r website www.jaypeebrothers.com, for detailed information on pediatric books, visit our website www.jaypeebrothers.com

PEDIATRIC ALLERGY



Celebrating 50 YEARS
Passion, Quality and Innovation in Healthcare Publishing

MANUAL OF PEDIATRIC ALLERGY

SECOND EDITION



Editor-in-Chief
Major K Nagaraju

Foreword
A Parthasarathy

JAYPEE

Contents

1. Approach to an Allergic Child **1**
Major K Nagaraju
Chief Complaints *2*
Triggers/Precipitating Factors *2*
Environment *2*
Drug History *3*
Physical Examination *5*

2. Sensitization: Epidemiology and Pathophysiology **12**
Mahesh PA, Amrutha D Holla
Epidemiology *12*
Epigenetic Modifications *17*
Pathophysiology *17*
Antigen-presenting Cells *18*
Cd4 Lymphocytes *19*
Airway Epithelium *19*
Toll-like Receptors *19*
T-regulatory Cells *20*

3. Diagnosis of Allergic Diseases **23**
Major K Nagaraju
Allergy Skin Testing *23*
History of Allergy Testing *24*

4. In Vitro Testing for Specific IgE **36**
Major K Nagaraju, N Satya Srivatsav
Characteristics of an Ideal IgE Test *36*
Methods *36*
Principle of Allergen-specific IgE Immunoassay *37*
Indications for IgE Testing *37*
Why In Vitro Testing is Needed? *37*
Classification of Specific IgE Antibody Immunoassays *37*
Types of Immunoassays *38*
Factors Influencing the Accuracy of In Vitro IgE Testing *38*
Techniques Commonly Available in India—which One to Choose? *38*
Points to Remember while Ordering and Interpreting the Results *38*
Merits of In Vitro-specific IgE Testing *40*
Limitations of In Vitro-specific IgE Testing *41*
When to Repeat In Vitro-specific IgE Tests? *41*
Component Resolved Diagnosis *42*

Multiplex System (Semiquantitative) *43*
Cell-based Technologies *43*

5. Atopic Dermatitis **45**
Major K Nagaraju
Epidemiology *45*
Disease Course *46*
Role of Aeroallergens *49*
Food Allergy and Atopic Dermatitis *49*
Microorganisms and Atopic Dermatitis *50*
Climate and Atopic Dermatitis *50*
Psychological Factors and Atopic Dermatitis *51*
Irritants and Atopic Dermatitis *51*
Mechanism of Pruritus *51*
Clinical Features *51*
Diagnosis *52*
UK Working Party's Diagnostic Criteria *53*
Scoring for Atopic Dermatitis *53*
Diagnosis of Atopic Dermatitis *54*
Variants of Atopic Dermatitis *54*
Investigations *54*
Treatment *55*
Complications *64*
Prognosis *65*
When to Refer to a Dermatologist or Allergist? *65*

6. Urticaria and Angioedema **69**
Major K Nagaraju
Classification *69*
Pathophysiology *70*
Etiopathogenesis *71*
Differential Diagnosis *73*
Diagnosis *73*
Approach to Urticaria *77*
Treatment *78*
Pharmacotherapy *79*
Complications *81*
Prognosis *82*

7. Contact Dermatitis **84**
Suresh Anne
Definition *84*
Prevalence *84*
Classification *85*
Diagnosis of Allergic Contact Dermatitis *92*

Treatment *95*
Prognosis *96*
Prevention *96*

8. Cow's Milk Allergy **98**
Major K Nagaraju
Epidemiology *99*
Mechanism of Cow's Milk Protein Allergy *100*
Clinical Features *101*
Immediate Cow's Milk Protein Allergy *101*
Diagnosis *105*
Allergen Elimination Test *107*
Treatment *109*
Prognosis *111*

