
CME review

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Cross-reactivity of pollen allergens: impact on allergen immunotherapy

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Objective: To provide guidelines for the rational formulation of allergen immunotherapy extracts based on knowledge of pollen allergen and epitope cross-reactivity.

Data Sources: A PubMed search was performed for articles published from 1966 to 2007 using the keywords *pollen*, *allergen*, and *cross-reactivity*. Older literature was found through cross-referencing of older articles and older reviews on pollen cross-reactivity.

Study Selection: Articles that dealt with crude pollen extracts and characterized allergens that addressed cross-reactivity were selected for inclusion in this review.

Results: In addition to unique allergens, several families of botanic proteins have similarities that allow them to act as pan-allergens. Although frequently these are minor allergens, in some circumstances they may also be major allergens. Recent studies have investigated nonspecific lipid transfer proteins, calcium-binding proteins, pathogenesis-related protein families, and profilins. Calcium-binding proteins and nonspecific lipid transfer proteins are responsible for pollen-fruit interactions and pollen cross-reactivity. Clarification of pollen allergen enzymatic activity helps explain the ubiquitous nature of these proteins.

Conclusion: Characterization of specific pollen allergens and their protein families has provided insight into cross-reactivity. Clarification of these relationships allows for consolidation or substitution in formulation of inhalant extracts.

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INTRODUCTION

Formulation of inhalant allergen immunotherapy is affected by the relationships of pollen allergens, a crucial issue with diminishing availability of pollen extracts. As optimal allergen doses become clarified, cross-reactivity should affect formulation. Adverse reactions due to inadvertent overdosing can occur if cross-reactivity is ignored. Plant systematics (taxonomy) is becoming more precise secondary to techniques such as amino acid and gene sequencing.¹ Cloning of recombinant allergens has identified homologous proteins and clarified functions. It has now been suggested that protein family content (molecular classification) rather than botanical

taxonomy is a superior way to address cross-reactivity issues.² However, as has been shown with profilins, even a high degree of amino acids homology does not always mean strong cross-reactivity.³

This review was performed to provide guidelines for the rational formulation of allergen immunotherapy extracts based on knowledge of pollen allergen and epitope cross-reactivity. A PubMed search was performed for articles published from 1966 to 2007 using the keywords *pollen*, *allergen*, and *cross-reactivity*. Older literature was found through cross-referencing of older articles and older reviews on pollen cross-reactivity. Articles that dealt with crude pollen extracts and characterized allergens that addressed cross-reactivity were selected for inclusion in this review.

For the purposes of this review, it remains useful to discuss pollen cross-reactivity and the implications on allergen extract formulation in terms of botanical groupings. Although there is much research on pollen and plant-food interactions

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due to shared allergen families, this topic is less germane to extract formulation and is therefore not discussed in detail herein. In addition, readers should remember that older techniques of raising animal antisera (IgG cross-reactivity) and IgE-binding immunoblots that use human antisera may show disparate results. IgG techniques such as passive double immunodiffusion (Ouchterlony technique) and crossed immunoelectrophoresis tended to suggest higher levels of cross-reactivity, whereas IgE-binding immunoblots or radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA) inhibition curves tended to show lesser degrees of cross-reactivity.

CONIFERS: GYMNOSPERMS

In distinction to the relative insignificance of the pine family, Pinaceae, the cypress family, Cupressaceae, is the most allergenic family in the order Coniferales. This family, which includes the subfamily Taxodioideae, contains cypress (*Cupressus* and *Chamaecyparis* spp), cedar and juniper (*Juniperus* spp), bald cypress (*Taxodium distichum*), redwood and sequoia (*Sequoia* spp), and Japanese red cedar (*Cryptomeria japonica*) (Table 1). Members are strongly cross-reactive, with animal antisera and human IgE antibodies studies demonstrating consistent cross-inhibition. Older literature has demonstrated the interchangeability of Cupressaceae member crude extracts.⁴ Strong homology has been demonstrated between the major (group 1) allergens of the various species. Although amino acid sequences are highly homologous among group 1 allergens, glycosylation sites may differ.⁵ Midoro-Horiuti and coworkers⁶ have mapped 2 of 3 major linear IgE epitopes of Jun a 1 to a highly conserved region of a pectate lysate catalytic site, an enzyme important during

