Report on Long-term on EAACI research fellowship.

Dear EAACI Headquarters,

I would like to thank for the unique opportunity to conduct research in one of the leading research institutions - Guy's and St Thomas NHS Foundation Trust, London, United Kingdom.

I have been in Department of Paediatric Allergy (Professor Gideon Lack) for the period of 12 months, since 7th of May 2016 until 30th of April 2017. The title of my fellowship was "Characterizing patterns of anaphylaxis; comparison between food-induced and peri-anaesthetic reactions" supervised by George Du Toit, the Clinical lead - Children' Drug Allergy Service & Children' Urticaria & Angioedema Service.

My project has required significant collaboration;

Collaborators & Participating Academic Centers:

1. Amber Franz, Seattle Children's Hospital, Seattle, USA.
2. Nicola Jay, Sheffield Children's NHS Foundation Trust, Sheffield, UK.
3. Haque Rubaiyat, Guy's and St Thomas' NHS Foundation Trust, London, UK.
4. Henry T. Bahnson, Benaroya Research Institute, Seattle, USA.
5. Pascal Demoly, Exploration des Allergies - Maladies Respiratoires - INSERM, Hopital Arnaud de Villeneuve, University Hospital of Montpellier, France.
6. Jonathan North, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK.
7. Gideon Lack, Guy's and St Thomas NHS Foundation Trust, London, UK.
8. Sophie Farooque, St Mary's Hospital, London, UK.
9. Robert Boyle, St Mary's Hospital, London, UK.
10. Antony Aston, St Mary's Hospital, London, UK.
11. Lene Heise Garvey, Allergy Clinic, Danish Anaesthesia Allergy Centre, Copenhagen University Hospital Gentofte, Gentofte, Denmark.

1. Introduction.

The EAACI Nomenclature Committee proposed the following definition for Anaphylaxis – Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. Given the obvious severity of this condition, it is surprising that relatively little is known of the pathophysiological mechanisms that underlie anaphylaxis in humans.

The mainstay of allergy management is identification and avoidance of the known allergen. In addition, patients and their family/carers are trained in the identification and management of acute severe allergic reactions. Whilst the vast majority of food and drug-induced allergic reactions are of a mild to moderate severity; life threatening anaphylactic reactions are possible, to all allergens, but are usually treatable. In order to optimize the identification and management of anaphylaxis, it is important that health care practitioners, patient and family are able to differentiate mild-moderate symptoms that will resolve with minor interventions, from severe reactions, that must be treated with adrenaline and more. We aim to identify clinical patterns of allergic reactivity, if indeed they exist.

Given the relatively controlled environment of the operating theatre, severe allergic reactions that occur in the peri-anaesthetic setting are well monitored and symptoms and signs are well documented on operative charts. This data therefore presents a perfect opportunity to better understand the pathophysiological changes that occur during anaphylaxis in a controlled setting. A second phase of this project was the collection of data for food-induced allergic reactions. This allows the comparison of reactions, in different settings, and to different allergens.

The design of this study represents a safe opportunity, using novel statistical modelling methodologies, to better understand the pathophysiological mechanisms that underlie anaphylaxis.

2. Proposed aim, objectives and inclusion criteria.

Aim:
Document time-dependent symptoms and signs that occur during anaphylaxis in the peri-anaesthetic environment. Drug induced peri-anaesthetic agents will be the focus of this initial project. It was extended to a comparison with food-induced severe allergic reactions in a second project.

Objectives (Part 1):
- To review the clinical characteristics of anaphylactic reactions, that occurs within the peri-anesthetic environment.
- To determine patterns of clinical reactivity and graphically display these patterns as a set of distinct clinical phenotypes.
- Assess for demographic factors, e.g. age, sex, and ethnicity, associated with the occurrence of anaphylaxis or milder forms of clinical reactions.

Objectives (Part 2):
A similar approach was adopted to above documentation of allergic reactions, but this project was restricted to food-induced allergic reactions.

3. Work performed during the fellowship.

My work on this project was an extremely large responsibility, as this study convenes 7 collaborators' hospitals across UK and USA. I organised honorary contracts for all visits across the country for the purposes of data collection.

We performed a retrospective audit of patients with peri-anaesthetic and food-induced anaphylaxis. Audit approval for the study was obtained from the Quality and Standard Department in each collaborated centre.

