Respiratory Allergen-Immunotherapy



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Any One Can Do Allergy Skin Tests & Blood Specific IgE Test

Few Do It Well, & Can Interpret The **Positivity** by Allergy Skin Test & Blood Specific IgE Test as Sensitization vs. Clinical Allergy

> Fewer Still Can Interpret clinically & Select The Allergens For Specific Immunotherapy

> > Dr. P.C Kathuria

Allergic Respiratory Diseases

- Allergic rhinitis (IgE)
 Allergic asthma (IgE)
- Allergic Bronchopulmonary Aspergillosis -> (IgE + IgG)
- Hypersensitivity Pneumonitis -> (IgG + Lymphocytosis)
- Aspirin exacerbated respiratory disease (Non IgE)





Influence of Anti-Allergic Drugs



These options only provide symptomatic treatment

Global Prevalence Of Sensitivity To Allergens In Allergic Rhinitis (% Of Allergic Population)

Allergen US EU 52% 56% Grasses 45% House dust mite 49% Ragweed 49% n/a 23% 14% Birch Weed 27% n/a Japanese cedar 10% n/a 39% 30% Cat 19% Dog n/a





Percentage Prevalence of Allergens



Environmental Factors: Action - Advice on allergens avoidance

-Animals outside the home (cats, dogs, hamsters) Dust Mites: Allergy Waterproof Cases Damp cloth and vacuum Home Humidity <50% No carpets in the bedroom Washing with hot water weekly Pollens: Close windows in time of pollination Snuff: Avoid smoking and passive exposure Fungi: Remove mildew stains on the walls Avoid wood stoves, smoke, air fresheners, etc..

Avoid w









These precautions alone are insufficient for significant improvements in symptomology.



Allergen Immunotherapy: What can we expect?

Improved efficacy over symptomatic medication

Cost-effectiveness over symptomatic treatment

Early onset of efficacy

Sustained/increasing efficacy

Long-lasting effect

Prevention of sensitizations

Prevention of asthma

Reduction for the need of steroids in asthamatic children

Matricardi PM et al., JACI 2011;128:791-9. Wahn U et al., J Allergy Clin Immunol 2012;130:886-93. Kuna P et al., JACI 2011;127:502-8. Jacobsen et al. Allergy 2007: 62: 943–948. Bozek et al., J Allergy Ther 2014, 5:4. Zielen S et al., J Allergy Clin Immunol 2010;126:942-9. Meadows A et al. Health Technol Assess 2013 Jul;17(27):1-336. Eng PA, et al. Allergy 2006;61:198-201.

Efficacy Data: Cochrane Review & Cochrane method Meta-analyses



$\frac{\text{Mechanism of Action of Allergen Immunotherapy}}{\text{Immuno regulatory cytokines} \longrightarrow (IL-10 \& TGF-\beta)}$



Source: Immunotherapy © 2012 Future Medicine Ltd.

Improvement of Symptoms and Reduction in Medication and Bronchial Hyperrespoonsiveness after Immunotherapy*

Outcome measure	Immunotherapy	<u>target</u>
	House-dust mite*	Other Allergens*, #
Symptom improvement	2.7 (1.7 – 4.4)	4.8 (2.3-10.1)
Reduction in medication	4.2 (2.2 – 7.9)	ND
Reduction in bronchial hyperresponsiveness	13.7 (3.8-50.0)	5.5 (2.8-10.7)

ND – Not done. * Odds ratio (95% Confidence intervals), # Pollen, mold or animal dande Data from Abramson et al. 74

Injection Allergen Immunotherapy For Asthma Eighty-eight trials were included (13 new trials) 42 house dust mite allergy 27 pollen allergy 2 animal dander allergy cladosporium mould allergy 10 2 latex allergy 6 multiple allergens

The Cochrane Library 2010, Issue 8

NHLBI guidelines for managing asthma in 5-11 yrs of age, adolescents (≥12 yrs) and adults

- Evidence B for
 - HDMs
 - Animal danders
 - Pollens
- Evidence weak or lacking for
 - Molds
 - Cockroaches
- Evidence is strongest for IT with single allergens

Allergens of Proven Efficacy

Allergen	Level of Evidence	Availability of Data
House Dust Mite	А	++++
Pollen	А	++++
Mould	А	++
Animal Epithelia	А	++
Hymenopteral venom	А	++
Cockroach	В	+

++++ = Multiple long-term randomized controlled trials available; ++ = Few randomized controlled trials available + = Limited data; no placebo-controlled trials

> Cox et al. J Allergy Clin Immunol 2011;127:S1-55 Kleine-Tebbe et al. *Allergologie, Jahrgang 33, Nr. 1/2010*

NHLBI guidelines for managing asthma in 5-11 yrs of age, adolescents (≥12 yrs) and adults



NHLBI Guidelines for the diagnosis and treatment of asthma: The National Asthma Education and Prevention Program JACI 2007

SIT: GINA Executive Summary

Eur REspir J 2008;31:143-178 www.ginasthma.com

- Allergen specific immunotherapy
- Appropriate immunotherapy requires the identification of a single well-defined clinically relevant allergen
- The value of IT using multiple allergens does not have support
- Side effects range from local reactions to anaphylaxis
- Abramson Cochrane Database Syst Review 2003:
 - symptoms reduce
 - asthma medications reduce
 - BHR (allergen specific and non-specific) reduces
- Calamita Cochrane Collaboration Method Allergy 2006:
 - SLIT results equal to ref. Abramson

