Anaphylaxis

Steve Adams
University of Auckland
Royal New Zealand Navy
King Menes(?2460 ?3400 BC) died after a single bee sting\(^1\) or crocodile or wild dog bite or hippopotamus attack\(^2\)

Portier and Richet (1902) found that dogs immunised to anemone venom produced fatal reactions to a dose of venom that was not previously harmful\(^3\)

\textit{anaphylaxis} = removal of protection

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History 2

Penicillins (1940) > increasing incidence of anaphylaxis

1980-2007 s > growth in food allergies

History 3

![Graph showing incidence of Drug and Food over age]

- Incidence
- Age
Definition

“A clinical syndrome of severe hypersensitivity reaction of type I or type IIIi characterised by cardiovascular collapse and/or respiratory compromise”\(^5\)

There were 4 major headings and 26 subheadings in the ICD-9 classification

There are no universally accepted clinical criteria

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Anaphylaxis?

Case 1:
Family unwell 1 hour after eating pancakes
“Flour was off”
¾ Family members felt itchy
Two had urticarial rash
One has wheeze and hypotension
Case 2: 42 year old man
Took paramax for migraine
Swollen blue tongue
Difficulty speaking ?SOB
Similar reaction to prochlorperazine in past
Anaphylaxis?

Case 3:
22 year old male
Extensive L upper dental work today
Taken Naproxen after local wore off
Swollen, oedematous L side of face
History of swelling up in face after fighting
Anaphylaxis?

Case 1:
Anaphylaxis
To mite found in flour

Case 2:
Dystonia of tongue
Interestingly said to respond to adrenaline

Case 3:
C1 Esterase Inhibitor Def Angio-oedema
Doesn’t respond to adrenaline
Anaphylaxis?

Case 4:
40 yr old with known penicillin allergy has been given IV flucloxacillin

SOB, pulse 120/min, BP low, O₂ sat 90%
Adrenaline

- What route?
- What dose?
- When to repeat?
Adrenaline

Survey of Hospital Drs in NZ:

Correct dose circled for IM and IV administrations.
## Offending Agent 2006

**United States Study:**

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. (%) of cases (N = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>356 (59)</td>
</tr>
<tr>
<td>Food</td>
<td>131 (22)</td>
</tr>
<tr>
<td>Medication</td>
<td>69 (11)</td>
</tr>
<tr>
<td>Exercise</td>
<td>31 (5)</td>
</tr>
<tr>
<td>Latex</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Catamenial</td>
<td>4 (1)</td>
</tr>
<tr>
<td><em>Chrysops</em></td>
<td>3 (0.5)</td>
</tr>
<tr>
<td><em>Triatoma</em></td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Chrysops – Horse fly

Triatoma – insect known as “kissing bug”

# Food allergies 2006

<table>
<thead>
<tr>
<th>Food</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shellfish</td>
<td>45</td>
</tr>
<tr>
<td>Peanuts</td>
<td>25</td>
</tr>
<tr>
<td>Food additives or spices*</td>
<td>15</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>13</td>
</tr>
<tr>
<td>Beef</td>
<td>8</td>
</tr>
<tr>
<td>Almonds or peaches</td>
<td>5</td>
</tr>
<tr>
<td>Pork</td>
<td>4</td>
</tr>
<tr>
<td>Cashews</td>
<td>4</td>
</tr>
<tr>
<td>Eggs</td>
<td>3</td>
</tr>
<tr>
<td>Tuna</td>
<td>1</td>
</tr>
<tr>
<td>Banana</td>
<td>1</td>
</tr>
<tr>
<td>Cranberry</td>
<td>1</td>
</tr>
<tr>
<td>Milk</td>
<td>1</td>
</tr>
<tr>
<td>Kiwi</td>
<td>1</td>
</tr>
<tr>
<td>Wheat</td>
<td>1</td>
</tr>
<tr>
<td>Cheetos†</td>
<td>1</td>
</tr>
<tr>
<td>Orange</td>
<td>1</td>
</tr>
<tr>
<td>Apples</td>
<td>1</td>
</tr>
<tr>
<td>Olean sesame seeds</td>
<td>1</td>
</tr>
<tr>
<td>Fish</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>133</strong></td>
</tr>
</tbody>
</table>

16: Webb, LM Libermann P Anaphylaxis a review of 601 cases Ann 2006 Jul v97 i1 p3 Allergy Asthma Immunol
# Drug anaphylaxis

