Insect Sting Allergy

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Monday 17 June 2010

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1. Epidemiology
2. Aetiology (meet the insects)
3. Clinical presentation
4. Risk of future systemic reactions
5. Investigations
6. Management
    a) Prevention
    b) Local reactions
    c) Systemic reactions
    d) Venom immunotherapy

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Epidemiology

- Large localised reaction
  - Frequency estimated to be 10% in adults[1]
- Systemic allergic reactions
  - Reported by up to 3% of adults[2]
  - Severe sting reactions in up to 1% of children[3]

1. Golden DBK. Immunol Allergy Clin N Am 2007;17:261-272
2. Golden et al. JAMA 1989;262:240-4.
3. Settipane et al. J Allergy 1972;50:146-50.

Epidemiology

- Admissions
  - In Australia, approximately 1200 admissions per year attributed towards hornet, wasp or bee stings (2002-2005)
- Fatalities
  - In Australia, approximately 2 cases per year (20 cases between 1997-2005).
  - In USA, >50 cases per year.

1. Bradley C. Australian Institute of Health and Welfare; 2008. Catalog no. INJCAT 110.
2. Liew et al; JACI 2009;123:434-42.
3. Barnard JH. JACI 1973;52:259-64.

Liew et al. Anaphylaxis fatalities and admissions in Australia. JACI 2009;123:434-42.