Allergen Immunotherapy in Asthma Indications

- FEV1>70%
- Not controlled with allergen avoidance and pharmacotherapy
- Nasal and bronchial symptoms
- Do not wish long term pharmacotherapy
- Have undesirable side effects from pharmacotherapy



Is Allergen Immunotherapy Effective in Asthma? Abramson AJRCCM 95;151:969

- 20 RCT placebo studies allergen IT in asthma
- Asthma symptoms, medications required, lung function, BHR
- Symptom scores combined OR 3.2 (2.2-4.9)
- Reduced medications for HDM 4.2 (2.2-7.9)

Mean 7.1% improvement in FEV 1

 But noted possible publication bias, but additional 33 negative studies required to overturn results

Q. WHY IMMUNOTHERAPY?

Efficacy of specific immunotherapy

Early effect

reduction in symptoms(60%)/need for medication(70%)

Progressive effect

- reduction in symptoms/need for medication
- reduction in hyperresponsiveness/late phase response

Persistent effect

- Iong-term reduced symptoms/need for medication
- Iong-term reduced hyperresponsiveness/late phase response

Preventive effect

 prevention of new sensitivities and exacerbation of disease (rhinitis into asthma)

Immunological effect

immunomodulation

Treats the symptoms, not the underlying disease

After treatment symptoms usually re occur and there are no long term benefits

→ Continued life-long treatment

Q. WHY IMMUNOTHERAPY? IT: prevention of new sensitizations New sensitizations after 3 years: 55% SIT group vs 100% control group.

Des Roches et al, JACI 1997

New sensitizations after 3 years: 25% SIT group vs 67% control group.

Pajno et al, Clin Exp Allergy 2001

New sensitizations after 4 years 23% SIT group vs 68% control group. Purello D'Ambrosio et al, Clin Exp Allergy 2001

Q. WHY IMMUNOTHERAPY?

Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study.

G. B. PAJNO*, G. BARBERIO*, Fr. DE LUCA*, L. MORABITO*, and S. PARMIANI[†]

	Number of patients		
	SIT Group	Control Group	
Female	42	38	
Male	33	25	
age: yrs (range)	7.14 (6-8)	6.38 (5-7)	
duration of y before nent: yrs	3.6	3.2	
toms	Intermittent asthma/ intermittent asthma and rhinitis	Intermittent asthma/ intermittent asthma and rhinitis	
ization	house dust mite	house dust mite	
	Female Male age: yrs (range) duration of y before nent: yrs toms	Female 42 Male 33 age: yrs (range) 7.14 (6-8) duration of 3.6 y before 3.6 nent: yrs Intermittent asthma/ intermittent asthma and rhinitis tization house dust mite	





Sensitization rates after 6 yrs: SIT: 24.6% ; CG : 66.7%

Q. WHY IMMUNOTHERAPY?

Prevention of allergic asthma

Primary prevention

- Allergen avoidance
 - prevention of allergic sensitisation and symptoms
- Prevention by infant allergen vaccination (ITN)
- Secondary prevention
 - ETAC/EPAAC
 - prevention of asthma in AD children (antihistamines)

Asthma symptoms

- Immunotherapy
 - prevention of asthma in rhinitis (PAT)
 - prevention of new allergies
- Tertiary prevention
 - START
 - prevention of asthma exacerbations (steroids)

Allergy Prevention by AIT Age-Dependent Windows of Opportunity



Mother, fetus and infant interaction In the development of allergy



Allergen, IgE, Th2 promoters

Fetal Swallowing

IgE facilitated allergen uptake and sensitization

New Born infants immune response dominated by TH2 ,genetically controlled.

A 'Designer' Allergic Infant





Age (in relation to Allergic march

The Allergy March Atopic Disease Progression



Atopic History

A 5-year old male presents with a history of seasonal nasal <u>symptoms and recurrent otitis media</u> for the last 2.5 years with intermittent ear pain. His nasal symptoms include rhinorrhea, congestion, itching, repetitive sneezing, and watery/ itchy eyes, and are present primarily during spring and fall . he has had decreased hearing and five episode of otitis media over the last two years, which were treated with antibiotics because of prolonged fluid in the middle ear. The patient's father has allergic rhinitis. The patients has two <u>indoor cats</u>, the patients had <u>atopic dermatitis</u> as an infant during physical examination, it is observed that he is a mouth breather, and repeatedly wipes his nose. The upper airway reveals a pale blue and boggy nasal turbinate with clear rhinorrhea. The patient has a *nasal crease and dark* circles under the eyes. Examination of the ear reveals a dull immobile tympanic membrane bilaterally. There is cobble stoning in the posterior pharynx with clear postnasal drip. the chest is clear on auscultation.