fertilization. A carbohydrate epitope, found also in unrelated pollens, is present in high density in the pollen exine.⁷ However, van Ree⁸ has recently suggested that only a few sensitized patients recognize the carbohydrate moiety as an IgE epitope. Japanese cedar Cry j 2 has been identified as a polymethylgalacturonase, a member of an enzyme family found in both pollen and fruits.⁹ Tinghino and coworkers¹⁰ found that Jun o 4 from prickly juniper, *Juniperus oxycedrus*, is a calcium-binding protein. Emphasizing the ubiquity of these proteins, immunoblotting studies revealed inhibition by family members and the unrelated pollens olive (*Olea europaea*) and ryegrass (*Lolium perenne*), with lesser inhibition by pellitory (*Parietaria officinale*).

GRASSES: MONOCOT ANGIOSPERMS

Results from crude extract inhibition studies can be summarized as follows: Pooideae subfamily members (northern pasture grasses) strongly cross-react; Chloridoideae members Bermuda (*Cynodon dactylis*), grama (*Bouteloua gracilis*), and salt grass (*Distichlis stricta*) are cross-inhibitory, with Bermuda being the most potent; and Panicoideae members Johnson (*Sorghum halepense*) and Bahia (*Paspalum notatum*) grasses show a mixed pattern⁴ (Table 2). Fourteen grass allergen groups have been fairly well characterized; groups 1, 2/3 (groups merged), and 5 (old group 9), and probably groups 4 and 11 as well, are major allergens.¹¹ Group 1 allergens are β -expansins, papain-related cysteine proteinases.¹² Older work demonstrated homology within group 1 allergens and to group 2/3 allergens; additionally, T-cell epitopes are shared between group 1 and group 5 allergens.⁴ Explaining lack of cross-reactivity between temperate and southern grasses, Smith and colleagues¹³ found group 1 al-

Table 1. Conifer Order (Coniferales) Pollen Interrelationships

Family or subfamily and genus and species	Common name	Comments
Cupressaceae		Strong cross-allergenicity within family based on marked homology of group 1 and 2 major allergens. Weak cross-allergenicity with angiosperms may be due to group 4 calcium-binding proteins.
<i>Juniperus ashei</i>	Mountain cedar	
<i>Juniperus oxycedrus</i>	Prickly juniper	
<i>Cupressus arizonica</i>	Arizona cypress	
<i>Chamaecyparis lawsonia</i>	Port Orford cypress	
<i>Thuja plicata</i>	Western red cedar	
Taxodioideae		
<i>Cryptomeria japonica</i>	Japanese red cedar	
<i>Taxodium distychum</i>	Bald cypress	
<i>Sequoia sempervirens</i>	Coast redwood	
Pinaceae		Weak cross-allergenicity with angiosperms may be due to calcium-binding proteins.
<i>Pinus sylvestris</i>	Scotch pine	
<i>Pinus radiata</i>	Monterey pine	
<i>Pinus strobus</i>	White pine	
<i>Picea abies</i>	Norway spruce	
<i>Tsuga canadensis</i>	Eastern hemlock	
<i>Pseudotsuga menziesii</i>	Douglas fir	

Table 2. Grass Family (Poaceae) and Grass Allergen Pollen Interrelationships

Family or subfamily and genus and species	Common name	Comments
Pooideae		Strong cross-allergenicity based on marked homology of group 1, 2/3, and 5 major allergens. Timothy and sweet vernal may each have unique allergens.
<i>Poa pratensis</i>	Kentucky blue	
<i>Phleum pratense</i>	Timothy	
<i>Dactylis glomerata</i>	Orchard	
<i>Festuca rubra</i>	Fescue	
<i>Anthoxanthum odorata</i>	Sweet vernal	
<i>Lolium perenne</i>	Perennial ryegrass	
<i>Phalaris canariensis</i>	Canary	
Chloridoideae		Cross-reactivity among members, with Bermuda the strongest inhibitor. Lack of group 2 and 5 allergens accounts for little cross-allergenicity with Pooideae.
<i>Cynodon dactylis</i>	Bermuda	
<i>Buchloe dactyloides</i>	Buffalo	
<i>Distichlis stricta</i>	Salt	
<i>Bouteloua gracilis</i>	Grama	
Panicoideae		Lack of group 2 and 5 allergens accounts for little cross-allergenicity with Pooideae. More cross-reactivity with Pooideae than Chloridoideae.
<i>Sorghum halepense</i>	Johnson	
<i>Zea mays</i>	Corn	
<i>Paspalum notatum</i>	Bahia	
<i>Saccharum officinarum</i>	Sugarcane	
Juncaceae		Cross-allergenicity within families. No cross-reactivity with Poaceae.
<i>Juncus effusus</i>	Soft rush	
Cyperaceae		
<i>Cyperus esculentus</i>	Yellow nutsedge	
<i>Carex aquatilis</i>	Sedge	
Typhaceae		
<i>Typha latifolia</i>	Cattail	
<i>Typha angustifolia</i>	Narrowleaf cattail	
Areceae		
<i>Phoenix dactylifera</i>	Date palm	

