Anaphylaxis

- Loss of consciousness
- Hives
- Swelling of tongue, inability to swallow
- Rapid swelling of throat tissues
Anaphylaxis

- Anaphylaxis comes from the Greek and means against or without protection. 
  “ana” - against 
  “phylaxis” – protection 

As opposed to prophylaxis 
“for protection” i.e prevention

Anaphylaxis Levin June 2012
Anaphylaxis

• a sudden, severe, potentially fatal, systemic allergic reaction.
• skin, respiratory tract, gastrointestinal tract, and cardiovascular system.
• Symptoms occur within minutes to two hours after contact with the allergy-causing substance.

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Anaphylaxis

Allergic

IgE mediated

Complement

Non IgE Mediated

IgG

Immune complexes

Non allergic)

Other

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Sensitization Stage

1. Antigen (allergen) exposure

2. Plasma cells produce IgE antibodies against the allergen

3. IgE antibodies attach to mast cells and basophils

Antigen

Plasma cell

IgE

Mast cell with fixed IgE antibodies

Granules containing histamine

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Anaphylactic Reaction

④ More of same allergen invades body

⑤ Allergen combines with IgE attached to mast cells and basophils, → degranulation and release of histamine and other chemical mediators

Antigen

Mast cell granules release contents after antigen binds with IgE antibodies

Histamine and other mediators

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Anaphylaxis

Immediate Release
Granule contents:
- Histamine
- TNF-α
- Proteases
- Heparin

Over Minutes
Lipid mediators:
- Prostaglandins
- Leukotrienes

Over Hours
Cytokine production:
- Specifically, TNF-α, IL-4, IL-13

Cell recruitment

Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes
Wheezing
Bronchoconstriction
Mechanisms Central role of mast cells

IgE mediated → sensitization & re-exposure → mast cells

Non IgE mediated → Complement → mast cells
→ Direct histamine release
→ Exercise induced anaphylaxis
(food dependent and nonfood dependent)

Non IgE, NOT mast cell mediated

Immune complex mediated
Arachidonic acid metabolism
Idiopathic anaphylaxis
Cold induced anaphylaxis
Anaphylaxis

• Many mediators and mechanisms
  – Histamine
  – Tryptase
  – Chymase
  – Mast cell carboxypeptidases
  – Platelet activating factor
  – Others
  – Prostaglandins, leukotrienes and cytokines
Platelet Activating Factor

• The most potent lipid mediator
  – Active at $10^{-12}$ molar
  – Transmits outside-in signals to intracellular transduction systems and effector mediators
    – Increases vascular permeability
    – Decreases cardiac output
    – Smooth muscle contraction: bronchoconstriction
    – Circulatory collapse

• More SEVERE manifestations (histamine produces the non life-threatening)

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Platelet Activating Factor

• PAF receptor
  – Transmembrane receptor
  – G protein coupled
  – Engages multiple signalling pathways
  – Receptor modulated by phosphorylation

• Normal mice get anaphylaxis when exposed to exogenous PAF

• PAF receptor knockout mice are resistant to exogenous PAF

• PAF receptor knockout mice are resistant to all anaphylaxis
Platelet Activating Factor

• PAF is degraded / inactivated by an enzyme PAF-AH (acetyl hydrolase)
• PAF-AH is a “protective enzyme”
• In mice either pretreatment with recombinant PAF-AH or post-event treatment can abrogate anaphylaxis
• In humans severity of anaphylaxis is correlated with PAF levels and
• Inversely correlated with PAF-AH levels

Platelet Activating Factor

A histogram of the serum PAF-AH activity of a sample of 3106 healthy Japanese

- PAF AH levels could be used to predict severity of anaphylaxis in at-risk individuals? (Anaphylaxis Levin June 2012)
Nitric Oxide

- NO is generated by NO synthase
- Principal mediator of hypotension induced by PAF
- Constitutive rather than inducible form of NO synthase mediates the NO involved in PAF induced anaphylaxis
- This is the final pathway
- Methylene blue inhibits NO synthase
IgE-mediated anaphylaxis