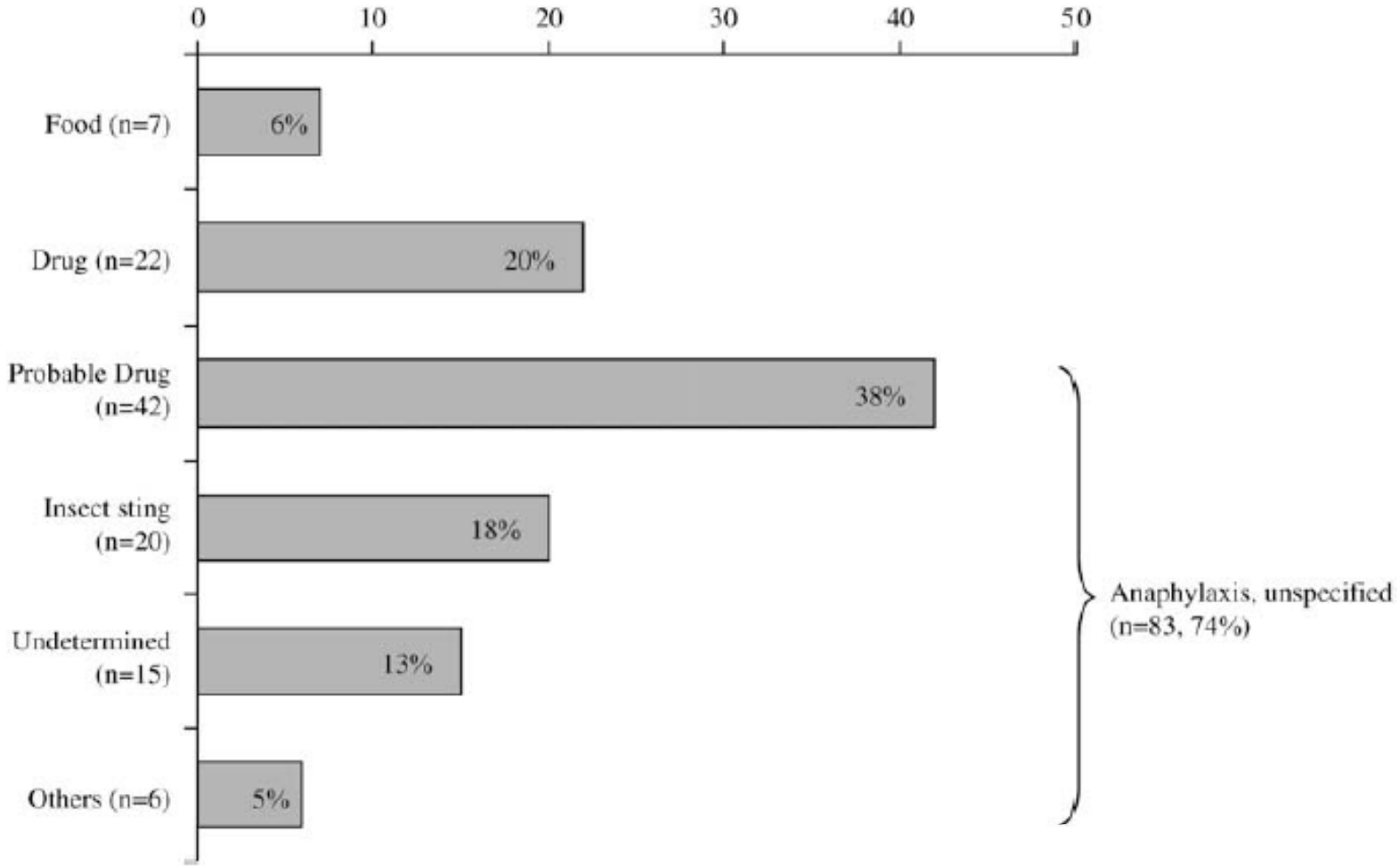


FIG 1. Causes of anaphylaxis deaths. There were 112 deaths between 1997 and 2005 in Australia. Causes are shown.

Liew et al. Anaphylaxis fatalities and admissions in Australia. JACI 2009;123:434-42.