lergens in both Pooideae and Panicoideae; however, they did not find group 5 allergens in other than the Pooideae subfamily, and some epitopes were not even found outside the tribe Poeae. Davies and colleagues¹⁴ examined ryegrass, canary (*Phalaris canariensis*), Bahia, and Bermuda grasses with IgE antibodies to Lol p 1 and Lol p 5 and demonstrated reactivity with the former but not the latter 2 grasses; timothy, canary, and ryegrass could inhibit ryegrass and Bahia; Bahia, Johnson, and Bermuda did not inhibit ryegrass.

Grass group 7 minor allergens are 2-EF hand calcium-binding proteins, with cross-reactivity seen among Phl p 7, Cyn d 7, Bet v 4, Aln g 4, Ole e 3, and Bra n 1.^{15,16} Lol p 11 is 32% homologous with soybean trypsin inhibitor without the active enzyme site: despite not being homologous with other grass allergen groups, similarity was found with orchard (*Dactylis glomerata*), fescue (*Festuca rubra*), and timothy (*Phleum pratense*) grasses and with corn (*Zea mays*) and tomato (*Solanum lycopersicum*) pollen proteins. In addition, Lol p 11 was 44% homologous with the major olive allergen, Ole e 1.¹⁷ Bermuda grass profilin, Cyn d 12, shares B-epitopes with sunflower (*Helianthus annuus*) profilin.¹⁸ Niederberger and associates,¹⁹ using rPhl p 1, rPhl p 2, rPhl p 5, and birch profilin rBet v 2,

found that IgE to the 4 recombinant proteins accounted for a mean 59% of grass pollen specific IgE. Polygalacturonases have been recently identified as important grass pollen allergens and designated as group 13.²⁰ These pectin-degrading enzymes have been isolated as food allergens as well.

Other monocots show within family cross-reactivity but little to no cross-inhibition with grasses.⁴ Asturias and co-workers²¹ demonstrated a date palm (*Phoenix dactylifera*) major allergen, Pho d 2, to be a profilin. IgE cross-reactivity was shown with perennial ryegrass, olive, and annual mercury (*Mercurialis annua*).

TREES AND WEEDS: TRICOLPATE ANGIOSPERMS

The tricolpate angiosperm group includes most flowering trees and weeds. There are 3 large subgroups of the core tricolpate clade with major interest to allergists: the superorder Caryophyllanae, the Rose subclass Rosidae, and the Aster subclass Asteridae¹ (Table 3 and Table 4).

Platanaceae is a family that contains sycamore (*Platanus occidentalis*) and plane tree (*Platanus acerifolia*), lying within the separate basal tricolpate clade. Three allergens from

