Severe and refractory anaphylaxis in paediatric intensive care unit.

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To the Editor,

Data regarding severe anaphylaxis (SA) are limited. A new entity called refractory anaphylaxis (RA) has emerged in the literature, although there are subtle differences between the three definitions proposed (Table S1).[1–3] A 21-member panel of experts in United States (US) has proposed RA to be defined as reactions treated with ≥3 appropriate doses of adrenaline (or initiation of an intravenous [IV] adrenaline infusion) in addition to symptom directed medical management (Table S1).[3] RA appears to be rare, around 2% of anaphylaxis.[4]

We previously reported a cohort of 166 children (<18 years) admitted to pediatric intensive care units (PICU) for anaphylaxis (2003–2013).[5] In the current study, we identified which of these children met the US definition for RA, and how they compared with those who were treated with ≥2 adrenaline doses and additional therapy which we defined as SA, and determined risk factors for either SA or RA (Methods in Appendix S1).

Data were missing for 32 children, and so the analysis cohort consisted in children, of whom 70 (51%) had SA and 52 (38%) had RA (Table 1). Drugs were the most common elicitor for both SA and RA, followed by foods. SA and RA occurred mainly in hospital (67% and 71%, respectively) and in operating theatre (36% and 40%), or during an oral food challenge (OFC) (13% and 12%).

The treatment and clinical symptoms according to organ system involvement from the first medical rescue to the first 24 h in PICU are described by time periods in children with either SA or RA (Figure 1 and Figure S1). Rapid clinical recovery has been reported with a normal examination within the first 6 h from PICU admission in the majority of children. However, three fatal anaphylaxis have been recorded, all related to foods and one following an OFC.

Children with RA were less likely to have a history of asthma ($p = .04$) or prior anaphylaxis ($p = .05$), although these were not significant at multivariate logistic analysis, possibly because these are less common in children with drug-induced anaphylaxis. RA-cases were more likely to receive IV bolus adrenaline ($p < .001$), IV adrenaline infusion ($p < .001$), and mechanical ventilation ($p = .015$) during the first 24 h in PICU (Table S2). With regards to adrenaline route according to elicitors and places of reaction, a majority of children treated with IV adrenaline had a drug-related anaphylaxis (58%) mostly in a perioperative setting (76%) (Tables S3 and S4). IM adrenaline was mostly used for food-related anaphylaxis (39%) and rarely in a perioperative setting (7%). In a multivariate logistic analysis, hypotonia at first medical rescue was the only factor predicting both SA (OR: 4.05; 95% CI: 1.24–13.28; $p = .02$) and RA (OR: 5.73; 95% CI: 1.62–20.26; $p = .01$) (Table S5).

Our data are the first to describe in details a series of children admitted to PICU for SA and even RA regarding their main characteristics, the time course of clinical manifestations and treatment. Whereas food is the main elicitor of anaphylaxis in children, drug was here the most common elicitor of both SA and RA, mainly in a perioperative setting, which is also reported by the European Anaphylaxis Registry.[2] However, foods are common in SA. SA occurred during an OFC in 9/51 (18%) food-related anaphylaxis cases and RA in 6/51 (12%), which reinforce the need to follow a rigorous procedure for OFC implementation with a team trained to manage SA. In RA, the use of IV adrenaline infusion and fluid therapy was insufficient in contradiction with current guidelines.[1] Our data highlight how difficult it is to identify the patients the most at risk of SA or even RA, as previously reported.[6] However, we found that hypotonia at first medical rescue was a critical characteristic independently associated with either SA or RA.

A worldwide consensus on RA definition is now urgently required as well as registries from childhood to elderly to better characterize risk factors and specificities according to age or elicitors.

The French Group for Paediatric Intensive Care and Emergencies members are in Appendix 1.

TABLE 1 Characteristics and elicitors of 70 children admitted to pediatric intensive care units with severe anaphylaxis (treated with ≥2 adrenaline doses and additional therapy) including 52 children with refractory anaphylaxis and comparison to children with non-severe anaphylaxis ($n = 68$) and non-refractory anaphylaxis ($n = 86$).