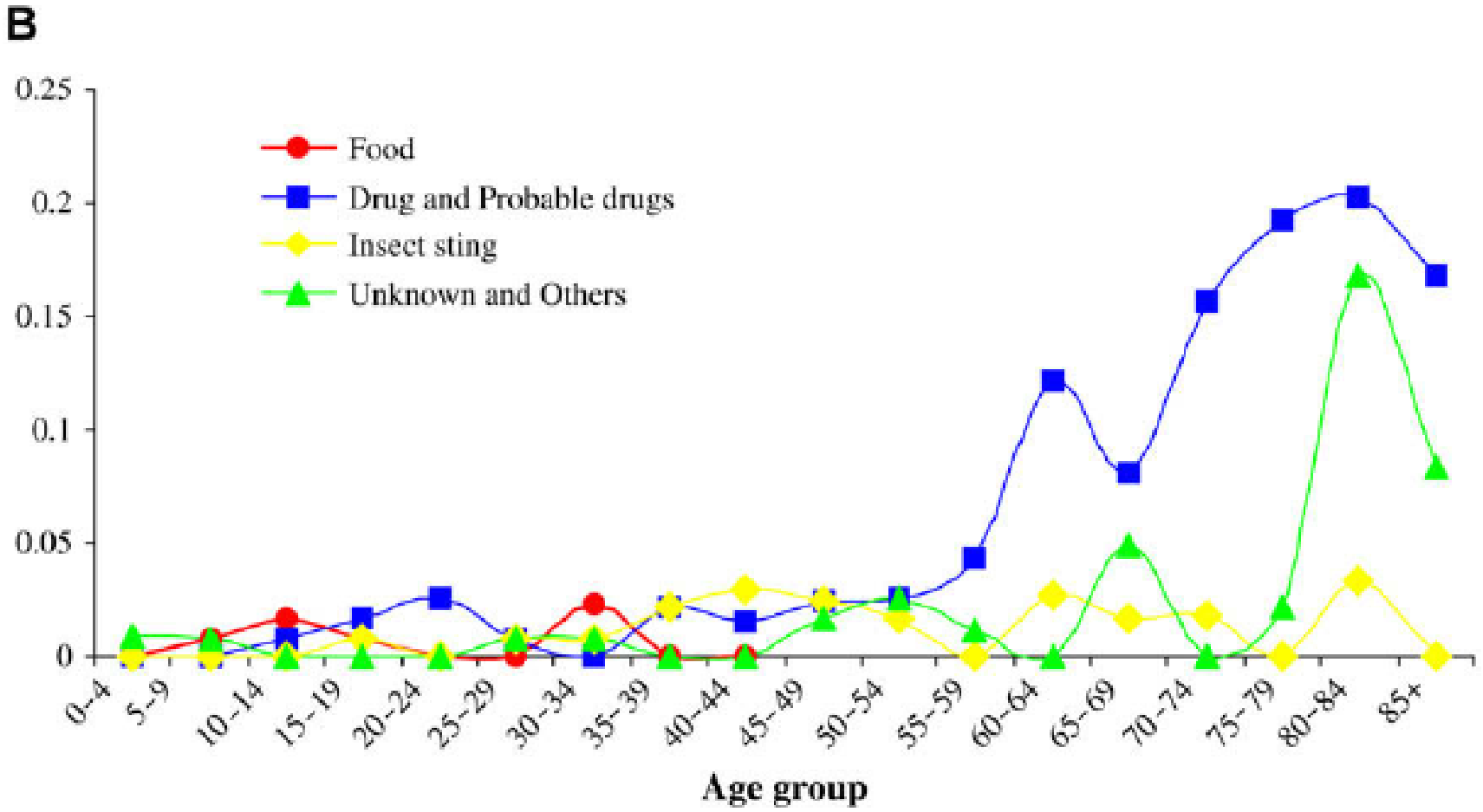
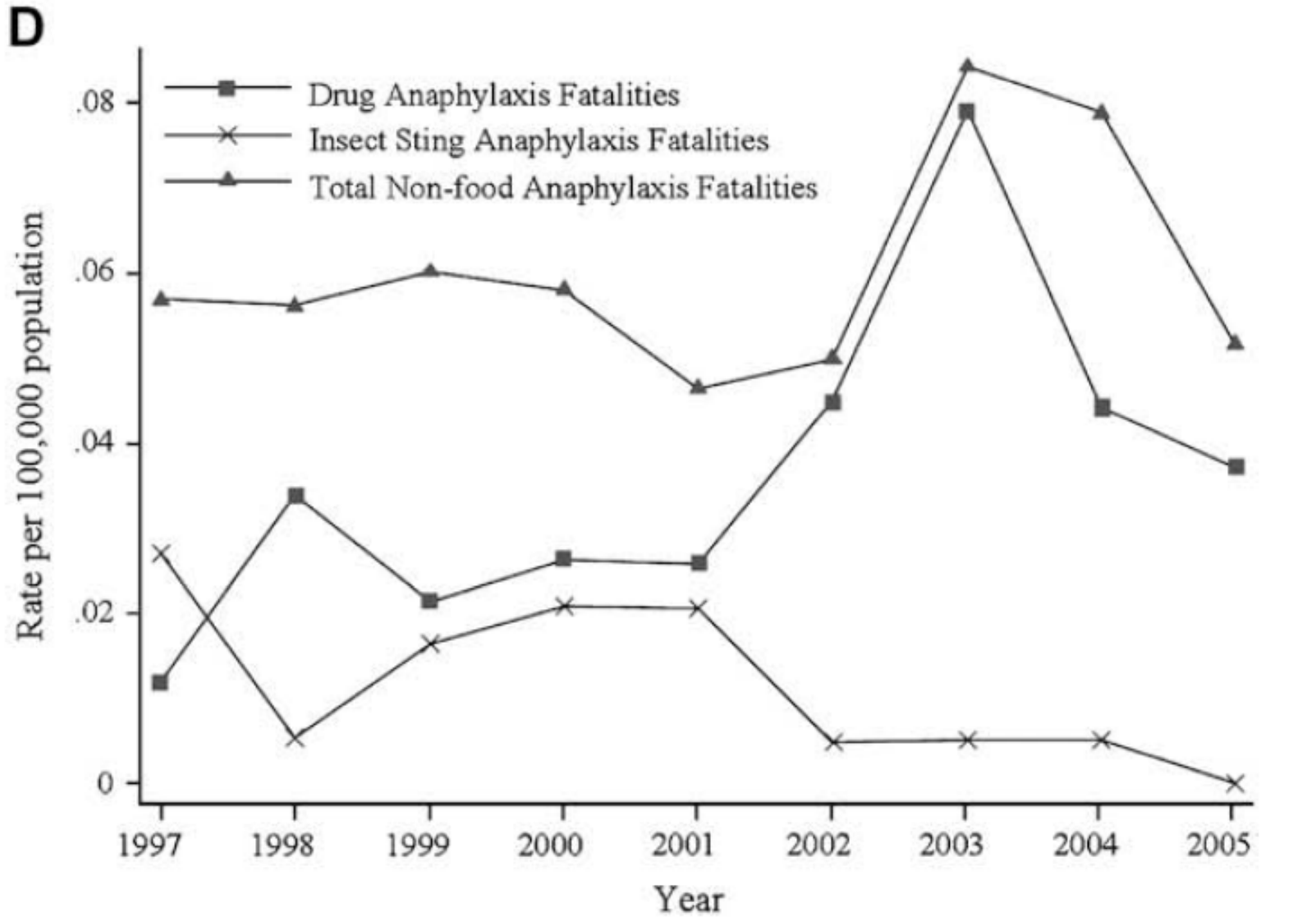


FIG 2. Anaphylaxis fatalities. **A**, Absolute number of anaphylaxis deaths by cause and age group. **B**, Anaphylaxis death rates by cause and age group. All but 1 food-induced anaphylaxis death occurred in the 10- to 35-year age groups (1 death at 8 years), most insect sting–induced anaphylaxis deaths occurred between

Liew et al. Anaphylaxis fatalities and admissions in Australia. JACI 2009;123:434-42.



