

# **Risk Factors in Severe Anaphylaxis**

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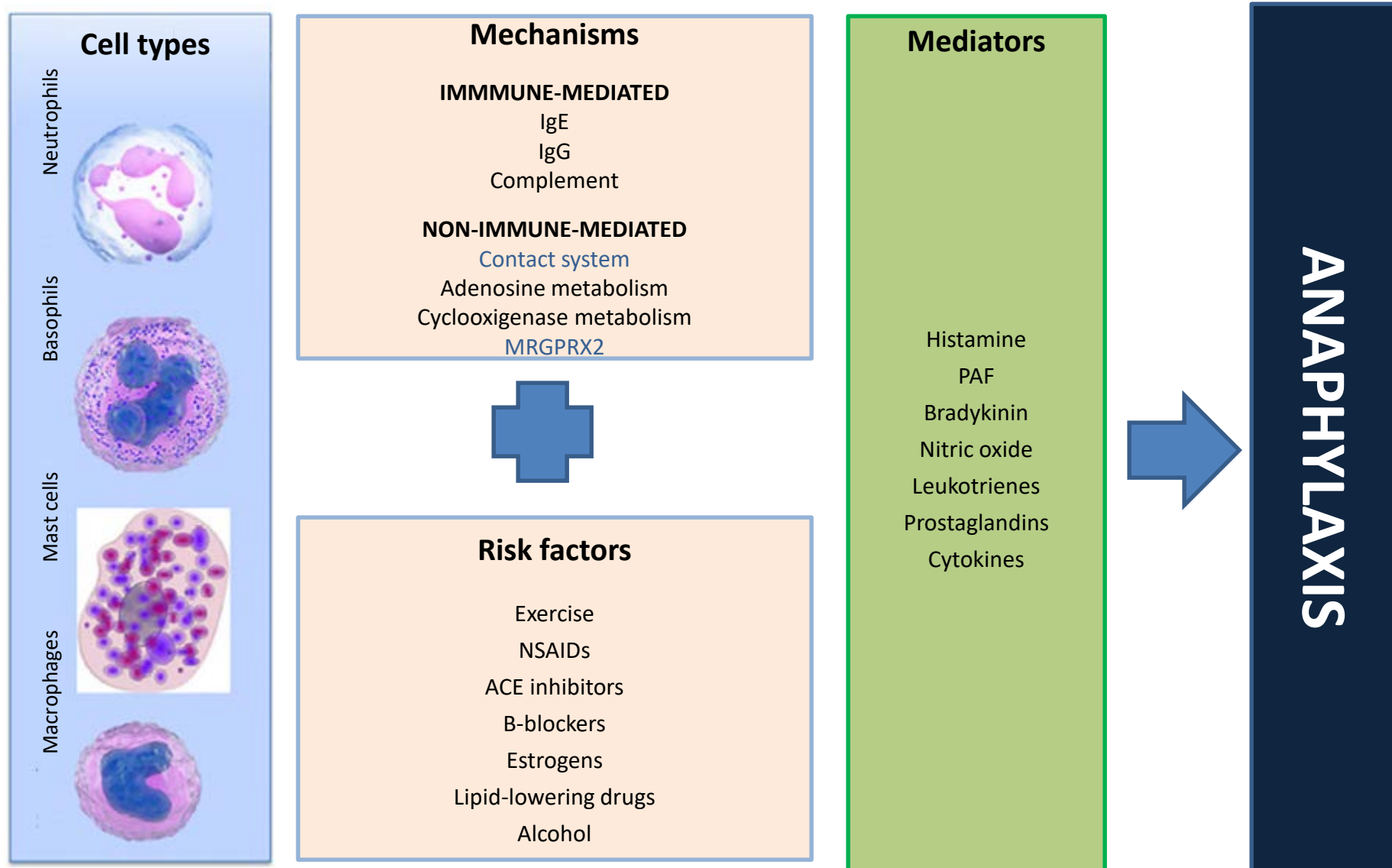
# Anaphylaxis- General data