• Foods
  – peanut, fish, egg, legumes, metabisulphites

• Insect venoms
  – Bees, wasps, hornets, fire ants

• Latex

• Medications
  – Antibiotics: B lactams, bactrim, vanco, chloramph, ampho
  – Vaccines
  – muscle relaxants, steroids, insulin, ACTH

• Immunotherapy
  – Insect venom
  – Inhalant allergens

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Non IgE mediated anaphylaxis

- Immune complex or complement
  - Blood products: blood, plasma, immunoglobulins
  - Methotrexate

- Arachidonic acid
  - Drugs: aspirin, NSAIDS
  - Additives: tartrazine, benzoates

- Direct histamine release
  - Radiocontrast media, opiates, vancomycin

- Unknown
  - Cold, idiopathic
Manifestations

- Urticaria, angioedema 88%
- Upper airway oedema 56%
- Wheeze, dyspnoea 47%
- Flush 46%
- Many others ................. far lower %
Clinical criterion 1

- Acute onset of illness (minutes to 2 hours) with
- involvement of the skin, mucosal tissue, or both

AND either:

- Respiratory compromise
- Reduced blood pressure or major systemic symptoms

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Clinical criterion 2

- Known allergic patient exposed to likely allergen:
- Two or more of the following occurring rapidly after exposure:
  - Involvement of the skin-mucosal tissue
  - Respiratory compromise
  - Reduced BP or associated symptoms
  - Persistent GI symptoms
Clinical criterion 3

- Reduced BP occurring rapidly after exposure to known allergen for that patient
  - Low systolic BP* or greater than 30% decrease in systolic BP from baseline

- 1 month to 1 year: <70 mm Hg
- 1 to 10 years: < (70 mm Hg + [2 X age])
- < 11 and adult: <90 mm Hg
Variation in manifestations

- Multiple systems involvement without skin / mucous membranes
- Hypotension only $\rightarrow$ shock, seizures, syncope
- Bradycardia
- Myocardial infarction
- Ventricular tachycardia
Variation in manifestations

**Perioperative anaphylaxis**
- less skin manifestations
- More CVS effects

**Non IgE mediated anaphylaxis**
- More skin effects
- Less CVS effects
- Less bronchospasm
- Lower degrees of severity
- Less death

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Patterns of anaphylaxis

• Uniphasic: Subsides within 1 to two hours after onset of symptoms either with or without therapy.

• Biphasic: Symptoms resolve after treatment but return between 30 minutes and 72 hours later

• Protracted: Symptoms do not resolve with treatment and may last up to 32 hours despite aggressive treatment
Biphasic anaphylaxis

- Usually after 2 – 24 hours
- Adults 5 – 20 %
- Children 3 – 6 %
- Classic late phase response
- Treatment wearing off
- Prolonged allergen exposure
- Late activation of PAF
Exercise-induced anaphylaxis

- Exercise → warmth, pruritus, urticaria →
- Hypotension and upper airway obstruction
- Pathophysiology unknown
  - increased tissue enzyme activity, changed epitope recognition, altered gastrointestinal permeability and autonomic dysregulation
- Not associated with food
- Associated with any meal
- Associated with food allergies
  - wheat ω-5 gliadin, celery, nuts, shellfish)
Cold-induced anaphylaxis

• Drastic lowering of the whole body temperature
  – Swimming
• Cold exposure leads to urticaria →
• Hypotension, collapse and drowning.
• Mechanism: unknown
Factors affecting incidence

• Age
  – Food allergy: Children > adults, teenagers at risk
  – Drugs: adults > children esp radiocontrast media, plasma expanders, anesthetics

• Gender
  – Overall females > males
  – Latex, aspirin, and muscle relaxants females > males
  – Hymenoptera stings males > females

• Atopy
  – Risk ingested antigens, latex, exercise and idiopathic anaphylaxis
  – Not a risk factor for insulin, penicillin, and venom induced reactions.
Factors affecting incidence

• Socioeconomic status
  – Higher adrenaline dispensing rates among rich

• Drugs:
  – Route of administration: probability and severity less via oral route

• Constancy of administration
  – The longer the interval, the less likely the recurrence for many allergens.
Epidemiological Studies

- 63 fatal cases of anaphylaxis
- All but 1 were known to have food allergy before the event
- All but 1 had asthma
- All were accidental ingestions
- Only 7 of the 63 were given adrenaline.

Epidemiological Studies

• 13 patients with fatal and near-fatal anaphylaxis
• 12 of the 13 had asthma
• All accidental ingestions
• All known food allergies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adrenaline early</th>
<th>Adrenaline late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Survived</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Epidemiological Studies

- 51 milder grades of anaphylaxis
- 0.98 reactions / child / year since receiving epipen prescription
- 63% of these were classified as anaphylaxis
- Only 16% severe with loss of consciousness
- Further 28% moderate (fainting / dizziness)

Epidemiological Studies

• No deaths
• Children in whom the epipen was used
  – less likely to be given adrenaline in hospital
  – Less likely to require subsequent admission
• When used in milder grades of anaphylaxis
  adrenaline prevents morbidity


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Epidemiological Studies

- 123 deaths
- All food allergic fatal reactions caused difficulty breathing
- Often treated for asthma rather than anaphylaxis
- Only 20% of patients given adrenaline received this before they arrested
- Late adrenaline cannot reverse established anaphylaxis
- Early administration is vital.

Epidemiological Studies

- 48 cases of fatal anaphylaxis
- Most had asthma
- Almost a third had current asthma exacerbation
- Over half had no advice related to their food allergy
- Adrenaline auto-injector had been provided to 40%
- Over half of the deaths occurred in patients in whom previous reactions had been mild


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Epidemiological Studies

- Pens used correctly by 9 subjects (19%)
- 2 had expired
- 6 failed to deliver an because of the depth of fat
- Pens were used too late in the reaction by 5 subjects
- Pens were not carried on that occasion by 4 subjects
- Pen was misused by 1


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Epidemiological Studies

- 126 severe allergic reactions
- Food was implicated in 89%
- Asthma risk for more severe reactions
- Recent exacerbation not associated with severity
- Self-injectable adrenaline poorly utilised
- Patients with adrenaline administered it in 35% of severe and 13% of non-severe reaction!

Canada 0.95 % of population prescribed adrenaline at some stage

2 % of young children … decreases slowly

Australia Underutilised: injected in only 32 % of episodes that fitted criteria

H1 antagonists given in 54 % of episodes where adrenaline should have been used
Risk factors for fatal anaphylaxis

- Previous anaphylactic reaction
- History of asthma
- Current poor asthma control
- Reactions with trace exposure
- Peanut > age 5
- Adolescents
- Remote from medical help
- Highly atopic
Differential diagnosis

• Vasovagal syncope
• Anxiety
• Acute urticaria, angioedema
• Acute asthma, vocal cord dysfunction, RDS
• Other causes of shock
• Leukaemia
• Hydatid cyst rupture
Causes of flushing

• Medications
• Alcohol
• Menopause
• Systemic mastocytosis
• Tumours
  – Carcinoid
  – VIPoma
  – Phaeochromocytoma
  – Thyroid carcinoma
Food associated syndromes

- Scombroid poisoning
- Anisakis
- Sulphites
Diagnosing Anaphylaxis

- Careful history
- Serum tryptase
  - Specific for mast cell degranulation
  - Remains elevated for up to 6 hours
- Other tests to rule out other diagnoses
- Refer to allergist for specific testing
Number of subjects

Tryptase µg/l

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Identify specific causes by:
- Skin tests
- ImmunoCAP
- BAT
- CAST
- Challenge tests
- Modified challenge tests
Treatment of Anaphylaxis

- Airway
- Breathing
- Circulation
- Disability
- Specific treatment: Adrenaline

GIVE ADRENALINE
AND BASIC LIFE SUPPORT
SIMULTANEOUSLY

Anaphylaxis Levin June 2012
Treatment of Anaphylaxis

• Immediate treatment with adrenaline imperative
  – No contraindications in anaphylaxis
  – Failure or delay associated with fatalities
  – IM produces more rapid, higher peak levels vs SC
  – Must be available at all times
Adrenaline is an essential drug
Catecholamines increased via camp
Narrow therapeutic window
Evidence for efficacy, though strong, is anecdotal.
(No RCT possible)

\[ \alpha_1 \rightarrow \uparrow \text{constriction, } \uparrow \text{PV resistance, } \downarrow \text{oedema} \]
\[ \alpha_2 \rightarrow \downarrow \text{insulin, } \downarrow \text{noradrenaline} \]
\[ \beta_1 \rightarrow \uparrow \text{inotrope, } \uparrow \text{chronotrope} \]
\[ \beta_2 \rightarrow \uparrow \text{bronchodilation, } \uparrow \text{vasodilation, } \uparrow \text{glycogenolysis} \]
\[ \downarrow \text{mediator release from mast cells} \]
S/C vs IMI

IMI   2136 pg/ml
     tmax 8  +-  2 minutes

S/C   1802 pg/ml
     tmax 34  +-  14 minutes


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**MDI administration**

<table>
<thead>
<tr>
<th>Previous thought</th>
<th>Less side effects, Painless</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Accepted by parents</td>
</tr>
<tr>
<td></td>
<td>Multiple doses</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>Number of inhalations to get systemic effects very high</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most kids could not inhale a full dose</td>
</tr>
<tr>
<td></td>
<td>Late peak</td>
</tr>
<tr>
<td></td>
<td>Adverse effects: cough, taste, dizziness</td>
</tr>
</tbody>
</table>

Epipen

Adrenaline not always available
Ampoules more widely available than injectors

Cost ?
Prescription ?
Dosing ?

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Epipen

Dose is 0.01 mg / kg / IMI

Injectors come in

- epipen 0.3 mg
- epipen jnr 0.15 mg

← R 880.00

R 1.63 →

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Vial & Syringe

Parents slower than doctors / nurses
Parents doses varied 40 fold !!
Parents times 142 secs +/- 13 secs

Simons FER, Chan ES, Gu X, Simons KJ. Epinephrine for the out-of-hospital (first aid) treatment of anaphylaxis in infants: is the ampule/syringe/needle method practical?

J Allergy Clin Immunol 2001;108:1040-4
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Expiry date

↓ adrenaline content correlated with months post – date

Heat sensitive / labile

In date adrenaline Clear solution

Outdated adrenaline Pink or brown solution and oily, BUT only in a minority


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Mild reactions

- Urticaria with or without angioedema
- Chlorpheniramine (allergex) 0.2 mg/kg or cetirizine 0.25 mg/kg (dose in ml is weight/2)
- Asthmatic? give salbutamol prophylactically
- Prednisolone to “prevent late phase reaction”
Wheeze or stridor without distress

- Oxygen
- Salbutamol (wheeze) or adrenaline (stridor) nebuliser
- Observe very closely
- Any respiratory compromise: adrenaline
Anaphylaxis without shock

- Airway, breathing, circulation
- Adrenaline neat 0.01 ml/kg IMI max 0.5ml
- Antihistamines
  - Allergex 0.2mg/kg PO
- Observe 5 minutes
Anaphylaxis without shock

- After 5 minutes
- Repeat Adrenaline
- Repeat nebulisations
- Corticosteroids
  - Prednisone PO
Anaphylaxis with shock

• Airway, breathing, circulation, position
• Adrenaline neat 0.01 ml/kg IMI max 0.5ml
• Call red box
• IV / IO access
• 20ml/kg bolus of fluid, 0.9% NaCl

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Anaphylaxis with shock

- Antihistamines
  - promethazine / phenergan 1mg/kg IV
- Steroids
  - Hydrocortisone 4mg/kg IVI
- If no response in 5 minutes,
- Repeat IM adrenaline
- Call ICU
  - Dopamine, adrenaline infusion
Poor response

Delay in injection

Once shock is established (50 % of MAP in dogs)
Adrenaline does not reverse shock.
No sustained recovery over 180 minutes

Wrong dose or route

β Blockers may be unresponsive to adrenaline:
intravenous glucagon may reverse hypotension.

α Blockers or ACE inhibitors

PAF acetyl-hydrolase levels, ACE levels

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Adrenaline

• Delay in administration leads to lower effectivity
  – Sampson 1992 Those who died had adrenaline > 30 mins
  – Bock 2001 Most who died did not have adrenaline immediately available
  – Pumphrey 2000 Adrenaline used in 62% of fatal reactions BUT before arrest in only 14%

Anaphylaxis Levin June 2012
Adrenaline

• Interactions between adrenaline and PAF
• PAF involved in vascular smooth muscle
• PAF causes PGE2 release
• Adrenaline treatment before, during or after PAF induction of anaphylaxis blunts the PGE2 release in a dose dependent manner
• Part of adrenaline mechanism of action is blunting PAF activity
Therapy

• Adrenaline: conventional first line therapy

• Case reports exist for successful treatment of RESISTANT anaphylaxis with methylene blue

• In mice pretreatment with PAF inhibitor or combined antihistamine / PAF inhibitor can abrogate anaphylaxis, but NOT antihistamine or antileukotriene alone


• Role of rupatadine? SM-12502?
Treatment of Anaphylaxis

• Observe for a minimum 8-12 hours
  – Insure F/U with PMD,
  – Benadryl for 24 hours.

• Rebound or persistent
  – Repeat adrenaline if symptoms persist
  – Repeat antihistamine ± H₂ blocker

• Risk management
Risk management

• Teach specific avoidance measures
• Keep an adrenaline kit (e.g. Epipen) and antihistamine on hand at all times
• Teach how to recognise severe reactions early, and give appropriate treatment
• Medic Alert bracelets should be worn.
• Emphasize the need for follow-up care
• Venom immunotherapy

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<table>
<thead>
<tr>
<th>NAME</th>
<th>HOSPITAL NO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Emergency contact numbers:**

|      |             |

**I am allergic to:**

|      |             |

**My medic alert number is:**

|      |             |
## MINOR REACTION

<table>
<thead>
<tr>
<th>Face and Skin – Itching, redness, hives (&quot;bommels&quot;), swelling of face, eyes, hands and feet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach – stomach pain, vomiting, diarrhoea</td>
</tr>
<tr>
<td>MAJOR REACTION</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Airway</strong> – difficulty breathing, coughing, wheezy, choking, noisy breathing, voice change</td>
</tr>
<tr>
<td><strong>Total body</strong> – change of colour, floppy, sense of impending doom, loss of consciousness, sleepy</td>
</tr>
</tbody>
</table>
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MINOR REACTION
(Face / Stomach / Skin)

GIVE ANTIHISTAMINE DOSE..........................

If asthmatic give Asthavent 4-6 puffs via spacer

Consult your doctor as soon as possible
MAJOR REACTION
(Airway / Total Body)

BREATHING DIFFICULTY OR CHANGE OF CONSCIOUSNESS

GIVE IMMEDIATELY

ADRENALINE / EPIPEN

DOSE: .................

ANTIHISTAMINE DOSE......................

If asthmatic give Asthavent 4-6 puffs via spacer

CALL 10177
say “ANAPHYLAXIS”

Get to closest doctor/clinic/hospital immediately

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Emergency kit

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Needle and syringe

- Open syringe
- Attach blue needle
- Open adrenaline
- Draw up adrenaline..........ml
- Hold syringe with needle facing up : air will be in syringe
- Flick syringe till air is at the top
- Inject the air out
- Stick needle straight down into upper outer thigh
- Inject dose into muscle
- Repeat after 5 minutes if no response
Epipen

- Hold epipen with blue top pointing upward
- Pull off blue top
- Do NOT put thumb over blue cap
- Jab orange tip into upper outer thigh
- Hold for 10 seconds
Take home messages

Many mechanisms of anaphylaxis

Unsure? 3 x tryptase levels

Adrenaline is life saving

Not easily available, often not used

Avoidance, medic Alert, Action plan

Antihistamines for isolated cutaneous reactions

Adrenaline 0.01 mg/kg = 0.01 ml/kg IMI