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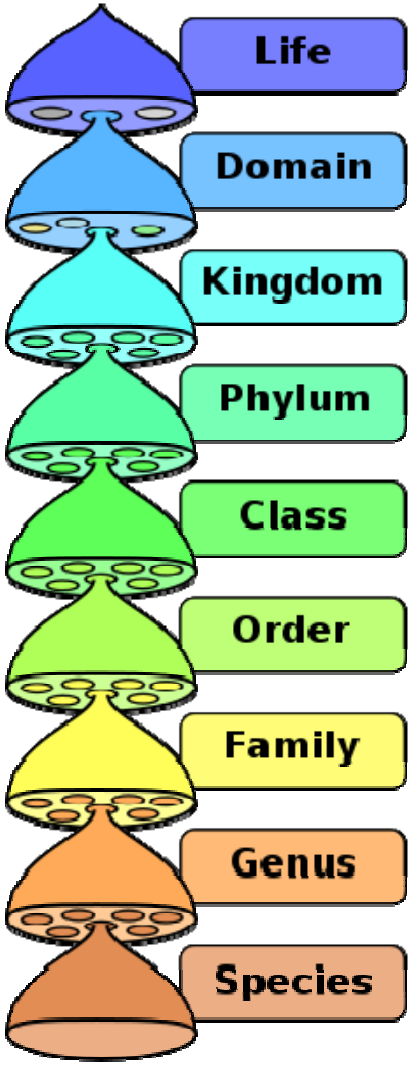
Aetiology (the insects)



ORDER: HYMENOPTERA	
Family	**Genus/Species**
Apidae (Bees)	• Apis (Honeybee) • Apis mellifera (European honeybee) • Bombus (Bumblebee)

Vespidiae (Wasps)	• Vespula and Dolichovespula (Yellow jackets or 'wasps')
	  • Vespula germanica (European/German Wasp)
	  • Vespula vulgaris (Common wasp)
	• Vespa (Hornets)
	• Polistes (Paper wasps)

Formicidiae (Ants)	• Myrmecia (Bull ants) • Myrmecia pilosula (Jack jumper ant)

Courtesy Peter Halasz.
http://commons.wikimedia.org/wiki/File:Biological_classification_L_Pengo_vflip.svg

Honeybees

- Major allergen *Api m 1* (phospholipase A2)
- Tan and black
- Hairy thorax and smooth abdomen
- Most mild-mannered of Hymenoptera
- Usually will not sting unless stepped or sat upon
- Presence of sting usually identifies honeybee (differential are the yellow jacket species)

Bumblebees

- Black and yellow
- Both thorax and abdomen are hairy
- Rarely cause sting reactions (slow and noisy thus easy to avoid)
- Not found in mainland Australia but common in Tasmania

Yellow jackets

- Major allergen *Ves v 5* (antigen 5)
- Yellow and black in colour
- Smooth thorax and abdomen
- Ill tempered
- Nests concealed in the ground or behind siding or retaining walls
- Scavenge for rotting fruit (found near garbage cans, dumpsters and orchards)
- Most common cause of insect sting reactions because they are disturbed when gardening and lawn mowing

Photograph courtesy Alex Wild.
http://www.myrmecos.net/ants/MyrmeciaPilo1.html

Jack Jumper Ants

- Colour is black, or red-and-black
- Yellow/orange legs, antennae and mandibles
- Most common in Tasmania. In Victoria, they are found in rural areas
- Have a characteristic jumping motion when agitated
- Highly territorial and may fight with ants from the same/other colonies.

Cross-reactivity

Honeybees have limited cross-reactivity to bumblebee and the vespid venoms[1]

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Formicidiae (Ants)	• Myrmecia (Bull ants) • Myrmecia pilosula (Jack jumper ant)

1. Golden DBK. JACI 2005;115:439-47.

Cross-reactivity

Yellow jackets and hornets are closely related and highly cross-reactive

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Cross-reactivity

In paper wasp allergy, less than half are completely cross-reactive with yellow jacket and honey bee venom.

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Clinical presentation of sting reactions

- Non-allergic: Pain, itching and swelling
- Allergic reactions[1]
  - Large localised swellings
    - Late-phase IgE-dependent reaction, develops after 12-48 hours, resolves over 5-10 days
    - Often > 15 cm
  - Systemic reactions
    - Cutaneous: generalised urticaria, angioedema, flushing, pruritus (only symptom in 68% of children vs 12% of adults)[2]
    - Gastrointestinal: abdominal pain, vomiting
    - Respiratory: laryngeal oedema, wheeze, stridor, hoarse voice, coughing
    - CVS (less common): bradycardia, tachyarrhythmias, cornoary vasospasm, hypotension

1. Golden DBK. JACI 2005;115:439-47.
2. Schuberth et al. J Pediatrics 1982;100:546-51.

History – important aspects

- Current sting
  - Identify the particular insect involved
    - Single (bee) versus multiple stings (wasp)
    - Presence of sting (honeybee or Yellow jacket)
  - Time of onset of reaction
  - Signs of anaphylaxis (note: hoarse voice, coughing)
- Previous stings
  - Severity of previous reactions
  - Number of stings
- Other allergies: especially asthma
- Social history
  - Risk of future sting? E.g. beekeepers
  - Time to nearest hospital?