Table 3. Rose Subclass (Rosidae) Pollen Interrelationships

Family or subfamily and genus and species	Common name	Comments
Sapindaceae		Disparity between <i>Acer negundo</i> and other <i>Acer</i> spp.
<i>Acer negundo</i>	Box elder	
<i>Acer rubrum</i>	Red maple	
Malvaceae		
<i>Tilia americana</i>	Basswood (linden)	
Brassicaceae		
<i>Brassica napus</i>	Oilseed rape	
Euphorbiaceae		
<i>Mercurialis annua</i>	Annual mercury	
Salicaceae		Strong skin test correlations.
<i>Salix nigra</i>	Black willow	
<i>Populus deltoides</i>	Eastern cottonwood	
<i>Populus tremuloides</i>	Aspen	
Fabaceae		
<i>Prosopis juliflora</i>	Mesquite	
Elaeagnaceae		Questionable cross-reactivity with Oleaceae.
<i>Elaeagnus angustifolia</i>	Russian olive	
Urticaceae		Little cross-reactivity.
<i>Urtica dioica</i>	Nettle	
<i>Parietaria judaica</i>	Pellitory	
Ulmaceae		
<i>Ulmus americana</i>	American elm	
Celtidaceae		
<i>Celtis occidentalis</i>	Hackberry	
Moraceae		
<i>Morus rubra</i>	Red mulberry	
Juglandaceae		Strong to moderate skin test correlations.
<i>Juglans nigra</i>	Black walnut	
<i>Carya ovata</i>	Shagbark hickory	
<i>Carya illinoensis</i>	Pecan	
Betulaceae		Strong cross-allergenicity among Betulaceae members based on homology of group 1 and 2 allergens. Fairly strong cross-allergenicity between Betulaceae and Fagaceae members based on homology of group 1 and 2 allergens.
<i>Betula verrucosa</i>	Silver birch	
<i>Alnus glutinosa</i>	European alder	
<i>Corylus avellana</i>	Hazelnut (filbert)	
<i>Carpinus betulus</i>	Hornbeam	
<i>Ostrya virginiana</i>	Eastern hophornbeam	
Fagaceae		
<i>Fagus sylvatica</i>	European beech	
<i>Quercus alba</i>	White oak	
<i>Quercus rubra</i>	Red oak	

London plane tree have been identified: the major allergen Pla a 1 is an 18-kDa invertase inhibitor, Pla a 3 is a 10-kDa lipid transfer protein (LTP), and Pla a 2 is a 43-kDa polygalacturonase.²² Pla a 2 is reactive with 84% of plane tree-sensitized patient sera, representing 52% of total IgE-binding capacity of *P. acerifolia* extract. Cross-reactivity of IgG antibodies has been shown with tomato and Cupressaceae pectate lyases. Studies of *P. acerifolia* profilin show that it cannot account for cross-inhibition of plane tree pollen extracts and food allergens.²³ Pla a 3 shows differing IgE specificity than the LTP from peach (*Prunus persica*), Pru p 3.²⁴

Superorder Caryophyllanae

Older literature concerning cross-allergenicity within the latter shows almost complete allergenic identity of the *Amaranthus* species redroot pigweed (*Amaranthus retroflexus*) and Palmer's amaranth (*Amaranthus palmerii*) and among *Atriplex* scales. Other members of Chenopodioideae show greater diversity, and Russian thistle (*Salsola pestifer*) appears to possess significant unique allergens.⁴ Lamb's quarter (*Chenopodium album*) appears to have cross-reactivity with *Amaranthus* and *Atriplex* genera, as well as other family members.⁴ Despite 27% to 45% identity with members of the Ole

Table 4. Tricolpate Angiosperm Pollen Interrelationships^a

Family or subfamily and genus and species	Common name	Comments
Plantanaceae		
<i>Platanus acerifolia</i>	Plane tree	
Caryophyllanae		
Amaranthaceae		Strong cross-allergenicity among amaranths. Strong cross-allergenicity among <i>Atriplex</i> species. Chenopodioidae members show greater diversity, with variable degrees of reactivity. Russian thistle may possess unique allergens.
<i>Amaranthus palmeri</i>	Palmer's amaranth	
<i>Amaranthus retroflexus</i>	Redroot pigweed	
Chenopodioidae		
<i>Chenopodium album</i>	Lamb's quarter	
<i>Kochia scoparia</i>	Burning bush	
<i>Salsola pestifer</i>	Russian thistle	
<i>Atriplex canescens</i>	Wingscale	
<i>Atriplex wrightii</i>	Annual saltbush	
Polygonaceae		
<i>Rumex acetosella</i>	Sheep sorrel	
Asteridae		
Plantaginaceae		
<i>Plantago lanceolata</i>	English plantain	
Oleaceae		
<i>Olea europaea</i>	Olive	Strong cross-allergenicity among Oleaceae members due to homology of group 1 allergens. Group 3 calcium-binding proteins cross-react within and across families.
<i>Fraxinus excelsior</i>	European ash	
<i>Ligustrum vulgare</i>	Privet	
<i>Syringa vulgaris</i>	Lilac	
Asteraceae		
<i>Ambrosia artemisiifolia</i>	Short ragweed	Strong cross-allergenicity among short, giant, western, and false ragweeds.
<i>Ambrosia trifida</i>	Giant ragweed	Strong cross-allergenicity across <i>Artemisia</i> species. Minor to little cross-reactivity among ragweeds and mugwort, marshelder, or cocklebur.
<i>Ambrosia psilotachya</i>	Western ragweed	
<i>Ambrosia acanthicarpa</i>	False ragweed	
<i>Ambrosia tenuifolia</i>	Slender ragweed	
<i>Ambrosia bidentata</i>	Southern ragweed	
<i>Ambrosia ambrosioides</i>	Canyon ragweed	
<i>Xanthium communis</i>	Cocklebur	
<i>Iva xanthifolia</i>	Burweed marshelder	
<i>Helianthus annuus</i>	Sunflower	
<i>Artemisia vulgaris</i>	Mugwort	
<i>Artemisia tridentata</i>	Giant sagebrush	