9. Food Allergy **114**
Major K Nagaraju, N Satya Srivatsav
Prevalence *114*
Definitions *115*
Classification *116*
Pathophysiology *116*
Phenotypes of IgE-mediated Food Allergy *122*
Clinical Features *124*
Diagnosis *126*
Treatment of Food Allergy *134*
Prevention *137*
Recent Developments in Prevention of Food Allergy *138*
Problems of Food Allergies in India *139*
Prognosis *139*

10. Anaphylaxis **143**
Major K Nagaraju
Epidemiology *143*
Definitions *144*
Risk Factors *144*
Pathophysiology *145*
Etiology *146*
Clinical Features *148*
Symptoms and Signs *149*
Diagnosis *149*
Treatment *152*
Caution *155*
Prognosis *156*

11. Ocular Allergies **158**
Major K Nagaraju, Srinivas K Rao
Prevalence *158*
Definitions and Classification *158*
Pathophysiology *160*
Clinical Features *161*
Diagnosis *163*
Treatment *163*

12. Clinical Features and Diagnosis of Allergic Rhinitis **169**
Major K Nagaraju
Definition of Allergic Rhinitis *169*
Clinical Classification *169*
Clinical Features *170*
Diagnosis *171*
Investigations *175*
Allergic Rhinitis in Preschool Children *177*
Local Allergic Rhinitis *178*
Allergic Rhinitis and Asthma *179*
Allergic Rhinitis and Sinusitis *180*
Allergic Rhinitis and Otitis Media *181*
Allergic Rhinitis and Quality of Life *182*
Progression of Allergic Rhinitis *183*

13. Treatment of Allergic Rhinitis **185**
Major K Nagaraju, VV Kasyapi
Treatment *185*
Pharmacotherapy *187*
Oral Steroids *199*
Newer Drugs *199*
Monitoring *199*
Remission in Allergic Rhinitis *202*

14. H1 Antihistamines in Pediatric Practice **205**
Major K Nagaraju
Histamine *205*
Classification of Antihistamines *205*
Mechanism of Action *207*
Pharmacokinetics and Pharmacodynamics *207*
Side Effects *208*
Contraindications *211*
Drug Interactions *212*
Therapeutic Uses *212*
Antihistamines as Preventive Role for the Development of Allergic Disease *216*
Myths about Antihistamines *216*

15. Genetics of Allergy and Asthma **219**
Esra Birben, Cansin Sackesen, Omer Kalayci
Genetic Approaches for Studying Allergy and Asthma *219*
Epigenetics *226*
Future Directions *227*

16. Preschool Asthma **232**
D Vijayasekaran
Prevalence of Asthma *232*
Asthma Onset *232*
Phenotypes of Asthma in Clinical Practice *233*
Investigations in Asthma *235*
Modified Asthma Predictive Index *236*

17. Diagnosis of Asthma **238**
NC Gowrishankar
Measurement of Airflow Obstruction—Spirometry *239*
Peak Flow Monitoring *241*
Impulse Oscillometry *242*
Biomarkers *243*
Exhaled Breath Temperature *244*
Exhaled Breath Condensate *244*
Bronchial Provocation Tests *244*

18. Persistent Bronchial Asthma **247**
TU Sukumaran
Mechanism of Bronchial Obstruction in Bronchial Asthma *247*
Diagnosis *248*
Investigations *249*
Differential Diagnosis *252*
Pathophysiology of Asthma *253*
Cells in Asthma *256*
Classification of Persistent Bronchial Asthma *257*
Aims of Treatment *257*
Nonpharmacological Measures *260*
Patients and Parents Education on Bronchial Asthma *260*

19. Acute Asthma Exacerbations in Childhood **271**
George V Guibas, Nikolaos G Papadopoulos
Triggering Pediatric Asthma Exacerbations *271*
Preventing Pediatric Asthma Exacerbations *273*
Treating Pediatric Asthma Exacerbations *274*
Concluding Remarks *274*

