Selection and Preparation of Allergen Vaccines (Extracts)

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Case History Number One

- 22 year old male with perennial allergic rhinitis and conjunctivitis caused by 3 cats in his home.
- Skin prick test very positive to cat extract

Single Allergen Associated With Allergic Disease

Patient allergic and symptomatic only to one.

⇒ Possible examples of single allergen vaccines: cat; olive; cedar; birch; short ragweed; dust mites; or northern grasses (timothy) In this case you can just use optimal doses of cat extract for vaccine.

Decision simple because patient sensitive to only one allergen.

Case History Two

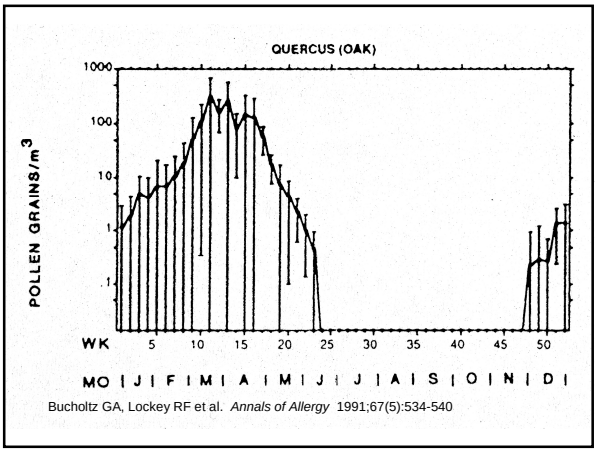
- 33 year old female with perennial allergic rhinitis, conjunctivitis, and asthma, worse in the spring and fall of the year.
- Patient also becomes very systematic when exposed to cat.
- Patient significantly skin test reactive to major trees, grasses, weeds, cat, and dust mites.

This patient is symptomatic + allergic to the major spring allergens in Florida

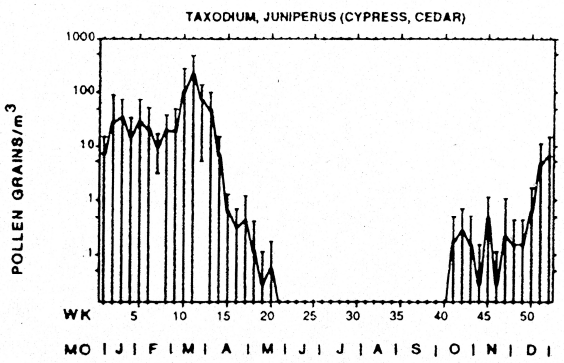
- For example:

1. Trees: oak, cedar, cypress, Australian pine, bayberry

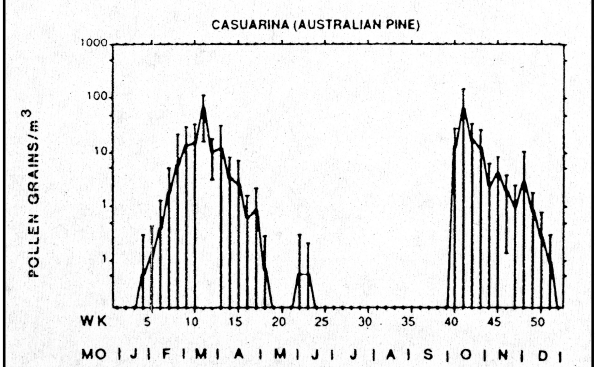
⇒ Do you need all of them?



Bucholtz GA, Lockey RF et al. *Annals of Allergy* 1991;67(5):534-540



Bucholtz GA, Lockey RF et al. *Annals of Allergy* 1991;67(5):534-540



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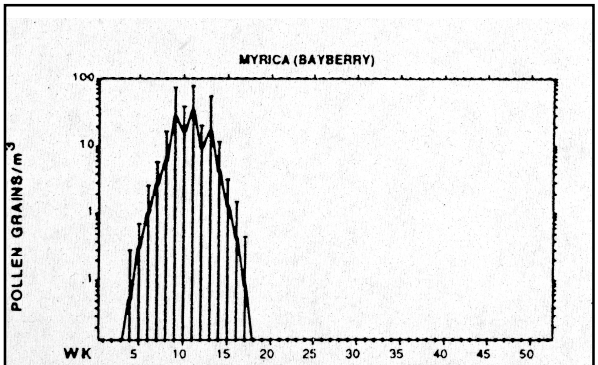

Bucholtz GA, Lockey RF et al. *Annals of Allergy* 1991;67(5):534-540

What Do We Know About Cross-Reactivity and Taxonomy?

Kingdom
Order
Family
Genus
Species

- Examination of plant taxonomy, allergenic cross-reactivity, and geographic distribution of plant species provides useful guidelines for selection of allergens
- May decrease number of allergens in an IT vaccine
- There is rarely significant cross-allergenicity between two families
- There is generally a high degree of cross-allergenicity among species of the same genus
- Taxonomic names don't always convey allergic relationships
  - Excellent cross-reactivity among 3 tree genera with very different names:
    - Birch – genus ***Betula***
    - Alder – genus ***Alnus***
    - Hazlenut – genus ***Corylus***

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Cross-Reactivity

What is a Species?