^a Rosidae subclass: see Table 3.

e 1-like protein family, no significant IgE cross-reactivity has been found between Che a 1 and Ole e 1, with only low-level IgG cross-reactivity.²⁵ Barderas et al²⁶ isolated and sequenced Che a 2, a profilin, and Che a 3, a polcalcin, which they believe are of greater relevance than Che a 1. Strong cross-reactivity was found between the corresponding olive allergens Ole e 2 and Ole e 3 and 65% to 82% identity with similar proteins from birch (*Betula verrucosa*), alder (*Alnus glutinosa*), rapeseed (*Brassica napus*), and timothy pollens.

Subclass Rosidae

Crude extracts of pellitory (*Parietaria judaica*) and nettle (*Urtica dioica*), despite being in the same family (Urticaceae), do not cross-react. The major *P. judaica* pollen allergens, Par j 1 and Par j 2, are nonspecific LTPs (nsLTP) and exhibit significant sequence homology.²⁷ Another mem-

ber of Urticaceae, *Holoptelea integrifolia*, although not containing a Par j 1 homolog, shows immunoblot cross-inhibition with pellitory.²⁸ Asero and colleagues²⁹ could not show cross-inhibition between profilins of pellitory, grass, or birch, whereas Asturias and associates³⁰ reported cross-reactivity with recombinant profilin Par j 3.

The Euphorbiaceae member annual mercury has a profilin major allergen, Mer a 1, which shares B-epitopes with sunflower profilin, reacting also with olive and castor bean (*Ricinus communis*) pollens.³¹ *Hevea brasiliensis* latex profilin is highly cross-reactive with ragweed but not annual mercury profilin.³² Ragweed (*Ambrosia* spp), mugwort (*Artemisia vulgaris*), and timothy extracts can inhibit IgE binding to latex immunoblots, but Bet v 1 and birch profilin Bet v 2 cannot.³³

Older studies on Salicaceae that used P-K neutralization, passive hemagglutination inhibition, and skin tests suggest strong cross-reactivity within the family and moderate cross-reactivity with Fagales.⁴ Older skin test comparisons between shagbark hickory (*Carya ovata*) and pecan (*Carya illinoensis*) show high correlations and moderate correlations with these and black walnut (*Juglans nigra*).⁴ Skin test correlations, RAST, P-K neutralization, and RAST inhibition support the cross-reactivity between Betulaceae and Fagaceae, with the former containing members such as birch, alder, hazel (*Corylus avellana*), and hornbeam (*Carpinus* spp) and the latter containing beech (*Fagus* spp), oak (*Quercus* spp), and chestnut (*Castanea sativa*). RAST inhibition studies support some cross-reactivity between Fagales members and ash (*Fraxinus* spp), elm (*Ulmus* spp), and willow (*Salix* spp).⁴