20. Management of Acute Asthma **279**
Somu Sivabalan, Srinath MV
Pathophysiology *280*
Clinical Display and Judgment *281*
Pharmacotherapy *282*
Nonpharmacologic Management *287*
Summary of Acute Asthma Management *288*

21. Difficult to Treat Asthma **292**
H Paramesh
What is Difficult to Treat Asthma? *292*

22. Drug Allergy **296**
Major K Nagaraju
Epidemiology *296*
Classification *297*
Drug Allergy *297*
Approach *298*
Pathophysiology *299*
Factors Influencing Drug Allergies *299*
Clinical Features in Skin *300*
Clinical Spectrum Other than Skin Involvement *303*
Diagnosis of Drug Allergy *306*
Management *309*
Prognosis *311*
Prevention *311*

23. Allergens **313**
Major K Nagaraju
Terminology of Allergens *313*
Aeroallergens *313*
Indoor Allergens *315*
Outdoor Allergens *326*
Common Stinging Insects in India *330*

24. Clinical Importance of Standardization of Allergens **335**
Major K Nagaraju
Standardized Allergen Extracts *335*
Units of Nonstandardized and Standardized Extracts *337*
Guideline Recommendations *338*

25. Environment and Respiratory Allergies **341**
H Paramesh
Environmental Issues *342*
Air Pollution *342*

Climate Change and Air Pollution Interact on Respiratory Health *348*
Environment Control in Prevention Allergic Disease *348*

26. Allergen-specific Immunotherapy 351
Major K Nagaraju
Mechanism of Immunotherapy *353*
Allergen Extracts to be Used in Immunotherapy *353*
Safety and Efficacy of Immunotherapy *353*
Adverse Reactions *356*
Schedule of Immunotherapy *360*
Age Appropriate to Begin Immunotherapy *361*
Allergens *361*
Cost-effectiveness of Allergen Immunotherapy *361*
Biomarkers *361*
Routes of Administration of Immunotherapy *362*
Future of Immunotherapy *364*
Passive Immunization Allergen-specific Immunotherapy *365*
Unmet Needs *365*

27. Approach to Primary Immunodeficiency Diseases 370
Major K Nagaraju
Epidemiology *370*
Genetics of Primary Immunodeficiency Diseases *370*
Classification *370*
Diagnosis *371*
Treatment 378
Prenatal Diagnosis *380*

28. Vitamin D and Allergy 385
Major K Nagaraju, N Karthik
History *385*
Vitamin D Metabolism *386*
Fallacies of Vitamin D Insufficiency *386*
Vitamin D and Fetal Lung *388*
Vitamin D and T Regulatory Cells *388*
Allergic Diseases *388*

29. Role of Probiotics in Allergic Diseases 397
Major K Nagaraju
Choice of Probiotic *400*
Role of Probiotics in Different Allergic Diseases *401*
Probiotics in the Prevention of Allergic Diseases *405*
Safety of Probiotics *406*
Foods Rich in Probiotics *406*
Unmet Needs *406*

30. Rheumatology in Allergic Diseases **409**
Kavitha Mohanasundaram, Saranya Chinnadurai
T-cell Subsets *409*
Diseases with Th Dominance *410*
Urticarial Vasculitis *411*
Systemic Lupus Erythematosus *412*
Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss Syndrome) *413*
Investigations for Possible Rheumatological Illness *415*

31. Drugs Commonly Used in Allergy and Asthma **419**
Major K Nagaraju, N Karthik

32. Selected Laboratory Values in Allergy and Immunology **428**
N Karthik, Major K Nagaraju
Nitroblue Tetrazolium *428*
Test for Phagocytosis *428*

33. Devices in Allergy and Asthma **434**
Major K Nagaraju, N Karthik
Metered Dose Inhaler *434*
Nebulizers *439*
Dry Powder Inhalation Devices *442*
Intranasal Steroid Device *445*
Peak Expiratory Flow Meter *445*

