# **Anaphylaxis**: Mechanisms and management

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## Anaphylaxis

- Epidemiology
- Clinical features
- Morbidity/Mortality
- Pathophysiology
- Management
  - Acute
  - Long term (prevention)
  - Pitfalls

## A[na]phylaxis

- Originates from Greek, meaning against or without protection.

  *As opposed to prophylaxis for protection*

- A rapidly evolving, generalised multi-system reaction characterized by one or more symptoms or signs of respiratory, cardiovascular and other systems such as the skin and/or gastrointestinal tract.

ASCIA

## WAO Definition



**TABLE 1.** Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING:
   A) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   B) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg. hypotonia [collapse], syncope, incontinence) OR
2. Two or more of the following that occur rapidly after exposure to *a likely allergen*[a] *for that patient* (minutes to several hours)
   A) Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
   B) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   C) Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   D) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting) OR
3. Reduced blood pressure after exposure to *known allergen*[b] for that patient (minutes to several hours)
   A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure[c]
   B) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF: peak expiratory flow.
[a]Or other trigger, for example, immunologic but IgE-independent, or nonimmunologic (direct) mast cell activation.
[b]For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or, in a similar example, during allergen immunotherapy, after injection of a known allergen for that patient, generalized urticaria (only one body organ system affected) might be the only initial manifestation of anaphylaxis.
[c]Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80–140 beats/min at age 1–2 years; from 80–120 beats/min at age 3 years; and from 70–115 beats/min after age 3 years. Infants are more likely to have respiratory compromise than hypotension or shock, and in this age group, shock is more likely to be manifest initially by tachycardia than by hypotension.
Clinical criteria 1, 2, and 3 are taken from reference 2.
References 33 and 34 support footnotes b and c, respectively.

## Epidemiology

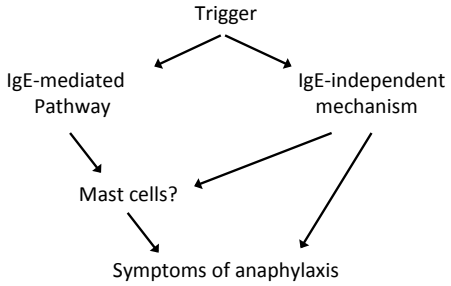
- Uncommon
- Incidence:
  8.4 - 21 per 100,000 patient years[1]
- Australian parents report 1:170 children have had one episode of anaphylaxis[2]

[1]Brown et al., MJA (2007); Sampson et al. JACI (2005)
[2]Boros et al., J Paediatr Child Health (2000)

## Causes

- Foods (most common in children)
- Insect Stings
- Latex
- Drugs; Anaesthetic Agents; IV Contrast
- Seminal Fluid
- Exercise
- Idiopathic

## Pathophysiology




## Pathophysiology

IgE mediated:

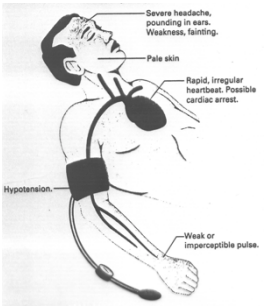
- **Haptens:**
  - **Penicillins, Antibiotics (most)**
- **Complete Antigens:**
  - **Venoms, Allergen extracts**
  - **Food**
  - **Insulin**
  - **IVIg**
  - **Others…**

IgE-independent / non-allergic:

- **Non-immune mast cell activators**
  - Radiocontrast, opiates, neuromuscular relaxants
- **Complement-mediated (anaphylatoxins)**
  - **Blood Tx, IgA deficiency**
- **Modulators of arachidonic acid metabolism**
  - **NSAIDs**
- **Other:**
  - **exercise, idiopathic**

## Clinical Manifestations

- Skin:
  - Flushing
  - Pruritus
  - Urticaria
  - Angioedema
- Cardiovascular system:
  - Tachycardia (bradycardia)
  - Hypotension/shock (Pale/floppy child)
  - Arrhythmias
  - Ischaemia, chest pain