Betulaceae pollen allergen studies show strong homology between Bet v 1, a pathogenesis-related protein group 10 member, and the other family group 1 allergens.^{34,35} Bet v 2 is a profilin, and Bet v 3 and Bet v 4 are calcium-binding proteins.^{36,37} Bet v 5, an isoflavone reductase-related protein, has cross-reactivity to pear (*Pyrus communis*) and lychee (*Litchi chinensis*) food allergens.³⁸ Bet v 2, Bet v 3, Bet v 4, and Bet v 5 are all minor allergens. Cross-reactivity among birch, mugwort, and celery (*Apium graveolens*) has been demonstrated with Bet v 1, Bet v 2, and 46- to 60-kDa allergens.³⁹ Recombinant Aln g 2 cross-reacts with an oilseed rape allergen, whereas the polcalcin Aln g 4 shares IgE epitopes with allergens from various pollens.^{40,41} According to Neudecker and coworkers,⁴² structural similarity accounts for the strong IgE cross-reactivity between Bet v 4 and Phl p 7, despite differences in oligomerization. Hazel pollen Cor a 10 is a heat shock protein 70 family chaperon luminal binding protein that shows 88% to 92% sequence identity with similar proteins from soy (*Glycine soja*), tobacco (*Nicotiana tabacum*), corn, and tomato.⁴³

Two oilseed rape pollen allergens are a calcium-binding protein homologous to Aln g 2 and a profilin.⁴⁴ Higher-molecular-weight allergens are glycoproteins that inhibit timothy grass group 4 allergens. Immunoblot inhibition with mesquite, *Prosopis juliflora*, shows relationships with *Ailanthus excelsa*, *Cassia siamea*, and *Salvadora persica*, all common trees in India.⁴⁵

Subclass Asteridae

Oleaceae shows strong cross-reactivity among family members such as olive, ash, *Forsythia*, lilac (*Syringa vulgaris*), and privet (*Ligustrum vulgare*).⁴ Ten olive allergens have been characterized: Ole e 2 is a profilin, Ole e 5 is a Cu/Zn superoxide dismutase, Ole e 3 and Ole e 8 are calcium-binding proteins, 2- and 4-EF hand, respectively, and Ole e 9 and Ole e 10 have 1,3- β -glucanase activity.⁴⁶⁻⁴⁸ Obispo and colleagues⁴⁹ raised monoclonal antibodies against the 17- to 19-kDa major allergen of olive, Ole e 1, and showed by crossed radioimmuno-electrophoresis and sodium dodecyl sulfate-polyacrylamide gel electrophoresis antigenic and allergenic epitope sharing among Ole 1, Fra e 1, Lig v 1, and Syr

v 1. N-terminal sequencing showed identity of the first 20 amino acids among these allergens. Martin-Orozco and associates⁵⁰ demonstrated that all 4 had 18- and 20-kDa Ole e 1 isoallergen homologues and forsythia had a 50- to 55-kDa cross-reactive protein. Ole e 1 has a single glycosylation site, which is an IgE-binding epitope.⁵¹ Antibodies directed against this glycan moiety cross-react with horseradish peroxidase, bromelain, and ascorbate oxidase. Study of the calcium-binding motifs of Ole e 3 and Ole e 8 did not reveal any significant IgE cross-reactivity.⁴⁶ Ole e 9 and Ole e 10 have 53% identity, the latter sharing IgE B-cell epitopes with several pollen and vegetable proteins.⁴⁸ Numerous ash allergens have been demonstrated by Niederberger and colleagues: Fra e 1, the Ole e 1 homolog; a profilin homolog of Bet v 2; a 2-EF hand calcium-binding protein cross-reactive with Phl p 7; a 35-kDa allergen cross-reactive with birch, ragweed, and olive; and high-molecular-weight components.⁵² The lilac polcalcin, Syr v 3, shows cross-reactivity with Ole e 3, Che a 3, and Phl p 7.⁵³ Older ELISA inhibition studies suggested that Russian olive (*Elaeagnus angustifolia*) in Elaeagnaceae cross-reacts with members of Oleaceae.⁵⁴ However, Sastre and coworkers⁵⁵ in Spain showed that *E angustifolia* could not inhibit olive (*O europaea*), whereas the latter inhibited the former up to 40%.

