Cross-Reactivity in Immunotherapy
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Introduction:

The vast majority of allergic patients in the United States are poly sensitized versus mono sensitized posing a dilemma for the physician as to what to choose for effective immunotherapy. A solid understanding of cross-reactivity and how it relates to making patient therapy vials is vital in achieving efficacious therapy levels.

The purpose of this CME article is to provide primary care clinicians with a basic knowledge of cross-reactivity utilizing established models in the current literature to prescribe adequate allergenic allergens in patient therapy vials from skin test results.

Objectives of this article are:

1. Understand relationships of family, tribe, genus and species in cross-reactivity models.
2. Choose most indigenous allergen to specific region when numerous ones are indicated.
3. Configure patient immunotherapy using cross-reactive models.

Understanding Cross-Reactivity and the Therapeutic Models it Presents:

Cross-reactivity: Cross-reactivity is the ability of the immune system to recognize similarities between different allergens, such that allergic antibodies produced against one allergen will also react against another, similar allergen. In other words a person whom is allergic to shrimp may also be allergic to Lobster or other shell fish because of cross-reactivity. This holds true for numerous aero allergens, mammalian allergens, insect allergens, basidiospores, foods and fungi.

The purpose of this study module is to address these relationships and how they can be utilized to minimize the number of allergenic allergens in patient therapy vials. Understanding cross reactivity models gives the physician useful guidance in choosing allergenic allergens best suited for the patient and minimizing the total number of allergenic allergens in a patient therapy vial. This results in greater concentrations of individual allergens in patient vials thus providing more efficacious dosing. New therapeutic models for effective immunotherapy are well represented in current medical literature. In 2011 the AAAAI published its third Immunotherapy Practice Parameter and suggested dosing requirements to establish effective symptom relieving therapy. (See table IX) (available by going to JCAAI website practice parameters). These parameters addressed the need for using fewer allergens in patient therapy vials and seeking high levels of individual allergens in said vials. This can only be accomplished by understanding and utilizing cross-reactivity models due to the high number of allergenic allergens present in the United States. Using one grass to cover numerous grasses enables the clinician to achieve proper BAU dosing.
The efficacy of immunotherapy (especially in allergic rhinitis) has been well defined over the last 92 years. Many patients who are symptomatic in the United States are poly sensitized versus mono sensitized and will skin test positive to a wide variety of allergens. In order for effective immunotherapy to be achieved in poly sensitized individuals a firm understanding of cross-reactivity is vital. Understanding the relationships between classes, sub class order, family, sub family, tribe, genus and species aides in discerning cross-reactive models.

For example strong cross-reactivity happens at the species level and genus level with varying degrees the further away from the species level you go. Current literature also shows relationships between foods, pollens, insects and mammals. These relationships are based on the identification of commonly shared proteins called pan allergens. Common pan allergen proteins are profilins, tropomyosin, and lipocalins. Pan allergens are often cited in the literature as being responsible for cross-reactivity between vastly different species and also with in species.

In examining cross-reactivity among major allergenic causing allergens a number of important factors can be surmised. In the pollen producing plants (weeds, trees, grasses) high degrees of cross-reactivity is clearly evident. Cross reactivity occurs within the Ambrosia, Chenopodium, Atriplex, Amaranthus weed family (see Table 1 below). The tree families shown to be cross-reactive are Cupressaceae, Betulaceae, Fagaceae, Oleaceae, and Populus (table 1). Grasses have shown significant cross reactivity within the Pooids, Panicoids and the Chloridoids. (see figure 1 below).

Sophisticated analytical laboratory tests such as RAST inhibition, ELISA, SDS Page, and Immunoblots have assisted in defining cross-reactivity of many aero allergens, inhalants and fungi. 3-D mapping of protein molecules will further refine cross-reactivity models enabling the clinician to, sometime in the future, choose fewer immunogenic allergens to cover numerous trees, weeds, grasses, mites, mammals, foods and fungi.