- Upper respiratory:
  - Congestion
  - Rhinorrhoea
  -
- Lower respiratory:
  - Throat/chest tightness
  - Hoarseness
  - Bronchospasm
  - Wheeze, cough
- Gastrointestinal tract:
  - Oral pruritus
  - Cramps, nausea, vomiting, diarrhoea


## Frequency of Manifestations

| | |
|---|---|
| • Cutaneous | 90% |
| – Urticaria and Angioedema | 85-90% |
| – Flushing | 45-55% |
| • Respiratory | 40-60% |
| – Dyspnea and Wheeze | 45-50% |
| – Laryngeal Angioedema | 50-60% |
| – Rhinitis | 25-20% |
| • Dizziness, syncope, hypotension | 30-35% |
| • Abdominal (n+v, colic, diarrhoea) | 25-30% |

Lieberman P et al JACI 2005;115(3):S483-S523

## Mortality

- **About 1 per 1 - 3 million population p.a.**
- **In ED: 1 per 100-200 episodes**
- Approx 20-30 deaths p.a. in UK, probably an underestimate.
- Most due to medication or blood Tx, sometimes to insect stings, rarely to food.

Brown et al., MJA (2007)

## UK causes of fatal anaphylaxis

| | | |
|---|---|---|
| Sting | 47 | 29 wasp, 4 bee, 14 unidentified |
| Nuts | 32 | 2 almond, 2 brazil, 1 hazel, 10 peanut, 6 walnut, 11 mixed or unidentified nuts |
| Food | 13 | 1 banana, 2 chickpea, 2 fish, 5 milk, 2 crustacean, 1 snail |
| Food? | 18 | 1 ?fish, 5 during meal, 1 ?grape, 3 ?milk, 3 ?nut, 1 ?sherbet, 1 ?strawberry, 1 ?yeast, 1 ?nectarine |
| Antibiotic | 27 | 1 benzypenicillin, 10 aminopenicillin, 12 cephalosporin, 1 ciprofloxacin, 1 vancomycin, 2 amphoteracin |
| Anaesthetic | 35 | 19 suxamethonium, 7 vecuronium, 6 atracurium, 7 at induction |
| Other drug | 15 | 3 ACE inhibitor, 6 NSAID, 5 gelatines, 2 protamine, 2 vitamin K, 1 diamox, 1 etoposide, 1 pethidine, 1 heroin, 1 kabikinase, 1 local anaesthetic |
| Contrast media | 11 | 9 iodinated, 1 technetium, 1 fluorescine |
| Other | 4 | 1 latex, 1 hair dye, 1 hydatid, 1 idiopathic |

## Mortality

Anaphylaxis is not uncommon,

but death from anaphylaxis is very rare.

Brown et al., MJA (2007)

## Risk factors for death from food-induced anaphylaxis

- Trigger: Peanut / tree nut / fish most common
- Asthma (even well controlled), cardiac disease
- Mastocytosis
- Previous allergic reaction to same food
- Biphasic course
- Not at home when reaction occurs
- Non-timely delivery of adrenaline *but mortality not prevented by early adrenaline alone*

Sampson et al, NEJM (1992)
Pumphrey, Curr Opin Allergy Clin Immunol. (2004)

## Risk assessment

Who is at risk of anaphylaxis?

- Previous anaphylaxis?
- In patients with previous mild reactions,
  44-80% of subsequent reactions are severe[1,2]
- sIgE / SPT do not predict severity
  (CRD may prove to be more useful)

➢ **Can thresholds be useful?**

Are patients who react to minimal doses of allergen more likely to develop anaphylaxis?