Index *453*

2
CHAPTER

Sensitization: Epidemiology and Pathophysiology

Mahesh PA, Amrutha D Holla

JAYPEE BROTHERS

INTRODUCTION

Sensitization to different allergens is a prelude to the development of clinical allergies in different age groups. Early sensitization to inhalant allergens predicts development of wheezing and asthma until adolescence. The development of sensitization needs a multifactorial interplay of various host factors such as a genetic predisposition, immunological pathways skewed toward the Th2 phenotype, and a gut microbiome with predominant Firmicutes and less of Xylanibacter and Prevotella of the Bacteroides species, and environmental factors including diet, early life exposures related to the hygiene hypothesis, allergen characteristics and load, and parasitic infestations. Vegetarian diet and diet rich in 3-omega fatty acids are likely strong factors influencing expression of clinical allergies, and both of these modify the gut microbiome. Strachan generated the hygiene hypothesis to explain that early life exposures that could increase microbial exposure in childhood affect sensitization and is relevant in both children and adults.

EPIDEMIOLOGY

Prevalence of Sensitization

The prevalence of sensitization varies in different geographies and different populations. The prevalence also varies depending on the allergen being evaluated and whether the studies are being done in the community or in diseased subjects in the hospital. Few studies have shown an increase in the prevalence of sensitization over time, though the exact reasons for such an increase are not clear. Table 1 lists the prevalence of sensitization in different countries. The summary of the key factors involved in the epidemiology of sensitization is listed in Figure 1.

Genetics of Sensitization

It was discovered in the early 20th century that allergies and asthma were heritable. Hopp estimated that around 50% of the risk of developing atopy and allergy was genetic and the other half due to environmental exposures. Atopy is a complex trait and is influenced by several genes with each gene carrying a small

Table 1: Prevalence of aeroallergen sensitization in different countries—key studies.

Year	*Country*	*Prevalence*	*Antigens*
2004 Adults	ECRHS, multicenter study, Europe, USA, and Australia *N* = 13,558	USA (43%), Australia (45%), New Zealand (46%), UK (44%), Netherlands (41%), Germany (40%), France (43%), Sweden (32%), Italy (30%), Spain (42%), Iceland (23%), Estonia (18%)	Any allergen House dust mite, cat, timothy grass, *Cladosporium herbarum*, and birch, *Parietaria judaica*, ragweed
2008 Children	ISAAC, multicenter study *N* = 54,178	Albania (12.4%), Brazil (12.1%), China (22.9%), Hong Kong (45.2%), Ecuador (18.1%), Estonia (12.6%), Georgia (27.4%), Ghana (1.6%), Greece (9.2%), India (5.8%), Spain (41.5%), Palestine (10.3%), Norway (20.1%), Turkey (15.8%), UK (10.6%)	Any allergen Tree pollen, grass pollen, house dust mite, cat hair, Alternaria