	Severe anaphylaxis $N = 70$ (%)	Non severe anaphylaxis $N = 68$ (%)	*p*	Refractory anaphylaxis $N = 52$ (%)	Non refractory anaphylaxis $N = 86$ (%)	*p*
Male gender, *n* (%)	41 (59)	34 (50)	.40	26 (50)	49 (57)	.53
Mean age, year (SD)	8.9 (5.3)	7.9 (5.6)	.28	8.95 (5.58)	8.06 (5.43)	.36
Median age, year (IQR)	10.2 (4.4–13.2)	7.3 (2.8–13)	.28	10.9 (4.12–13.35)	7.9 (3.12–12.97)	.38
Age <6 years	24 (34)	30 (44)	.24	19 (37)	35 (41)	.15
6–11 years	17 (24)	19 (28)		10 (19)	26 (30)	
Age >11 years	29 (41)	19 (28)		23 (44)	25 (29)	
Medical history						
Asthma	21 (30)	24 (35)	.63	11 (21)	34 (40)	.04
Food allergy	22 (331)	23 (34)	.76	14 (27)	31 (37)	.29
Prior anaphylaxis	6 (9)	5 (7)	1	1 (2)	10 (15)	.047
ICU admission for anaphylaxis	3 (4)	3 (4)	1	1 (2)	5 (6)	.41
Elicitors						
Foods	25 (36)	26 (37)		14 (27)	37 (43)	
Peanut	8 (11)	8 (12)		5 (10)	11 (13)	
Cow's milk	6 (9)	7 (10)		4 (8)	9 (10)	
Tree nuts	6 (9)	4 (6)		3 (6)	7 (8)	
Other foods	5 (7)	7 (10)		2 (4)	10 (12)	
Drugs	35 (50)	35 (51)		28 (54)	42 (49)	
Antibiotics	8 (11)	10 (15)		5 (10)	13 (15)	
Contrast media	4 (6)	2 (3)		3 (6)	3 (3)	
Cancer chemotherapy	3 (4)	4 (6)		2 (4)	5 (6)	
NMBA	3 (4)	1 (6)		3 (6)	1 (1)	
Other drugs	17 (24)	18 (26)		15 (29)	20 (23)	
Other elicitors	10 (14)	7 (10)		10 (19)	7 (8)	
Insect venom	2 (3)	2 (3)		2 (4)	2 (2)	
Latex	2 (3)	1 (1)		2 (4)	1 (1)	
Foods vs drugs vs others			.77			.058
Place of the reaction						
In hospital	47 (67)	42 (62)	.63	37 (71)	52 (60)	.28
Operating theatre	25 (36)	17 (25)	.40	21 (40)	21 (24)	.31
OFC	9 (13)	8 (12)		6 (12)	11 (13)	

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NC, non calculated; NMBA, neuromuscular blocking agent; OFC, oral food challenge; SD, standard deviation.