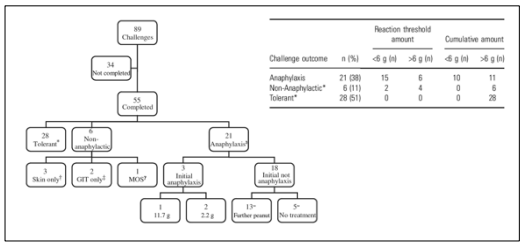
1 2



PEDIATRIC ALLERGY AND IMMUNOLOGY

Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level

Bryon Kevin Wainstein[a,f], Jennie Studdert[b], Mary Ziegler[c] and John B. Ziegler[d,e]
[a]Department of Immunology and Infectious Diseases, Sydney Children's Hospital, High Street, Randwick, Sydney, New South Wales, Australia, [b]School of Women's and Children's Health, University of New South Wales, Sydney, New South Wales, Australia




| | | Reaction threshold amount | | Cumulative amount | |
|---|---|---|---|---|---|
| Challenge outcome | n (%) | <6 g (n) | >6 g (n) | <6 g (n) | >6 g (n) |
| Anaphylaxis | 21 (38) | 15 | 6 | 10 | 11 |
| Non-Anaphylactic* | 6 (11) | 2 | 4 | 0 | 6 |
| Tolerant* | 28 (51) | 0 | 0 | 0 | 28 |

21/27 children with +ve OFC developed anaphylaxis:

- 3 as initial symptom
- 13 with subsequent peanut exposure.

Threshold dose for peanut: Risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals

Steve L. Taylor[a,*], D.A. Moneret-Vautrin[b], Rene W.R. Crevel[c], David Sheffield[d], Martine Morisset[b], P. Dumont[b], Benjamin C. Remington[a], Joseph L. Baumert[a]

Food and Chemical Toxicology 48 (2010) 814–819

$ED_{10}$ doses* for whole peanut as assessed by the log-normal probability distribution model for Severity Grade.

| Severity grade | Total no. of peanut-allergic individuals | $ED_{10}$ | 95% CI |
|---|---|---|---|
| Severe[a] | 40 | 10.4 | 4.8, 22.6 |
| Non-severe[b] | 123 | 10.2 | 6.4, 16.1 |
| No prior history[c] | 123 | 27.0 | 17.4, 42.0 |

All values reported in mg whole peanut.
* Statistically valid $ED_{05}$ estimates could not be provided due to the limited number of subjects in all of the severity grade classes.
[a] Severe reactions include three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension.
[b] Non-severe reactions include one or two organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, non-laryngeal angioedema, and/or mild asthma (peak flow rate <80%).
[c] History of prior allergic reactions and severity of reactions were not available.

NB: Subjects with prior severe reactions were not excluded.

## Risk assessment

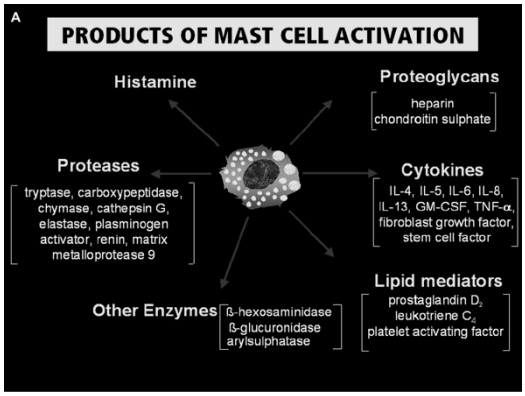
Predicting severity…

- Previous anaphylaxis ?
- Up to ¾ of peanut-allergic children will experience anaphylaxis if given sufficient dose
- Patients with anaphylaxis do not appear to be more sensitive i.e. same threshold