General

Kingdom	Plant	Plant
Order	Asterales	Asterales
Family	Asteraceae	Asteraceae
Genus	Ambrosia	Artemesia
Species	artemesifolia	vulgaris
Species	trifida	tridentata

Short Ragweed
Mugwort
Specific
Giant Ragweed
Common Sagebrush

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Cross-Allergenicity Among Trees

- Family Fagaceae: beech, oak & chestnut

⇒ Significant cross-reactivity between family Betulaceae pollens and oak of the family Fagaceae has been demonstrated

⇒ Use major local species

Mothes N et al. "Tree Pollen Allergens". In: *Allergens and Allergen Immunotherapy.* Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp. 165-184

Weber RW. *Ann Allergy Asthma Immunol* 2007;99(3):203-11

Cross-Allergenicity Among Trees

- Strong cross-reactivity within the following family:
  - Family Cupressaceae: mountain & eastern red cedar, bald cypress, prickly juniper, Japanese cedar

⇒ One member should suffice

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Bayberry and Australian Pine

- These tree pollens contain unique allergens.

Mixture of Vaccine A

- Oak, bayberry, Australian pine, and cedar added to vaccine

Other Sensitivities

Patient also symptomatic + allergic to other allergens

- For example:

1. Trees: oak, cedar, cypress, Australian pine, bayberry (spring) (Florida)

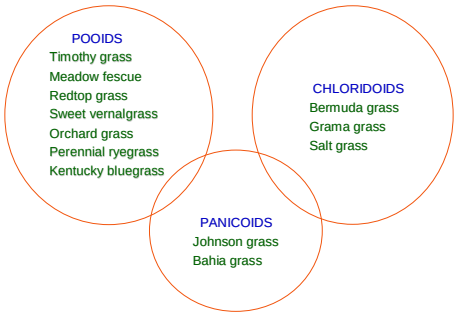
- **Also allergic to:**

2. **Grasses: Bahia, Bermuda (spring, summer, fall)**
3. **Weeds: short ragweed, pigweed family, and lamb's quarters (summer, fall)**
4. **Animal: cat (perennial)**
5. **Dust mites: *D. pteronyssinus, D. farinae* (perennial)**

Do you need to have all allergens in the vaccine?

YES – multiple allergens are necessary in this vaccine.

Grass Cross-Reactivity



Esch RE. "Grass Pollen Allergens". In: *Allergens and Allergen Immunotherapy.* Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp. 185-206

Vaccine A

- Oak, bayberry, Australian Pine, cedar
- Add Bahia grass and Bermuda grass

Examples of Relevant Weeds of the World*

Country	Weeds
Argentina	Short ragweed
Australia	Capeweed, wattle, plantain, dock, goosefoot family, Paterson's curse, wild mustard
Egypt	Goosefoot and pigweed families
France	Ragweed, sagebrush, plantain, pellitory, goosefoot and pigweed families
Hungary	Plantain, dock, goosefoot, hemp, ragweed, sagebrush, pigweed, cocklebur
India	Cocklebur, hemp, sagebrush, dock, goosefoot and pigweed families, castor bean, mugwort
Japan	Sagebrush, ragweed
Romania	Goosefoot, sages, ragweed

*Table represents a sampling of allergenically relevant weeds from countries throughout the world.

Mohapatra SS and Lockey RF. "Weed Pollen Allergens". In: *Allergens and Allergen Immunotherapy*. Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp 175

Cross-Reactivity Among Weeds

- Family Asteraceae (Compositae), genus *Ambrosia*: ragweeds-most cross-react extensively but:
  - 90-95% of ragweed allergic people react to Amb a 1 & Amb a 2
    - Decreasing amounts in short, western, southern, slender, giant and false ragweed
    - Southern and slender ragweed do not cross-react as well
    - Allergenic differences between major and minor allergens of short and giant ragweed that might be clinically significant.

⇒ One species, or better yet, a mixture between short and giant ragweed, may suffice but differences based on locale

Mohapatra SS and Lockey RF. "Weed Pollen Allergens". In: *Allergens and Allergen Immunotherapy*. Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp 207-222

Weber RW. Ann Allergy Asthma Immunol 2007;99(3):203-11

Cross-Reactivity Among Weeds

- Family Asteraceae (Compositae)
  - Genus *Artemisia*: sages, wormwood, mugworts
    - No Amb a 1 in cocklebur, marshelder, sages, or mugwort
    - Studies suggest strong cross-reactivity among family Artemisia species (ELISA-INH, immunoblotting).