The flow diagram 1, describing the number of selected patients with peri-anaesthetic and food anaphylaxis, as well as patients in control groups.

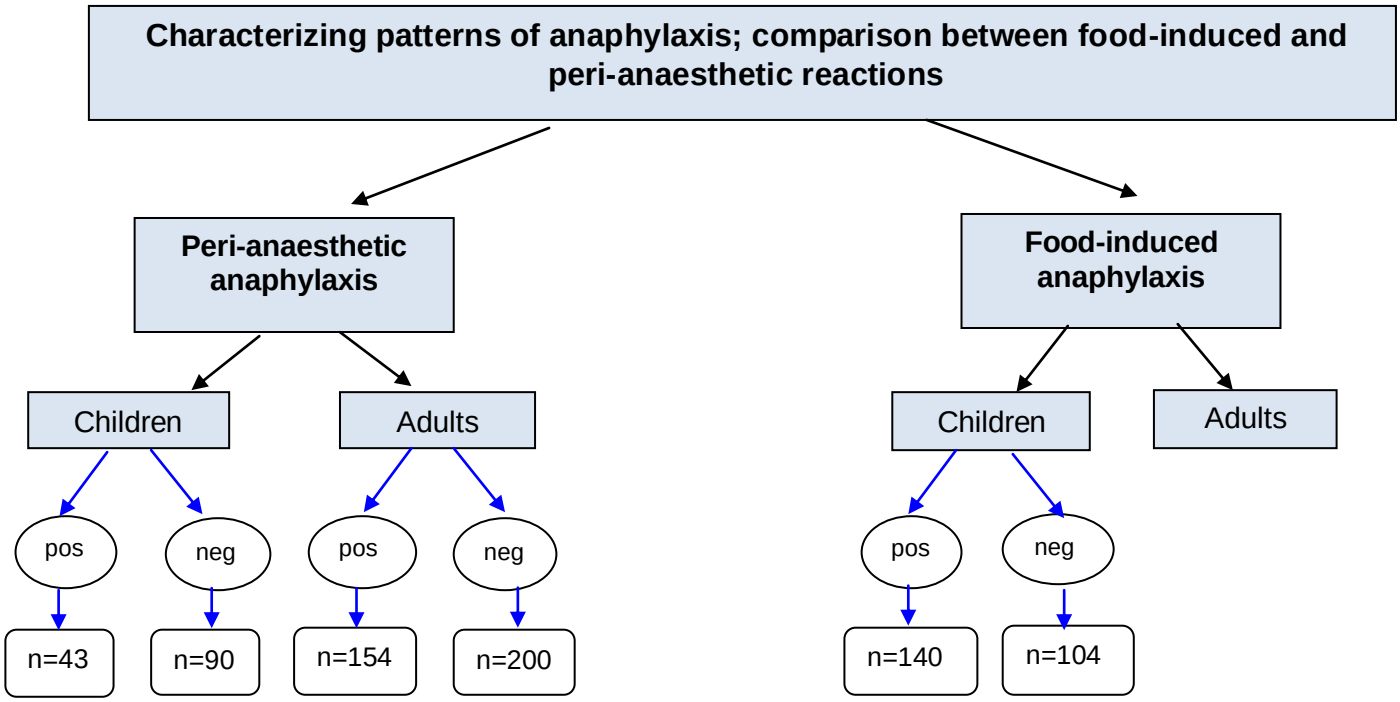

Fig.1. Design of the study. Pos= patients with anaphylaxis; neg=control group.

A. Peri-anaesthetic anaphylaxis

The diagnosis of peri-anaesthetic anaphylaxis remains challenging, given its clinical setting, exposure to multiple medications, and rarity. We included patients with confirmed diagnosis of peri-anaesthetic anaphylaxis and we didn't make any assumptions regarding the diagnosis.
Records were retrieved from databases of drug challenges and/or performed skin tests (ID and/or skin prick test) and/or drug allergy clinic. We put no restriction on the year of the reaction.