1. Golden DBK. Immunol Allergy Clin N Am 2007;17:261-272

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Risk of systemic reaction

- Asymptomatic patients with a positive diagnostic venom test (skin test or sIgE)
  - 15-25% of adults have a positive venom test[1]
  - This is commonly transient, with 12% of subjects becoming negative every year[2]
  - The risk of systemic reaction to a subsequent sting was 17% (11/65 subjects), compared to 0% in patients with a negative skin test (0/160)[2]
  - An explanation may be that a variable proportion of these IgE antibodies are directed against the CHO determinants that cross-react with foods and inhalants.

1. Golden et al. JAMA 1989;262:240-244
2. Golden et al. JACI 1997;100:760-6.
3. Hemmer et al. JACI 2001;108:1045-52.

Golden et al. Insect sting allergy and venom immunotherapy: A model and mystery. *Journal of Allergy and Clinical Immunology* 1997;100:760-6.

TABLE I. Risk of systemic reaction in untreated patients with a history of sting anaphylaxis and positive venom skin test responses

Original sting reaction		Risk of systemic reaction	
Severity	**Age**	**1-9 y**	**10-20 y**
No reaction	Adult	17%	
Large local	All	10%	10%
Cutaneous	Child	10%	5%
Systemic	Adult	20%	10%
Anaphylaxis	Child	40%	30%
	Adult	60%	40%

Sensitised and never stung

Reprinted with permission from Adkinson NF, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER, editors. Insect allergy. In: *Middleton's Allergy: Principles and Practice*. 6th ed. St Louis: Mosby; 2003. p. 1475-86.

Investigations

- Who to investigate?
  - Diagnostic tests are indicated when the risk future of anaphylaxis is judged to be high (i.e. >10%)
  - These are subjects where immunotherapy is being considered

Golden et al. Insect sting allergy and venom immunotherapy: A model and mystery. *Journal of Allergy and Clinical Immunology* 1997;100:760-6.

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Anaphylaxis	Child	40%	30%
	Adult	60%	40%

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Investigations

- Options
  - Insect venom skin test
  - Insect venom specific IgE
  - Sting challenge

Investigations

- Options
  - Insect venom skin test
  - Insect venom specific IgE
  - Sting challenge
    - Considered impractical and unethical[1,2]
    - Even when sting challenge causes no reaction → there remains a 15-20% chance of a systemic reaction from a subsequent sting[3]

1. vanderLinden et al. JACI 1994;94:151-9
2. Reisman RE. JACI 1993;91:1100
3. Franken et al. JACI 1994;93:431-6

Investigations

- Insect venom skin test
  - Method[1]
    - Intradermal skin test – start with lowest concentration (0.001 mcg/mL) and increase to highest (1mcg/mL)
    - Skin prick test – may be used initially for patients with a history of severe reaction (at no higher than 1 mcg/mL)

1. Golden DBK. Immunol Allergy Clin N Am 2007;27:261-272

Investigations

- Insect venom skin test
  - The preferred diagnostic method
  - High degree of sensitivity (>65%) and proven safety[1,2]
  - Use in complement with venom sIgE
    - 15-20% with positive skin tests have negative sIgE[3,4]
    - 5-10% with negative skin tests have positive sIgE[4]

1. Hamilton RG. Curr Opin Allergy Clin Immunol 2004;4:297-306
2. Allergen immunotherapy: a practice parameter second update 2007;JACI;120:S25-S85.
3. Sobotka et al. J Immunol 1978;121:2477-84
4. Golden et al. JAMA 1989;262:240-4.

Investigations

- Possible reasons for a negative skin test in a patient with a convincing insect sting allergic reaction
  - True reaction but false negative skin test[1]
  - Loss of skin test sensitivity with time[2]
  - Anergic phase (if performed within several weeks of a reaction)[3]
- Action
  - Double check with serum venom sIgE[4]
  - Repeat skin tests 1-6 months later[3]
  - Where both skin test and sIgE is negative (1% of patients) → consider proceeding straight to immunotherapy, with or without a sting challenge[1,5]

1. Golden DBK. JACI 2005;115:439-47.
2. Golden et al. JACI 2001;107:897-901.
3. Goldberg et al. JACI 1997;100:183-4.
4. Finegold I. Curr Opinion Allergy Clin Immunol. 2008;8:343-347
5. Allergen immunotherapy: a practice parameter second update 2007;JACI;120:S25-S85.

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Management

1. Prevention measures (ASCIA)
   - Cover up - wear long sleeves & trousers (when gardening), and shoes outdoors
   - ‘Don’t be a flower’ – avoid perfumes, bright coloured clothing and flowery prints
   - Avoid drinking blindly from drink cans (wasps)
   - Remove nearby nests professionally (home & school)
   - Drive with windows up

http://www.allergy.org.au/content/view/172/154/

Management

2. Local reactions
   - Acute management[1,2]
     - Oral H1-antihistamines : use second generation, less-sedating antihistamines
     - Oral corticosteroids: consider if oedema is spreading
     - Ice pack and simple analgesia
     - Antibiotics are rarely required
   - Reassure and explain natural history of 10% chance of future systemic allergic reaction

1. Moffitt et al. JACI 2004;114;869-86.
2. Severino et al. Current Opinion in Allergy and Clinical Immunology 2009;9:334-337

Management

3. Anaphylactic reactions
   - Prescribe Epipen Junior or Epipen
   - Optimise asthma management
   - Anaphylaxis action plan
   - Immunotherapy

ascia
australasian society of clinical immunology and allergy inc.
www.allergy.org.au

ACTION PLAN FOR Anaphylaxis (Insect allergy)

for use with EpiPen® or EpiPen® Jr adrenaline autoinjectors

Name: _____

Date of birth: _____

Photo

Insect allergies: _____

Other allergies: _____

Family/carer name(s): _____

Work Ph: _____

Home Ph: _____

Mobile Ph: _____

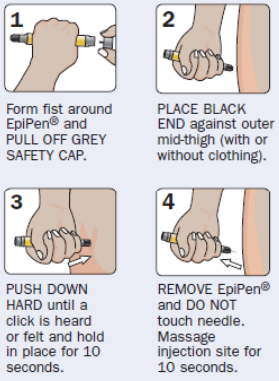
Plan prepared by:

Dr _____

Signed _____

Date _____

How to give EpiPen® or EpiPen® Jr



1. Form fist around EpiPen® and PULL OFF GREY SAFETY CAP.
2. PLACE BLACK END against outer mid-thigh (with or without clothing).
3. PUSH DOWN HARD until a click is heard or felt and hold in place for 10 seconds.
4. REMOVE EpiPen® and DO NOT touch needle. Massage injection site for 10 seconds.

MILD TO MODERATE ALLERGIC REACTION

- swelling of lips, face, eyes
- hives or welts

ACTION

- **if sting can be seen, flick it out immediately (but do not remove ticks)**
- stay with person and call for help
- give medications (if prescribed) .....
- locate EpiPen® or EpiPen® Jr
- contact family/carer

Watch for any one of the following signs of Anaphylaxis

ANAPHYLAXIS (SEVERE ALLERGIC REACTION)

- abdominal pain, vomiting
- difficult/noisy breathing
- swelling of tongue
- swelling/tightness in throat
- difficulty talking and/or hoarse voice
- wheeze or persistent cough
- loss of consciousness and/or collapse
- pale and floppy (young children)

ACTION

1. **Give EpiPen® or EpiPen® Jr**
2. **Call ambulance*- telephone 000 (Aus) or 111 (NZ)**
3. **Lay person flat and elevate legs. If breathing is difficult, allow to sit but do not stand**
4. **Contact family/carer**
5. **Further adrenaline doses may be given if no response after 5 minutes (if another adrenaline autoinjector is available)**

If in doubt, give EpiPen® or EpiPen® Jr

EpiPen® Jr is generally prescribed for children aged 1-5 years.
*Medical observation in hospital for at least 4 hours is recommended after anaphylaxis.