When numerous aero allergens are involved, efficacious dosing can be achieved by using cross – reactivity models. These models are well defined in current literature and have shown to be well accepted in the allergy community. Advancements in assay technologies and 3-D mapping of protein structures will lead to further in depth understandings of the immunogenicity of allergen extracts and their relationships to each other. The future immunotherapy model may simply be a few proteins representing many.
Table 1. Cross-reactive relationships in family/genus:

<table>
<thead>
<tr>
<th>Ambrosia</th>
<th>Cupressaceae</th>
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</thead>
<tbody>
<tr>
<td>Short ragweed</td>
<td>Juniper</td>
</tr>
<tr>
<td>Giant ragweed</td>
<td>Cedar</td>
</tr>
<tr>
<td>False ragweed</td>
<td>Cypress</td>
</tr>
<tr>
<td>Western ragweed</td>
<td>Betulaceae</td>
</tr>
<tr>
<td>Artemisia</td>
<td>Birch</td>
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<tr>
<td>Sages</td>
<td>Alder</td>
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<tr>
<td>Wormwood</td>
<td>Hazel</td>
</tr>
<tr>
<td>Mugworts</td>
<td>Hornbeam</td>
</tr>
<tr>
<td>Chenopodiacea</td>
<td>Hophornbeam</td>
</tr>
<tr>
<td>Russian thistle</td>
<td>Fagaceae</td>
</tr>
<tr>
<td>Lambs quarter</td>
<td>Beech</td>
</tr>
<tr>
<td>Kochia (Burning bush)</td>
<td>Oak</td>
</tr>
<tr>
<td>Atriplex</td>
<td>Chestnut</td>
</tr>
<tr>
<td>Wingscale</td>
<td>Oleaceae</td>
</tr>
<tr>
<td>Salt bush</td>
<td>Ashes</td>
</tr>
<tr>
<td>Amaranthus</td>
<td>European olive</td>
</tr>
<tr>
<td>Pigweed</td>
<td>Privit</td>
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<tr>
<td>Red root pigweed</td>
<td></td>
</tr>
<tr>
<td>Amaranth</td>
<td></td>
</tr>
<tr>
<td>Populus</td>
<td>Dust Mites</td>
</tr>
<tr>
<td>Aspen</td>
<td>D. farinae</td>
</tr>
<tr>
<td>Poplar</td>
<td>D. pteronyssinus</td>
</tr>
<tr>
<td>Cottonwood</td>
<td>Cockroach</td>
</tr>
<tr>
<td></td>
<td>American</td>
</tr>
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<td></td>
<td>German</td>
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</tbody>
</table>

Cross-reactivity exists in these families and within the genus. Example family Salicaceae, genus Populus one of the three trees covers the others.
North American grasses and their cross-reactivity relationships. The POOIDS are highly cross-reactive with each other as are the Chloridoids and the Panicoids. The Panicoids are also cross-reactive with the Pooids and the Chloridoids. The Pooids are significantly different from the Chloridoids and allergenically distinct requiring separate diagnosis and immunotherapy.

Figure 1. North American Grasses-Cross Reactivity
**Fungi Cross-Reactivity:**

The fungal allergens are more difficult to discern cross-reactive models and literature is almost nonexistent in showing solid cross-reactivity. There are however some relationships which have been established by RAST, Immunoblots, Immunoprints, CIE, and CRIE. These relationships show differing levels of cross reactivity with the strongest being at the species level and decreasing the further away from the species level you go. An example of this would be Alternaria- species are probably highly cross-reactive with each other. Whereas the family Deuteromycetes maybe cross-reactive on a lesser degree with other species such as Helminthosporium.

Vijay et al. showed these relationships in chart form in the second edition of Allergens and Allergen Immunotherapy. It is from his work certain fungi can be said to be cross reactive with others by utilizing the aforementioned assays (see figure 2 below, Ref. #8). Cross-reactivity of fungi species is difficult to ascertain due to a number of limiting assays to examine major allergen content of specific fungi, lack of potent immunogenic allergens and the mutating nature of these allergens. Most fungal allergen extracts are of poor quality and lack sufficient potency to develop adequate skin test models for cross-reactivity and to date only a few proteins have been identified.

A number of shared proteins exist in different mold species which may account for cross-reactivity within species and also families. These proteins are alkaline serine protease, serine protease, enolase and vacuolar serine protease (9). Continued efforts at identifying and mapping mold molecular structures, manufacturing stronger well defined extracts, and utilizing monoclonal antibody technology should further our understanding of mold immunotherapy and also cross-reactivity of molds.

To date the most common fungi found in air sampling are Alternaria, Aspergillus, Cladisporium, and Penicilium. Less abundant are Rhizopus, Yeasts, Epicoccum, and Fusarium. Therapeutically the two fungi which have some literature showing efficacy are Alternaria and Cladisporium. Most of the other fungi have little peer reviewed literature showing efficacy and lack double blinded placebo controlled studies. To further complicate matters many molds are referred to by numerous synonyms (e.g. Alternaria tenius /alternaria alternata). Another significant issue with the current fungi available for therapy and diagnostic purposes is the vast differences in manufacturing process and even the ability of mycologists to agree on species determination.
The understanding of the cross-reactivity of fungi assists the physician in making sound therapeutic decisions when prescribing immunotherapy. Using one species to cover many provides more efficacious dosing levels. Alternaria to cover Helminthosporium, Curvularia and Spondylocladium exemplifies this concept.