## MECHANISMS OF ANAPHYLAXIS

## Mast Cells

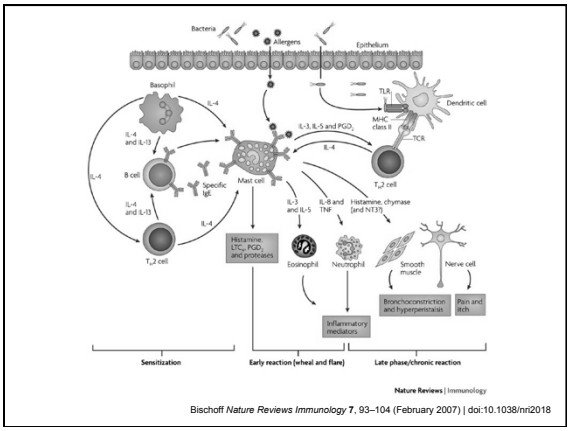
- Originate in the bone marrow, reside in connective tissues where they mature
- Increase host response to parasitic infections
- Contain immunological mediators in granules
- 2 populations that vary in granule content and activity:
  - Connective tissue
  - Mucosal
- Has high affinity for IgE molecules (105 IgE/cell)



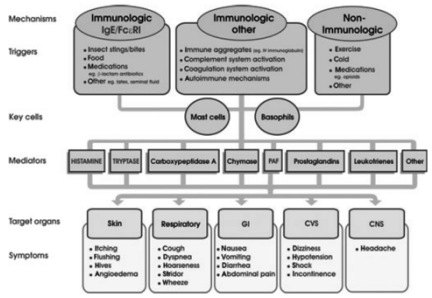

## Histamine

- Coronary vasoconstriction
- Bronchoconstriction
- Vascular permeability
- Intestinal smooth muscle contraction
- Increased secretion of gastric and mucosal cells
- Dysrhythmias

But histamine receptor blockade does not prevent anaphylaxis in man



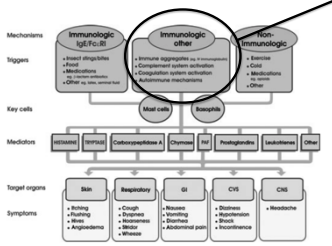

Bischoff *Nature Reviews Immunology* **7**, 93–104 (February 2007) | doi:10.1038/nri2018

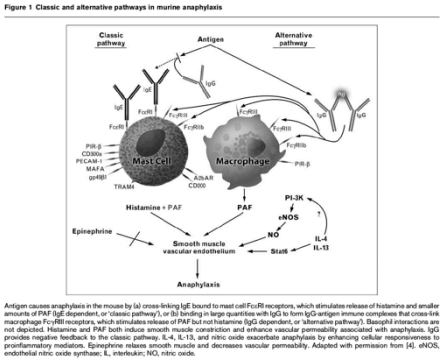



(Simons, 2011)

## Gaps in knowledge…

IgE-independent mechanisms in murine models of anaphylaxis…

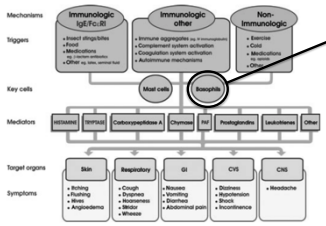





Antigen causes anaphylaxis in the mouse by (a) cross-linking IgE bound to mast cell FcεRI receptors, which stimulates release of histamine and smaller amounts of PAF (IgE dependent, or 'classic pathway'), or (b) binding in large quantities with IgG to form IgG-antigen immune complexes that cross-link macrophage FcγRIII receptors, which stimulates release of PAF but not histamine (IgG dependent, or 'alternative pathway'). Basophil interactions are not depicted. Histamine and PAF both induce smooth muscle constriction and enhance vascular permeability associated with anaphylaxis. IgG provides negative feedback to the classic pathway. IL-4, IL-13, and nitric oxide exacerbate anaphylaxis by enhancing cellular responsiveness to proinflammatory mediators. Epinephrine relaxes smooth muscle and decreases vascular permeability. Adapted with permission from [4]. eNOS, endothelial nitric oxide synthase; IL, interleukin; NO, nitric oxide.