Additional information _____

Venom Immunotherapy

- Aims
  - Indicated in patients with positive diagnostic test and systemic reaction to a sting[1]
  - Ultimate goal is to prevent fatal anaphylaxis[2]

1. Moffitt et al. JACI 2004;114;869-86.
2. Golden DBK. JACI 2005;115:439-47

Venom Immunotherapy

- Regimen
  - Build-up phase
    - Varies between 6 hours to 4 months[1]
    - The more rapid regimens of VIT appear to have the same or greater safety as traditional regimen[2,3,4]
  - Maintenance phase
    - The target dose is 100 mcg 4-weekly[1]
    - Some patients are eventually stretched out to 8-12 weekly[5,6]

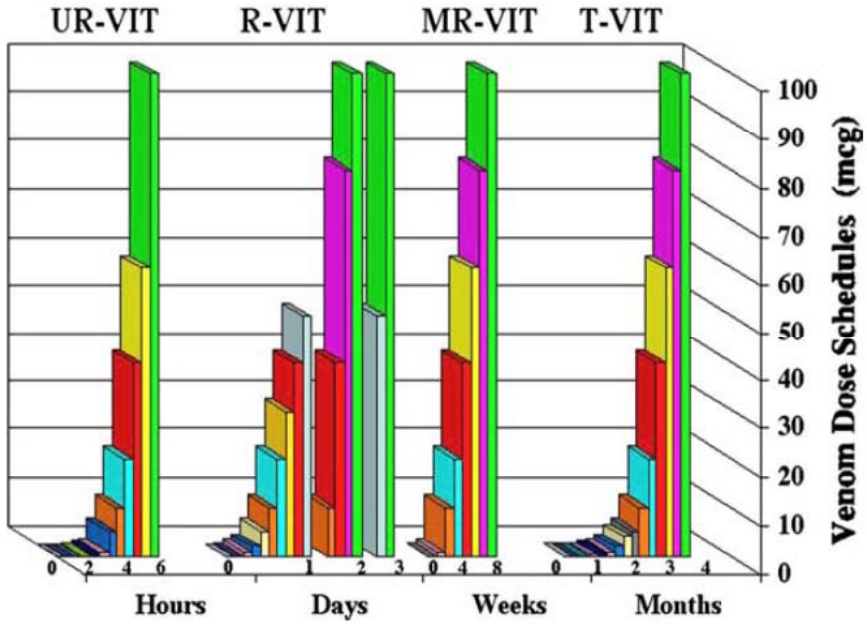


FIG 2. Four dose regimens reported for VIT depicting each dose given during the initial build-up stage of treatment. In the ultrarush schedule *(UR-VIT)* doses are given every 30 minutes to reach the full dose in 6 hours. In the rush schedule *(R-VIT)* doses are given every 30 minutes for 10 doses on day 1, 4 doses on day 2, and 2 doses on day 3. The modified rush schedule *(MR-VIT)* is given once weekly for 8 weeks, and the traditional schedule (T-VIT) is given weekly for 4 months or more.

1. Golden DBK. JACI 2005;115:439-47 (Figure).
2. Bernstein et al. Ann Allergy 1994;73:423-8.
3. Birnbaum et al. Clin Exp Allergy1993;23:226-30.
4. Yunginger et al. JACI 1979;63:340-7.
5. Moffitt et al. JACI 2004;114:869-86.
6. Goldberg et al. JACI 2001;107:902-6.

Venom Immunotherapy

- Efficacy
  - Without VIT, risk of anaphylaxis is 40-60% after a systemic allergic reaction[1]
  - With VIT, risk of systemic allergic reaction reduced to 5% (wasps) to 15% (honeybees)[2]