**Fungi (mold) spore cross-reactivity:**

There is data to suggest cross-reactivity with in classification and also species/families. The basidomycetes are cross reactive within themselves however no conclusive data they cross-react with the other fungi (see figure 2 below).

![Figure 2. Fungi Cross-Reactivity](image)

- Aspergillus fumigatus
- Alternaria
- Cladosporium
- Stemphylium
- Aspergillus glaucus
- Aspergillus flavus
- Curvularia
- Alternaria
- Helminthosporium
- Spondylocladium
- Basidiomycetes
  - Lentinus /Psilocybe
  - Agaricus
  - Pleurotus/ Coprinus
Mammalian Cross-Reactivity:

In the mammalian family the most prominent species causing allergic symptoms are:

- Domestic horse
- Domestic cattle
- Dog
- Cat (house)
- Old world rabbit
- Guinea pig
- Norway rat
- Mouse (house)

There is little data on cross-reactivity within these species or across the species however some data exists to show all dogs have the major allergen can f 1. Cats all have the major allergen fel d 1 and the other species all have similar major allergens. Horses have equ 1, Guinea pig cav p 1, Mouse mus m1, Rabbit ory c 1, and Rat has rat n 1 (10).

Recently there has been some discussion in the scientific literature as to cross-reactive links between species especially in allergens found in there albumin. This allergen is a lipocalin and may account for cross-reactivity between Cat and Dog (10).

The literature to date is cloudy and drawing any conclusions for cross reactivity is at best weak to moderate. Therefore until adequate data is published mammalian allergens should be considered individualized for immunotherapy and proper selection should be based on current practice standards (11).

Food Cross-reactivity:

Numerous foods have been shown to cross react with air borne pollinated plants. This cross-reactivity is usually due to profilins, carbohydrate determinants and lipid transfer proteins. Relationships often are within species and in some instances go beyond species to families. It is thought most fish species are cross-reactive and also most crustaceans. There are models of cross-reactivity which show relationships between air borne pollens (trees, weeds, grasses) and fruits/vegetables.

Birch has been shown to cross react with apple, cherry, apricot, pear, peach, plum, almond, hazelnut, mango, kiwi, strawberry, carrot, celery, parsley, chilli pepper, soybean and peanut. Mugwort with
mango, celery, carrot and some spices; grass with melon, watermelon, kiwi, orange, tomato, potato and peanut; ragweed with melon, watermelon, cantaloupe, banana, courgette and cucumber. Avocado, banana, chestnut, kiwi and fig have shown cross-reactivity to latex (12).

There appears to be some cross-reactivity between walnut, pecan, and brazil nut. Peanut is not in the nut family and is considered a legume. Peanut is a potent allergen and has a high incidence of sensitization in food allergic patients (13).

A basic understanding of food allergy can assist the clinician in making good clinical decisions when prescribing Aero allergen immunotherapy. Understanding some foods cross-react with Aero allergens can be beneficial during the immunotherapy program. For instance one may want to advise patients who receive ragweed immunotherapy to be aware of the cross-reactivity of certain foods with ragweed to possibly prevent adverse reactions.

**Examples:**

1. Patient T.W. has been skin tested and is positive to the following Aero allergens:
   - Timothy grass, Kentucky grass, Sweet vernal grass, Redtop, Johnson grass, Bermuda grass.
   - Cottonwood, Popular, Mt. Cedar, Cypress and Oak trees.
   - Russian Thistle, Kochia, and Pigweed.
   - Using cross reactivity models his therapy vial could contain the following allergens:
   - Timothy, Johnson and Bermuda grasses. Cottonwood, Mt. Cedar and Oak trees. Kochia and Pigweed. (14 allergens covered by 8.)

2. Patient S.W. has been skin tested and is positive to the following Aero allergens and fungi.
   - Alternaria, Hormodendrum Cladisporides, Penicilliam, Aspergillus, Curvularia, Fusarium, Ragweed, Oak, Timothy grass, Bermuda grass, Mite, Cat.
   - Utilizing cross-reactivity the molds could be trimmed down to Alternaria and Aspergillus.
References:


