

Anafilassi: ciò che è essenziale sapere



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Benevento, 14 gennaio 2016

Questo è essenziale

TABLE 1. Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

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*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than $(70 \text{ mm Hg} + [2 \times \text{age}])$ from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Absolute indications:

- Previous cardiovascular or respiratory reaction to a food, insect sting or latex.
- Exercise induced anaphylaxis.
- Idiopathic anaphylaxis.
- Child with food allergy and co-existent persistent asthma*.

Relative indications:

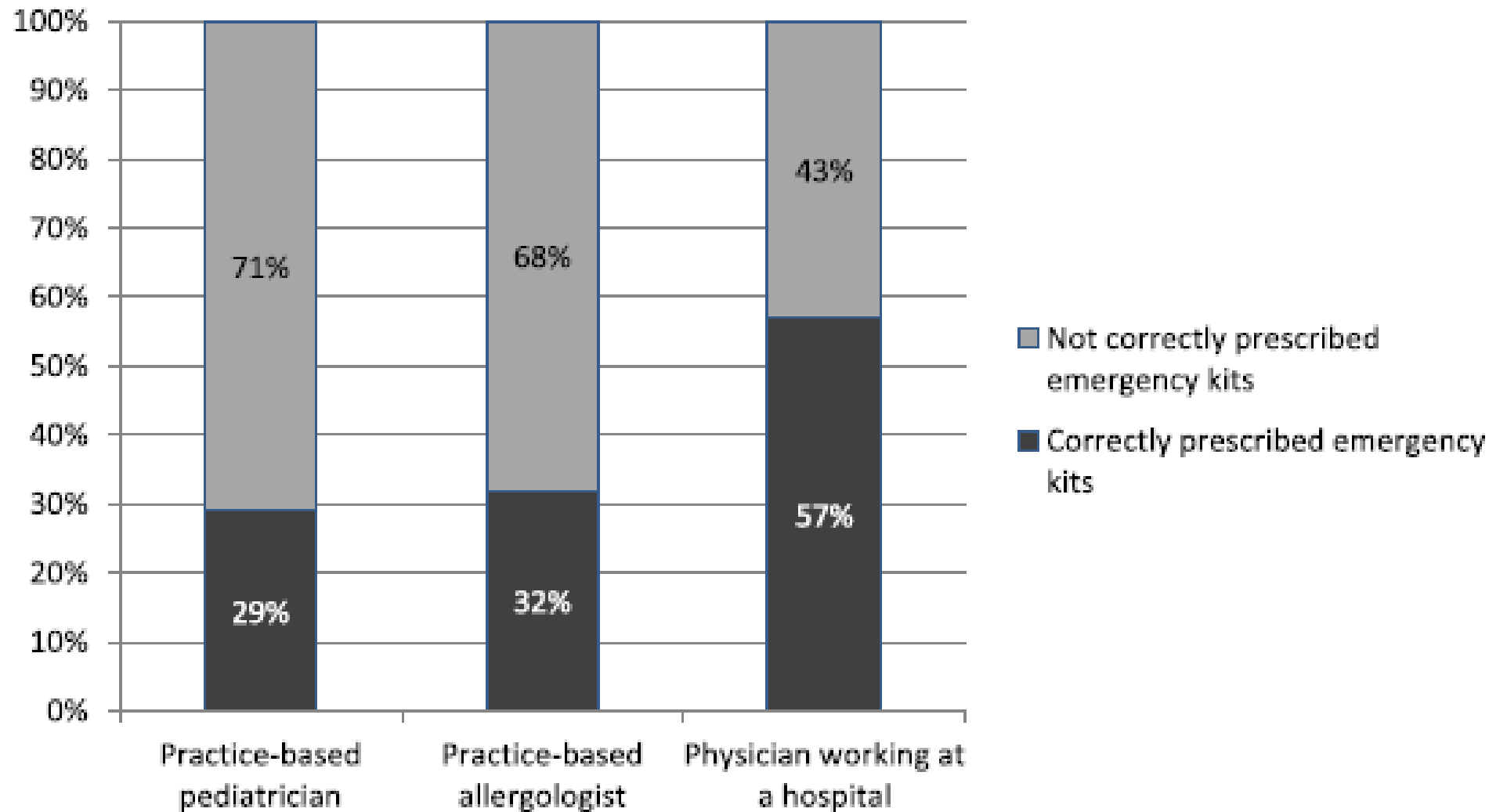
- Any reaction to small amounts of a food (e.g. airborne food allergen or contact only via skin).
- History of only a previous mild reaction to peanut or a tree nut.
- Remoteness of home from medical facilities.
- Food allergic reaction in a teenager.

Chi non si occupa di anafilassi la conosce poco

Anaphylaxis	Allergists	Nonallergists
Common	44.3	16.4
Rare	55.4	82.2
No evidence	0.2	1.4

Martelli A. Anaphylaxis in the emergency department: a paediatric perspective. Curr Opin Allergy Clin Immunol 2008;8:321-9.

Il doppio dei Medici in H prescrive correttamente



Kilger M et al. Acute and preventive management of anaphylaxis in German primary school and kindergarten children. *BMC Pediatr.* 2015;15:159.

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Anafilassi da carne rossa

TIPO DI ALLERGIA	CARATTERISTICHE
allergia alla carne	IgE mediata. allergeni: sieralbumine bovine/ovine.
pork-cat syndrome	cross-reattività carne di maiale & epitelio del gatto. allergene: sieralbumina.
milk-beef syndrome	cross-reattività latte & carne di manzo. allergene: sieralbumina bovina.
FDEIA food-dependent exercise-induced anaphylaxis	anafilassi da carne dopo esercizio fisico. allergeni: proteine della carne.
anafilassi ritardata da carne di mammifero	anafilassi ritardata (3-7 h) dopo assunzione di carni di mammiferi (carni bovine, suine, ovine). allergene: α-gal

Planisfero con i casi alfa-gal



★ = Location of published reports of mammalian meat allergy due to sIgE to galactose-alpha-1,3-galactose detailed in Table I

Commins SP et al. Delayed anaphylaxis to alpha-gal, an oligosaccharide in mammalian meat. *Allergol Int.* 2016;65:16-20.

I tempi della reazione

Country	Suspected tick species	Timing of reactions	Implicated foods	Reference
Australia	<i>Ixodes holocyclus</i>	1–6 h	N-PMM, kangaroo, horse, gelatin	16,17
France		0.5–5 h	N-PMM, pork kidney, horse	8,9
Germany	<i>Ixodes ricinus</i>	0.25–5 h	N-PMM, pork kidney, gelatin	12,13
Japan		>2 h	N-PMM	11
Panama	<i>Amblyomma cajennense</i>	1.5–6 h	N-PMM	15
Spain	<i>Ixodes ricinus</i>	2–6 h	N-PMM	10
Sweden	<i>Ixodes ricinus</i>	1.5–6 h	N-PMM, moose	14,26
United States	<i>Amblyomma americanum</i>	2–6 h	N-PMM, squirrel, gelatin	6,7,22,24

N-PMM, non-primate mammalian meat = e.g., beef, pork, lamb, goat, venison, rabbit.

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I segni respiratori nell'anafilassi

Respiratory tract symptoms

Dyspnea/difficulty breathing	60 (44.8)
Tightness/fullness of the throat	57 (42.5)
Wheezing/bronchospasm	31 (23.1)
Cough	15 (11.2)
Hoarseness/raspy voice	11 (8.2)
Rhinitis	8 (6.0)
Laryngeal edema	5 (3.7)
Cyanosis	4 (3.0)
Stridor	3 (2.2)
Aphonia	3 (2.2)

Campbell RL et al. Prescriptions for self-injectable epinephrine and follow-up referral in emergency department patients presenting with anaphylaxis. *Ann Allergy Asthma Immunol* 2008;101:631-6.

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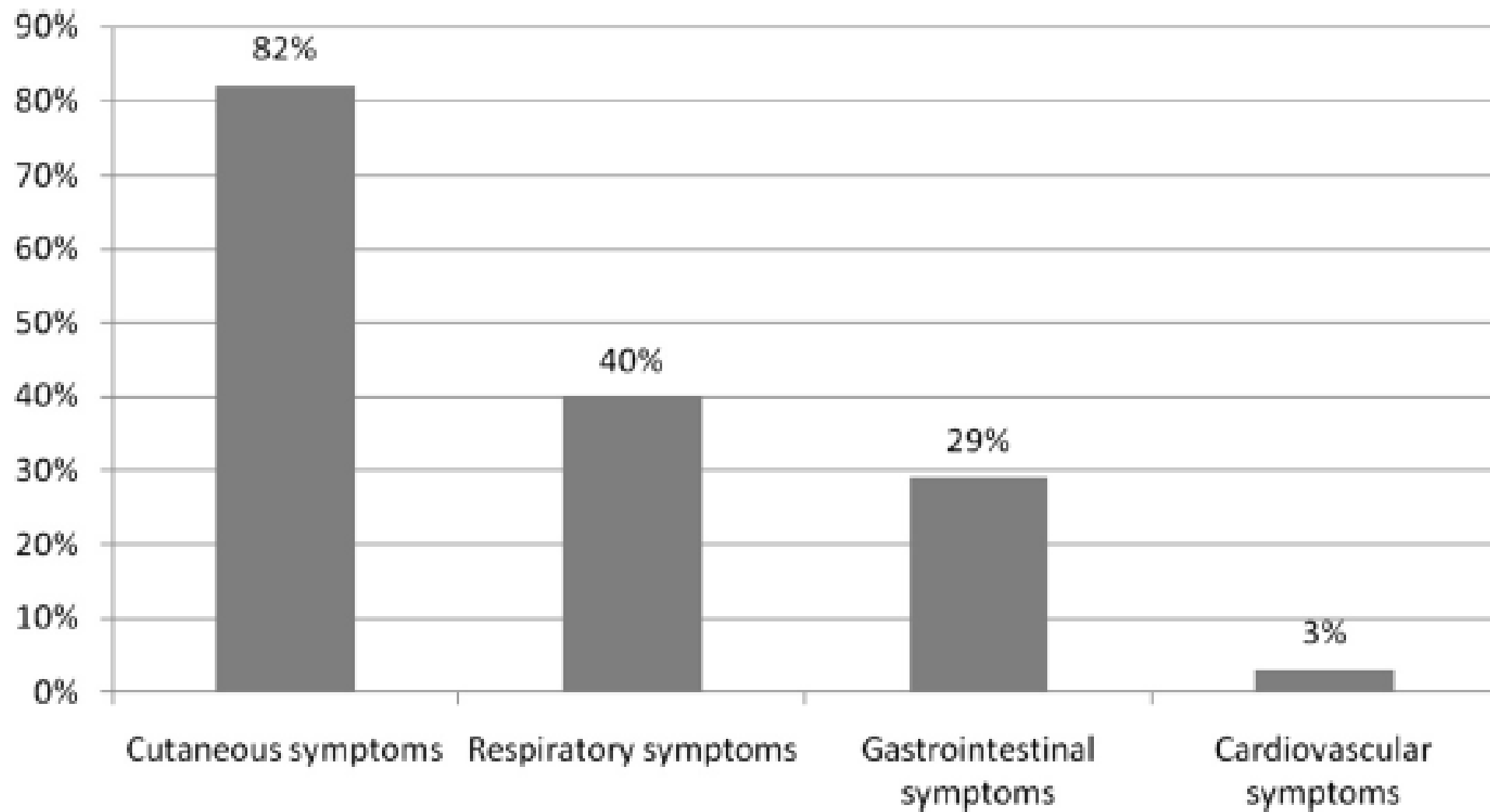
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Apparati coinvolti

Segni e sintomi iniziali	N(%)
Tegumentario	33(60)
Respiratorio	14(25)
Gastrointestinale	3(5)
Neurologico	2(4)
Cardiovascolare	1(2)
Altri	2(4)

Segni e sintomi globali	N(%)
Tegumentario	51(93)
Respiratorio	51(93)
Cardiovascolare	14(26)
Neurologico	14(26)
Gastrointestinale	7(13)

Meno segni respiratori



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Cosa vuol dire “likely allergen”?

Allergene probabile

- Che ha un intervallo temporale breve
- La reazione si è ripetuta per lo stesso alimento senza ancora aver fatto diagnosi
- Reazione che si è verificata per un nuovo alimento probabilmente cross-reattivo con l'alimento indice
- Si tratta di un alimento introdotto per la prima volta, ma molto allergizzante (frutta secca, pesce ecc.)

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Indicazioni assolute/relative per l'adrenalina

Absolute indications:

- Previous cardiovascular or respiratory reaction to a food, insect sting or latex.
- Exercise induced anaphylaxis.
- Idiopathic anaphylaxis.
- Child with food allergy and co-existent persistent asthma*.

Relative indications:

- Any reaction to small amounts of a food (e.g. airborne food allergen or contact only via skin).
- History of only a previous mild reaction to peanut or a tree nut.
- Remoteness of home from medical facilities.
- Food allergic reaction in a teenager.

Simons FER et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. *J Allergy Clin Immunol* 2011;127:593.e1- e22

Proposte per la prescrizione di Adrenalina in AA

History of an anaphylactic reaction to the corresponding food in the past

Patients with any systemic reaction to a food in combination with bronchial asthma

Systemic allergic reactions to foods with a high risk of severe reactions such as peanuts, tree-nuts, and seeds

Patients who exhibit clinical reactions even to tiny amounts of the food

Patients with underlying mastocytosis and food allergy

Concomitanti malattie cardiovascolari

	WAO Guidelines	AAAAI/ACAAI Guidelines	EAACI Guidelines
Definition of anaphylaxis	"a serious life-threatening generalized or systemic hypersensitivity reaction" and "a serious allergic reaction that is rapid in onset and might cause death"	"an acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils"	"a severe life-threatening generalized or systemic hypersensitivity reaction"
Epidemiology	not a major emphasis	not a major emphasis	summary of anaphylaxis epidemiology and clinical presentation; gaps in the evidence (Box 15)
Patient risk factors and co-factors relevant to anaphylaxis	describe vulnerability related to age, concomitant diseases (asthma, CVD, mastocytosis), concurrent medications (beta-blockers, ACE inhibitors); describe co-factors such as exercise, acute infection, emotional stress, premenstrual status, and ethanol or NSAID ingestion; Figure 1	describe concomitant diseases (asthma, CVD, mastocytosis), concurrent medications (beta-blockers, ACE inhibitors); mention premenstrual status as a co-factor	give examples of patient-specific factors, pre-existing conditions, medications and lifestyle factors; describe concomitant asthma in detail; Box 6

Simons FE et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J. 2014;7:9.

Indicazioni relative

- Ogni reazione a piccola dose? Dipende dall'alimento. Se ad esempio è il kiwi diventa difficile venire a contatto anche con piccole dosi.
- Reazione lieve, non moderata, a frutta secca. Le reazioni successive possono essere più marcate?
- Due fattori relativi fanno sempre uno assoluto?
- Airborne food allergy: caso del censimento. Non è la stessa cosa per cute e respiratorio?
- Per un teenager può bastare per la prescrizione solo una reazione all'alimento senza anafilassi?

La ragazza del censimento

- Reazione da inalazione di vapori di latte vaccino
- Non aveva adrenalina con sé
- E' andata a casa a prenderla
- Forse si sarebbe salvata se l'avesse avuta con sé

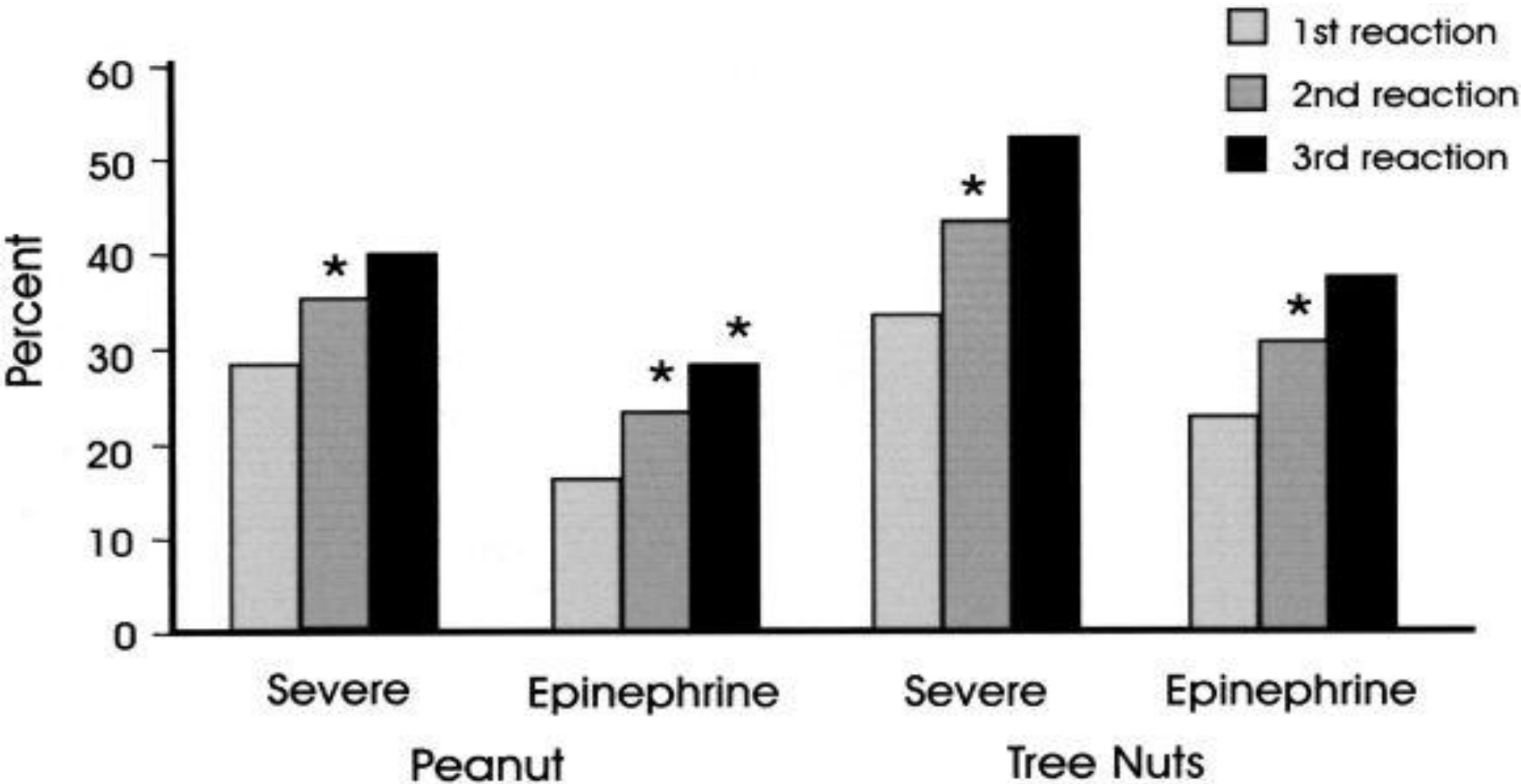
Barbi E et al. Fatal allergy as a possible consequence of long-term elimination diet. *Allergy* 2004;59:668-9.

Asma e asma severo

Topic	Clinical or basic research concerns	Advances and observations
Food allergy	Epidemiology	<ul style="list-style-type: none">• Childhood peanut allergy appears to have increased and exceeds a prevalence of 1%.• Delayed introductions of milk and egg are associated with increased risk of atopic outcomes.• Maternal ingestion of peanut during pregnancy was associated with increased risk of infant peanut sensitization among a cohort of atopic infants.
	Pathophysiology	<ul style="list-style-type: none">• Allergen-induced <i>IL4</i> expression was related to milk allergy in the absence of <i>GATA3</i> expression.
	Diagnostic testing	<ul style="list-style-type: none">• Binding to Ara h 2 provided the best peanut allergy diagnostic discrimination in a population-based cohort.• Studies of epitope binding provide insights on the prognosis, severity, and phenotypic expression of milk allergy.
	Treatment/management	<ul style="list-style-type: none">• Oral immunotherapy shows promise for the treatment of peanut allergy.• A preliminary study of epicutaneous immunotherapy with milk protein shows a trend toward efficacy.
Anaphylaxis	Epidemiology	<ul style="list-style-type: none">• A database of >1 million person-years shows increased risk for anaphylaxis among persons <u>with asthma, particularly severe asthma.</u>

Sicherer SH et al. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2010. *J Allergy Clin Immunol* 2011;127:326-35.

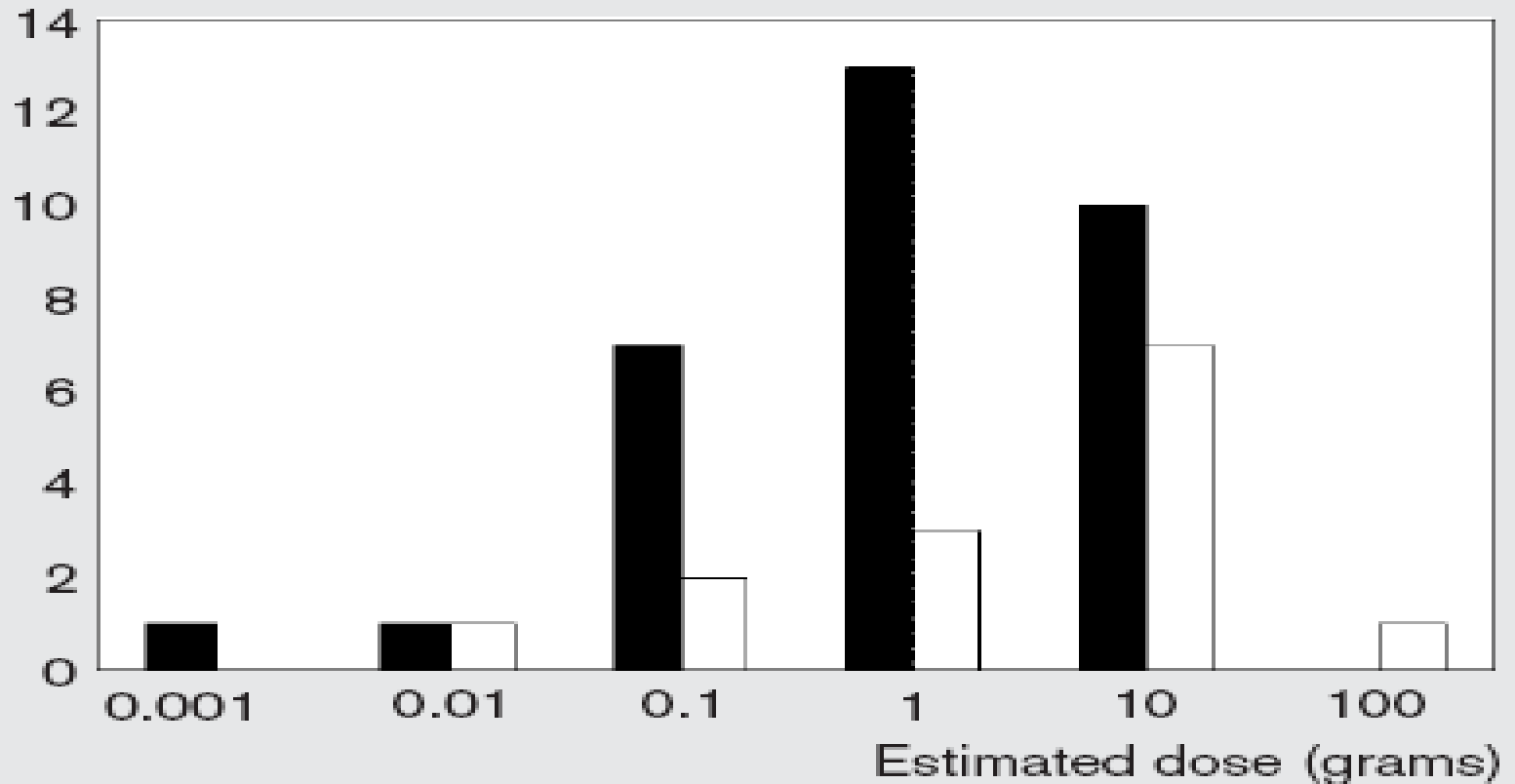
Anafilassi lieve non sempre resta tale



Simons FER. First-aid treatment of anaphylaxis to food: focus on epinephrine. *J Allergy Clin Immunol* 2004;113:837-844.

Anafilassi fatale: dose stimata di alimento come causa di morte

Number of deaths



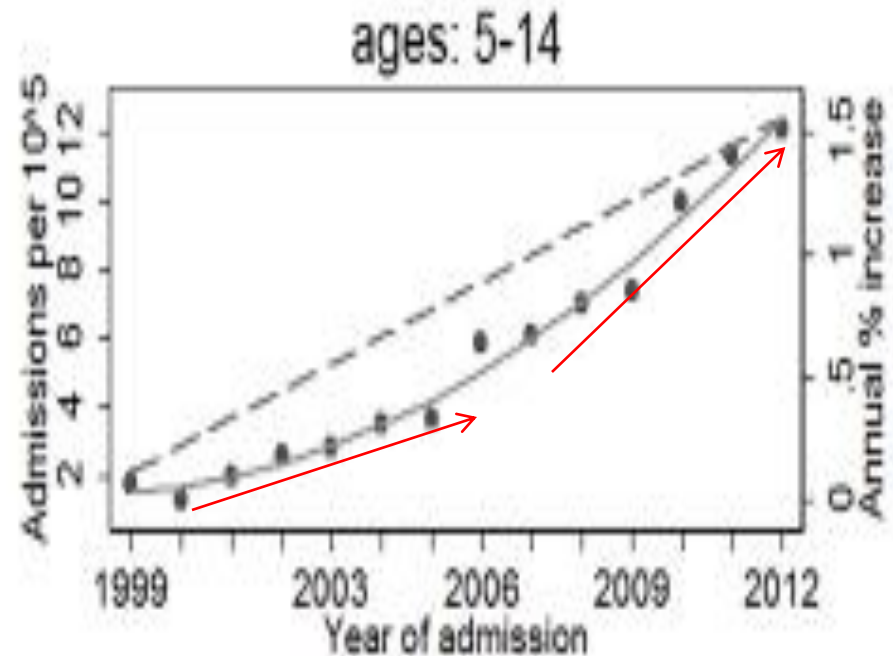
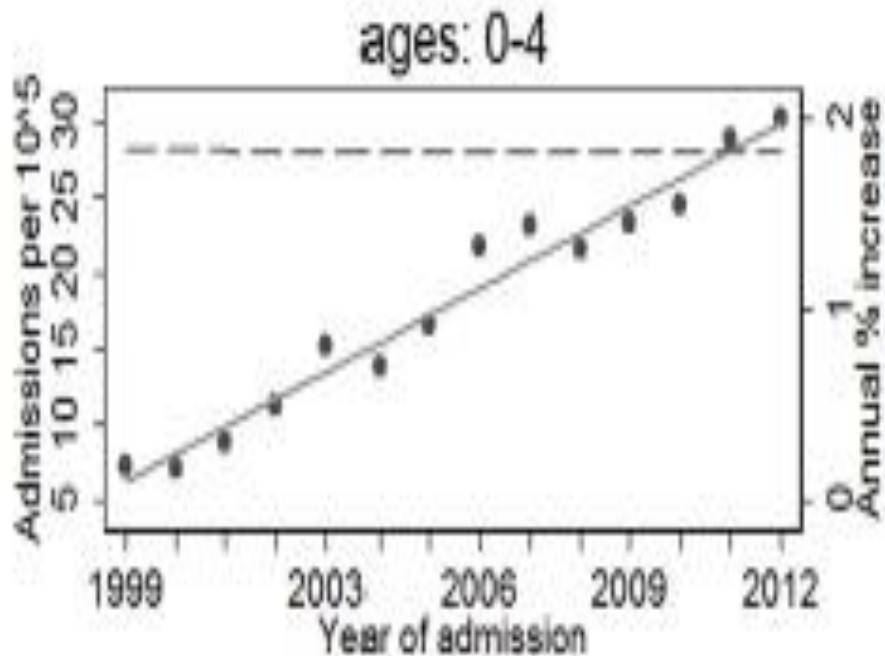
■ Nuts
□ Other food

Frutta secca e cross reattività

Food allergen	Potential clinical cross-reactivity
Peanut	Legumes (soy, lentils, chickpeas) High rate of cross-sensitization, but clinical cross-reactivity uncommon (5%) Multiple legume allergy may be associated with sensitization to lentil and chickpea
	Tree nuts Approximately one-third of patients with peanut allergy report clinical reactivity to tree nuts (not evaluated by DBPCFC) Significant cross-reactivity between peanut and certain tree nut epitopes (almond, walnut, pecan, hazelnut, Brazil nut)
	Seeds Co-sensitization is common, but clinical cross-reactivity unknown
	Other tree nuts Clinical reactivity to multiple tree nuts reported in up to one-third of patients (37%)
Tree nuts	Seeds Co-sensitization is common, but clinical cross-reactivity unknown
	Peanut (see above)
Walnut	Pecan – clinical cross-reactivity Coconut – homologous but clinical cross-reactivity rare
Cashew	Pistachio – clinical cross-reactivity

Lomas JM et al. Managing nut-induced anaphylaxis: challenges and solutions. J Asthma Allergy. 2015;8:115-123.

Ricoveri in H per anafilassi da alimento Aumentano nel bambino e nel teenager



Mullins RJ et al. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *J Allergy Clin Immunol.* 2015;136:367-75.

Quando prescriverne più di 1?

- 1 high body weight requiring a higher dose than delivered by one device, especially with the relatively low maximum dose of 300 µg available in most countries,
- 2 fear of a possible miss-firing,
- 3 a location without promptly available professional medical help,
- 4 concern that the first shot may not help sufficiently or for long enough,
- 5 protracted or recurrent clinical reactions in the past, and
- 6 persistent bronchial asthma.

Uso dell'adrenalina

Reference	Study design	Auto-injector prescription	Used an auto-injector during follow-up*	Reactions where initial intramuscular adrenaline dose was followed by additional doses**
(61)	Retrospective clinic population	All	4% (41/969) over a 12-month period	32% (13/41)
(88)	Retrospective clinic population	All	22% (15/68) over a 20-month period	15% (2/13)
(89)	Prospective clinic population	Not all	3% (23/785) over an average of 48 months	0% (0/23)
(84)	Prospective clinic population	Not all	19% (78/413) over an average of 24 months	19% (18/95)
(15)	Patient survey	Not all	27% (500/1885)	18% (90/500)
(83)	Patient survey	Not all	35% (22/63)	18% (4/22)

Notes

*Refers to individual patients.

**Refers to individual allergic reactions (often more than one per patient). Additional doses were usually given by a healthcare professional.

Muraro A et al. EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69:1026-45.

Adrenalina nei casi fatali

Epinephrine was injected before cardiac arrest in only 23 % of 92 individuals who experienced a fatal anaphylaxis episode [93].

In an observational study, data confirmed the safety of IM epinephrine injection, typically given through an epinephrine auto-injector. (adverse events 1 %, and no overdoses). In contrast, IV bolus injections were associated with significantly more adverse events (10 %) and overdoses (13 %) [99].

Simons FE et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015;8:32.

Problemi per l'utilizzo dell'autoiniettore

- An individual known to be at risk of anaphylaxis may not have their own AAI immediately available (e.g. expired, broken and used but misfired).
- A second dose of adrenaline may be required before an ambulance arrives.
- A previously diagnosed individual with mild or moderate allergy who was not prescribed an AAI has anaphylaxis.
- An undiagnosed individual, not previously known to be at risk of any allergic reaction, may have their first ever episode of anaphylaxis away from home.
- General use AAI should be considered as being *additional* to prescribed AAI, not a substitute for prescribed AAI.
- AAI may be purchased from pharmacies without prescription at full price.
- An AAI brand-specific ASCIA Action Plan (general) should be stored with the AAI.
- AAI should be replaced before their expiry date.
- The number of AAI required will consider issues such as the number of children at risk of anaphylaxis attending offsite activity compared with the number of children remaining at school, the number of simultaneous activities, the location of out of school activities (access to emergency care, mobile phone coverage and likelihood of exposure to allergic triggers, particularly food or insect stings).

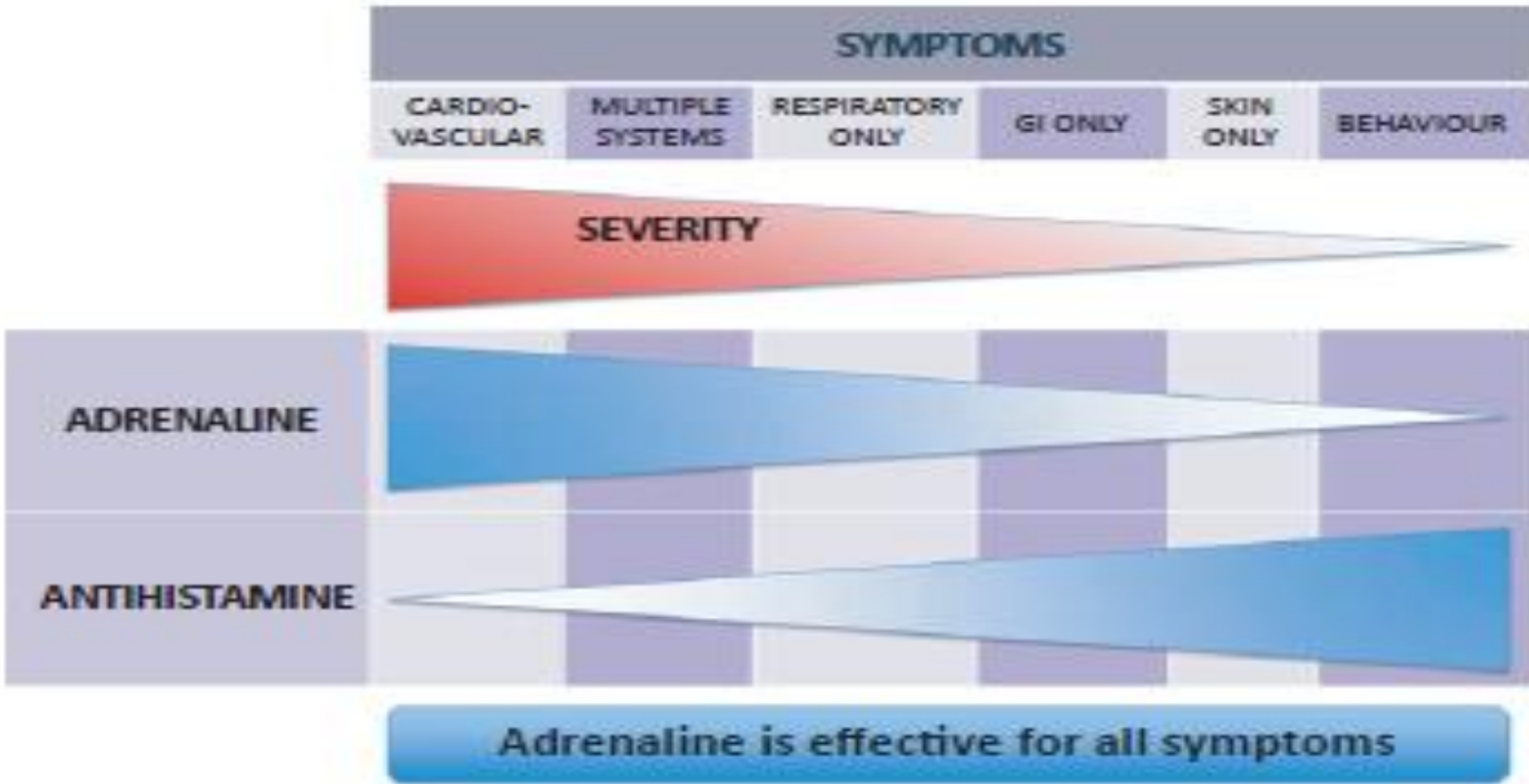
Vale S et al. ASCIA guidelines for prevention of anaphylaxis in schools, pre-schools and childcare: 2015 update. J Paediatr Child Health. 2015;51:949-54.

Evidenze per l' action plan

Recommendation	Evidence level	Grade
<p>Anaphylaxis management plan An anaphylaxis management plan should be used from the time of diagnosis to prevent future reactions, and aid recognition and treatment of any further reactions</p>	III	C
<p>Venom immunotherapy Subcutaneous venom immunotherapy is recommended in venom-allergic patients with a previous episode of anaphylaxis and adults with systemic cutaneous reactions</p>	I	A
<p>Training Training in the recognition and management of anaphylaxis should be offered to all patients and caregivers of children at risk of anaphylaxis ideally from the time of diagnosis</p>	V	D
<p>Training in the recognition and management of anaphylaxis, including the use of adrenaline auto-injectors, should be offered to all professionals dealing with patients at risk of anaphylaxis</p>	IV	C
<p>Training packages should be developed with the target groups</p>	V	D
<p>Training should cover allergen avoidance, symptoms of allergic reactions, when and how to use an adrenaline auto-injector, and what other measures are needed within the context of an anaphylaxis management plan</p>	V	D
<p>Training may involve more than one session to allow revision, an interactive scenario-based approach, a standardized program with manual and educational material and simulation tools. Content and language should be tailored to be understood and memorized</p>	V	D
<p>Psychological interventions Educational interventions should ideally incorporate psychological principles and methods to address anxiety so that children and families may function well at home, at school/work, and socially despite their risk of future reactions and should ideally be part of their educational training. This can be done in a group format. Some patients, with severe anxiety of ongoing duration, may need more in-depth one-to-one psychological intervention</p>	V	D

Muraro A et al. EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69:1026-45.

Cortisone non considerato



Muraro A et al. EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69:1026-45.

Perché non viene eseguita adrenalina autoiniettiva?

- 1 failure to recognize anaphylaxis,
- 2 uncertainty about autoinjector administration technique,
- 3 uncertainty about the indication to use, and
- 4 fear of side effects.

Piano d'azione per la reazione allergica da alimento

Nome e Cognome Mario Rossi

Data di nascita 1.1.2000

Insegnante.....

Allergico a: frutta secca.....

Asma bronchiale

x sì*

no

* elevato rischio per reazioni severe

Fotografia del
bambino

Da fare subito: guardare ed eventualmente trattare

Segni e sintomi

Terapia

Fastjekt

Antistaminico

Alimento appena assunto ma ancora nessun sintomo

sì

- **Cavo orale:** prurito, pizzicore, e/o gonfiore delle labbra, della lingua o della bocca

sì

-**Pelle:** prurito, rash pruriginoso, gonfiore del volto
-delle estremità (mani e piedi)

sì

-**Intestino:** nausea, dolori addominali, vomito o diarrea

sì

-**Gola†:** gola secca, senso di ostruzione, tosse abbaiante

sì

sì

- **Polmone†:** respiro breve e frequente, tosse ripetuta, fischio

sì

sì

- **Coscienza†:** offuscamento della vista, svenimento

sì

- **Cuore†:** polso frequente, bassa pressione arteriosa, pallore, cianosi

sì

sì

- **Altro** :.....

sì

sì

- **Se la reazione sta progredendo** (più sedi coinvolte)

sì

sì

La severità dei segni e dei sintomi può rapidamente cambiare.

† potenzialmente a rischio di vita

Contatti familiari di emergenza:

Nome /relazione con il bambino..... Telefono # 1 Telefono # 2

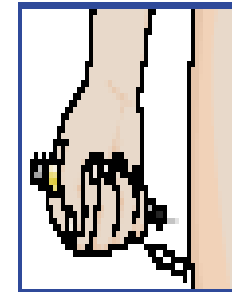
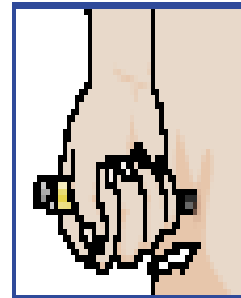
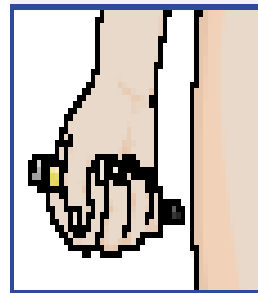
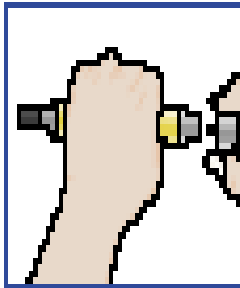
NON ASPETTATE DI TROVARE IL GENITORE O PARENTE! TRATTATE SUBITO E POI PORTATE IL BAMBINO
..... AL PRONTO SOCCORSO

CHI CERCARE AL CENTRO ALLERGOLOGICO:

Dottor o infermiere Telefono # 1 Telefono # 2

Come praticare l'adrenalina.

- 1 . Rimuovi il tappo grigio di attivazione
 - 2 . Appoggia con forza il tappo nero sulla parte laterale della coscia (sempre sulla coscia!)
 - 3 . Spingi con forza finchè scatta l' auto-iniezione. Tienilo pressato e conta con calma fino a 10.
 - 4 . Rimuovi Fastjekt e massaggia la zona di iniezione per 10 secondi.
- Porta in Pronto Soccorso anche il Fastjekt usato. Pianifica una osservazione in Pronto Soccorso.
- Per i bambini con allergie a più alimenti, considera di preparare piani di azione separati per ogni alimento.



Dosaggio:

Adrenalina: iniezione intramuscolare nella coscia

Fastjekt adulti

Antistaminico: somministra.....

farmaco, dose, via di somministrazione

Altro: somministra.....

farmaco, dose, via di somministrazione

Subito dopo il trattamento: chi chiamare

Chiamare il **118**. - Dite che c'è una reazione allergica grave in un bambino, e che è già in corso il trattamento

Firma dei genitori.....

Firma del medico.....

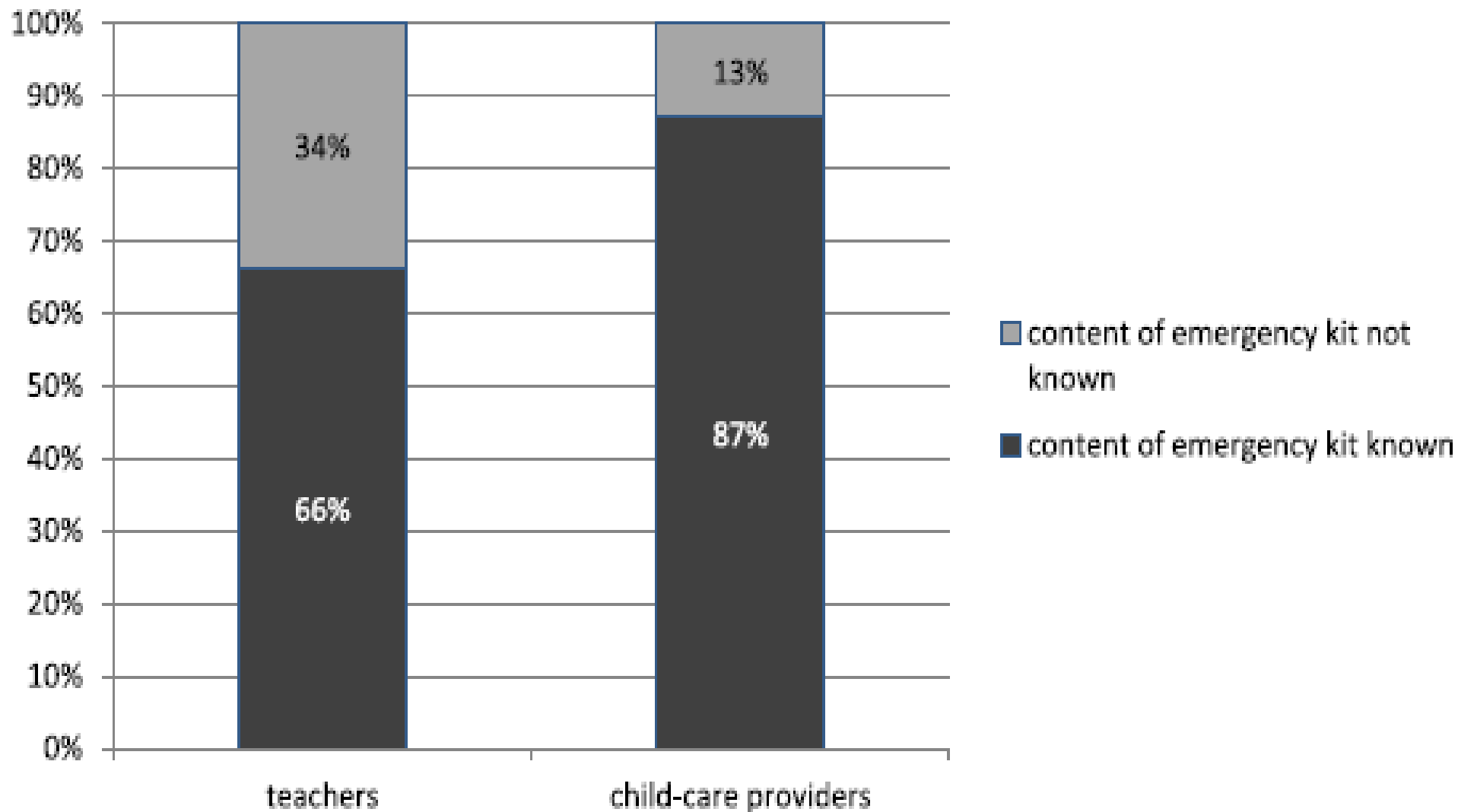


Più il cortisone dell'adrenalina

	Total number	Percentage
Content of emergency kits: corticosteroids	37	69.8 %
Content of emergency kits: antihistamines	33	62.3 %
Content of emergency kits: β 2-agonists	20	37.7 %
Content of emergency kits: adrenaline auto-injector	14	26.4 %

Kilger M et al. Acute and preventive management of anaphylaxis in German primary school and kindergarten children. BMC Pediatr. 2015;15:159.

Gli insegnanti sanno poco del kit



Kilger M et al. Acute and preventive management of anaphylaxis in German primary school and kindergarten children. BMC Pediatr. 2015;15:159.

Si ripetono: la necessità di parlarne ai parenti

Ratio Boys/Girls	50/37	57.5 %/42.5 %
Average age (in years) of children affected	7	
Children with a single episode of anaphylaxis	30	34.5 %
Children with 2 to 5 episodes of anaphylaxis	41	47.1 %
Children with more than 5 episodes of anaphylaxis	12	13.8 %
Missing data concerning episodes of anaphylaxis	4	4.6 %
Occurrence of the anaphylactic reaction: 6 months ago	9	10.3 %
Occurrence of the anaphylactic reaction: 12 months ago	10	11.5 %
Occurrence of the anaphylactic reaction: 18 months ago	9	10.3 %
Occurrence of the anaphylactic reaction: more than 24 months ago	56	64.4 %
Occurrence of the anaphylactic reaction: missing data	3	3.5 %
Site of occurrence of anaphylactic reaction: child's home	58	66.7 %
Site of occurrence of anaphylactic reaction: school or kindergarten	23	26.4 %
Site of occurrence of anaphylactic reaction: relative's/friend's house	19	21.8 %
Site of occurrence of anaphylactic reaction: on holiday	15	17.2 %

Kilger M et al. Acute and preventive management of anaphylaxis in German primary school and kindergarten children. *BMC Pediatr.* 2015;15:159.

Anafilassi da Ranitidina e.v.



Mori F, et al. Anaphylaxis to Intravenous Ranitidine in a Child. *Pharmacology*. 2015;95:240-242.

Anafilassi durante desensibilizzazione orale alla rifampicina



Syrigou E et al. Anaphylaxis during rapid oral desensitization to rifampicin. J Allergy Clin Immunol Pract. 2015 Oct 23.

Anche gli agenti biologici



Puxeddu I et al. Hypersensitivity reactions during treatment with biological agents. Clin Exp Rheumatol. 2016 Jan 9.

Delayed diagnosis of anaphylaxis secondary to ondansetron

A case report

Preeti Goyal, Kaggere Paramesh, Sarang Puranik, Mark Proctor and Mihir Sanghvi

Fatal Anaphylactic Shock Ceftriaxone-Induced in a 4-Year-Old Child

Gioacchino Calapai, MD, Selene Imbesi, MD,† Elvira Ventura-Spagnolo, MD,‡ Viviana Cafeo, MD,*
Livio Milone, MD,‡ Michele Navarra, PharmD,§|| and Sebastiano Gangemi, MD†¶*

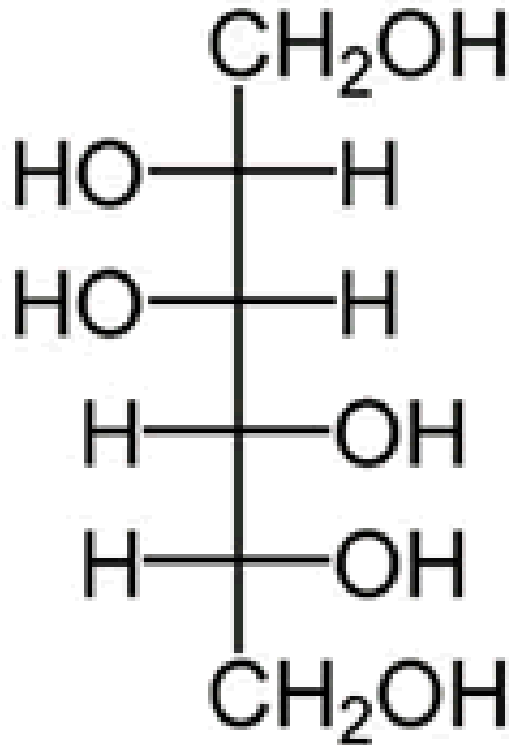
- Breve intervallo fra assunzione e anafilassi
- Pregressa esposizione a stessa cefalosporina e probabile sensibilizzazione
- Congestione poliviscerale e intensa eosinofilia all'esame istologico

6 casi di anafilassi con shock

- Beta-methasone
- Methylprednisolone
- Prednisolone
- Triamcinolone

Caduff C et al. Immediate hypersensitivity reactions to parenteral glucocorticoids? Analysis of 14 cases. Schweiz Med Wochenschr 2000 1;130:977-83.

Anafilassi a farmaco e.v. già assunto per os: è un problema di eccipienti



D-MANNITOLO



MANNA (linfa estratta dalla corteccia del frassino opportunamente incisa)

Jain SS et al. Anaphylaxis following intravenous paracetamol: the problem is the solution. *Anaesth Intensive Care*. 2015;43:779-81.

Effetti antiedemigeni cerebrali



Lightner DD et al. A case of mannitol hypersensitivity. J Pediatr Hematol Oncol. 2013;35:e274-5.



Diagnosi 2016

La spettrometria di massa



Poli C et al. Comparison of two enzymatic immunoassays, high resolution mass spectrometry method and radioimmunoassay for the quantification of human plasma histamine. *J Pharm Biomed Anal.* 2016;118:307-14.

Laboratory tests to be considered in the differential diagnosis of anaphylaxis

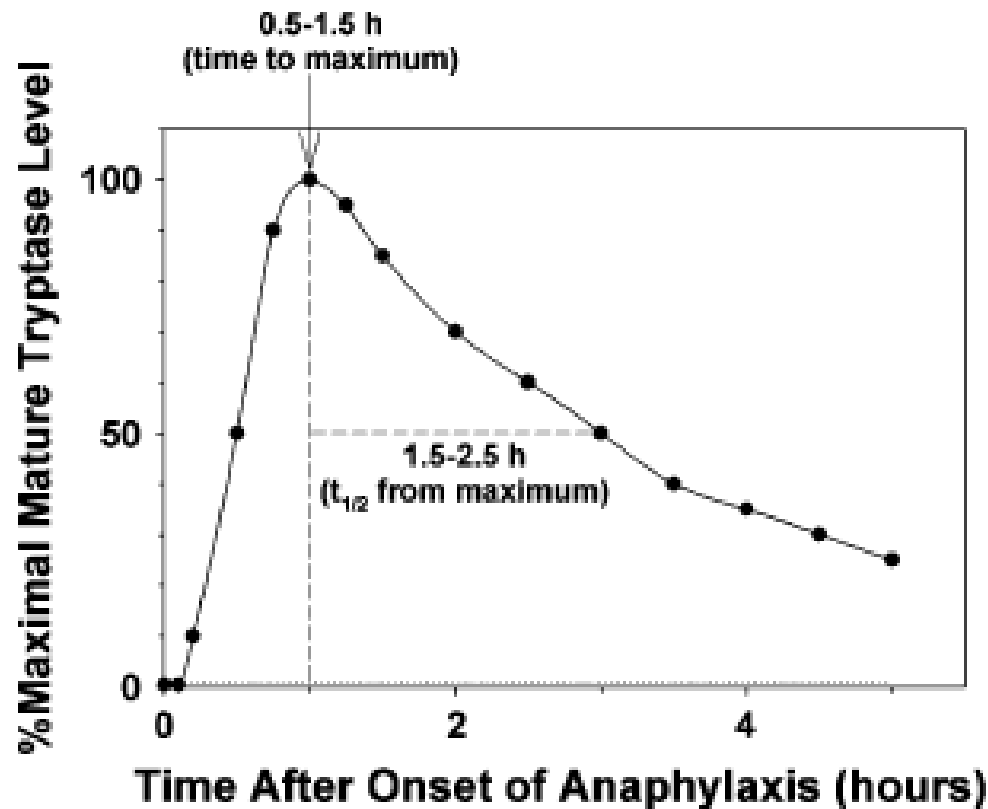
- **Serum tryptase levels**

peak 60-90 minutes after the onset of anaphylaxis and persists to six hours.
- **Plasma histamine levels**

begin to rise within 5-10 minutes and remain elevated only for 30-60 minutes.
- **24-hour urinary histamine (methyl histamine) and its metabolites**

are elevated for a longer period of time – up to 24 hours.

Andamento dei livelli ematici di triptasi: prelievo da 1 a 3 h dopo esordio





- Porcine angiotensin I converting enzyme (ACE I)
- Aminopeptidase N (AP-N).

Hilger C et al. Two galactose- α -1,3-galactose carrying peptidases from pork kidney mediate anaphylactogenic responses in delayed meat allergy. *Allergy*. 2016 Jan 5.

Terapia 2016

Adrenalina in film a rilascio immediato



Alayoubi A et al. Development of a fast dissolving film of epinephrine hydrochloride as a potential anaphylactic treatment for pediatrics. Pharm Dev Technol. 2016;7:1-5.



Abril-Gil M et al. Effect of a cocoa-enriched diet on immune response and anaphylaxis in a food allergy model in Brown Norway rats. *J Nutr Biochem.* 2016;27:317-26.

Conclusioni

- L'Anafilassi deve essere correttamente riconosciuta in base ai criteri internazionali di classificazione.
- La prescrizione dell'autoiniettore di Adrenalina è assoluta in alcuni casi ben specificati
- Solo in casi particolari può essere fatta una doppia prescrizione
- Bisogna continuare a fare educazione sanitaria per ridurre il rischio che l'adrenalina non venga iniettata quando occorre
- La doppia dose nello stesso iniettore, sarà messa in commercio nel nostro Paese nel 2017. Dovrebbe essere prescritta in casi selezionati

Più fra i teenagers

Clinical implications: Acceleration in the rate of increase in food-related anaphylaxis in older children and teenagers has implications for management of FA in these age groups, who are at greatest risk of fatal anaphylaxis.

Prescrizione per autoiniettore

Recommendation	Evidence level	Grade	Key references
Absolute indications for at least one adrenaline auto-injector			
Previous anaphylaxis triggered by food, latex, or aeroallergens	IV	C	(127, 128)
Previous exercise-induced anaphylaxis	IV	C	(58)
Previous idiopathic anaphylaxis	IV	C	(61)
Co-existing unstable or moderate to severe, persistent asthma and a food allergy*	IV	C	(15, 83–86)
Venom allergy in adults with previous systemic reactions (not receiving maintenance VIT) and children with more than cutaneous/mucosal systemic reactions	IV	C	(56, 129, 130)
Underlying mast cell disorders or elevated baseline serum tryptase concentrations together with any previous systemic allergic reactions to insect stings, even in VIT-treated patients	IV	C	(52, 56, 103, 130)
Consider prescribing at least one adrenaline auto-injector with any of the following additional factors (especially if more than one is present)			
Previous mild-to-moderate allergic reaction* to peanut and/or tree nut	IV	C	(51,79)
Teenager or young adult with a food allergy*	IV	C	(22, 45, 46, 63, 131)
Remote from medical help and previous mild-to-moderate allergic reaction to a food, venom, latex, or aeroallergens	V	D	(131); Expert consensus
Previous mild-to-moderate allergic reaction to traces of food*	V	D	(22, 45, 46, 63, 131)

Notes

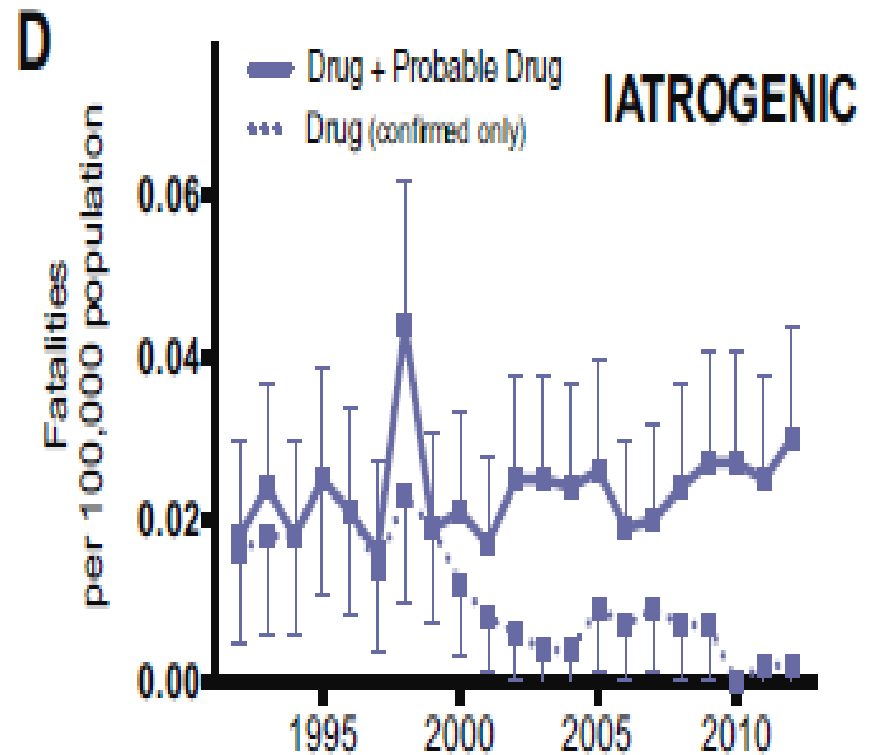
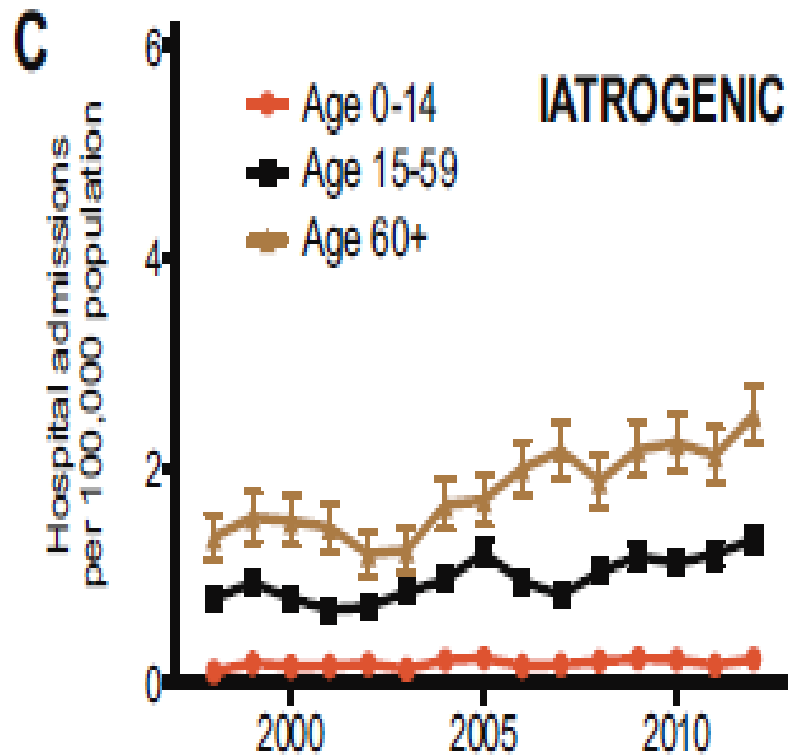
*Excluding pollen food syndrome (oral allergy syndrome).

Muraro A et al. EAACI Food Allergy and Anaphylaxis Guidelines Group. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69:1026-45.

Agaricus arvensis e Agaricus campestris



Ricoveri e decessi per anafilassi da farmaco. Quando la diagnostica migliora i casi calano

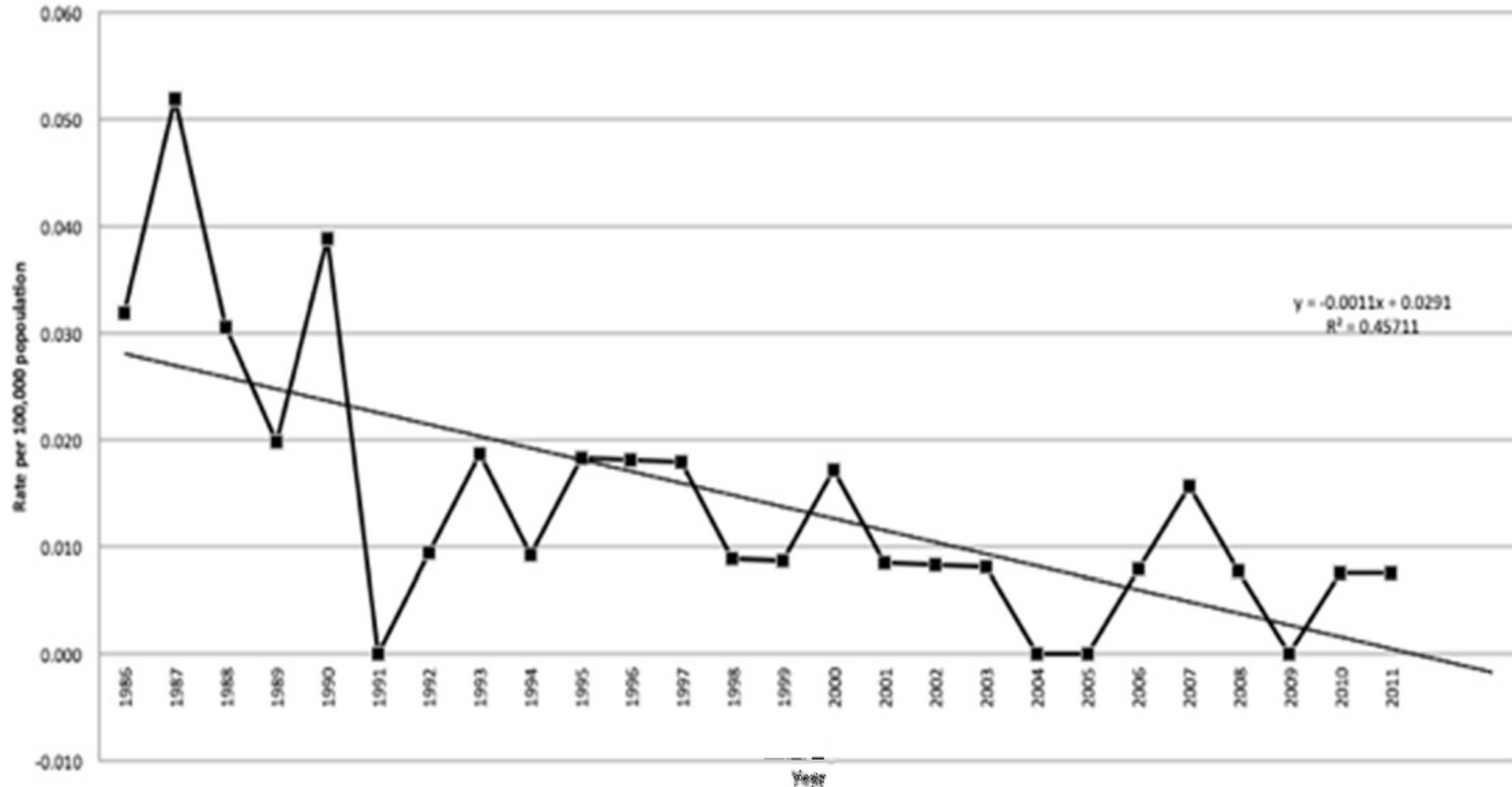


Turner PJ et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol.* 2015 Apr;135(4):956-63.e1.

Ontario: cause di eventi fatali da alimento

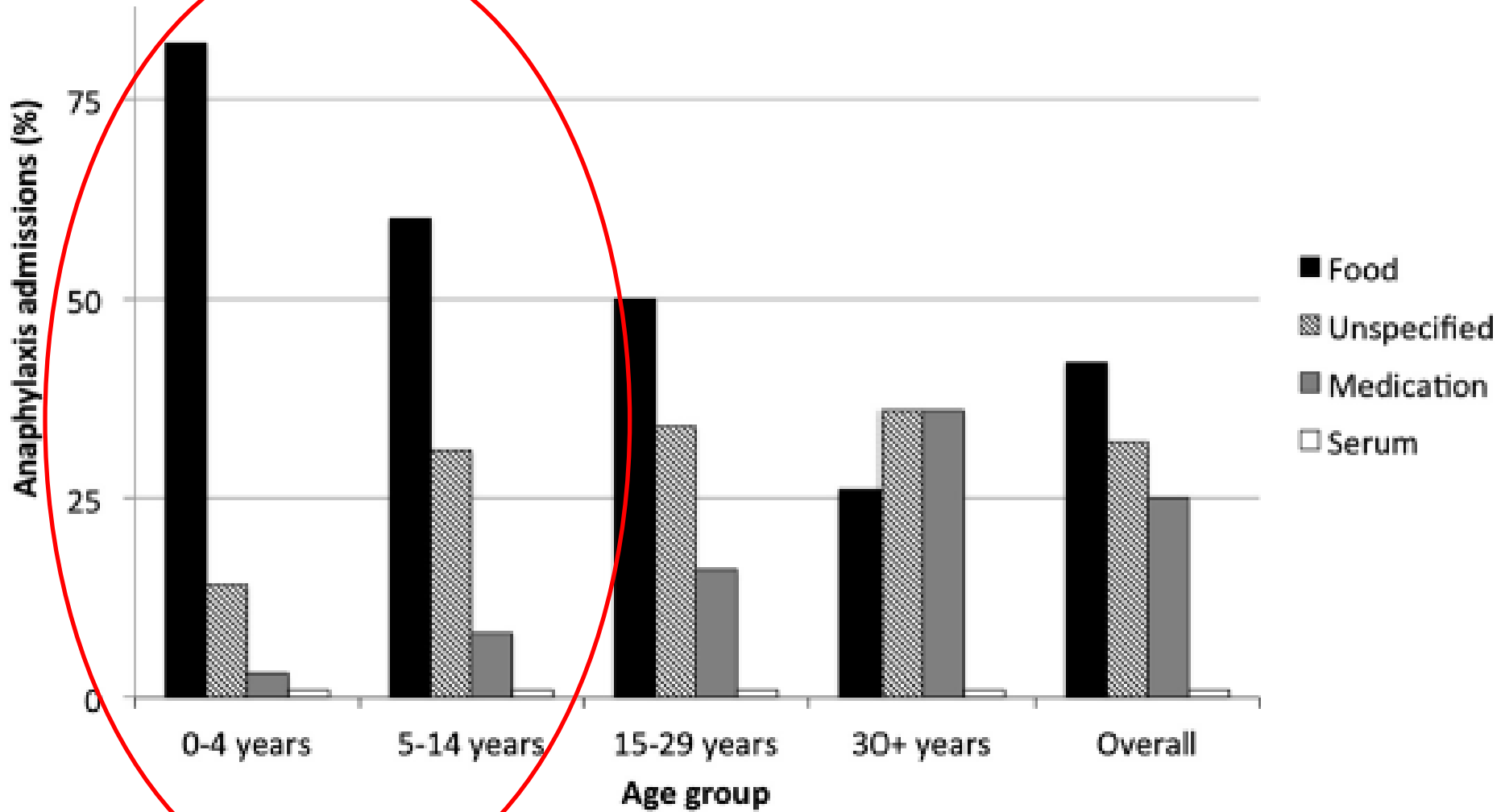
A

Time trend in food anaphylaxis fatalities



Xu YS et al. Anaphylaxis-related deaths in Ontario: a retrospective review of cases from 1986 to 2011. *Allergy Asthma Clin Immunol.* 2014;10:38.

Ricoveri in H per anafilassi in Australia



Mullins RJ et al. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *J Allergy Clin Immunol.* 2015;136:367-75.

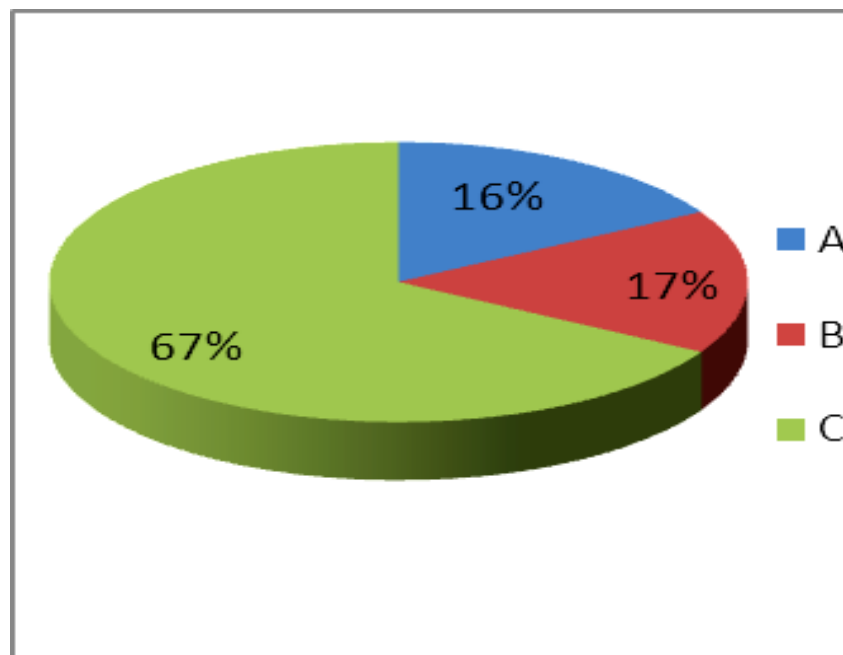
Prurito orale predittore di segni obiettivi durante DBPCFC per PLV

No.	Subjective symptom(s)	(Objective) symptom(s) preceded by OS
1	Transient localized erythema, sensation of pain in throat and mouth (OS)	Generalized pruritus with erythema and scratching, sneezing, rhinoconjunctivitis, dyspnoea
2	Oral pruritus tongue and throat (OS), nausea	Repetitive vomiting, wheezing, dyspnoea
3	Oral pruritus/tingling (OS)	Generalized urticaria
4	Transient localized pruritus face, pain in palate (OS), abdominal pain, nausea	Rhinorrhoea, conjunctivitis
5	Transient localized flushing, oral pruritus (OS)	Sensation of throat tightness, mild dyspnoea
6	Sensation of swelling lip, sensation of pruritus throat (OS), abdominal pain	Repetitive vomiting, rhinorrhoea
7	Oral pruritus tongue (OS)	Change in activity level (fatigue), malaise, pale skin
8	Pruritus throat (OS), abdominal pain	Conjunctivitis, generalized urticaria
9	Transient localized erythema, sensation of pain in mouth (OS)	Repetitive vomiting, generalized urticaria

Kok EE et al. Oropharyngeal symptoms predict objective symptoms in double-blind, placebo-controlled food challenges to cow's milk. *Allergy* 2009;64:1226-7

Quali sono le caratteristiche del paziente ideale?

- A. Anafilattici per tracce o per dosi molto basse
- B. Soggetti con una tolleranza parziale
- C. Entrambi



A	B	C
4	4	16

OR e fallimento precoce o tardivo della SOTI in APLV: non viene mai fatta

Background variable	6-month OIT induction phase OR (95% CI, p-value)	2 years after induction phase OR (95% CI, p-value)
Sex (male)	1.0 (0.2–5.7, p = 0.93)	1.2 (0.3–4.7, p = 0.80)
Asthma	13.7 (1.1–170, p = 0.041)	0.7 (0.2–3.1, p = 0.66)
Allergy to eggs and/or wheat	0.1 (0.03–0.77, p = 0.024)	0.6 (0.1–2.4, p = 0.46)
History of the use of <u>epinephrine</u> due to milk allergy	1.1 (0.2–6.2, p = 0.91)	1.6 (0.4–6.0, p = 0.47)
Age	1.0 (0.8–1.3, p = 0.96)	0.9 (0.7–1.1, p = 0.29)
Milk-specific IgE < 10 IU/L (before OIT)	1	1
Milk-specific IgE 10–100 IU/L (before OIT)	0.9 (0.1–7.1, p = 0.90)	2.0 (0.5–8.3, p = 0.33)
Milk-specific IgE > 100 IU/L (before OIT)	15.7 (1.8–137, p = 0.013)	4.7 (0.6–36.4, p = 0.14)

Kivistö JE et al. Half of the children who received oral immunotherapy for a cows' milk allergy consumed milk freely after 2.5 years. Acta Paediatr 2015;104:1164-8

Bene a 7 anni

Symptoms and rescue treatments	Questionnaire at three years (n = 20)	Questionnaire at four years (n = 17)	Questionnaire at five years (n = 13)	Questionnaire at seven years (n = 16)
Symptoms				
Intestinal	4	3	1	2
Oral	4	4	4	0
Dermal	8	5	3	1
Angioedema	1	0	2	0
Asthma	3	0	2	0
Conjunctival	1	0	0	0
Nasal	0	0	1	0
No symptoms	10 (50.0%)	10 (58.8%)	8 (61.5%)	13 (81.3%)
Treatment for symptoms				
Oral antihistamine	5	5	5	3
Oral corticosteroid	2	1	2	1
Adrenalin injection	1	0	0	0
No treatment for symptoms	15 (75.0%)	12 (70.6%)	8 (61.5%)	13 (81.3%)

Paasilta M et al. Children who were treated with oral immunotherapy for cows' milk allergy showed long-term desensitisation seven years later. *Acta Paediatr.* 2015 Oct 27.

Carne – α -Gal

Triggers

- Le reazioni di tipo ritardato avvengono dopo l'ingestione di carne rossa o frattaglie, cioè manzo, maiale, montone, vitello, cavallo, coniglio, cinghiale, lingua, fegato, rene, intestino, ma non pollo, tacchino o pesce
- I pazienti sono spesso in grado di tollerare piccole quantità di carne senza reazioni; quantità elevate come un doppio hamburger o 2 salsicce (86 g) possono indurre reazioni gravi
- Più la carne è grassa maggiore è il rischio
- Il rene è molto ricco in α -Gal e può indurre reazioni anche con minime quantità e talvolta non ritardate
- Sia la carne cruda che cotta può causare reazioni
- Molti pazienti allergici alla carne sono sensibilizzati alla **gelatina** (contiene α -Gal) che rappresenta quindi un rischio (presente in caramelle, addensanti alimentari, gelati, maionese, yogurt, salame, salsicce)
- α -Gal è contenuta anche nel frammento Fab dell'anticorpo monoclonale **Cetuximab**. È quindi consigliata la verifica di assenza di positività prima della somministrazione
- I co-fattori come le infezioni, l'esercizio fisico, l'alcol, i FANS, possono diminuire la dose di allergene necessaria per scatenare i sintomi



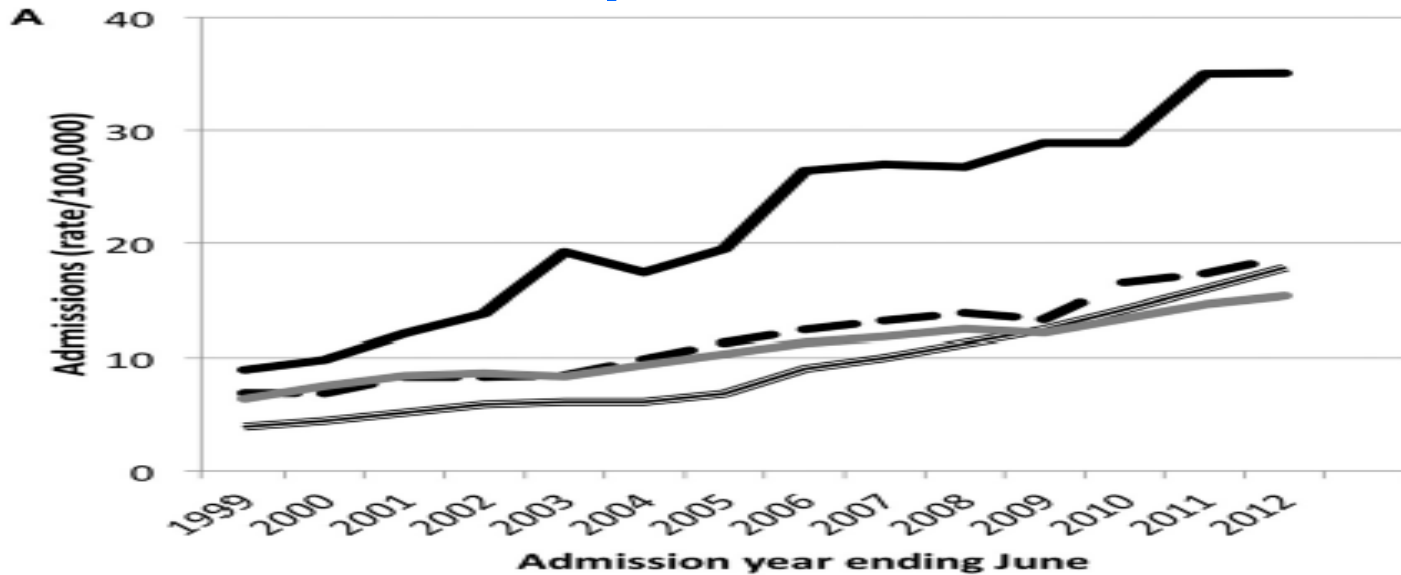
Ricoveri in H per anafilassi in Australia

Observed cases per 10⁶ population (fold increase from previous time point)

Age group (y)	1998-1999	2004-2005	2005-2006	2011-2012
All anaphylaxis				
All ages	6.3	10.6 (1.7)	12.2	17.7 (1.5)
0-4	9.0	19.5 (2.2)	26.4	35.1 (1.3)
5-14	3.9	6.9 (1.7)	9.0	17.8 (2.0)
15-29	6.9	11.3 (1.6)	12.4	18.8 (1.5)
≥30	6.4	10.3 (1.6)	11.3	15.4 (1.4)
Food anaphylaxis				
All ages	2.0	4.5 (2.2)	5.6	8.2 (1.5)
0-4	7.3	16.7 (2.3)	21.7	30.3 (1.4)
5-14	1.7	3.7 (2.1)	5.8	12.1 (2.1)
15-29	2.6	6.1 (2.4)	6.7	10.3 (1.5)
≥30	1.3	2.8 (2.1)	3.4	4.3 (1.3)
Unclassified anaphylaxis				
All ages	2.8	3.5 (1.2)	3.5	5 (1.4)
0-4	1.5	2.4 (1.6)	3.9	0.4 (0.1)
5-14	1.5	2.7 (1.8)	2.5	8.3 (3.3)
15-29	2.9	3.7 (1.3)	3.7	9.2 (2.5)
≥30	3.5	3.7 (1.1)	3.6	14.8 (4.1)
Medication anaphylaxis				
All ages	1.4	2.6 (1.8)	3.1	4.3 (1.4)
0-4	0.2	0.2 (1.0)	0.6	0.1 (0.2)
5-14	0.5	0.3 (0.4)	0.6	2.4 (4.0)
15-29	1.4	1.4 (1.0)	2.1	4.9 (2.3)
≥30	1.8	3.8 (2.1)	4.2	16.4 (3.9)
Serum anaphylaxis*				
All ages	0.06	0.09	3.0	0.15
0-4	0	0.2	1.0	0.03
5-14	0	0.2	0	0.2
15-29	0.02	0.05	8.0	0.3
≥30	0.06	0.07	12	0.4

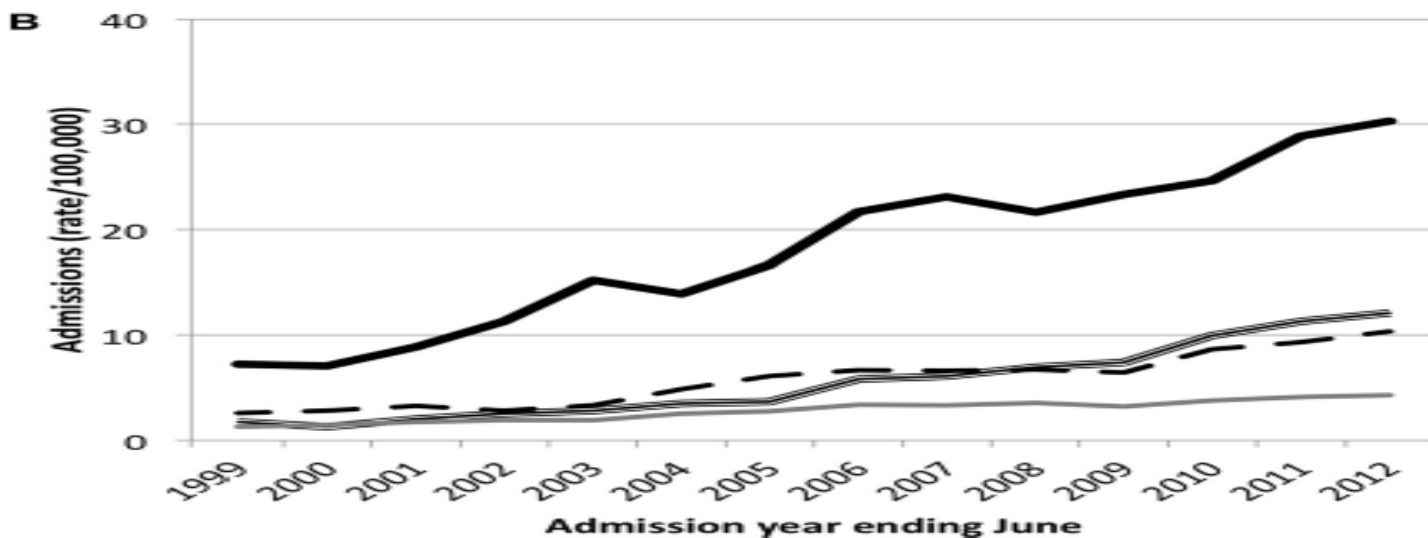
Mullins RJ et al. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. J Allergy Clin Immunol. 2015;136:367-75.

Ricoveri in H per anafilassi in Australia



Anafilassi totali

Anafilassi da alimento



Mullins RJ et al. Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012. *J Allergy Clin Immunol.* 2015;136:367-75.

II release

Parameter	Mast cells	Neurons
Granules	Secretory lysosomes	Specialized secretory granules
Granule size	300–1000 nm	50 nm
Granule number	Up to 1000/cell	200–500/nerve terminal
Ca ²⁺ requirements	1 μ M	200 μ M
PKC requirement	Yes	No
Time frame of exocytosis	Minutes	Milliseconds
Recycling time	Long (hours to days)	Very short (seconds to minutes)
Site of release	Multidirectional ^a	Active zone
Release characteristics	One single release, up to 100% of total granular content; multi-granular/compound mode	Multiple release one granule per fusion event

Blank U. et al. Vesicular trafficking and signaling for cytokine and chemokine secretion in mast cells. *Front Immunol.* 2014;5:453.

Pancake anaphylaxis



Adachi YS et al. A case of mite-ingestion-associated exercise-induced anaphylaxis mimicking wheat-dependent exercise-induced anaphylaxis. *Int Arch Allergy Immunol* 2013;162:181-3.

Indicazioni assolute

- Farmaci?
- Idiopatiche in generale o perché non capiamo noi?
- Asma persistente

Caso fatale a Messina

Tryptase can even be measured from a blood sample taken from any person who has died of the anaphylactic shock.

In the normal condition, the level of **tryptase** circulating in serum is at or close to zero.

Calapai G et al. Fatal Anaphylactic Shock Ceftriaxone-Induced in a 4-Year-Old Child. *Pediatr Emerg Care*. 2016;32:32-3.

Riduzione rischio di esposizione in FA

- Young children with FA ideally should only consume food provided by parents/guardians from home.
- Bottles, other drinks and lunch boxes provided by the parents for their children with FA should be clearly labelled with the name of the child for whom they are intended. This is of particular importance in infants with cows milk allergy to minimise consumption of incorrect baby formula.
- If food is purchased from the school canteen, parents should check the appropriateness of foods by speaking directly to the canteen manager.
- Where food is provided in OOHC settings, food preparation personnel should be educated about how to read labels for FA and instructed about measures necessary to prevent cross-contamination during the handling, preparation and serving of food. Examples include preparing food for children with FA first, careful cleaning (using warm soapy water) of food preparation areas after use and cleaning of utensils when preparing allergenic foods.
- Food should not be given to children with FA in childcare and primary school without parental engagement and permission (e.g. birthday parties, food treats).
- Where food needs to be consumed inside the classroom (e.g. lunches consumed inside classrooms on rainy days), the risk of accidental exposure to the allergic child should be minimised.
- Implement policies to avoid trading and sharing of food, food utensils or food containers.
- Unlabeled food poses a potentially greater risk of allergen exposure than packaged food with precautionary labelling suggesting a risk of contamination with allergen.
- Use of food in crafts, cooking classes, science experiments and special events (e.g. fetes, BBQs, assemblies, cultural events) needs to be considered and may need to be restricted depending on the allergies of particular children and their age.
- In craft, an appropriate alternative ingredient can be substituted (e.g. wheat-free flour for play dough or cooking) and substitution of non-food containers for egg cartons, particularly in younger children.
- When planning for out-of-school activities such as excursions (e.g. restaurants and food processing plants), or school outings or camps, catering requirements of the food allergic child and emergency planning (including access to emergency medication and medical care) should be considered early.

Vale S et al. ASCIA guidelines for prevention of anaphylaxis in schools, pre-schools and childcare: 2015 update. *J Paediatr Child Health*. 2015;51:949-54.

Multiplex CRD nell'anafilassi idiopatica?

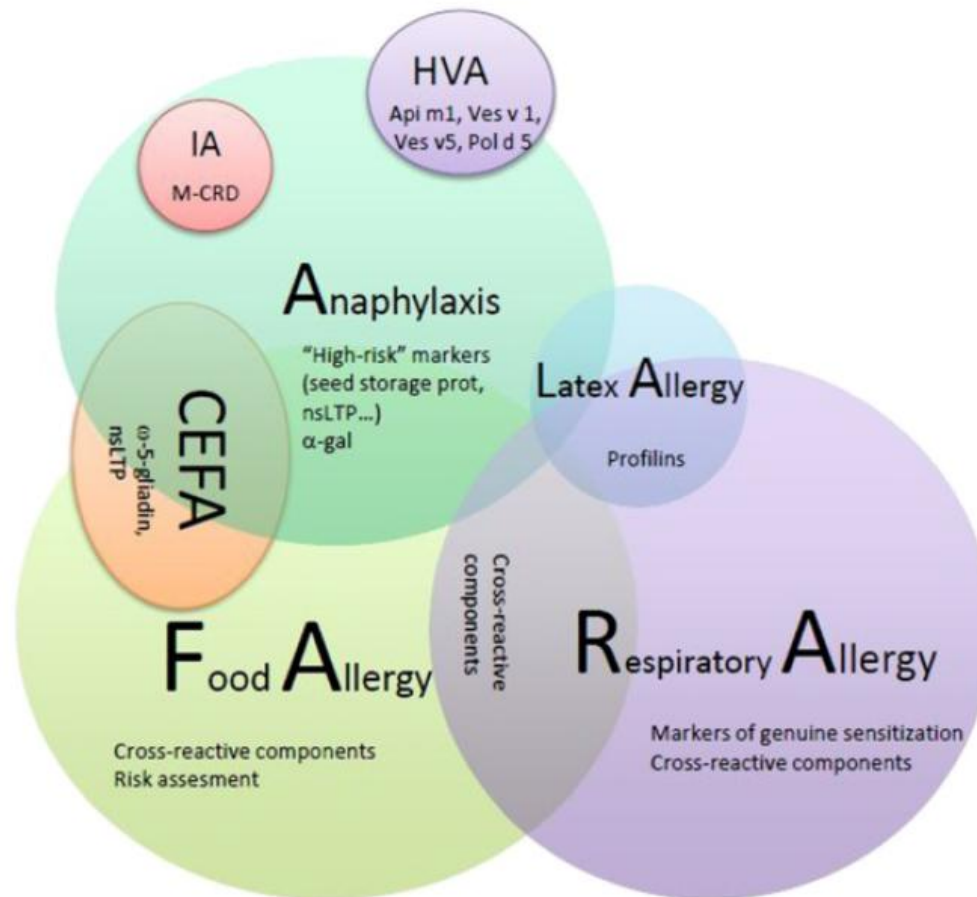


Figure 5 Hypothetical scheme representing the potential use of CRD. Represented by spheres are the allergic conditions in which molecular diagnosis may be of potential value, illustrating the potential overlap between different clinical reactions. Recommended components to be tested are listed; multiplexed CRD would be of special interest in idiopathic anaphylaxis and polysensitized patients. CEFA: cofactor-enhanced food allergy; HVA: hymenoptera venom allergy; IA: idiopathic anaphylaxis; M-CRD: multiplex CRD; nsLTP: non-specific lipid transfer proteins.