Allergenic similarity of short (*Ambrosia artemisiifolia*), giant (*Ambrosia trifida*), western (*Ambrosia psilotachya*), and false ragweed (*Ambrosia acanthicarpa*) crude extracts has been shown by various techniques.^{4,56} Short ragweed allergens Amb a 1, 2, 3, and 5 to 10 have been characterized; the most important is Amb a 1. Ninety to ninety-five percent of people allergic to ragweed will react to Amb a 1 and Amb a 2. The other allergens are minor: Amb a 3 and 7 are plastocyanins, Amb a 6 is an nsLTP, Amb a 8 is a profilin, and Amb a 9 and 10 are polcalcins. Amb a 1 has been found in short, giant, southern, and false ragweed, with minimal amounts in slender ragweed (*Ambrosia tenuifolia*), and no Amb a 1 was found in cocklebur (*Xanthium communis*), marshelder (*Iva xanthifolia*), sages and mugwort (*Artemisia* spp), or plantain (*Plantago lanceolata*).⁵⁷ Lee and Dickinson⁵⁸ found decreasing amounts of Amb a 1 in short, western, southern (*Ambrosia bidentata*), canyon (*Ambrosia ambrosioides*), slender, giant, and false ragweed, respectively, as well as in cosmos (*Cosmos bipinnatus*), but not in sunflower, narrowleaf marshelder (*Iva angustifolia*), or spiny cocklebur (*Xanthium spinosum*).

Katial and colleagues⁵⁹ found overlapping ELISA inhibition curves in 9 *Artemisia* species and virtually complete immunoblot inhibition. Brandys and coworkers⁶⁰ showed strong cross-reactivity between giant sagebrush (*Ambrosia tridentata*) and 5 Eurasian sages. Hirschwehr and associates⁶¹ demonstrated that Art v 1 was shared by short ragweed and there was cross-reactivity with Bet v 2. Art v 1 is a 10.8-kDa defensin-like glycoprotein that contains 2 unique O-glycans, one probably a cross-reactive carbohydrate determinant.^{62,63} Art v 2 is a 35-kDa glycoprotein, Art v 3 is a 13-kDa nsLTP with cross-reactivity to peach allergen Pru p 3, and Art v 4 is

a profilin.^{64,65} Asero and coworkers⁶⁶ looked at the skin test results of 372 ragweed and/or mugwort sensitized patients, and 42 patient serum samples were examined with several recombinant allergens from both plants using ELISA and immunoblot inhibition. They believed that their results supported cosensitization rather than cross-reactivity.

Thirteen allergens have been described in *H annuus* pollen, with two 24- to 25-kDa proteins reacting with 95% to 100% of the patient serum samples.⁶⁷ RAST and immunoblot inhibitions revealed greatest cross-reactivity with mugwort, then oxeye daisy (*Chrysanthemum leucanthemum*), dandelion (*Taraxacum officinale*), and goldenrod (*Solidago gigantea*), with short ragweed the least. Hel a 2 has been identified as a strongly cross-reactive profilin.⁶⁸

DISCUSSION

Based on these observations, certain recommendations can be made concerning allergen extract choices for diagnosis and immunotherapy. Such recommendations are meant as guidelines only, to be tempered by regional factors such as floral prevalence. Where related plants appear to have adequate cross-reactivity and extracts have similar potency, it appears wise to use the most prevalent local member.

Concerning conifers, the older literature showing interchangeability of extracts within the Cupressaceae family is well supported by recent allergen characterization. Therefore, a single family member, perhaps *Juniperus ashei*, would be adequate coverage in extract formulation. Pinaceae sensitivity, if clinically relevant, needs to be treated separately. No significant cross-reactivity is found between conifers and flowering plants; the minor reactivity seen, due to pan-allergens such as profilin, is not clinically important.

Within the Pooideae subfamily of northern pasture grasses, cross-allergenicity is strong because of the marked homology of major allergen groups 1, 2/3, and 5. Therefore, 1 of 2 members should suffice for treatment, and timothy has been shown to be an adequate choice to represent the subfamily and may possess some unique allergens based on older work. Use of additional members may be appropriate for optimal concentration of allergen groups. Consider sweet vernal where prevalent, since older work suggests some unique allergens; otherwise, June or perennial ryegrass are good choices. Panicoideae and Chloridoideae subfamilies have greater diversity, and the lack of group 2 and 5 allergens accounts for differences with northern pasture grasses. Therefore, members of these tribes should be tested for and treated separately. Southern grasses such as Bermuda, Bahia, and even Johnson grass need to be treated separately. Chloridoideae members are cross-reactive, with Bermuda grass being most potent, and the appropriate choice to cover other members such as certain prairie grasses. The cross-reacting profilins and calcium-binding proteins are minor allergens of grasses, of little practical consequence in vaccine formulation. Grass allies, such as palm or sedge, if thought to be clinically relevant, need to be treated separately.