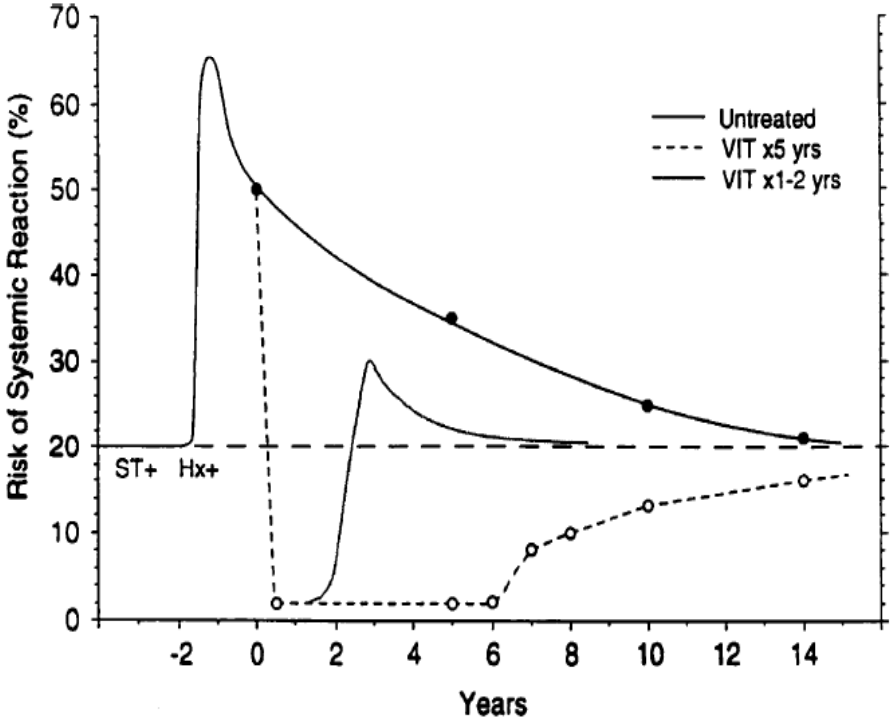


FIG 3. Natural history of insect sting allergy showing the risk of systemic reaction to a sting in untreated patients *(solid line)* and in patients who received VIT *(dashed lines)* for a duration of either 1 to 2 years or for a mean of 6 years. Reprinted with permission from Golden DBK, Kagey-Sobotka A, Lichtenstein LM. Survey of patients after discontinuing venom immunotherapy. J Allergy Clin Immunol 2000;105:389.

1. Golden DBK. JACI 2005;115:439-47.
2. Lerch et al. JACI1998;101:606-12.

Mosbech et al. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. Allergy 2000;55:1005-1010.

Table 1. Classification of abnormal sting reactions and side-effects. Modified from Mueller (4)

Type of reaction	Symptoms
0) Large local	Swelling >10 cm for >2 days
1) Minor	Itching, urticaria, edema, malaise, anxiety
2) General	Chest tightness, palpitations, dizziness, nausea, abdominal pain
3) Severe	Somnolence, respiratory difficulties, vomiting, diarrhea, incontinence
4) Anaphylactic	Confusion, drop in blood pressure, feeling of impending doom, unconsciousness, cyanosis, death

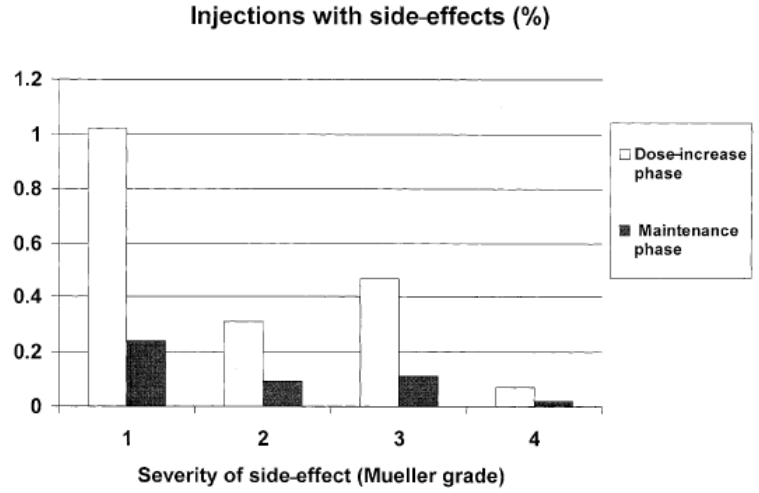


Figure 1. Side-effects during dose increase and maintenance phases classified according to severity.

- 19 centres, 840 patients, 26,601 injections
- 71% with *Vespula*- and 27% with honeybee venom extract
- Systemic side effects occurred in 20% of patients (1.9% of injections during build up phase and 0.5% of injections during maintenance)
- Majority of reactions are mild and only 1/3 required medical treatment

Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res 1966;3:331-333.

Venom Immunotherapy

- Risk factors for relapse[1-6]
  1. More severe allergic reaction on history
  2. Honey bee allergy
  3. Systemic reaction during VIT
  4. Less than 5 years of VIT

1. Muller et al. JACI 1992;89:529-35
2. Golden et al. JACI 1998;101:298-305
3. Golden et al. JACI 2000;105:385-90
4. Lerch et al. JACI 1998;101:606-12
5. Reisman et al. JACI 1993;92:831-6
6. Keating et al. JACI 1991;88:339-48

Summary

1. Majority of children (70%) develop isolated cutaneous symptoms when stung by a bee or wasp.
2. These children have a <10% risk of a future systemic allergic reaction.
3. Children who have had anaphylaxis are at a 40% risk of a future systemic allergic reaction and should be commenced on VIT.

Summary

4. VIT reduces the risk of a systemic allergic reaction to 5% (wasp) to 15% (bees)
5. Risk of relapse from VIT is increased in subjects who have had: 1) a more severe allergic reaction, 2) honeybee allergy, 3) systemic allergic reaction during VIT, and 4) < 5 years of treatment;
6. Venom skin test or serum sIgE is unhelpful as a screening tool for candidates for VIT.