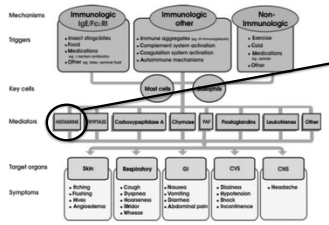
(Khan & Kemp, 2011)

## Gaps in knowledge…



- Mostly evidence from animal models
- Limited evidence of recruitment into airways after allergen challenge in man
- Increase in activated basophils in anaphylaxis following insect sting challenge in man
- Utility in Dx - BHT
- ?role in FA: bystander or contributor?

## Gaps in knowledge…



What other mediators are involved?

Antihistamines do not prevent severe allergic reactions in man

Antihistamines combined with PAF antagonist protect against murine PSA in some models

## PAF and Severe Anaphylaxis

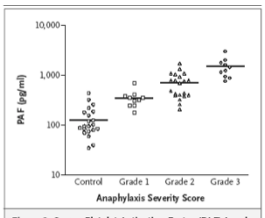



**Figure 2. Serum Platelet-Activating Factor (PAF) Levels as a Function of Anaphylaxis Severity Score.**
Untransformed values are plotted on a log scale.

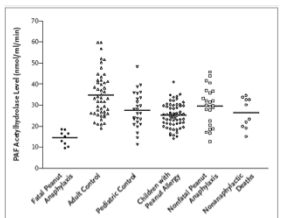
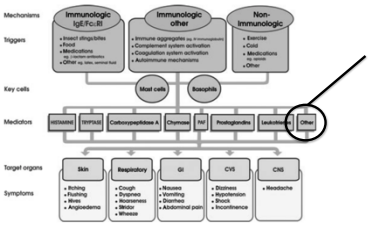



Figure 4. **Levels of Serum Platelet-Activating Factor (PAF) Acetylhydrolase Activity in Patients with Fatal Peanut Anaphylaxis and in Five Comparison Groups.**

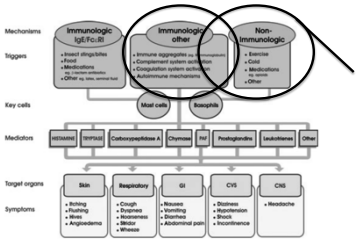
Vadas P et al. NEJM 2008;358:28-35

## Gaps in knowledge…




- Kinins
- Complement
- NO
- Cytokines

## Gaps in knowledge…



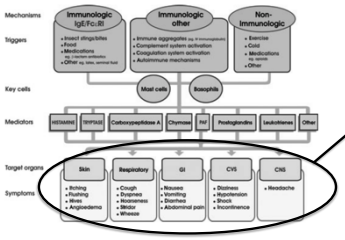

- Do external factor such as exercise and sleep deprivation interact with immunological interface?
- Or is this effect purely mediated through physiological means e.g. changes in GI permeabilty

| | Extrinsic factors | | | | | | |
|---|---|---|---|---|---|---|---|
| Subject # | Infection or other intercurrent illness | Exercise | Tiredness | Anxiety | Aero-allergen co-exposure | Menstruation | Total number of episodes | Symptoms |
| 1 | | 1 | | | 2 | | 3 | RC, W |
| 4 | 1 | | 3 | 1 | | | 5 | OI, W, SOB |
| 5 | | | 1 | | | | 1 | OI |
| 6 | 1 | 1 | >5 | | | | >5 | AP, V, A |
| 7 | | | 5 | | | | 5 | AP, RC, OI |
| 12 | | | | 1 | | | 1 | AP, W |
| 14 | 4 | | | | | | 4 | OI, AP, W |
| 15 | >5 | | | | | | >5 | OI |
| 17 | 1 | | >5 | | | | >5 | AP, N |
| 19 | 1 | 4 | 2 | | | | >5 | W, V |
| 20 | >5 | | 2 | >5 | | | >5 | OI, AP |
| 21 | >5 | | 1 | | | 3 | >5 | AP,U,W |

Subjects experiencing transient symptoms due to extrinsic factors (infection/underlying illness, exercise, tiredness, anxiety, aeroallergen exposure), total number of episodes of reactions with extrinsic factors for each subject and symptoms occurring during those episodes. 'Tiredness' is defined by reduced sleep duration on the previous night/nights. Subject 21 had three episodes of reaction during three consecutive menstrual periods.
OI, oral itching; AP, abdominal pain; W, wheeze; N, nausea; V, vomiting; A, angioedema; RC, rhinoconjunctivitis; U, urticaria; OIT, oral immunotherapy.