Diversity is the rule among tricolpate angiosperms, and lack of cross-reactivity is the rule even to the level of tribe. There are exceptions, with significant cross-reactivity across certain family boundaries. In Amaranthaceae weeds, *Amaranthus* and *Atriplex* species can each be represented by single members, but the other locally relevant members need to be addressed separately. Russian thistle possesses unique allergens and needs to be treated separately.

The order Fagales shows strong cross-allergenicity within the birch family and extending to the beech family. Use of the locally prevalent Betulaceae member, frequently birch or alder, should cover other family members as well. In areas where oaks are predominant, *Quercus* would be expected to cover birch. With other members of the Rosidae subclass, generally one member of a family can be expected to be adequate for immunotherapy, although there are exceptions such as nettle and pellitory, which share no significant cross-allergenicity.

Oleaceae members are strongly cross-reactive. In areas where European olive is grown, it seems the proper choice, whereas in areas where ash is prevalent, it should be adequate.

Asteraceae members show variable cross-reactivity. The 4 major ragweeds (short, giant, western, and false) strongly cross-react, and 1 or 2 are adequate. In areas where the sages (*Artemisia*) or marshelders (*Iva*) are common, these need to be handled separately. Since *Artemisia* species are strongly cross-allergenic, it is not necessary to skin test or treat with multiple members. In the Midwest and West, choose common sagebrush, *A tridentata*, whereas in the eastern states and Europe, mugwort, *A vulgaris*, seems most appropriate.

In conclusion, refinement of plant systematics with clarification of phylogenetic relationships has demonstrated that certain basic premises hold true: cross-allergenicity reflects taxonomy in most cases, with more distantly related plants showing fewer shared allergenic proteins. However, the contradictory observation of unexpected cross-reactivity between distantly related plants flies in the face of the premise that taxonomy dictates cross-reactivity. Advances in gene sequencing and cloning of proteins have illustrated that there are many tightly preserved proteins, even from plants to animals, such as profilins, LTPs, and pathogenesis-related proteins. The small differences that exist between these ubiquitous presumably vital proteins explain why these are frequently only minor allergens. Clarification of allergen groups in important aeroallergenic plant sources explains earlier clinical observations and cross-reactivity experiments with crude allergen extracts. It is hoped that these observations will provide a rational structure for decisions of extract formulation.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

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CME Examination

1–5, Weber RW. 2007;99:203–212.

CME Test Questions

1. The lack of significant cross-reactivity between northern pasture grasses (Pooideae) and southern grasses such as Bermuda (Chloridoideae) is due to which of the following?
 - a. strong homology of allergen groups 1, 2/3, and 5
 - b. lack of group 2 and 5 allergens in Chloridoideae
 - c. allergen uniqueness of timothy and sweet vernal grasses
 - d. strong reactivity between Chloridoideae and Panicoideae precludes reactivity with Pooideae
 - e. none of the above
2. Which of the following pairs have a major allergen group 1 protein shown to have pectate lyase activity?
 - a. *Parietaria* and *Urtica*
 - b. *Artemisia* and *Ambrosia*
 - c. *Ambrosia* and *Juniperus*
 - d. *Betula* and *Quercus*
 - e. *Olea* and *Chenopodium*
3. For which of the following weeds is a nonspecific lipid transfer protein a major allergen?
 - a. timothy grass
 - b. privet
 - c. forsythia
 - d. lamb's quarter
 - e. pellitory
4. Which of the following pairs show strong enough cross-reactivity not to require separate treatment?
 - a. Palmer's amaranth and redroot pigweed
 - b. pellitory and nettle
 - c. mugwort and short ragweed
 - d. Bahia and perennial ryegrass
 - e. Australian pine and Monterey cypress
5. Which of the following family pairs show strong homology of their group 1 allergens?
 - a. grass and palm
 - b. aster and plane tree
 - c. amaranth and olive
 - d. beech and birch
 - e. willow and elm

Answers found on page 231.