Inclusion Criteria:

- All allergic reactions that occur in peri-anesthetic environment
- Completed anesthetic chart with documentation of signs and symptoms of anaphylaxis
- UK ,USA, France patient base

We reviewed 700 cases and indentified 197 with anaphylaxis. From the 700 charts reviewed, cases 503 were not included in the analyses because of the following reasons: not meeting clinical criteria for peri-anaestetic anaphylaxis (166), lack of documentation and/or anaestetic chart (294), lost to follow-up (42).

Among the study population 108 (54.8%) were females and 89 (45.2%) were males. Out of them 43 is children and 100 is adults. The mean age and corresponding standard deviation (s.d.) were 8 (SD 5.27) years in paediatric group and 54.5 (SD 13.8) in adults group.

We recorded:
1. Demographic factors, including. age, sex, and ethnicity;
2. Previous history of allergic disorders and peri-anaestetic events;
3. Current medications, which may affect the severity of the reaction (B-blockers, ACE-inhibitors);
4. Weight and height (BMI);
5. Time sequence of clinical manifestations of peri-anaestetic anaphylaxis:
-cardiovascular symptoms: systolic and diastolic blood pressure, heart rate
-skin symptoms with affected area (hives, flushing, erytema etc)
-respiratory symptoms: saturation,airway pressures,wheezing,difficult to ventilate, bronchospasm, airway andioedema etc.
- gastrointestinal symptoms
- temperature;
6. Cardiovascular, respiratory vitals temperature before and after the surgery;
7. Completion of the surgery (completed or abandoned);
8. Healthcare unit where patient was transferred after surgery;
9. Treatment of the reaction and doses;
10. Tryptase levels (at least during 1 hour of reaction and after 24 hours);
11. Results of SPT/ID/sIgE;
12. Severity of the reaction (Modified Ring and Messmen Grading Scale);
13. Type of surgery (cardiovascular, orthopaedic and etc.).

There are 3 presentations of patients experienced anaphylaxis in peri-anaesthetic setting to different classes of drugs (neuromuscular-blocking agents, antibiotics, blue dyes).

Review 1.

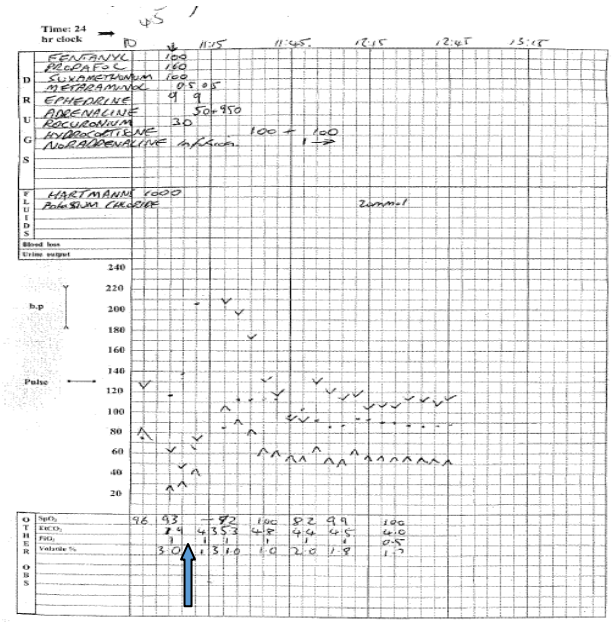

Fig.2. Suxamethonium/rocuronium-induced anaphylaxis.

A 59-year-old female patient was scheduled to undergo cholecystectomy. She has had a few successful general anaesthetics previously. This time, her induction was with fentanyl, propofol and suxamethonium. Immediately after intubation there was minimal chest movement, slight wheeze and quiet breath sounds. She desaturated to 81%. The decision was made to remove ETT. She was bag ventilated but it was difficult. She was reintubated and 30mg of Rocuronium

was given. She became cardiovascularly unstable with blood pressure 61/38 and heart rate of 115. She was given ephedrine and metaraminol, but her repeat blood pressure was even lower (45/32; HR 135).Adrenaline was eventually given IV and she started to recover. There was a diffuse erythematous rash. Her blood pressure improved to 205/105. No other infusion was given. Her baseline tryptase was 5. It is unfortunate that her acute tryptase had not been processed as it would have provided further confirmation of the allergic nature of her reaction. She is otherwise well, does not smoke, has no pets and is not allergic to any other drugs. Skin tests were strongly positive with suxamethonium, rocuronium and borderline positive to pancuronium; however, negative to atracurium, cisatracurium, mivacurium and propofol.

Review 2.

A 52-year-old female patient was scheduled to undergo a wide local excision of a breast lump. There were no immediate problems after induction. Approximately 20 minutes into the procedure, she received an injection of Patent Blue V subcutaneously for identification of the sentinel lymph nodes. Very soon afterwards, she became profoundly hypotensive and tachycardic. She received treatment for an allergic reaction with adrenaline, Hydrocortisone and Chlorphenamine. When she awoke she had generalised pruritus and angioedema of her hands and feet. Post-operatively she briefly went to the Intensive Care Unit before going back to the ward. Tryptase (ng/m) 2hours=20.2 and 3 hours=38.5, baseline=4.5. Her history strongly suggests an allergy to Patent Blue V and both skin prick testing and intradermal testing confirmed this.

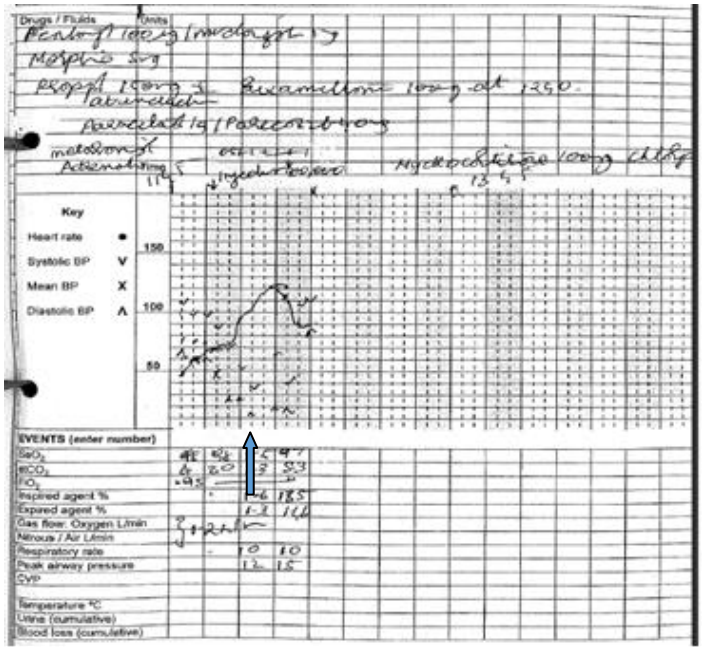

Fig.3. Patent Blue V-induced anaphylaxis.

Review 3.

A 55 years-old Female patient was scheduled to undergo Laparoscopic Cholecystectomy Cyclizine, Dexamethsone and iv Cefuroxime were given shortly after induction (with Propofol, Fentanyl and Rocuronium) and intubation. Five minutes into the operation her BP dropped significantly with associated tachycardia , She became erythematous and profusely sweaty. She was resuscitated appropriately with Adrenaline and steroids and serial tryptase levels were assessed and shown to be significantly elevated peri-operatively (immediate =85 mcg/L;1hr= 98 mcg/L and 24hr =8.8 mcg/L). Although skin prick testing to this drug was negative, at standard testing strengths,

intradermal testing revealed a significant increase in wheal diameter (>5mm) with tracking and with significant erythema confirming allergy to this drug.

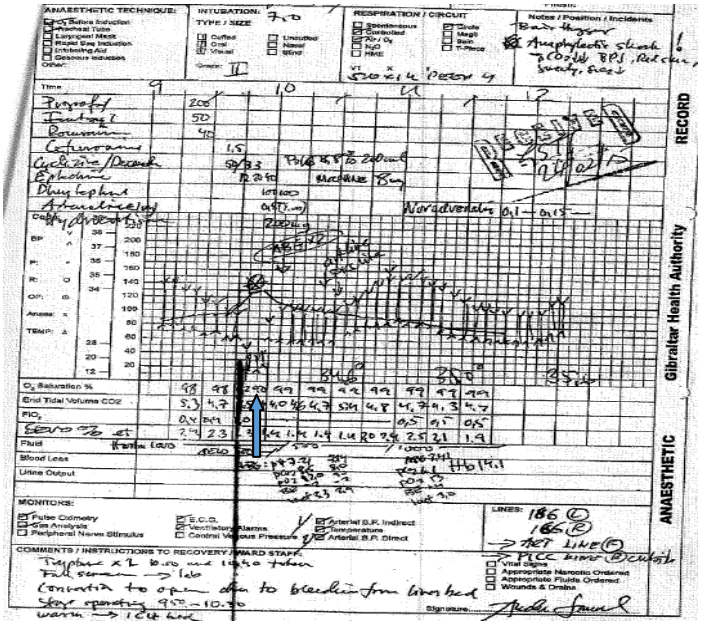

Fig.4. Cefuroxime-induced anaphylaxis.

For control group in peri-anaesthetic environment were included patients from stable (IE no cardiac, trauma, septic etc) elective surgery cases e.g. hernia's, elective T's and A's as well as with their baseline data (vitals before and after surgery, where applicable).

I was also working on the algorithm for the diagnosis of peri-anaesthetic allergic reactions, by defining patients in the groups based on patophysiological manifestations of anaesthetized patients with age-related levels of blood pressure (systolic and diastolic) and heart rate. Also we put information about other clinical manifestations based on severity of the reaction accompanied by data regarding level of tryptase and other immunological and skin tests.

B. Food-induced anaphylaxis

Patients with peanut allergy were selected from LEAP study who had anaphylaxis during peanut challenge with recorded vitals during this event.

We recorded:
1. Demographic factors, e.g. age, sex, and ethnicity;
2. History of allergic disorders;
3. Results of SPT/ID/sIgE;
4. Temperature along with cardiovascular and respiratory vitals before challenge;
5. Vitals during peanut challenge were recorded every 5 minutes (or less) and included:
-systolic and diastolic blood pressure
- heart rate
- temperature
-saturation
-respiratory rate
- PEFR
6. Symptoms during the challenge

7. Treatment of the reaction and doses
8. Amount of protein eaten before reaction
9. Severity of the reaction

During the research fellowship period, we managed to carry out all research activities proposed in the fellowship application as well as data collection. However, the majority of results still have to be calculated and analysed and, thus, these results cannot be included in this report.

4. Presentations and publications related to the fellowship.

I have presented early findings at National and International forums. This has allowed for collaboration with experts in the drug allergy field. In a joined presentation with my mentor George du Toit we presented in Inaugural meeting of the South Thames Paediatric Anaesthetic Network in London, September 2016.

This early findings of this project have been awarded several Travel grants allowing me to present preliminary results at international conferences including:

- Scholarship for the American Academy of Allergy, Asthma & Immunology Annual Meeting. Atlanta, USA, 3-6 March 2017. (Peri-Anaesthetic Anaphylaxis; Comparisons Between Cardiovascular and Skin Manifestations in Children and Adults. E.Khaleva, H. Bahnson, A. Franz, N. Jay, R. Haque, AT. Fox, G. Lack, G. du Toit .The Journal of Allergy and Clinical Immunology. Volume 139, Issue 2, Suppl,2017. AB44. Abstract №143.AAAAI Annual Meeting, Atlanta,USA)

- Scholarship for the World Allergy Organization International Scientific Conference (WISC) 2016. Jerusalem, Israel, 6-9 December 2016. (Peri-anaesthetic anaphylaxis; comparisons between cardiovascular manifestations in children and adults. E.Khaleva, H. Bahnson, A. Franz, L.H. Garvey, N. Jay, R. Haque, AT. Fox, G. Lack , G. du Toit . WAO Journal Suppl (in press). Abstract №1100. World Allergy Organization International Scientific Conference (WISC) 2016. Jerusalem, Israel, 6-9 December 2016)

5. Extracurricular research and educational activities.

I was interested in becoming more involved in research and was very supportive of on-going research projects within the academic department by helping other colleagues in the department with data collection, defining database and working with notes.

A. Together with Ana Prieto del Prado, who had clinical fellowship (awarded by EAACI),we collaborated on a project entitled 'Evaluation of using an adrenaline in children during an oral food challenge'. The aim of this study was to study in detail the clinical characteristics of anaphylaxis and time after first exposure to first symptoms in comparison with allergic background of the child.