Le considerazioni

- Several hours: anafilassi tardiva alla carne rossa
- Orticaria + edema dell'ugola: un solo apparato
- Compromissione respiratoria: deve esserci una sintomatologia severa
- SNC ipotonia e rilascio degli sfinteri
- I disturbi gastrointestinali sono persistenti

La diagnosi differenziale

Common diagnostic dilemmas	Flush syndromes
Acute asthma ^a	Peri-menopause
Syncope (faint)	Carcinoid syndrome
Anxiety/panic attack	Autonomic epilepsy
Acute generalized urticaria ^a	Medullary carcinoma of the thyroid
Aspiration of a foreign body	
Cardiovascular (myocardial infarction ^a , pulmonary embolus)	Nonorganic Disease
Neurologic events (seizure, cerebrovascular event)	Vocal cord dysfunction
	Hyperventilation
	Psychosomatic episode
Postprandial syndromes	
Scombroidosis ^b	Shock
Pollen-food allergy syndrome ^c	Hypovolemic
Monosodium glutamate	Cardiogenic
Sulfites	Distributive ^d
Food poisoning	Septic
Excess endogenous histamine	Other
Mastocytosis/clonal mast cell disorders ^e	Nonallergic angioedema
Basophilic leukemia	Hereditary angioedema types I, II, & III
	ACE inhibitor-associated angioedema
	Systemic capillary leak syndrome
	Red man syndrome (vancomycin)
	Pheochromocytoma (paradoxical response)

Anaphylaxis is a under recognized disease

- First episode
 - Trigger not apparent, hidden or not previously recognized
 - Idiopathic anaphylaxis

 - Failure to recognize (by patient or caregiver) because of:
 - Cognitive, visual or auditory impairment
 - Neurologic, psychiatric, or psychologic problems
 - Use of medications, including sedating H₁ antihistamines or recreational drugs, or use of ethanol

 - Failure to diagnose (by health care professional) because of:
 - Absence of skin symptoms and signs
 - Patient not undressed or fully examined
 - Vulnerable person: infant, elderly

 - Patient who cannot describe subjective symptoms because of being:
 - Aphonic or disphonic
 - Dyspneic
 - Unconscious
 - Reporting of serious or fatal anaphylactic events is not mandatory
- Simons FE. J Allergy Clin Immunol 2008;122:1166-8.

Overdiagnosis of anaphylaxis

- Subjective symptoms only

- Nonspecific signs

- Diagnostic error

Hyperventilation

Anxiety

Panic attack (difficulty breathing)

Vasovagal episode (faint)

Munchausen syndrome or by proxy (in children)

Scombroidosis

Anisakiasis

Administration of epinephrine for life - threatening allergic reactions in school settings

In 24% of the cases, the individual was not known to have a life-threatening allergy.



McIntyre CL. Pediatrics 2005;116:1134-40.

Definizione di anafilassi idiopatica

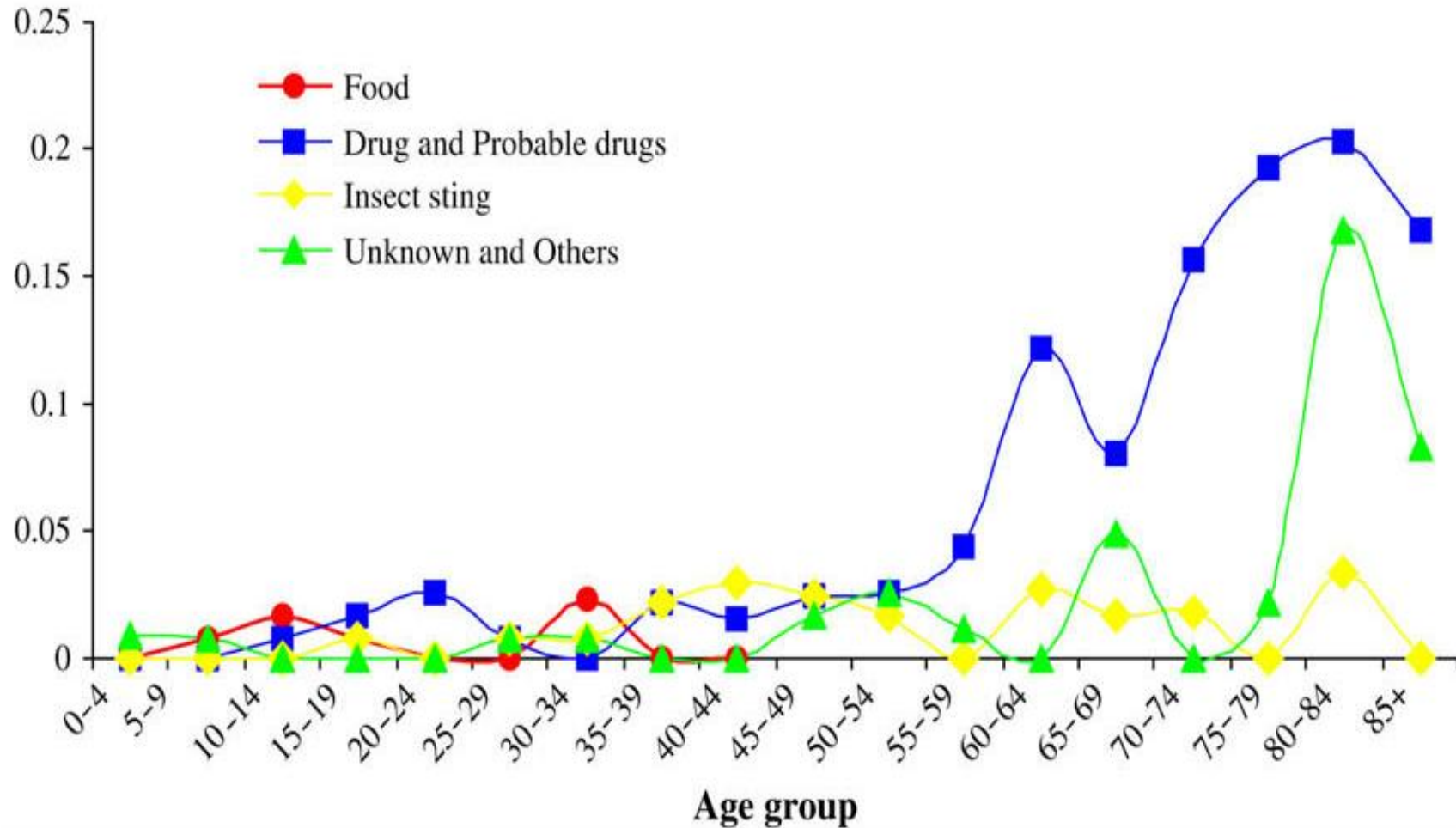
- L'anafilassi idiopatica è un'anafilassi non spiegata da una causa comprovata o presunta.
- Diventa una diagnosi di esclusione, dopo aver eliminato altre cause come ad esempio alimenti, farmaci, esercizio fisico, alimento + esercizio fisico, punture di insetti, mastocitosi, e deficit o ipoattività del C1 inibitore

La classificazione dell'anafilassi idiopatica

Terminology	Objective evidence for anaphylaxis
Idiopathic anaphylaxis—generalized	Yes
Idiopathic anaphylaxis—angioedema	Yes
Corticosteroid-dependent idiopathic anaphylaxis	Yes
Malignant idiopathic anaphylaxis	Yes
Undifferentiated somatoform idiopathic anaphylaxis	No ^a

Greenberger PA. Idiopathic anaphylaxis. *Immunol Allergy Clin North Am.* 2007; 27:273-93.

Cause di morte per anafilassi per età



L'identikit del paziente con anafilassi idiopatica

- Circa 10-60% di tutti i casi di anafilassi (rara nel bambino)
- Rapp. F/M 2:1
- Nel 35% dei casi notturna
- Sintomi cutanei presenti in \approx 100% dei casi
- Alta incidenza di associazione con anafilassi da causa nota e OC idiop.
- Recidive frequenti
- Frequente remissione spontanea entro alcuni anni
- Rari coinvolgimento cardiovascolare e fatalità
- Generalmente responsiva ai glucocorticoidi
- D.D. con molte patologie (in primis mastocitosi)

Ditto, AAI 1996;77:285

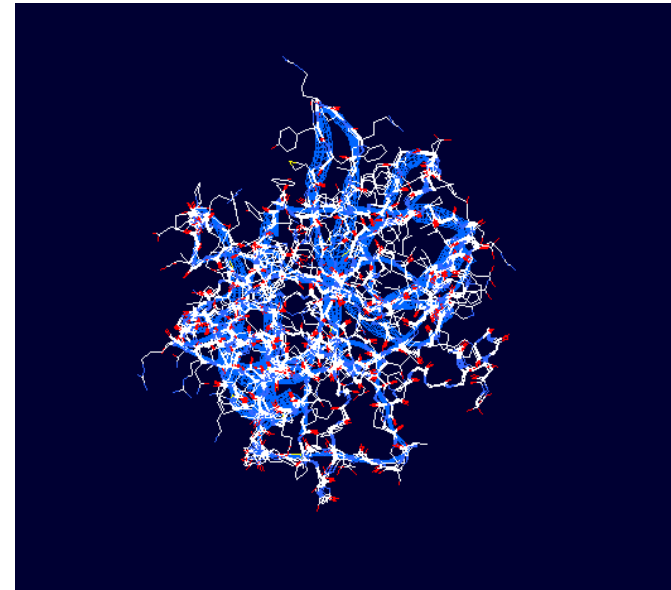
Ditto, JACI 1997;100:320

Tejedor-Alonso, AAI 2002;88:313

Greenberger, JACI Pract 2014;2:243

Tryptase levels

- **β tryptase precursors** seem to be continuously secreted by human mast-cells, with their levels in blood typically reflecting the burden or number of mast-cells.
- Mature tryptase (β - tryptase) is stored in in secretory granules and is secreted only during granule exocytosis, reflecting mast-cell activation.



Diagnostic Value of Tryptase in Anaphylaxis and Mastocytosis

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Table 1
Mature and total tryptase levels

Clinical condition	Tryptase levels (ng/mL)		Tryptase ratio (total/mature)
	Total	Mature	
Normal	1–15	<1	Not applicable
Systemic anaphylaxis (acute)	> Baseline	>1 ^a	<10
Systemic mastocytosis (nonacute)	>20 ^b	<1 to small elevations	>20

^a Level related to clinical severity (hypotension), timing of sample collection in relation to onset of signs and symptoms, and nature of the anaphylactic stimulus.

^b Speculated to reflect primarily the total body burden of mast cells.

Tanner A et al. Epinephrine Policies and Protocols Guidance for Schools:
Equipping School Nurses to Save Lives. NASN Sch Nurse. 2016;31(1):13-22.

Dal lavoro di Ondansentron

The incidence of anaphylaxis in anaesthesia has been estimated at between 1:10 000 and 1:20 000.^{1,2} It can be a very challenging condition to manage and is fatal in 10% of cases.

errors.⁵ In a Scandinavian study,⁶ 42 anaesthetists were tested on a high fidelity simulator and not one made the diagnosis of anaphylaxis within 10 min.

6 Jacobsen J, Lindekær AL, Østergaard HT, *et al.* Management of anaphylactic shock evaluated using a full-scale anaesthesia simulator. *Acta Anaesthesiol Scand* 2001; 45:315–319.