- Severe allergic reaction that is rapid in onset and may be fatal
- Majority reactions are not life threatening / **severe reactions do occur and are unpredictable !!!**
- **Diagnostic criteria - WAO/EAACI;**
- Diagnosis is based on:
  - Clinical findings and
  - Serum tryptase -6 h (not in all food anaphylaxis)
- **Severity Scoring Systems**
  - Müller, Muraro, Brown, Sampson, Mehl,
  - NIAID/FAAN (severe vs non-severe)
  - Ring and Messmer (grades I-IV)

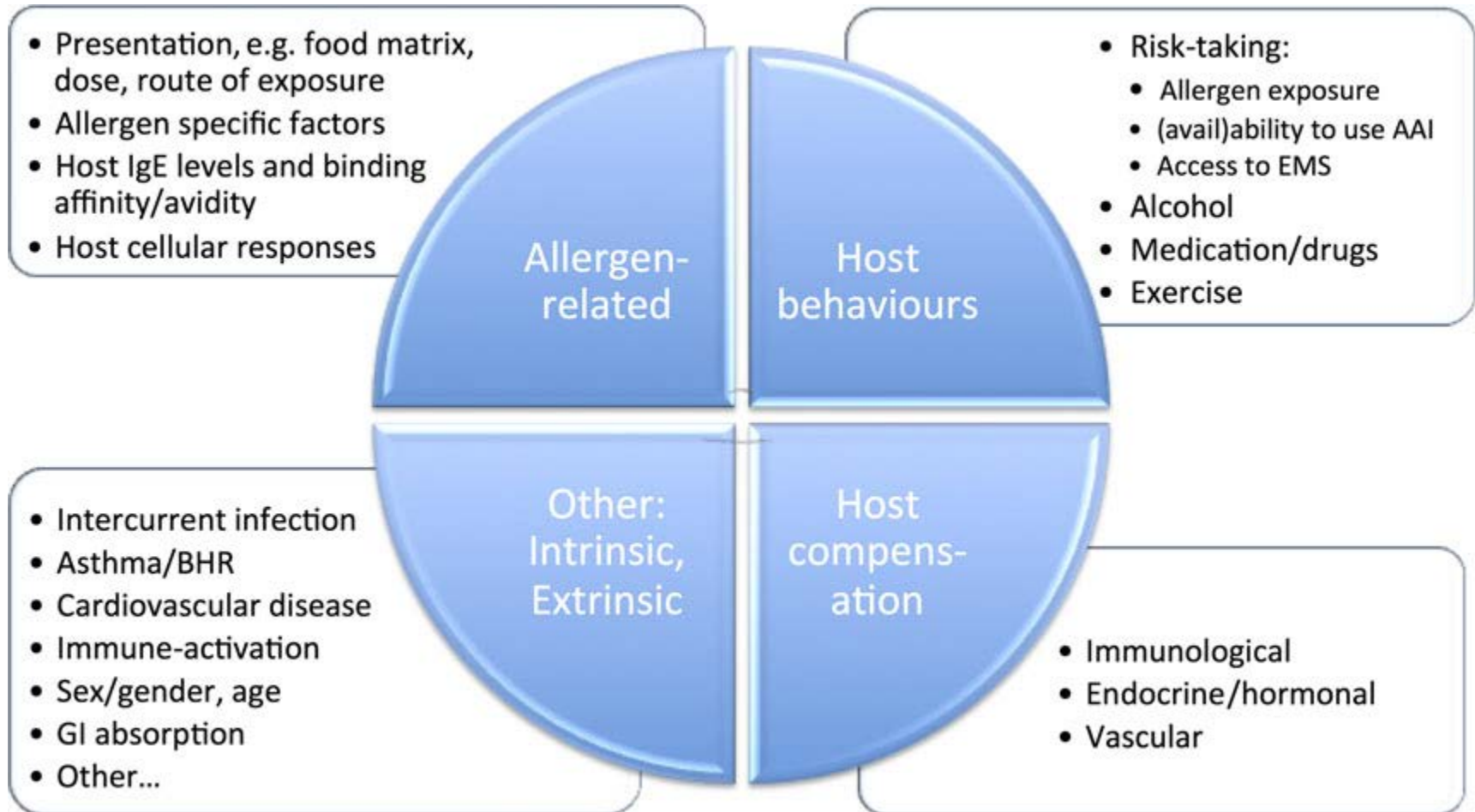
# Anaphylaxis (A) - General data

- Incidence is increasing!!!
- Variable incidence rate depending on the population and study design: 1,5-42 cases per 100000 person-years
- **Severe A: 12,2-42% X total A (fatal A: 0,1%)**
- The incidence in fatal A has not increased in line with that of A;
- Fatal drug A may be increasing but rates of fatal A to venom and food are stable!!!

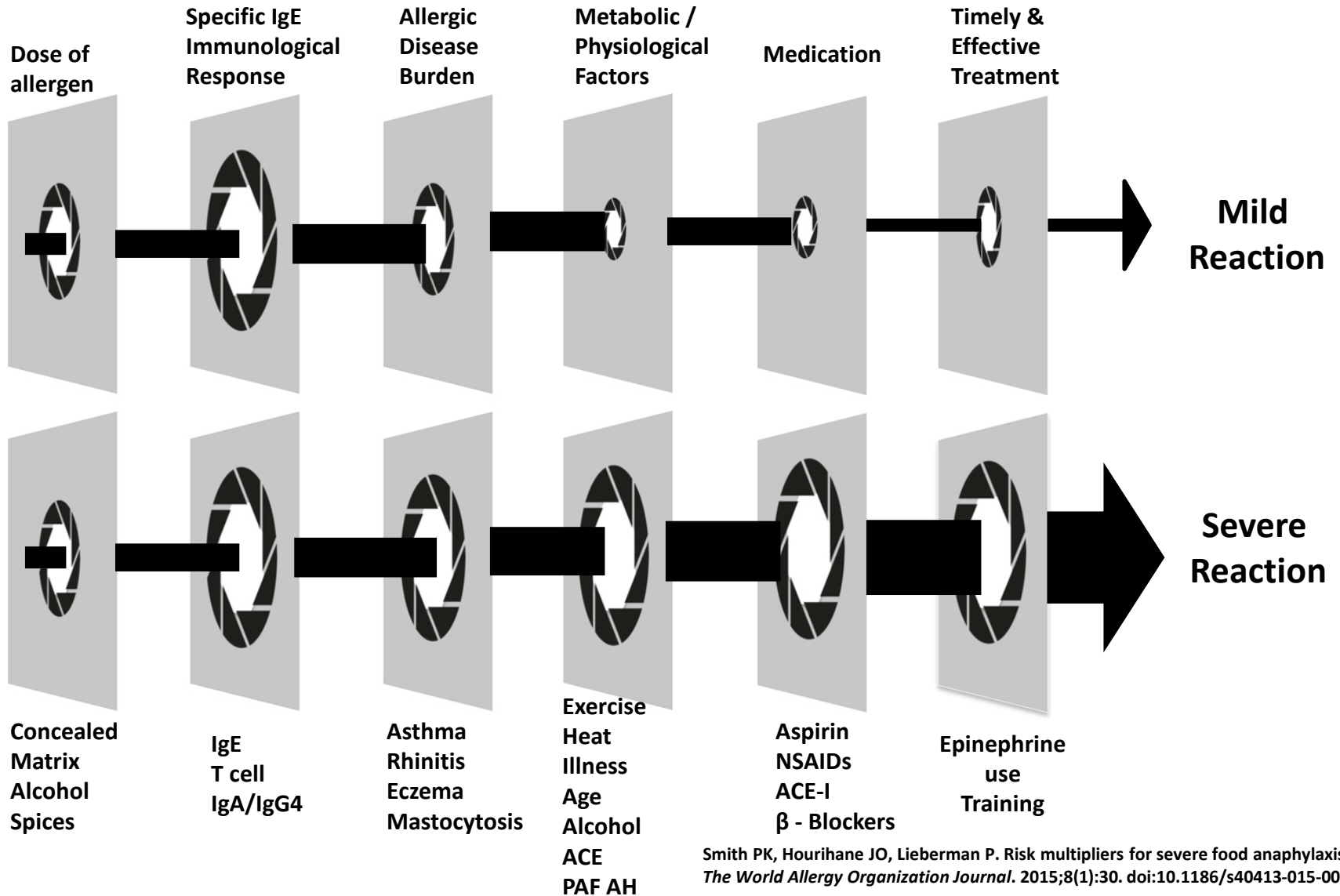
# Mechanisms and augmenting factors involved in anaphylaxis



# Risk factors for severe anaphylaxis



# Risk Multipliers for severe anaphylaxis






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ORIGINAL ARTICLE

Epidemiology and Genetics

WILEY Allergy EUROPEAN JOURNAL OF ALLERGY  
AND CLINICAL IMMUNOLOGY EAACI

# Patterns of anaphylaxis after diagnostic workup: A follow-up study of 226 patients with suspected anaphylaxis

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## Abstract

**Background:** Most published studies on anaphylaxis are retrospective or register based. Data on subsequent diagnostic workup are sparse. We aimed to characterize patients seen with suspected anaphylaxis at the emergency care setting (ECS), after subsequent diagnostic workup at our Allergy Center (AC).

**Methods:** Prospective study including patients from the ECS, Odense University Hospital, during May 2013-April 2014. Possible anaphylaxis cases were daily identified based on a broad search profile including history and symptoms in patient records, diagnostic codes and pharmacological treatments. At the AC, all patients were evaluated according to international guidelines.

**Results:** Among 226 patients with suspected anaphylaxis, the diagnosis was confirmed in 124 (54.9%) after diagnostic workup; 118 of the 124 fulfilled WAO/EAACI criteria of anaphylaxis at the ECS, while six were found among 46 patients with clinical suspicion but not fulfilling the WAO/EAACI criteria at the ECS. The estimated incidence rate of anaphylaxis was 26 cases per 100 000 person-years and the oneyear period prevalence was 0.04%. The most common elicitor was drugs (41.1%) followed by venom (27.4%) and food (20.6%). In 13 patients (10.5%), no elicitor could be identified. Mastocytosis was diagnosed in 7.7% of adult patients and was significantly associated with severe anaphylaxis. Atopic diseases were significantly associated only with food-induced anaphylaxis. Cofactors were present in 58.1% and were significantly associated with severe anaphylaxis.

**Conclusion:** A broad search profile in the ECS and subsequent diagnostic workup is important for identification and classification of patients with anaphylaxis. Evaluation of comorbidities and cofactors is important.

# Patterns of anaphylaxis after diagnostic workup: A follow-up study of 226 patients with suspected anaphylaxis

## Detailed distribution of cofactors by elicitors.

Elicitors	Cofactors			
	Infection n (%)	ASA/ NSAIDs n (%)	Exercise n (%)	Alcohol n (%)
<b>Drugs</b>				
B-lactam antibiotics n=24	24 (100)	6 (25)	5 (20.8)	2 (8.3)
ASA/NSAIDs n=10	1 (10)	N/A	1 (10)	2 (20)
Other drugs <sup>a</sup> n=17	7 (41.2)	5 (29.4)	1 (5.9)	1 (5.9)
<b>Food</b>				
Tree nuts, Peanut and Almond n=14	0	2 (14.3)	3 <sup>c</sup> (21.4)	0
Wheat (WDEIA) n=5	0	0	5 <sup>c</sup> (100)	1 (20)
Other <sup>b</sup> n=7	1 (14.3)	0	0	1 (14.3)
<b>Venom</b>				
Wasp n=26	0	4 (15.4)	8 (30.8)	9 (34.6)
Bee n=6	0	0	1 (16.7)	0
Other <sup>d</sup> n=2	0	0	0	0
Unknown n=13	4 (30.8)	3 (23.1)	2 (15.4)	1 (7.7)
<b>Total n=124</b>	<b>37 (29.8)</b>	<b>20 (16.1)</b>	<b>26 (20.9)</b>	<b>17 (13.7)</b>

Presence of one or more cofactors (self-reported) was significantly associated with severe anaphylaxis



# Clinical implications- role of allergist

- Identify the causative and risk factors for severe and potentially fatal A
- Prevent causative/risk factors re-exposure
- Prescription of and training in the use of epinephrine

## **Risk factors for severe anaphylaxis in patients receiving anaphylaxis treatment in US emergency departments and hospitals**

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### Abstract

#### BACKGROUND:

Although reported risk factors for severe anaphylaxis include older age, presence of comorbid medical conditions, and concomitant medications, previous studies have used varying definitions for anaphylaxis and heterogeneous methodology.