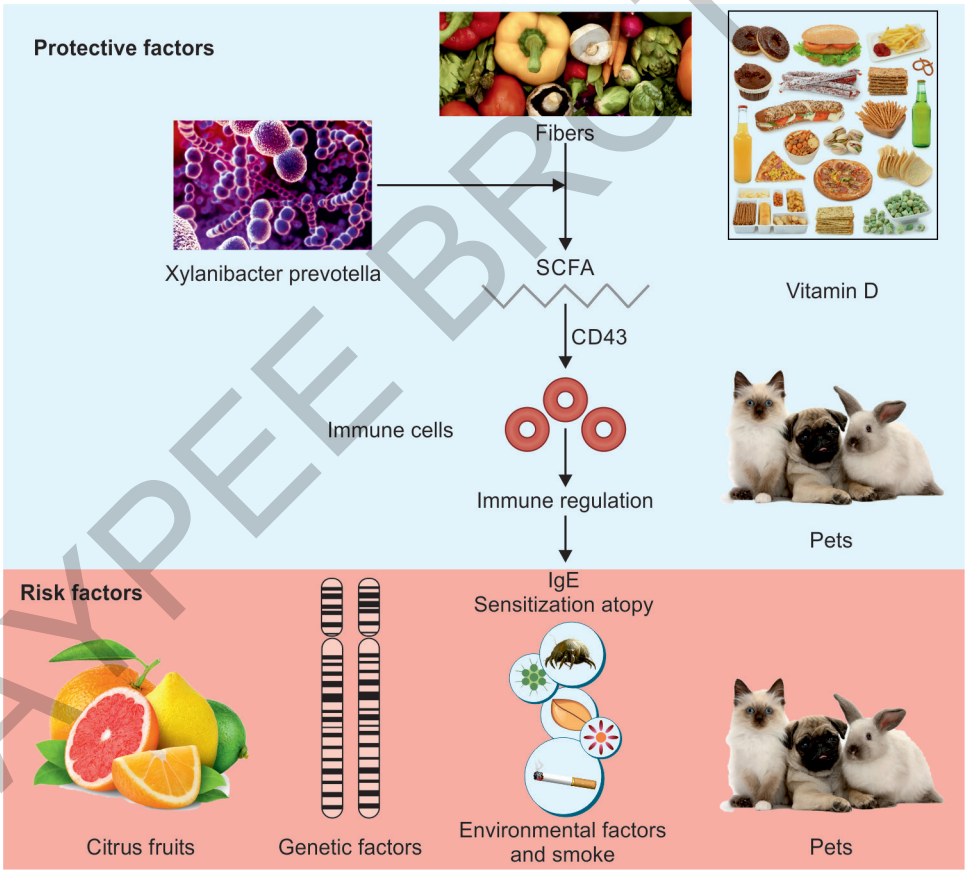

Fig. 1: Summary of various epidemiological factors involved in increasing the risk of sensitization and those offering protection against sensitization.

JAYPEE BROTHERS

weight and different genes being important at different levels in each individual. Most of the genes that are associated with atopy are present in the region of *Chromosome 5q* including regions encoding IL-3, IL-4, IL-5, IL-9, IL-13, and GM-CSF. The other important chromosome that is involved in regulating the total IgE is *Chromosome 12*. Major histocompatibility complex II (MHC II) is also involved in regulating specific IgE to different allergens such as grasses, ragweed, and mite antigen.

Diet and Sensitization

Evidence shows that diet is an important determinant of sensitization. The key pathway that connects diet and immune deviations is the alterations in the gut microbiome with alterations in the diet. It has been observed that even changes in the maternal diet can alter the sensitization profiles in children. In a Finnish birth cohort study, examining the effects of maternal diet and allergies until 5 years of age observed that increased consumption of Vitamin D decreased risk of sensitization to foods and increased consumption of citrus foods increased the risk of sensitization to inhalant allergens. Similar observations of increased maternal consumption of citrus fruits and increase in sensitization to both inhalant and food allergens in children until 2 years of age have been reported from Germany. Nutrients including allergens are transported to the fetus via the placenta and influence immune development in the offspring and the effect of diet starts in utero itself. The reasons for the relation between increased maternal citrus fruit consumption and increased risk of sensitization in the children could be due to the transfer of pan allergens such as Profilin- and Germin-like proteins, which are known to be important allergens in oranges and have strong proinflammatory properties. Other birth cohort studies from the United States have shown beneficial benefits in decreased sensitization in children with increased maternal consumption of Vitamin D and the study from the United Kingdom showed benefit on asthma but not on sensitization. The effect of supplementation of n-3 polyunsaturated fatty acid (PUFA), mainly from fish oils, on pregnancy and sensitization in children is controversial. Observational and randomized controlled studies have shown both benefits and no benefits.