## Table 3. Medications Associated With Anaphylaxis

<table>
<thead>
<tr>
<th>Medication</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>24</td>
</tr>
<tr>
<td>Other NSAIDs</td>
<td>15</td>
</tr>
<tr>
<td>β-Lactams</td>
<td>14</td>
</tr>
<tr>
<td>Insulin</td>
<td>7</td>
</tr>
<tr>
<td>Protamine</td>
<td>2</td>
</tr>
<tr>
<td>Codeine</td>
<td>2</td>
</tr>
<tr>
<td>Meperidine</td>
<td>1</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>1</td>
</tr>
<tr>
<td>Salmon calcitonin</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>69</strong></td>
</tr>
</tbody>
</table>

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

16 Webb, LM Libermann P Anaphylaxis a review of 601 cases Ann 2006 Jul v97 i1 p3 Allergy Asthma Immunol
Penicillin and Cephalosporin

- Found ~ 10% with early cephalosporins
  - penicillin used in manufacture
- Cross reactivity much less in later drugs
- Never reported in children
- It is safe to administer cephalosporin to a patient with penicillin allergy


Pathophysiology

- **Anaphylactic reaction**
  (Type 1 Immune Response):
  IgE mediated degranulation of mast cells

- **Anaphylactoid reaction**
  (Type 3 Immune Response):
  Direct displacement of histamine and other mediators from mast cells
Pathophysiology 2

No clinical difference acutely:
- Presentation identical
- Treatment currently the same
- Risk of morbidity high for both
Sensitisation

- Initial exposure to antigen or another antigen with similar structure

- Antigen specific IgE formed by plasma cells
Re-exposure

- Secondary exposure to antigen
  (may require further condition to be present eg: allergen+exercise)
- IgE-antigen complex binds to mast cell Fc receptors
- Delay
  - av 5/60 for drugs
  - 15/60 for stings
  - 30/60 for food

Other Triggers

- Anaphylactoid (Type III) reactions by direct action on mast cells (non immunological)

- NSAIDs with Cox-1 activity including aspirin appear to act further down the cascade on leukotrienes B4,C4,D4,E4
Mechanisms Overview

[Diagram of signal transduction pathways involving proteins such as Fyn, PI3K, Gab2, Lyn, SHIP, PLC-γ, DG, PKC, Ca²⁺, Histamine release, Cytokines, Syk, Shc/Grb2/Sos, Rac, Ras, JNK, ERK, and transcription factors.]
Mast Cell Activation

**Degranulation:**
- Histamine
- ECF-A
- NCF
- Enzymes inc
- Tryptase
- Proteoglycans

**Phospholipase A activation:**
- Prostaglandin D2
- Thromboxane A2
- Leukotrienes - B4,C4,D4,E4
- Platelet activating factor
- Cytokines
- Adenosine
- Free O2 Radicals

In Severe Anaphylaxis:

- Complement activation
- Coagulation cascade activation
- Kallikrein - kinin system
Actions of Mediators

- Negatively inotropic
- Vasodilatory
- Increased capillary permeability
- Bronchiolar constriction
- Hypotension
- Tachycardia
- Volume depletion
Symptomatology

- Skin 94%\textsuperscript{4}, 90%\textsuperscript{6}
- 78% respiratory \textsuperscript{3,6}
- 50% cardiac/shock \textsuperscript{3}

### Symptomatology 2

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Resp</th>
<th>Both</th>
<th>Shock</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>86</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Drugs</td>
<td>24</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>Venom</td>
<td>41</td>
<td>12</td>
<td>47</td>
</tr>
</tbody>
</table>

Time Course

Study of Fatal Reactions:
- Drugs 5 min to arrest
- Venom 15 min to arrest
- Food 30 min to arrest

Diagnosis 1

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

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus 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 BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP* b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baselinePEF, Peak expiratory flow; BP, blood pressure. * 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.

Box 1. Clinical criteria for the diagnosis of anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula).
   And at least one of the following:
   a. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia).
   b. Cardiovascular compromise (e.g. hypotension, collapse).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin or mucosal tissue (e.g. generalized hives, itch, flushing, swelling).
   b. Respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxia).
   c. Cardiovascular compromise (e.g. hypotension, collapse).
   d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting).
3. Hypotension after exposure to known allergen for that patient (minutes to several hours):
   Hypotension for children is defined as systolic blood pressure <70 mmHg from 1 month to 1 year [<70 mmHg + (2 × age)] from 1 to 10 years, and <90 mmHg from 11 to 17 years.
Diagnosis 3

Consider where two of these occur:

- Skin rash
- Upper airway swelling
- Bronchospasm
- Hypotensive shock
Differential

May present looking like:

- Severe asthma
- Collapse

May mimic:

- Myocardial infarct
- Pulmonary embolism
- Shock
Grading

1: Mild allergic reaction - involving skin only
2: Moderate severity
   - skin ± abdo pain/nausea ± dyspnoea ± systolic BP drop
3: Severe bronchospasm, laryngeal oedema, vomiting, defecation
4: Life threatening
   - shock, severe bronchospasm, airway obstruction, resp arrest, impaired GCS


Logistic regression analysis: minimum set of predictors for documented hypotension, ranked by odds ratio

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Documented hypotension</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinence</td>
<td>13 (1.2-143)</td>
<td>.033</td>
<td></td>
</tr>
<tr>
<td>Collapse (includes LOC)</td>
<td>6.3 (3.1-13)</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>4.0 (1.9-8.5)</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Cyanosis or SpO₂ &lt; 92%</td>
<td>3.4 (1.3-8.4)</td>
<td>.010</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.9 (1.5-5.6)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Dizziness (presyncope)</td>
<td>2.7 (1.4-5.3)</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.1 (1.2-3.7)</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2.2 (1.1-4.2)</td>
<td>.018</td>
<td></td>
</tr>
</tbody>
</table>

LOC, Loss of consciousness.
Logistic regression analysis: minimum set of predictors for cyanosis or $\text{SpO}_2 \leq 92\%$

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Documented cyanosis or $\text{SpO}_2 \leq 92%$</th>
<th>Odds ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td></td>
<td>9.9 (1.3-77)</td>
<td>.028</td>
</tr>
<tr>
<td>Stridor</td>
<td></td>
<td>3.8 (1.4-10)</td>
<td>.008</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>2.9 (1.4-5.7)</td>
<td>.003</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>2.9 (1.3-6.8)</td>
<td>.013</td>
</tr>
<tr>
<td>Wheeze</td>
<td></td>
<td>2.2 (1.1-4.6)</td>
<td>.028</td>
</tr>
</tbody>
</table>

Grading system based on predictors for hypotension and hypoxia / cyanosis
Correlates with adrenaline mean dose

Treatment Gd1 (NZRC in orange)

- Remove source eg: sting
- Call for help
- Lie patient supine
- Place IV line, observe until clearly settling
- High flow Oxygen

Antihistamine: promethazine slow IV/IM:
- Adult: 12.5-50mg
- Child: 5mg
- Preschooler: 2.5mg
Treatment Gd2

- High flow $O_2$
- Start monitoring $SaO_2$, ECG, BP
- Adrenaline IM$^{12}$
  - Adult: 0.25 - 0.5mg (1:1000)
  - Child: 5 - 10µg/kg
- Place large bore IV while IM adrenaline absorbed
- Rapidly infuse Normal Saline
  - Adult: 1000ml
  - Child: 20ml/kg

Treatment Gd2 NZRC

- High flow O₂
- Adrenaline IM
  - Adult: 0.5mg (1:1000)
  - Child: 10µg/kg
- Place large bore IV
- Rapidly infuse Normal Saline
  - Adult: 1000ml
  - Child: 20ml/kg
- Promethazine 25mg slow IV or IM
- Hydrocortisone 250 µg/kg
Treatment Gd3 (NZRC)

- Hypotension: Adrenaline IV/IO
  - Adult: 0.1mg-0.2mg (100µg/min)
  - Child: 10µg/kg in 5/60

- Upper airway:
  - Nebulised adrenaline 1mg

- Bronchospasm:
  - Salbutamol IV: 0.1mg-0.25mg

Seek assistance as airway compromise may be imminent.
Treatment Gd4

- Intubation should be initiated early but in impending upper airway obstruction:
- Surgical airway may be required - equipment should be readied (eg minitrach)
- Barbiturate induction for intubation should be avoided (direct cardiac depression)
- Opiate, Etomidate, Ketamine preferred

Treatment

Adrenaline infusion and other vasopressors (Metaraminol, Noradrenaline) may be needed to support the circulation.
Problems 1

Tricyclic antidepressants:
Adrenaline sensitivity

Try reducing dose to 20% \(^{14}\)

Problems 2

**Beta blockers:**

Adrenaline resistance or differential block with α-adrenergic overdrive

- **Glucagon 1mg** 20-30μg IV q5/60
- **Ranitidine 50mg** 1mg/kg IV q5/60


Postacute

Steroid:
- Hydrocortisone 200-259 mg stat +
- Prednisone 40mg-2mg/kg od 5/7

H1 Antagonist:
- Loratidine 10mg-0.2mg/kg od
- Cetrizine 10mg -0.2mg/kg od

H2 Antagonist:
- Ranitididine 300mg od
How Long?