Anagnostou et al, 2009

## Gaps in knowledge…

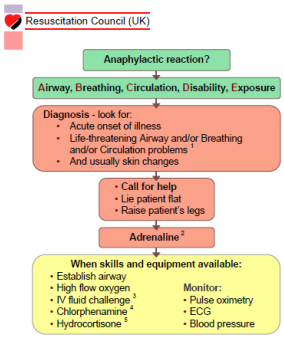



What is the effect of an allergic response to food on the vasculature?

Local vs systemic?

| Murine models | | Human |
|---|---|---|
| 10-30% | **Neutrophils in peripheral blood** | 50-70% |
| Monomeric, low serum levels | **IgA** | Mono- & dimeric, abundant in serum |
| + | **Presence of IgE** | + |
| + | **FceRI on mast cells and basophils** | + |
| No | **FceRI on macrophages and Langerhans cells** | + |
| + | **FcgRIIb on mast cells** | + |
| + | **FcgRIII on macrophages** | + |
| No | **Presence of FcgRIIA, FcgRIIIA, and FcgRIIIC** | + |
| + | **Mast cell production of histamine** | + |
| + | **Sensitivity to histamine** | ++++ |
| + | **Macrophage production of PAF** | + |
| + (weak) | **Activation of mast cells by IgG** | No |
| + | **IgE binding to FcgRIIb and FcgRIII** | + |
| Relatively high doses: 200mg (=1000 peanuts!) | **Oral induction of anaphylaxis** | Very low doses - mgs |

## MANAGEMENT



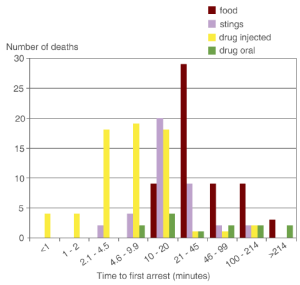

## Pitfalls in management

1. Recognition
2. Biphasic reaction
3. Failure to treat refractory anaphylaxis aggressively
4. Inappropriate use of drugs
5. Suboptimal management at/after discharge

## 1) Recognition

| MILD TO MODERATE ALLERGIC REACTION |
|---|
| • swelling of lips, face, eyes<br>• hives or welts<br>• tingling mouth<br>• abdominal pain, vomiting (these are signs of a severe allergic reaction to insects) |
| **ANAPHYLAXIS (SEVERE ALLERGIC REACTION)** |
| • difficult/noisy breathing<br>• swelling of tongue<br>• swelling/tightness in throat<br>• difficulty talking and/or hoarse voice<br>• wheeze or persistent cough<br>• loss of consciousness and/or collapse<br>• pale and floppy (young children) |

**All fatal food-induced anaphylactic reactions cause respiratory difficulties**




Time to respiratory / cardiac arrest following exposure to trigger
(Data from Pumphrey, *Clin Exp Allergy* 2000;30:1144-50.)

## 2) Biphasic reactions...

- May appear within seconds, or as late as 2 hours after ingestion of trigger food.
- Up to one third have a biphasic reaction.
- Initial symptoms → apparent resolution
  → recurrence of symptoms after 1-3 hours
- Observe for <u>minimum</u> 4-6 hours in hospital
  - 90% of biphasic reactions occur within 4 hrs[1]
  - Caution in those with severe asthma, previous biphasic reactions, geographical isolation

[1]Lee et al, Pediatrics 2000.