#### OBJECTIVE:

To describe risk factors for severe anaphylaxis among US patients treated in emergency departments (EDs) or hospitals for anaphylaxis.

#### METHODS:

Individuals with an ED visit/hospitalization for anaphylaxis were identified from 2 MarketScan Research Databases using an expanded International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code algorithm. Eligibility for the current study required continuous medical and prescription coverage for at least 1 year before and after the index date. Severe anaphylaxis was defined as a reaction requiring hospital admission.

### RESULTS:

**Among 11,972 individuals, 2,622 (22%) had severe anaphylaxis. Unadjusted analysis showed that severe anaphylaxis was associated with older age and higher comorbidity burden.** These patients were also less likely to have filled an epinephrine autoinjector (EAI) prescription or visited an allergist/immunologist, but more likely to have had an ED visit/hospitalization (any cause). On multivariable analysis, filling an EAI prescription (odds ratio [OR], 0.64; 95% CI, 0.53-0.78) or visiting an allergist/immunologist (OR, 0.78; 95% CI, 0.63-0.95) before the index event was associated with a lower risk of severe anaphylaxis, while any previous ED visit (OR, 1.18; 95% CI, 1.07-1.30) or hospitalization (OR, 1.55; 95% CI, 1.36-1.75) was associated with a higher risk of severe anaphylaxis.

### CONCLUSIONS:

In this large cohort with an ED visit or hospitalization for anaphylaxis, 22% had severe anaphylaxis. **Pre-index preventive anaphylaxis care (ie, EAI prescription fill and allergist/immunologist visit) was associated with a significantly lower risk, supporting the benefits of preventive anaphylaxis care in real-world practice.**

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# Factors increasing the risk for a severe reaction in anaphylaxis: An analysis of data from The European Anaphylaxis Registry

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# Factors increasing the risk for a severe A: data from **The European Anaphylaxis Registry**

- **Objectives:**

- identify
  - prioritize
  - avoid
- } factors associated with an increased risk of developing severe A

- **Methods:**

## Database and cohort

- data from the European Anaphylaxis Registry (status for may 2017)
- cases of immediate hypersensitivity reactions from 122 centers/ 11 countries;
- questionnaire developed by an expert panell ( factors that can influence the severity of A: elicitors, concomitant diseases, medications, lifestyle)

## Statistical analysis:

- logistic regression was performed to identify factors increasing the risk of developing severe A
- outcome variables = *severity grades (NIAID/FAAN; Ring and Messmer)*
- predictor variables = *age, sex, concomitant diseases, concomitant medication, reaction elicitor, lifestyle, first or subsequent anaphylaxis;*

# Factors increasing the risk for a severe A: data from **The European Anaphylaxis Registry**

## • **RESULTS**

- 10212 cases: 8055 dg A (NIAID/FAAN criteria)
- Elicitors: 1. venoms;  
2. drugs;  
3. food .
  - **Drugs** (though being a non-homogeneous group of elicitors) increase the severity of A
  - Of insect stings, **yellow jackets elicited cases were more severe than bee sting elicited cases.**

- **Age** was the most important predictor risk factor for severe anaphylaxis (multivariable analysis)
- **Male sex** was associated with a higher risk of severe A
- **Mastocytosis** was a concomitant disease in 120 pts (1,64%) and increased the odds of developing severe A

# Factors increasing the risk for a severe A: data from **The European Anaphylaxis Registry**

- **Mastocytosis:**
  - Previous studies suggested that mastocytosis is one a potential factor increasing the risk of severe IgE- dependent A as it has been linked to fatal A in pts stung by Hymenoptera
  - This data support the finding that mastocytosis is one of the most potent co-factors for severe A
  - The European Anaphylaxis Guidelines recommend the **prescription of an adrenaline auto-inj in all** mastocytosis pts.