If Pharmaco therapy fails with risk factors

- Topical nasal corticosteroids
- Nasal cromonyl sodium
- Environmental control
- Oral non sedating anti-histamine

Would you consider this patient a good candidate for Immunotherapy? :- YES



Diagnosis: Allergic rhinoconjunctivitis to suspicion of bronchial asthma

House dust Mite- Positive by SPT & specific IgE

- 5 year old boy is admitted to hospital in June with acute wheezy bronchitis and dyspnea
- Itchy eyes and runny nose since early June
- Wheezy bronchitis in March of same year treated with oral salbutamol
- Both parents allergic to grass pollen, father with seasonal asthma

• Discordance >15 % in Aero allergns between SPT & specific-IgE

Early HDM **sensitisation** and **multiple LRI** are the main risk factors for wheeze at **5 years**

Negative control (Saline)NegativePositive control (Histamine)+++ (5/7)NoAero-AllergensResultSpecific

ALLERGY SKIN TEST

NU	Aero-Allergens	Result	specific ige
1	Dermatophagoides farinae	+++ (5/14)	20 kU/L
2	Dermatophagoides pteronyssinus	+++ (6/15)	25kU/L

Initiation of House dust Mite, immunotherapy? Administration route? SLI /D Age Issue?

SLIT Efficacy/ Risk /Dose/Duration?

Total IgE **530** kU/L

Immunotherapy is the only treatment that may affect the natural course of allergic diseases, and it also may prevent the development of asthma in patients with allergic rhinitis

WHO Position Paper in 1998.

Allergen immunotherapy: therapeutic vaccines for allergic diseases

Long-Term Study on Children



14-year study on preventive effects of immunotherapy published in *Pediatrics*

Allergy shots reduced number of children who developed asthma

Source: Johnstone DE, Dutton A. Pediatrics 1968

Prevention of Asthma 14 Years Later



Development of Bronchial Hypersensitivity



Source: Bauer CP. 1993
Bronchial Hyperresponsiveness After Immunotherapy



Allergy Prevention by AIT Age-Dependent Windows of Opportunity



Respiratory Allergies

Allergic rhinitis



32% of rhinitis patients develop asthma

40-50% of patients with allergic rhinitis also have asthma

Allergic asthma



50% of patients with asthma alone develop rhinitis

70-90% of patients with asthma also have rhinitis

World Allergy Organization http://www.worldallargy.org/public/allergic_diseases_center/caras

Rhinitis as a Risk Factor for Asthma



Differential Diagnosis of AR

Consistent With AR

- Nasal symptoms
- Comorbidities
- Pallor
- Turbinate edema
- Clear mucous

Rule Out

- Infection
- Occupational allergy
- Drug-induced
- Hormonal
- Mechanical

Seidman MD, et al. Otolaryngol Head Neck Surg. 2015;152:s1-s43.

Comorbid Conditions



Seidman MD, et al. Otolaryngol Head Neck Surg. 2015;152:s1-s43.

Case Presentation

- 22-year-old woman
- Year-round allergic symptoms for 3 years
 - Nasal stuffiness and rhinorrhea
 - Fatigue
 - Minimal seasonal fluctuations
- Past medical history:
 - Recurrent clinically diagnosed sinusitis
 - No asthma nor pneumonias



- Social history:
 - Nonsmoker
 - Resides in older carpeted apartment
 - Forced air heat and window air conditioning
 - No pets

(cont)

- Physical Examination:
 - Infraorbital edema
 - Turbinate enlargement
 - Pallor and clear mucous

- Current treatment:
 - OTC first-generation antihistamines nightly
 - OTC second-generation antihistamines as needed



Is It Truly an Allergy?



When knowledge of the causative allergen is needed to target therapy

HDM Sensitisation: in allergic rhinitis Risk Factor for progressive Disease

History : House Du Alle	st Mite Allergy in orgy Rhinitis
In vivo:	In vitro:
SPT (wheal/flare in mm):	Total IgE 200 kU/I
histamine (5/7)	Spec. IgE
Dermatophag. pter. 6/15	D. pter. 20 kU _A /I
Dermatophag. Farinae 7/15	Dermatophag. Farinae. 25 kU A/I
NPT: D. pter. positive	

House Dust Mite Allergy and Allergic Rhinitis

- HDMs are the most common cause of perennial AR
- 22% to 80% of the population are sensitized to HDM
- 10% to 30% of adults and 40% of children are affected by AR

- AR is associated with comorbidities, including:
 - Asthma
 - Sinusitis
 - Decreased quality of life
 - Sleep disorders



Calderon MA, et al. J Allergy Clin Immunol. 2015;136:38-48; Bousquet J, et al. Allergy. 2008;63:8-160; Nathan RA. Allergy Asthma Proc. 2007;28:3-9.

HDM Facts

- HDM are arachnoids
- Invisible to the naked eye
- Dermatophagoides (skin-eaters)
 - D pteryonyssinus
 - D farinae



- Require heat and humidity for growth
- Live on skin scales, organic debris, and fungi
- Lifecycle:
 - Reach adulthood in 3 to 4 weeks
 - Can colonize a home in 1 year
 - HDM bodies and feces are the allergens

Mites-Seafood

Sensitization to tropomyosin

Sensitization to arginine kinase and sarcoplasmic binding protein

Environmental Controls for HDM Allergy

- Reduce household humidity to <50%
- Encase mattresses, box springs, pillows with covers that are
 <20 microns
- Wash all bedding, drapes, etc in hot water
- Remove carpeting (if possible), otherwise vacuum weekly
- Freeze stuffed toys for 24 hours once weekly



These precautions alone are insufficient for significant improvements in symptomology.

Calderon MA, et al. J Allergy Clin Immunol. 2015;36:38-48.

Conventional Treatment of HDM Allergy





Seidman MD, et al. Otolaryngology Head Neck Surgery. 2015;152:s1-s43.

AIT for House Dust Mite (HDM) Allergy: Why?

HDM allergens play a major part of allergic disease

45 to 85% of asthmatics are sensitized to mites

In the Copenhagen Allergy Trial

50%	of HDM-induced rhinitis patients had HDM induced asthma
95%	of HDM-induced asthma patients also had HDM-induced rhinitis



Curr Allergy Asthma Rep (2014) 14:482

HDM AIT Proves Beneficial in Monosensitized and Polysensitized Patients

- Thirty AR patients polysensitized to both HDMs and seasonal allergens (group A) and 30 patients sensitized to HDMs only (group B) were enrolled in this study.
- All subjects who received immunotherapy against HDMs for more than 2 years



Fig. 2. Comparison of total nasal symptom scores pre- and post-treatment between Groups A and B (*P<0.05).

Group A: sensitized to both HDMs and seasonal allergens Group B: sensitized to HDMs only

Fig. 4. Comparison of mean medication scores pre- and post-treatment between groups A and B (**P*<0.05).

Allergy Asthma Immunol Res. 2014

Concluding Remarks

- House dust mite allergy is a common condition
- Proper evaluation and treatments are paramount
- Immunotherapy offers the ability to lead to improved outcomes for patients suffering with this condition

Nine Yrs Follow-up in 35 Patients of Persistent Allergic Rhinitis & Intermittent Br. Asthma after discontinuation of H.D. Mites (D.farinae/D.pteronyssinus) Immunotherapy (SCIT)

> Dr. P.C. Kathuria, Dr.Neelam etal. NATIONAL ALLERGY CENTRE DELHI -8Ph: 09312285947 SENIOR CONSULTANT : BLK Super Speciality Hospital Tel. : 30403040

Nine year Follow-up of 35 patients of Persistent **Allergic Rhinitis and Intermittent Bronchial Asthma after Discontinuation of HDM SCIT**

Conclusions

 Specific Allergen immunotherapy - DOSE & Duration- dependent 2. Standardized Allergen Extract of Mites (Df&Dp)

> after 6 Months

- 170% Symptoms Scoring
- 50% Medication Scoring

- 50% Repeat Skin Test Wheal Size by SPT - 10% Diuranal Variability by PEFM

after 1yr

and Considerable Improvement by Physician's Assessment of Patients ' Condition

3. Specific Allergen immunotherapy - Long Lasting Effect for 6 yrs after 3yrs of Standardized Allergen Extract of Mites (Df&Dp)

Polysensitization - not an obstacle

Subcutaneous Immunotherapy (SCIT)

- Systematic review of 74 RCTs
- High strength evidence support the use of SCIT

Symptoms	Number of Trials	N
Rhinitis, rhinoconjunctivitis	26	1764
Conjunctivitis	14	1104
Nasal, ocular, bronchial	6	591
Rhinitis, rhinoconjunctivitis, asthma	11	768
Rhinoconjunctivitis disease-specific quality of life	6	889

AHRQ website.

Long-lasting efficacy of IT: controlled studies

AUTHOR	ALLERG	ROUTE	DISEASE	LONG - LASTING
Mosbech 1988	Grass	SCIT	Rhinitis	6 yrs
Hedlin, 1995	Cat/dog	SCIT	Rhin/Asthma	3 yrs
Jacobsen, 1997	Birch	SCIT	Rhin/Asthma	6 yrs
Ariano, 1999	Pariet	SCIT	Rhinitis	4 yrs
Durham, 2000	Grass	SCIT	Rhinitis	5 yrs
Eng 2002	Grass	SCIT	Rhinitis	3 yrs

Data kindly provided by Canonica (2003)

Allergy Prevention by AIT Age-Dependent Windows of Opportunity



Seasonal Br. Asthma A 13 YEAR OLD MAN H/O RECURRENT **EPISODES OF** allergic rhinitis C/O Severe, Recurrent Sneeze, Nonproductive Cough & Wheezing Worst months – March, April, September , October **Skin Test - Positive (Pollens & Mites) Specific IgE-Positive** (Pollens & Mites) **Total IgE 500Iu PFT** – **Normal** Medication- LABA+ICS X sos **SPECIFIC IMMUNOTHERAPY : SCIT X 3yrs** IgE inflammation