We review study of 3979 patients undergoing the food challenge were conducted at tertiary Allergy Centre and identified all patients for whom adrenaline was administered for food-induced anaphylaxis between 2008-2016 year and analyzed demographic characteristics such as age, gender, type of food given in the challenge, time after first exposure to first symptoms, treatment required, skin prick test, specific lgE and allergic co-morbidities.

- This audit reveals that anaphylaxis during OFC's in a bust tertiary Allergy Centre seldom results in the need for adrenaline administration for the treatment of allergic reactions.

However, all foods are capable of producing anaphylaxis in this setting of which milk was the commonest cause.

- Reactions can occur soon after allergen exposure, especially when the challenge is undertaken to nuts.
- It is difficult to predict who most at risk for severe allergic reactions is; all children in this audit had allergic co-morbidities and food allergy was the most frequent one. Children who have both asthma and a food allergy are at greater risk for anaphylaxis.
- Severe reactions requiring treatment with adrenaline was common, but 5 children required multiple doses of adrenaline.
- OFC's, which serve as the gold standard diagnostic modality are generally safe but severe reactions do rarely occur for which adrenaline treatment is required.

Ana presented at 4th Food Allergy and Anaphylaxis Meeting 2016. Rome, Italy. (Prieto del Prado A.,Khaleva E., Du Toit G. Clinical and Translational Allergy 2016, 6(Suppl 1):PP26.)

B. Under the supervision of Dr Alexandra Santos, Consultant in Paediatric Allergy, I classified the severity of allergic reactions according to different scales and has gathered the cumulative and discrete threshold dose for all the positive challenges in the LEAP study.

C. I helped Dr Lauri-Ann Van der Poel, Consultant in Paediatric Allergy, to conduct an audit concerning safety of prescribing fish oil supplements in patients with fish or selfish allergy. My task was to define database, identify patients based on inclusion criteria and create questionnaire for further phone calls. We are planning to submit results for EAACI congress 2018.

D. During my stay in the department, to expand my knowledge base in various topics in allergy by attending educational sessions in Allergy Academy:

19th May 2016: Update in Paediatric Allergy
4th Oct 2016: Practical Allergy in Primary Care
11th Oct 2016: Asthma in Practice
1st Nov 2016: Practical Management of food allergies in children
4th Nov 2016: Hot topics in drug allergy
8th Nov 2016: Allergy and Skin Study day
17th Jan 2017: Anti-IgE and Immunotherapy in Allergy Study Day

E. I completed a 'Designing Clinical Research course', King's College London to further enhance the skills in data analysis and design such that I could structure, calculate and illustrate the findings in my projects in the best way possible.

6. Conclusion.

I am extremely grateful for the opportunity given by the EAACI Long Term Research Fellowship. This has provided me an unforgettable professional experience with an outstanding training in the United Kingdom. The project gave me the opportunity not only to learn more about translational research but also to work with excellent teams across the UK. I am excited to continue the scientific collaboration with further projects in the future.

I'm planning to present the results of this fellowship at the PAAM 2017, BSACI 2017 and annual EAACI congress 2018, in addition to that we will write a two scientific papers according the data obtained during the fellowship.

I am now motivated to apply for a PhD position to enhance my knowledge in anaphylaxis.

7. <u>Acknowledgement.</u>

I would like to express deepest gratitude to my scientific supervisor George du Toit and Gideon Lack, He of the department, for their supervision and hospitality, their dedication and passion for scientific research and teaching, which always serve as an example to me.

I wish to convey my sincerest thanks to other members of the GSTT/KCL Paediatric Allergy Team for their support and guidance. My sincere thanks goes to: Dr Lauri-Ann Van Der Poel, Dr Alexandra Santos, Dr Susan Chan, Dr Suzanna Radulovic, Dr Helen Brough, Pr Adam Fox, Dr Kate Swan, Dr Rosie Wells, Dr Tom Mars, Dr Marta Krawiec, Dr Lizanne Naronha.

I also want to mention the other international fellows: Dr Joana Belo Gomes (Portugal), Dr Olympia Tsilochristou (Greece) and Dr Farah Hannachi (France) who made my stay more social and interesting.