⇒ One species should suffice

Mohapatra SS and Lockey RF. "Weed Pollen Allergens". In: *Allergens and Allergen Immunotherapy*. Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp 207-222

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Cross-Reactivity Among Weeds

- Family Amaranthaceae: pigweed, red pigweed, amaranth
  - Using rabbit antisera & double diffusion, RAST inhibition and comparative skin testing amaranth family has strong cross-reactivity

⇒ Single allergen should suffice

Mohapatra SS et al. "Weed Pollen Allergens". In: *Allergens and Allergen Immunotherapy*. Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp. 207-222

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Cross-Reactivity Among Weeds

- Family Chenopodiaceae: Russian thistle, Kochia, lamb's quarters, *Atriplex* species
  - More heterogeneity: by P-K inhibition: lamb's quarters & Russian thistle inhibit each other 50% & 75% of the time but no effect on amaranth specifies

⇒ Use locally relevant member(s)

⇒ Russian thistle may have unique allergens but appears to have most cross-reactivity

Mohapatra SS et al. "Weed Pollen Allergens". In: *Allergens and Allergen Immunotherapy*. Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp. 207-222

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Vaccine A

- Oak, bayberry, Australian Pine, cedar
- Bahia grass and Bermuda grass
- Add short ragweed, pigweed family, & lamb's quarters

Cat Allergen

- Unique allergen, not cross-reactive with other mammalian allergens

Vaccine A

- Oak, bayberry, Australian Pine, cedar
- Bahia grass and Bermuda grass
- Short ragweed, pigweed family, & lamb's quarters
- Add cat allergen

Cross-Reactivity Among Dust Mites

- *D. pteronyssinus*
- *D. farinae*

  Extensive cross-reactivity
- *B. tropicalis* – shares some cross-reactivity and species specific allergens.
- Many others (*E. maynei, L. destructor*, T. *putrescentiae, G. domesticus* (with some shared or unique allergens)

⇒Use mixture of *D. pteronyssinus* and *farinae. B tropicalis should be included if prevalent mite.*

Fernández-Caldas E et al. "Mite Allergens". In: *Allergens and Allergen Immunotherapy.* Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed, Marcel Dekker, 2004, pp. 251-270

Allergen Vaccine B

- Add Dust Mite (Dt and Df) mixture

Final Two Vaccines for Patient Two

The patient is symptomatic and allergic to many allergens

- For example:

  Vaccine A
  - Trees: oak, cedar, cypress, Australian pine, bayberry
  - Grasses: Bahia, Bermuda
  - Weeds: short ragweed, pigweed, lamb's quarter
  - Cat

  Vaccine B
  - Dust mites: *D. pteronyssinus, D. farinae*

Cross-Reactivity Between Cockroaches

- German and American cockroaches cross-react.

⇒ Equal mixture, but one or the other would suffice.

Helm RM and Pomés. "Cockroach and Other Inhalant Insect Allergens". **In: *Allergens and Allergen Immunotherapy.* Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp. 271-296**

Cox L (ed), Li J, Nelson H, Lockey R (co-eds). *Allergen Immunotherapy: A Practice Parameter Second Update. JACI* 2007;120:S25-85

Weber RW. Ann Allergy Asthma Immunol 2007;99(3):203-11

Cross-Reactivity Among Molds/Fungi

- Sampling from around the globe: most common airborne fungi: *Cladosporium*, *Alternaria*, *Penicillium*
- "Indoor": *Aspergillus, Penicillium,* and *Alternaria*
- *Cuvularia* 7th most prevalent - similar frequency also *Epicoccum, Helminthosporium*
- Some cross reactivity is found among *Alternaria*, *Stemphyllium*, and *Curvularia.*

Vijay HM and Kurup VP. "Fungal Allergens". In: *Allergens and Allergen Immunotherapy.* Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp. 223-250.

Cross-Reactivity Among Molds/Fungi

- *Fusarium* has some cross reactivity with *Alternaria*, *Penicillium*, and *Aspergillus.*
- Varying degrees of cross-reactivity among *Penicillium species*
- *Penicillium* species cross-reacts with *Aspergillus*

⇒ Molds should be used individually for optimal results.

Vijay HM and Kurup VP. "Fungal Allergens". In: *Allergens and Allergen Immunotherapy.* Lockey RF, Bukantz SC, Bousquet J (eds), 3rd ed., Marcel Dekker, 2004, pp. 223-250.

Separation of E**xtracts** with High Proteolytic Enzyme Activities, such as Fungi (Mold Spores) and Cockroach from Other Extracts/Vaccines Such as Pollens

- Mold/fungi extracts mixed with other extracts cause loss of potency of grass, cat, birch, white oak, box elder and some weeds and in some studies dust mite allergens.
- Cockroach had a similar effects on pollen extracts in some studies.
- Short ragweed –conflicting data on mixing with mold/fungi
- Dust mite extracts do not appear to have a deleterious effect on pollen allergens.

⇒These studies suggest that pollens, dust mites and cat can be mixed together.

Conclusions

1) Single allergens, where possible

2) In U.S.A., single allergens rarely possible. For multiple allergen vaccine:
   a) knowledge of most important allergens
   b) understand cross-reactivity
   c) prescribe optimal doses
   d) prescribe proper mixtures to avoid proteolytic degradation

Thank you!