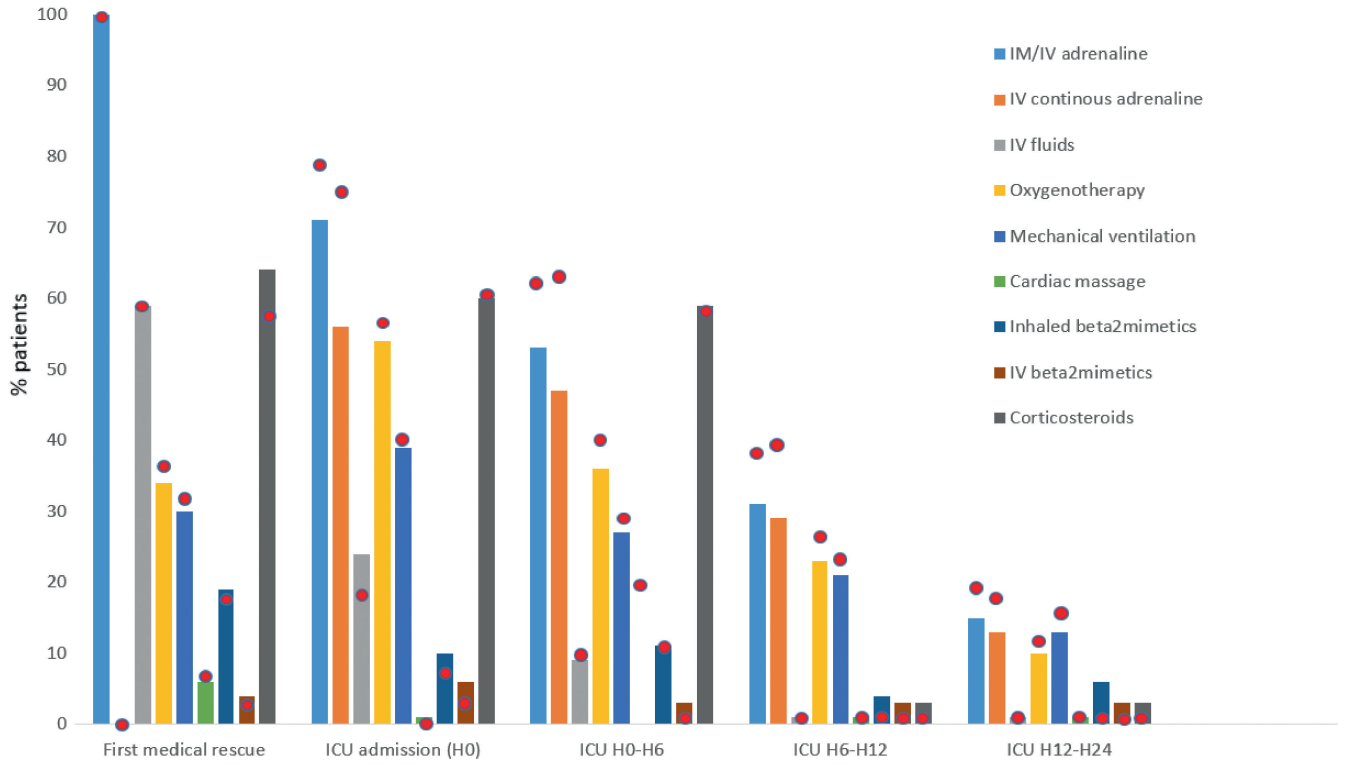

FIGURE 1 Therapy administered in 70 children with severe anaphylaxis (bar graph) including 52 with refractory anaphylaxis (red points) from first medical rescue to the first 24 h in pediatric intensive care admission (ICU) (by time periods at first medical rescue, at admission to pediatric ICU -H0-, from H0 to 6 h –H6-, from H6 to H12, from H12 to H24). IM, intramuscular; IV, intravenous.

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CONFLICT OF INTEREST STATEMENT

GP has provided consultation and speaker services for Aimmune Therapeutics/Nestlé, Bausch and Lomb, Stallergenes, Novartis, ALK-Abello, Bioprojet; serves as a medical consultant/advisor for Bioprojet and AI Therapeutics/Nestlé. AD reports personal fees from Novartis, ALK, GSK, Sanofi, Regeneron, Aimmune Therapeutics, DBV Technologies, Nestlé, Stallergenes Greer, DBV Technologies, Nutricia. Grant from Fondation du Souffle, Conseil Régional Hauts-de-France Research Program 2014–2018, outside the submitted work. The other authors declare to have no conflict of interest. The other co-authors declare no conflict of interest in relation with this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX 1

Collaborators of the French Group for Pediatric Intensive Care and Emergencies

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Microbes, antibodies, and breastfeeding as the trans-generational axis of microbiota maturation

To the Editor,

It is well established that in a newborn, the microbiota and immunity engage in constant interactions that can set an individual on a trajectory toward health or disease.

Apart from vaginal delivery, breastfeeding is a powerful way mothers use to influence the health of their offspring. The importance of breast milk in preventing infant mortality has been known for more than a century[1] and has been attributed, at least in part, to the immune exclusion of pathogenic bacteria by secretory immunoglobulin A (sIgA).[2] One such example includes the binding of maternal sIgA to *Enterobacteriaceae*, which prevents the development of necrotizing enterocolitis in preterm infants.[3]

The popularization of next-generation sequencing (NGS) in the first decade of the 21st century has started a revolution in unraveling the impact of commensal microbes on human health. Given a tight association between the microbiota and IgA, new roles for breastmilk sIgA have started to be proposed. By combining advances in flow cytometry and NGS, Sterlin et al., showed that milk sIgA binds bacteria, which are associated with the infant's health and thrive early in life, for example, *Bifidobacterium longum*.[4] This observation was not in line with the immune exclusion function of sIgA (although the exact consequences of antibody coating, in this case, were not unraveled). Also, details behind *B. longum* – sIgA interactions have not been fully elucidated but might involve the recognition of microbial glycans by the variable regions of sIgA.[4] Understanding the functional impact of sIgA – *B. longum* interactions is particularly important in light of the health benefits this commensal brings to the host. The examples include dampening intestinal inflammation (in a process involving the induction of a negative regulator of Th2 and Th17 cell function, galectin-1, by *B. longum*-derived indole-3-lactic acid[5]), and the protection against enteropathogenic infection (in a process involving bacterial production of acetate[6]). Earlier studies have also indicated the roles of breastmilk sIgA that extend beyond the immune exclusion. For example, Rogier et al., noted that, in addition to preventing the translocation of aerobic bacteria from the gut to the mesenteric lymph nodes, sIgA-containing milk imprinted broad and long-lasting changes in the microbiota composition of the offspring.[7]

It is interesting to note that antigen specificity of sIgA in breast milk may be influenced by the mother's gut microbiota. For example, Usami et al., indicated the presence of *Bacteroides acidifantis*-specific IgA^+ plasma cells in lactating mammary glands, which were of Peyer's patches origin.[8] This observation opens up a possibility that sIgA imprints certain microbial changes in the neonatal intestinal tract based on the mother's gut microbiota. Identifying further examples, and unraveling the functional impact of antibody