I would also like to acknowledge my local and international collaborators for their assistance and guidance:

1. Amber Franz, Seattle Children’s Hospital, Seattle, USA.
2. Nicola Jay, Sheffield Children's NHS Foundation Trust, Sheffield, UK.
3. Haque Rubaiyat, Guy's and St Thomas' NHS Foundation Trust, London, UK.
4. Henry T. Bahnson, Benaroya Research Institute, Seattle, USA.
5. Pascal Demoly, Exploration des Allergies - Maladies Respiratoires - INSERM, Hopital Arnaud de Villeneuve, University Hospital of Montpellier, France.
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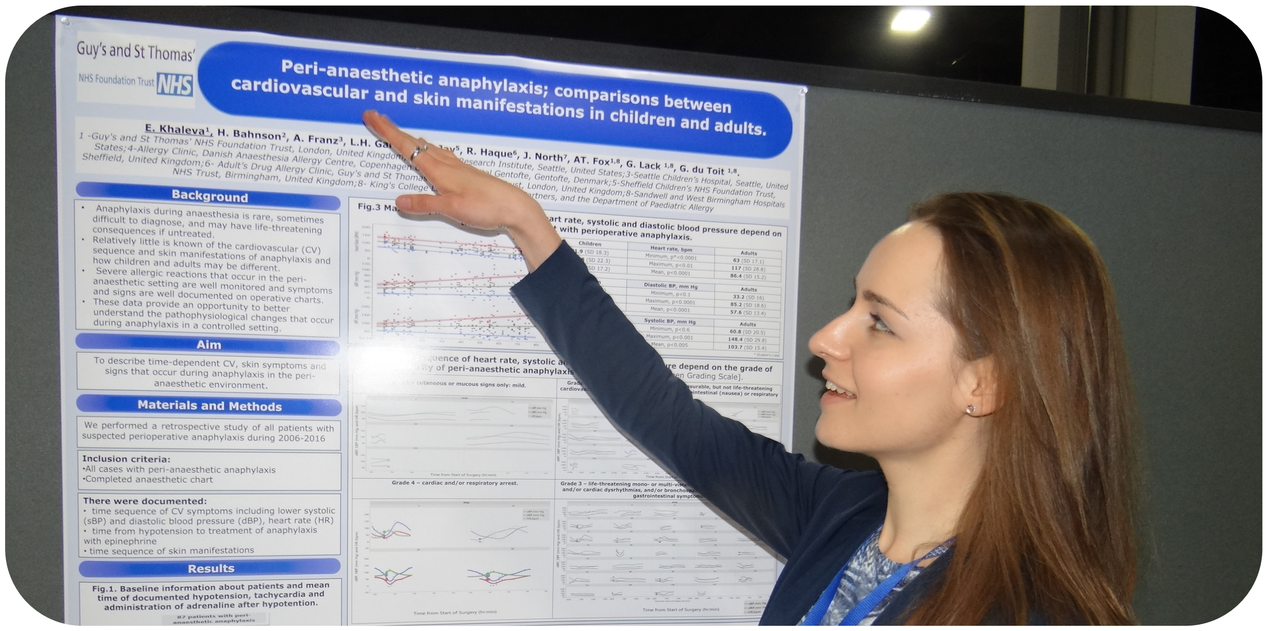
11. Lene Heise Garvey, Allergy Clinic, Danish Anaesthesia Allergy Centre, Copenhagen University Hospital Gentofte, Gentofte, Denmark.

I am very thankful to my home supervisor Professor Gennady Novik (Saint-Petersburg) for my training in Paediatric Allergy and approving my leave, which allowed me to conduct this project in London.

Finally, I would like to express all my gratitude to the EAACI Scientific Committee for their education program, which allows fellows like me the opportunity of building future research at the international level. The role of this Fellowship in my career and self-development cannot be underestimated.

I encourage everyone with an interest in research, allergy and clinical immunology to apply for an EAACI fellowship.


Welcome to St Thomas' Hospital


Guy's and St Thomas'
NHS Foundation Trust
Peri-anaesthetic anaphylaxis; comparisons between cardiovascular and skin manifestations in children and adults.
Background
Aim
To describe time-dependent CV, skin symptoms and signs that occur during anaphylaxis in the peri-anaesthetic environment.
Materials and Methods
We performed a retrospective study of all patients with suspected perioperative anaphylaxis during 2006-2016
Inclusion criteria:
•All cases with peri-anaesthetic anaphylaxis
•Completed anaesthetic chart
There were documented:
Results