# Factors increasing the risk for a severe A: data from **The European Anaphylaxis Registry**

- **RESULTS:**

- **Concomitant medication** (beta blocker and ACE inhibitor) increase the risk of severe A independent of elicitor
- **Vigorous exercise** (during or prior) increase the risk in 3 elicitor groups; when the model was restricted to food, the risk was corresponding to the level of exercise
- **Psychological burden** was more often associated with severe A

# Factors increasing the risk for a severe A: data from **The European Anaphylaxis Registry**

## Elicitation factors

- **venoms**
- **drugs**
- **food** (more common in children)

## Augmentation factors (co- factors)

### Intrinsic

- higher age
- male sex
- concomitant mastocytosis

### Extrinsic

- vigorous exercise
- psychological burden
- drugs(i.e. beta-blockers and ACE-I)



# Factors increasing the risk for a severe A: data from **The European Anaphylaxis Registry**

- The first study with calculation of a relative risk of endogenous and exogenous factors influencing the severity of A based on a large dataset.

*The Journal of Allergy and Clinical Immunology:*

# In Practice

Clinical Commentary Review

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## **Fatal Anaphylaxis: Mortality Rate and Risk Factors**

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# POPULATION-BASED DATA FOR RATE OF FATAL ANAPHYLAXIS TRIGGERED BY DRUGS

Region	Data Source	Total deaths	Gender predominance	Leading causal drugs	Risk factors identified
Australia (1997-2013)	Australian Bureau of Statistics and National Coroners Information System	147 cases in total 84 (57%) triggered by drugs	Male > female	Antibiotics 43% General anesthetic 35% Radiocontrast 18%	Age Cardiovascular disease 71% Known penicillin allergy 11% (33% of beta-lactam fatalities)
Canada (Ontario) (1986-2011)	Ontario Coroner's database	92 total 16 (17%) drugs Coroner reports searched	38% male	Antibiotics 44% Radiocontrast 25%	Age Known allergy to the drug in 1 of 5 cases with data available (20%)
France (2000-2011)	French National Pharmacovigilance Database*	84 (0.04% of total anaphylaxis cases)	Male > female	Not stated	Male gender Hypertension and Cardiovascular comorbidities Obesity Beta-blocker use
United Kingdom (1992-2012)	National fatal anaphylaxis registry	479 total 263 drugs (55% of total)	Not stated	Not stated	Older age
United States (1999-2010)	National Center for Health Statistics MCDD	2458 total 1446 (59% of total)	None	Antibiotics (mostly beta-lactams) Contrast agents Antineoplastic drugs	African American ethnicity Older age

*MCDD, National Center for Health Statistics' Multiple Cause of Death Data.*

*\*Reported data were only on neuromuscular blocking agents.*

# Practical implication of fatal drug anaphylaxis data

- Drug-induced anaphylaxis is the most common cause of fatal anaphylaxis in most regions
  - The incidence of fatal drug anaphylaxis may be increasing
  - People *older than 50 years with pre-existing cardiovascular morbidity* - at highest risk for fatal drug anaphylaxis
  - Beta-lactam antibiotics
  - Muscle relaxants (general anesthesia)
  - Injected radiocontrast medium
- the commonest triggers of fatal drug anaphylaxis

# POPULATION-BASED DATA FOR RATE OF FATAL ANAPHYLAXIS TRIGGERED BY FOOD

Region	Data Source	Total deaths	Gender predominance	Leading causal foods	Risk factors identified
Australia (1997-2013)	Australian Bureau of Statistics and National Coronial Information System (NCIS)	324 (119 with known cause) 23 (19%) food	No	Seafood 50% Nuts 32%	Known food allergy 91% Asthma 68% Alcohol or recreational drugs 27% Upright posture 68% Delayed use of epinephrine
Canada (Ontario) (1986-2011)	Ontario Coroner's database	92 total 40 (43%) food Coroner reports searched;	No	Peanut	Delayed use of epinephrine Known allergy to the culprit food in all 34 cases where this information was available (100%)
United Kingdom (1992-2008)	National fatal anaphylaxis registry	479 total 124 (26%) food	Male (under 15 y) Female (over 15 y)	Peanut or Tree nut 73%	Known food allergy 69% Asthma 78% Change in posture
United States (1999-2009)	3 national databases (NIS, NEDS, MCDD)	2229 total approximately 122 (5%) food	Not stated	Not stated	Not stated
United States (1999-2010)	National Center for Health Statistics MCDD	2458 total 164 (7%) food	Male > female	Not stated	African American ethnicity

MCDD, National Center for Health Statistics' Multiple Cause of Death Data; NCIS, Australian National Coronial Information System; NEDS, Nationwide Emergency Department Sample, from the Healthcare Cost and Utilization Project; NIS, Nationwide Inpatient Sample, from the Healthcare Cost and Utilization Project.