Duration of observation?
- 4-24 hours after acute symptoms settled
- Should be warned of the possibility of a biphasic reaction
Course/Prognosis

- **Death**
  - respiratory arrest ~86%
  - cardiac arrest ~25%
  - hypoxic brain injury ~28%  

- **Prolonged reaction (5-32hr)** 28%  

- **Biphasic reaction (4-12hr)** 20% - 7%  

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Controversies 1

Adrenaline route (SC, IM, IV)

IM had significantly faster absorption than SC in atopic children\(^{11}\)


Controversies 2

Adrenaline route (SC, IM, IV)

- IV use still controversial\(^{12,13}\)
  - higher rate of VT in particular
  - myocardial infarction
  - acute congestive failure
  - no good studies to clearly show greater efficacy or hazard


Controversies 3

- Use of Vasopressin
  - case reports of use where adrenaline effect inadequate 23

- Use of H₂ Antagonists
  - Advocated to augment adrenaline (NZRC)
  - no evidence of effectiveness
  - but may improve cutaneous Sx¹⁵

Adrenaline Ampoules

Generally available in:

- 1:1000  1ml
- 1:10000 10ml

Both contain 1 mg adrenaline
Dilution of Adrenaline

Various dilutions of adrenaline are advocated in different situations.

Trade off between ability to finely measure and

Increased risk of wrong dose with non standard dilutions
Future Directions

- **Serotonergic blockers**
  - trials negative

- **Nitric oxide synthetase inhibitors**
  - animal studies promising

- **Blocking Ep1 Ca sensitive K+ channels**
  - works if blocked prior to reaction

- **Blocking cyclic GMP**
  - methylene Blue reduces hypotension
  - new cGMP blockers in development
Follow Up

It is worth taking blood acutely for:

- Histamine  15- 60 min after onset
- Tryptase  15-180 min after onset

Plain tube
Follow Up

Consider
- Allergy testing?
- Carry drugs?
  - Antihistamine
  - Adrenaline self-injector
- Medic alert
- Management plan
Referral

Immunologist

Should refer new patients with anaphylaxis

- Allergy testing
- Recommendations on management
- Desensitization?
Adrenaline Self Injector 1

Absolute indications:

- Resp or CVS reaction to food, drug or sting
- Exercise induced anaphylaxis
- Idiopathic anaphylaxis
- Food allergy and coexisting persistent asthma

17. European guidelines for Paediatric Anaphylaxis Allergy Aug 2007 v62 p857-871
Relative indications:

- Reaction to a small amount of food allergen
- Mild reaction to peanut or tree nut
- Remoteness from medical facility
- Food allergy in a teenager

Epipen
- 0.3mg (Adult)
- 0.15mg “Jr” (Child)
Adrenaline Autoinjector

Retail = $160
Administration

Requires familiarity and practice
Management Plan

Adrenaline self injector
- Spares?
- Other person to carry eg teacher
- Ongoing practice

Documentation

Patient support organizations
Management Plan

Individualized anaphylaxis management plan:

- **Personal identification data**: name and address; emergency contact details
- **Clear identification of the allergens** to be avoided
- **Copies of plan** to be kept by the child, his/her relatives, school staff, family and stored with the emergency medication.
- **Individualized instructions written clearly** in simple, nonmedical language
- **Stepwise approach** with simple instructions for each step
- **Clear description of symptoms of bronchospasm and laryngeal oedema** in nonmedical language so can rapidly administer adrenaline and call emergency medical services.
- Detailed instructions, possibly with photographs, on how to correctly administer the child's particular self-injectable adrenaline device.
- Recommendation to inject a second dose of adrenaline if there is no apparent improvement after 5–10 min.

17. European guidelines for Paediatric Anaphylaxis Allergy Aug 2007 v62 p857-871
References


References ....2


References ....5