## Risk factors for biphasic reaction

- >1 dose adrenaline[1]
- Fluid bolus[1]

- Delayed administration of adrenaline[2]
- ? use of subcutaneous adrenaline[2]

[1]Mehr et al. Clin Exp Allergy 2009 39:1390.
[2]Lee & Greenes, Pediatrics 2000 106:762.

## 3) Failure to treat refractory anaphylaxis aggressively

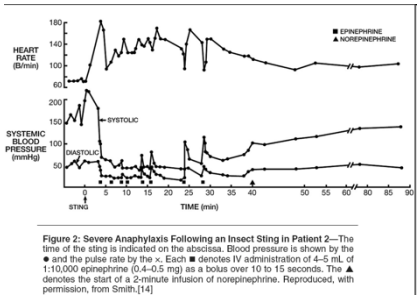



**Figure 2: Severe Anaphylaxis Following an Insect Sting in Patient 2**—The time of the sting is indicated on the abscissa. Blood pressure is shown by the ● and the pulse rate by the ×. Each ■ denotes IV administration of 4–5 mL of 1:10,000 epinephrine (0.4–0.5 mg) as a bolus over 10 to 15 seconds. The ▲ denotes the start of a 2-minute infusion of norepinephrine. Reproduced, with permission, from Smith.[14]

## 3) Failure to treat refractory anaphylaxis aggressively

- Repeated IM adrenaline ± infusion
- Fluid bolus – repeated if poor response
- Inotropes
- Glucagon if on beta-blockers
- IV hydrocortisone

- Admit for <u>at least</u> 24hrs if patient requires more than 1 dose adrenaline or fluid bolus etc.

## 4) Inappropriate use of drugs

- Wrong drug
- Wrong dose
- Suboptimal or dangerous route of administration

**Antihistamines**

– Slow onset of action – at least 30 mins+
– Don't block all histamine receptors
– Don't inhibit other mediators released
– Appear to be mostly active against skin symptoms (little effect on CVS / RS)
– Cannot inhibit "Mast cell leukocyte cytokine cascade"

– Can be useful to treat urticaria and pruritus
– ?more effective if combined with H2 antagonists
– May have prophylactic value (eg before IT)

**(Glucocortico)steroids**

– Onset of action 4 - 6 hours

– Will inhibit the "Mast cell leukocyte cytokine cascade"
– Administer only after initial stabilisation
– Potentially influence biphasic response
– Evidence limited
– Benefit
  - Patients with asthma (steroid responsive diseases)
  - Prophylaxis for idiopathic anaphylaxis

**Salbutamol (Ventolin)**

– Fails to treat all the other symptoms of anaphylaxis
– Will not inhibit the "Mast cell leukocyte cytokine cascade"
– Will not prevent further deterioration

– Administer only after initial stabilisation
i.e. if the onset of wheeze might be due to anaphylaxis, give IM and nebulised adrenaline.

## Role of adrenaline (epinephrine)

- $\alpha$1-adrenergic effects:
  - Vasoconstriction
  - Increased peripheral vascular resistance
  - Decreased mucosal oedema
- $\beta$2-adrenergic effects:
  - Bronchodilatation
  - Decreased mediator release from mast cells and basophils

**1st line drug of choice**

## Dose

0.01 ml/kg
(10 mcg/kg)
1:1000 Adrenaline

OR

| | |
|---|---|
| < 1 yr | 0.05 - 0.1ml |
| 1 – 2 yrs | 0.1 ml |
| 2 – 3 yrs | 0.15 ml |
| 4 – 6 yrs | 0.2 ml |
| 7 – 10 yrs | 0.3 ml |
| 10 – 12 yrs | 0.4 ml |
| > 12 yrs | 0.5 ml |

IM doses of 1:1000 adrenaline (repeat after 5 min if no better)
- Adult: 500 micrograms IM (0.5 mL)
- Child more than 12 years: 500 micrograms IM (0.5 mL)
- Child 6 -12 years: 300 micrograms IM (0.3 mL)
- Child less than 6 years: 150 micrograms IM (0.15 mL)