# Practical implication of fatal food anaphylaxis data

- Fatal food anaphylaxis is rare.
- Identification of patients at ↑ risk of fatal food A is not currently possible!!!
  - egg allergy or no asthma appear to be at lowest risk
  - highest risk in the second and third decades of life
- Fatal outcome associated:
  - ◇ upright posture
  - ◇ delayed use of epinephrine.

# POPULATION-BASED DATA FOR RATE OF FATAL ANAPHYLAXIS TRIGGERED BY INSECT VENOM

Region	Data Source	Total deaths	Gender predominance	Leading causal insects	Risk factors identified
Australia (1997-2013)	Australian Bureau of Statistics and National Coronial Information System (NCIS)	324 (119 with known cause) 41 (13%) insect	90% male	Honeybee 73% Ants 9% Ticks 9% Wasp 6%	Age Male sex Cardiovascular disease 45% Upright posture 30% Known venom allergy 48% Squeezing tick bites associated with death in all tick cases
Canada (Ontario) (1986-2011)	Ontario Coroner's database	92 total 30 (33%) insect Coroner reports searched	80% male	Not stated	Age Male sex Known venom allergy in 11 of 21 (52%) cases where this information was available
United Kingdom (1992-2008)	National fatal anaphylaxis registry	479 total 92 (19%) insect	Not stated	Not stated	Not stated
United States (1999-2009)	3 national databases (NIS, NEDS, MCDD)	2229 total 295 (13%) insect	Not stated	Not stated	Not stated
United States (1999-2010)	National Center for Health Statistics MCDD	2458 total 374 (15%) insect	80% male 88% white	Not stated	Age White race Male sex

MCDD, National Center for Health Statistics' Multiple Cause of Death Data; NCIS, Australian National Coronial Information System; NEDS, Nationwide Emergency Department Sample, from the Healthcare Cost and Utilization Project; NIS, Nationwide Inpatient Sample, from the Healthcare Cost and Utilization Project.

Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal Anaphylaxis: Mortality Rate and Risk Factors. *The Journal of Allergy and Clinical Immunology in Practice*. 2017;5(5):1169-1178.

# Practical implication of fatal venom anaphylaxis data

- The risk of fatal venom A for venom allergic pts is **low**:  
3 to 6 cases per million person years
- Risk factors for fatal venom anaphylaxis are:
  - middle age;
  - male sex;
  - white race;
  - pre-existing cardiovascular disease;
  - mastocytosis.
- Fatal venom A is associated with *upright posture*
- Fatal tick bite A associated with *squeezing ticks for removal*
- These risk factors should be considered, together with quality of life impairment, when making treatment decisions in venom allergic patients.



# Risk Factors for fatal A

## Conclusions

- The incidence of fatal A has not increased in line with hospital admission for A
- Fatal drug A may be increasing but rates of fatal A to venom and food are stable
- Risk factors for fatal A vary according to the cause (drugs/food/venoms)
- The rarity of fatal A (less than 1% of total mortality risk) and the significant QoL impact suggest that QoL impairment should be a key consideration when making treatment decision in pts at risk for A

# General conclusions

- **Intrinsic and extrinsic factors may facilitate or aggravate anaphylaxis**
  - Higher age, male sex and concomitant mastocytosis
  - Vigorous exercise, vulnerability to psychological burden and drugs (beta-blockers and ACE-I)
  - The presence of more co-factors is associated with severe anaphylaxis
- **EAI prescription and allergist/immunologist visit was associated with a significantly lower risk**

# Conferința Națională de Alergologie și Imunologie Clinică

“Practica clinica in alergologie: focus pe  
ghiduri si consensuri”



17 - 19 mai 2018  
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