and first symptoms of perioperative anaphylaxis in children.

I.V.-intravenous; NSAID - non-steroidal anti-inflammatory drugs; ND - not done; NA - not available; IDT - intradermal test. Skin testing was performed and interpreted according to local protocols. Text in italics refers to suspected causative drug.

[§]Aprotin is the likely causal medication given the strong temporal relationship between administration and allergic symptoms, and negative testing to other medications.

[†]During the first hour.

[¶]Subsequent surgeries were tolerated in absence of the suspected causative drug; in addition, in patient № 28, IDT were performed 10 days after PA due to urgency.

[^]Vitals and signs were recorded every 5 minutes in most of the cases unless specified in the notes or taken from the electronic charts.