## Where & how

- IM anterolateral thigh > IM or SC deltoid

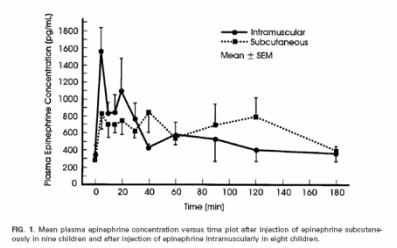



FIG. 1. Mean plasma epinephrine concentration versus time plot after injection of epinephrine subcutaneously in nine children and after injection of epinephrine intramuscularly in eight children.

(Simons et al, JACI 1998)

- Infusions reserved for refractory cases

## In-hospital treatment

- ABC
- A incl. adrenaline IM if needed
- B - Oxygen
- IV access - IV fluids if ongoing hypotension
- ± H1 antagonist and corticosteroids
  (may help reduce biphasic response)
- nebulised salbutamol may be used for lower airway obstruction
- Further doses of adrenaline
- IV adrenaline infusion for refractory symptoms

## Further Management

- Other drugs
  - Glucagon if patient is on beta-blockers
  - Vasopressors e.g. dopamine if poor response to repeated IM adrenaline + fluid boluses
- Observe for <u>minimum</u> 4 hours in hospital
  - 90% of biphasic reactions occur within 4 hrs[1]
- Recommended discharge meds
  - ? Antihistamine ?steroid for 48 hours
  - Adrenaline Auto-injector device

[1] Lee et al, Pediatrics 2000.

## Adrenaline Autoinjectors

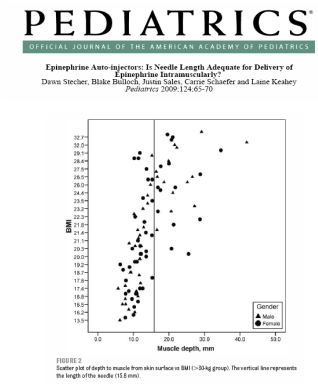
## Beware of needle size!

- Medicine needs to get to muscle.
- We are getting fatter!

| Standard UK needle gauges and lengths | | |
|---|---|---|
| Brown | 26G | 10 mm |
| Orange | 25G | 16 mm or 25 mm |
| Blue | 23G | 25 mm |
| Green | 21G | 38 mm |

- Generally recommend 25G (orange), 25mm
- May need blue needle in some children.
- Autoinjector devices may have too short needles for some children![1]

[1]Stecher et al, Pediatrics 2009 124:65-70.




## IV Adrenaline

- IV adrenaline can cause life-threatening hypertension, tachycardia, arrhythmias, and myocardial ischaemia in patients with a spontaneous circulation
- Use of IV adrenaline in cardiac arrest totally different
- Risk of incorrect dose, inappropriate usage.
- Reserved for patients who require repeated IM doses.
- If used:
  - Call expert help
  - Monitoring essential:
    continuous ECG, O2 Sats and <5minutely BP
  - Titrate dose of 1mcg/kg against response. Requires very careful dilution – hence IM preferred
  - Infusion more appropriate.

## 5) Suboptimal management at discharge

- ?antihistamine ?steroid for 48 hours
- Adrenaline Auto-injector device vital
- Appropriate dietary advice
  - Avoid trigger
    - If Cow's Milk, don't recommend:
      - Lactose-free
      - Partially hydrolysed formula
      - Caution with Soy, Extensively hydrolysed formula
- Referral!!

## Adrenaline Auto-injectors

- Recommended for all children with previous anaphylaxis
- Training essential
- Anaphylaxis action plan essential
- Seek advice if needed.


## NOT Recommended:

- Asthma without anaphylaxis or systemic allergy
- Positive skin or RAST test only
- Family history of anaphylaxis
- Local reactions to insect stings
- Generalised skin rash (only) to bee or wasp stings in children
- Resolved food allergy