Case Dr. P. C. Katuria NATIONAL ALLERGY CENTRE Diplomin & E. MD Hann, Mick JOTCD. PCAL RCCP, 13. East Parel Nager. N. Delhi-6 Consultant Allungar & Chest Mysician Sector - Authors & Allwegic Stin Diseases SKIN TEST REACTION PRICK TESTS INTR ADERMAL TESTS (PATCHTEST / PROVOCATION TESTS / C.A.S.T. Patient's Name and U.A.Y.C. SIN Consultant Address: Delivery Actions : 24-Y Sector 17-A Gu RGOAN Tel-No: Delivery Actions : 24-Y Sector 17-A Gu RGOAN Tel-No: Delivery Actions : 24-Y Sector 17-A Gu RGOAN Tel-No: Detive of Skin Test : 7-1-0-6 Remio-	Dr Lal PathLabs Put Ltd. BUGNOSTIC CHITTLE C. 18, OLD D.F. COLONI, SECTOR 14 GURGAON 122 DDT HICKES 1917422 2250545857 FAX: 96174-22 2258 MAIN LADORACOMY TEKEN MODEL 54 HAMMANN FOAD, NEW DELHA-110 DDT DR ARNIND LAL MEESS D.C.P Which d'Salonatory Windows Philod of Salonatory Windows Philod Of Salonatory Philod	Dr. Aal P. SMACHONIC CENTR GURGADH-122 COI PHONES MAN LAGORATOPY: 155 ANY MARS. DCA MARS. DCA	athLabs Put Lta E CIB. OLD DLF COLONY. SECTOR. M IN MITA-202 2253548537 FAX. 35174-2221 HOUSE, 34 MANAMAN SCAO, NEW DELHART ALL ALL ALL ALL ALL ALL ALL AL	Star Saturna DR.V DR.V DR.V M DR.V M DR.V M M Thick second the sec	05 3926580 _PL-GURGAON ANDANA LAL BRA. M. Produ of Pathology ME INVICUING 26/12/05 26/12/05 26/12/05 9 P , Range
Treatment Set	ALLERGY COMPREHENSIVE PROFILE, PARDIATRIC		Paguit	Units	Ref.Range.
SKIN TEST RESULTS Negative Control (Saline) Positive Control (Histamine) +++	ALLERGY SCREEN Phadiatop Phadiatop Positiv Interpretation: Common allergens. This test differentiates between atopic a remarked.	DUST PANEL House Dust Cockroach Dermatop, pteromyssinus Dermatophagoides farinae	Negative Positive, 9,47 Negative Negative	kliA/L	(* 0.35)
No Allergen Skin Text Result IgEIC.A.S.T.	diseases. The test comprises a balanced mixture of relevant allergene that react with specific IgE antibodies in the patient serum.	FOOD PANEL	Result	Units	Ref.Range
I. J. Forinae +++ +ve 2. Cockreach. ++++ 3. PROSOPUE july floer ++ 4. Bransica ++ 5. PARTHENNUM ++	Immunoglobulin IgE, Total, Serum <u>247.00</u> IU/mL (1.00 - 181.00) Interpretation: Total serum IgE represents a small fraction of total serum immunoglo- bulins. Concentration of IgE is dependent on age Infants have very low levels. A progressive increase in levels is seen in children upto 10 to 15 years of age followed by a decline to adult levels. High levels are seen in:	Egg White Milk Wheat Peanut Soyabean Shrimp Gluten Rice Chicken Fish	Negative - Negative -		
6. Agerālum ++	1. Ryper - IgE syndrome 2. Allergic brunchopulmonary aspergillosis 3. Parasitic diseases	ANTWAL DANEL	Repult	Units	lef.Range
I, Dr. P. C. KATHURIA with to order this testment set / meintenance vial. The above data has been checked by me and found to be correct. I further confirm that the hypothermore that the management of the property of the control of the control of the property of the property of the control of the control of the property of the control of the control of the property of the control of the property of the control of the co	4. Allergic Asthra 5. Allergic rhinitis SCIT X 3 yrs. = Remi ALLERGY PANELS:	Cat Epithellium & Dander Horse Sander SSHON Dog Lanner	Negative - Negative - Negative - Negative -		-
Nume of Instantion & Addres :	Mixed Panels Result		Result	Units	Ref.Range
11 NATIONAL ALLERGY CENTRE 1/3, East Pathi Negar, New Delhi's Ph.: 5785457	Dust Panel Positive Pood Panel Negative Animal Panel Negative Mold Panel Negative Grass Panel Negative Tree Panel Negative	MOLD PARE Penicillium notatum Cladosporium herbarum Aspergillus funigatus Candida albicans Alterneria tenuis	Negative - Negative - Negative - Negative - Negative -	-	

Page 2

House dust mite SCIT in asthma

• Daily fluticasone dose reduction after 2 years of SCIT



Zielen S et al., J Allergy Clin Immunol 2010;126:942-9.

NASO Bronchial Allergy with Bronchial Asthma **Bronchial Asthma Perennial** Seasonal Atopic Simple **Steroid dependent Atopic** Non atopic **Non-Atopic** Atopic **Steroid dependent Steroid dependent** Meta ABPA **Non ABPA** -Sulphite Aspirin - Cockroach Indoor - H.D. Mite Perennial - Food Allergen Allergen (Brittle type II)

Allergy Prevention by AIT Age-Dependent Windows of Opportunity



***27 YEARS OLD SIMPLE PERENNIAL BR.ASHTMA, FREQUENT ATTACKS WHICH** MAY TAKE HOURS TO DAYS TO REVERSE (MARCH – APRIL – AUG.- SEPT.) ***OFTEN NOCTURNAL SYMPTOMS AND** CHANGE OF SEASON ++ *P.E.F.R. VARI > 20% BUT NORMAL P.E.F.R. – >500 l/pm & F.E.V1 >70% WITH STEROIDS • SKIN TESTING- POLLEN, FUNGI & DUSTMITES INDUCED. **Ch. INFLAMMATION**

✓ SPECIFIC IMMUNOTHERAPY : SCIT

30 y old female patient,

She has sneezing, itching, runny nose and stuffiness for 4 years. She also has wheezing and chest tightness occasionally at nights. Her complaints are

- all the year around
- getting worst at spring and summer
- severity and frequency of her symptoms increased by the Change of season

Personal history

- Working in a bank covered with wall to wall carpet,
- Atopy in family history
- Dog owner for 7 years.
- Suffered with chronic urticaria for the last 10months

Taking LABA & ICS and antihistaminic tablets regularly.

History : Suggesting allergy ? YES NB Allergy with Br Asthma Which allergen(s) may be responsible for her respiratory symptoms? Perennial allergens? (mites?, Dog?, molds?) Seasonal allergens? (pollens?, molds?) How can we detect this allergen(s)? Skin tests? In vitro test ?

Positive Allergy Test V/s Challenge / Provocation Tests (95%)

J Allergy Clinical Immu. 1995:96:580-587

Respiratory Allergens

(S.P.T.)

•Seasonal Allergen > 32.4mm² •Dermatophagoides pt > 31.2mm² (H.D. MITES)

ALLERGY SKIN TEST

Allergen Size of the Wheal

Negative control (Saline)	Negative
Positive control (Histamine)	+++

No	Aero-Allergens	Result	specific IgE	
1	Dermatophagoides farinae	+++-	34.4 kUA/L	
2	Dermatophagoides pteronyssinus	++	26.5 kUA/L	
3	Blomia Tropicalis	++-		
4	Cockroach	++	Food allergens	
5	Pennisetum	++	PEANUT	++
6	Ricinius communis (castor)	+++-	EGG	++
7	cynodon dac	++-		

POLYSENSETIZATION

1/0 CNHQ	nood astnma,	dermatitis,	urticaria (C	ð TC
I/O PRCK TEST	S/INTRIDERMAL TEST / PATE	HIEST / PROVOCATION	TESTS/C.A.S.T.	
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Treatment Set 3.5 M - 3.1 M - 550 M No. POLLENS /	SKIN TEST Negative Control (Saline) Positive Control (Histami Allergen FUNGI / DUSTS / MITES / FOODS	RESULTS ine) Skin Test Result (mm) or (plus sign) +++	The-8500 Dhe-60,3 Aze-780 Ige/C.A.S.T. Pasitive	0,1)eu
Treatment Set 3.5 h - 3.1 h - 550 h No. POLLENS / 2	SKIN TEST Negative Control (Saline) Positive Control (Histami Allergen FUNGI / DUSTS / MITES / FOODS	RESULTS ine) Skin Test Result (mm) or (plus sign) ++++ ++++	The-8500 Dhe-60,3 Aze-780 Ige/C.A.S.T. Pasitive (326.00)	0,1)eu
Treatment Set 3.5 h - 3.1 h - 550 h No. POLLENS / 1 2 3 7050 h	Allergen FUNGI / DUSTS / MITES / FOODS	RESULTS ine) Skin Test Result (mm) or (plus sign) ++++ ++++ ++++	The-8500 Dhe-60,3 Aze-780 Ige/C.A.S.T. Pasitive (326.00)	0,1)eu
Treatment Set 3.5 h -3.1 h -550 h No. POLLENS / 1 2 3 70050 4	Allergen FUNGI / DUSTS / MITES / FOODS	RESULTS ine) Skin Test Result (mm) or (plus sign) ++++ ++++ ++++ ++++	The-8500 Dhe-60,3 Aze-780 Ige/C.A.S.T. Pasitive (326.00)	0,1)eu

wish to order this treatment set / maintenance NATHORIA ١., The above data has been checked by me and found to be correct. I further confirm that the vial. hyposensitisation treatment will be carried out by trained specialists in our clinic which is equipped with the necessary emergency kits, oxygen cylinder etc.

Doctor's Signature/Qualifications : _

POLYSENSETIZATION Immunotherapy –SCIT X 3 yrs.

Question: what do you do in polysenstized patients What happens to an allergic patient with an immune system that is already up-regulated in Th2 bias, (Increased total IgE & specific IgE) who becomes the recipient of chronic antibiotic usage and corticosteroids? □What are the therapeutic implications?

POLYSENSITIZED PATIENTS

- "Once an allergen, always a potential allergen"
- An allergen early in life causing an acute reaction (urticaria, eczema, asthma) may go into remission and then "resurface" in adulthood, causing symptoms once again often more insidious—and often in a different target organ

POLYSENSITIZED PATIENTS

Different allergenic triggers may "target" different end organ systems in the same patient

POLYSENSITIZED PATIENTS

When you do a "test" for "allergies," you are only measuring one of the two essential items that determine an allergic reaction:

Multiple symptoms, Multiple targets.. Think total load

Allergic Threshold Infectious

Nutritional

Hormonal

Pollen allergen

Fungal allergen

Dust mites & Cockroach allergen

Food Allergens



Day Number

Mix (IgE & Non - IgE mediated reaction)

Concept Six: Hidden Food Sensitivities

Important corollary:

Hidden food sensitivities worsen intestinal permeability AND increased intestinal permeability worsens hidden food sensitivities!



- Frequently eaten foods may be responsible for chronic, fluctuating symptoms in allergic patients
- No immediate reaction consistently reported after eating these foods
- Common hidden food sensitivities include milk, wheat, corn, soy, egg, yeast









1 B 1000



Combined Omalizumab & allergen immunotherapy



Safety of Accelerated Schedules of Cluster Allergen Immunotherapy with House dust mites in Sixty Five Patients with Perennial rhinitis & BR. Asthma Dr. PC. Kathuria, & Dr. Neelam et al

Allegy & Asthma Clinic, BLK Super-speciality Hospital, National Allergy Centre, New Delhi, INDIA

CONCLUSIONS

- Combined (anti IgE) omalizumab and cluster Immunotherapy is without an IgE mediated adverse systemic reaction & maintenance maximum tolerance dose (MTD) of 1000 / ml achieved in 3 visits in 36 days (> 1month) in our 9 patients
- Cluster Immunotherapy in 40 patients is efficacious, well tolerated than conventional immunotherapy of 4 months of single Allergen Injection as maintenance maximum tolerance dose (MTD) of 1000 - Au achieved in more than 75% in 4 visits of 46 days duration but 20% of patients in cluster Immunotherapy develop grade II/III adverse systemic reaction (J Allergy Clin Immunol 125:569-574, e567 2010)
- 3. Waiting period after allergen vaccine was one hour if there is H/O of large local reaction of >10cm, size of weal >7mm (HEP), positive specific IgE to D.farinae, and D pteronyssinus > 3.5 ku/ ml, Total IgE > 300 to 700 / ml, in poly - sensitized patients, On high doses of ICS (>1000ug) & variability in PEFM > 10% with FEV1 / FVC > 70%, In such cases Fexofenadine 180mg & Methyl - prednisolone 8mg was given three hours before cluster immunotherapy to minimize adverse systemic reaction
- In our patients, if there is > 50% reduction of weal size after repeat S.P.T (7mm to 3mm) and > 50% reduction of symptoms scoring, gives us an indirect measurement of MTD (maximum tolerance dose.)
- 5 We Could not find any influence of gender and numbers of allergy shots (injections) as development of adverse systemic reaction

Clinical Pearls

- Poly-sensitized patients struggling with multiple symptoms of multiple target organs with a personal past, current or family history of allergic - asthma disease should have allergy consultation. to down regulate the B-lymphocytic IgE inflammation by SLIT/SCIT & Diet Elimination.
- Is there evidence? Yes

Allergy Prevention by AIT Age-Dependent Windows of Opportunity



Polysensetization with comorbid-Diseses poorly reversible lung function

Patient –A 44 years old female with severe persistent BR. ASTHMA was diagnosed 10 years ago and had remained Pooriy controlled inspite of optimal inhaled and oral drougs inclouding corticosteroids.Her serum IgE level was 310 ku/l with a positive RAST (specific IgE) & SPT to house dust mite & Asp. fumigatus negative

<u>SPT : multiple sensitivity to pollens & HDM & fungi</u>

Symptoms presents for 3 months	Cormorbid diseses:
Frontal maxillary facial pain	
Green nasal discharge	HYPOTHYROIDISM
Post nasal drip	PEPTIC ULCER DISEASE
hoarseness	OSTEOPOROSIS
intermittent wheezing	DEPRESSION
	DEPRESSION IBS

•PMH:

- infant-atopic eczema from eggs& dairy products.
- Adolescence: allergic rhinitis
- Youngage- intolerance (diarrhoea) with recurrent sinusit &vaginitis



The peak flow rate was 180/min (the predicted value was 450 l/min. Pulmonary function tests showed a moderate severe obstructive defect with mild air trapping and hyperinflation .there was significant improvement in expiratory flow after bronchodilator inhalation (more than 18 %).

Therapy

- (a) Intranasal corticosteroid (1 sprays of mometasone furate monohydrate 50 mcg per nostril once daily)
- (b) oral antihistamine (10mg daily of cetirizine at bedtime)+montelukast 5mg.
- (c) antibiotic for acute or chronic infectious sinusitis(500mg ofciprofloxcin twice daily for 3weeks)
- (d) inhaled corticosteroid & LABA for hyper reactive airways (2 puffs of Budesonide 400 mcg & formetrol 6 mcg /puff two to three times daily vialupihaler)+doxyphyllina 400mg X BD oral steroids as per advised
- (e) inhaled beta2- agonist when needed for wheezing (salbutamol 2-4 puffs every 4-6 hours as needed)

SIT: SCIT-contra indication/SLIT??? Anti-IgE therapy?

House Dust Mite (D.farine D. Pteronyssinus) Immunotherapy in 45 patients of Perennial & Steroid dependent BR. Asthma



Follow up study upto 6 yrs during & after Immunotherapy

DR. P.C. KATHURIA

Conclusions Dust Mite Specific Immunotherapy

House Dust Mite Immunotherapy in 45 patients of Perennial & Steroid dependent BR. Asthma Follow up study upto 6 yrs — during & after Immunotherapy

- <u>Steroid Sparing, safe in Perennial BR. Asthma</u>
- But less Effective in Steroid dependent BR. Asthma
- There is improvement in BHR (PEFR variability & reversiblity) ψ in both the groups
- In steroid BR. Asthma 3 yrs during immunotherpy, BHR impove but after discontinuation the amount of drug intake increase indicative of ongoing inflammation and or new sensitization

History : Positive Perennial Allergic Br. Asthma Seasonal *Exacerbations In steroid dependent*

In vivo:

SPT (wheal/flare in mm):

All pollen positive i. e. pollen, mites, animal dander, molds

In vitro:

Which allergen sources require "additional" IgEtesting?

D/D Genuine /cross reactive positive ? Polysensitization

> *Vs.* polyallergic

History : Positive Perennial Allergic Br. Asthma Seasonal *Exacerbations In steroid dependent*

Total IgE 150 kU/I In vivo: Spec. IgE SPT (wheal/flare in mm): Phl p 12 (profilin) 3 kU_A/l Phl p 7 (polcalcin) 15 kU_A/I All pollen positive i. e. pollen, mites, animal da CRD (Component Resolved Diagnosis) Polysensitization Vs.

In vitro:

Poly allergic







General reasons why molecular allergy (MA) is applied to diagnostic methods (IgE testing) **Role Of Component-resolved Diagnostics (CRD)** A science that make it feasible to quantify IgE antibodies to specific allergen proteins on a molecular allergologic level **Component A Component B** Component C A mixture of allergens and non-allergenic substances Native/recombinant proteins A, B and C Whole Allergen Components, (Individual Allergenic Epitopes Molecules) **CRD** have been introduced in

order to increase the probability of

True Food/aero-allergens & insects Allergy diagnosis

Identify patients at high risk of reactions

Identify patients more prone to persistent disease

"Rule of thumb": How to use MA

Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, Ollert M et al. Pediatr Allergy Immunol 2016;27(Suppl.23):1-250 (free access)

- Suspected allergen from family with
 broad crossreactivity? i.e.
 - PR-10,
 - nsLTP
 - profilin
 - polcalcin
 - albumin
 - parvalbumin
 - tropomyosin

- Test specific IgE only to one representative member, i.e.
 - i.e. Bet v 1
 - Pru p 3
 - Phl p 12 or Bet v 2
 - Phl p 7 or Bet v 4
 - Fel d 2
 - Gad c 1
 - Pen a 1

"Rule of thumb": How to use IgE tests in MA

Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, Ollert M et al. Pediatr Allergy Immunol 2016;27(Suppl.23):1-250 (free access)

 Allergen from family with limited crossreactivity? (seed storage proteins, lipocalins)

2S albumins



- test suspicious member(s) and related ones*
- hierarchy indicates primary sensitizer
- *if negative, crossreactivity is unlikely

Screening for allergen-specific IgE sensitizations with pollen extracts



General reasons why molecular allergy (MA) is applied to diagnostic methods (IgE testing) Multiple sensitizations due to crossreactivity?





General reasons why molecular allergy (MA) is applied to diagnostic methods (IgE testing) Sorting our clinical cross-reactivity with history/oral challenges (if needed)

Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, Ollert M et al. Pediatr Allergy Immunol 2016;27(Suppl.23):1-250 (free access)



Cross-reactivity between pollen allergens?

Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, Valenta R, Hilger C, Hofmaier S, Ollert M et al. Pediatr Allergy Immunol 2016;27(Suppl.23):1-250 (free access)



Multiple sensitizations due to crossreactivity or true co-sensitization?



History : positive Perennial allergic Rhinitis Seasonal Exacerbations In Allergic Asthma

In vivo: SPT (wheal/flare in mm):

All pollen positive i. e. pollen, mites, animal dander, molds CRD (Component Resolved Diagnosis) Grass, trees, weeds. mites

In vitro: Total IgE 150 kU/I Spec. IgE PhI p 12 (profilin) 3 kU_A/I PhI p 7 (polcalcin) 15 kU_A/I Bet v 1 Ole e 1, Cup a 1, Pla a 1 Phl p 1, Phl p 5 Art v 1 Amb a 1

ysensitization

History : positive Perennial allergic Rhinitis Seasonal Exacerbations In Allergic Asthma In vitro: Total IgE 150 kU/I In vivo: Spec. IgE SPT (wheal/flare in mm): PhI p 12 (profilin) 3 kU_{Δ}/I All pollen positive Phl p 7 (polcalcin) 15 kU_A/I i. e. pollen, mites, animal Bet v 1 0.6 kU/l (0.4%) dander, molds Ole e 1, Cup a 1 < 0.35kU/I Allergen Phl p 1 30 kU₄/l (20%) Immunotherapy Phl p 5 15 kU_△/l (10%) **Of Grass & Mites** Art v 1 and Amb a 1 neg. Only

Der p1 – 15 kU/L Der f1 -10kU/L

polysensitization





Allergen molecule-based tests for accurate prescription of immunotherapy
Subcutaneous Immunotherapy

VS.

Pharmacotherapy

Subcutaneous Immunotherapy has demonstrated numerous benefits over and above the symptomatic pharmacotherapy provided to patients



Thanks

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TRAINING IN ALLERGY TESTING AND IMMUNOTHERAPY

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Three Day Training program in clinical history taking, skin prick tests (SPT, SIDT, PPT, APT, SAPT, PCK Technique), IgE measurements and Interpretations, allergen-immunotherapy (Combined cluster immunotherapy & anti-IgE (Omalizumab) therapy) SLIT, SCIT, RIT, ORAL DESENSITIZATION, DRUGS DESENSITIZATION, ASPIRIN DESENSITIZATION and Anaphylaxis will be organized by NATIONAL ALLERGY CENTRE under the guidance of National Experts. THE TRAINING WILL PROVIDE OPPORTUNITY FOR HANDS ON TRAINING AND CLINICAL MANAGEMENT OF ALLERGIC DISEASES WITH FREE ADVISE FOR FURTHER SIX MONTHS. Medical graduates/post graduates interested may apply with their curriculum vitae and certificates for consideration to Course Director Training, NATIONAL ALLERGY CENTRE, for further consideration.



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