There is some evidence regarding the role of Vitamin E, selenium, and flavonoids such as Quercetin in the diet, which along with their antioxidant effects also have specific effects on the Th differentiation. They promote Th1 differentiation and suppress Th2 differentiation and thus have an effect on decreasing sensitization. Human T cells exposed to physiologic amounts of Vitamin E show a reduced gene expression of IL-4 by inhibiting the transcription. The key age for their beneficial effects is likely to be during pregnancy and early childhood until 5 years of age. Therefore, supplementation studies in adults have not yielded any positive results. There is also a possible protective role of regular fruits and vegetable consumption, and decreasing consumption in a more westernized lifestyle could be associated with increasing sensitization and clinical allergies. However, further studies are needed to confirm these associations as true associations.

Gut Microbiome and Sensitization

There is a close relation between the diet and the gut microbiome of the individual, and this is one of the most exciting areas of research today. Ninety percent of the cells in the human body are not human but part of the microbiome, i.e. bacterial cells in the skin

JAYPEE BROTHERS

and oral cavity, and the highest numbers are present in the gut. There is very strong evidence that diet influences the gut microbiome, which can change quickly with changes in the diet. Higher fibers in the diet lead to higher proportion of the gut microbiome of the Bacteroids group, with predominance of the *Xylanibacter* and *Prevotella* species. These are highly beneficial gut microbes that help in the digestion of the insoluble fiber and help release short-chain fatty acids, one of the most important metabolites having very potent anti-inflammatory effects not only in the gut but also systemically that helps to reduce sensitization to allergens and clinical allergy. On the other hand, consumption of a more western diet with more of meat and refined wheat and less of fiber would lead to the predominance of Firmicutes in the gut microbiome, which increases the risk of systemic inflammatory disorders. Studies in mice have shown that introduction of a western diet would change the gut microbiome in a matter of few weeks. Studies in children from Burkina Faso (Africa) and Europe with their vastly different diets have shown similar changes in their gut microbiome with the children from Africa having predominantly *Bacteroides* species and the European children having the *Firmicutes* species. It is necessary to study the effect of the typical Indian diet and the gut microbiome and sensitization as it would help in the primary and secondary prevention of sensitization. The high consumption of fermented products in the Indian diet could contribute to a better and more beneficial microbiome.

Bacterial Infection, Parasitic Infestation, and Sensitization

Field studies investigating whether food-borne and orofecal infections affect sensitization have shown inconsistent results. Few studies in adults have supported the concept of hygiene hypothesis and observed that prior infection with hepatitis A, *Toxoplasma gondii*, and *Helicobacter pylori* lowers the risk of allergic sensitization and allergic diseases while other studies did not find significant association for *T. gondii* or Hepatitis A. Studies in young children observed protection against sensitization with prior infection with *T. gondii* and *H. pylori*, and not with Hepatitis A. Another study on hospitalized children found a protective effect of *salmonella* on respiratory allergies. In the EuroPrevall study evaluating the risk of sensitization and prior infection with Hepatitis A, *Salmonella*, and *T. gondii*, a significant positive association was found between prior exposure to hepatitis A and lower sensitization to food allergens, but not with *Salmonella* and Toxoplasma.

The hygiene hypothesis proposed that a reduced stimulation of the immune system by microbial infections and parasitic infestations due to better sanitation, use of antibiotics, and various lifestyle factors including a change in the diet, use of antiseptics, and decreasing number of siblings has contributed to increased risk of sensitization. A bacterial or a viral infection would shift the balance toward Th2, which would increase the risk of sensitization and allergic diseases. Even though helminthic infestation exerts a strong Th2 stimulus, there is a protective effect against sensitization. This dichotomy is due to the simultaneous strong stimulation of regulatory T cells, which increases IL-10 and TGF-beta that prevents development of sensitization and clinical allergies. Studies have observed that worm infestation can reduce the prevalence of sensitization by more than 25%.

Pet Ownership and Sensitization to Pets

There are conflicting evidences relating to the pet ownership and sensitization to the same

JAYPEE BROTHERS

pets. In some studies, owning a dog is shown to be protective, whereas in other studies, it is a risk factor for sensitization. Similar conflicting studies exist for cats as well. Presence of sensitization to other allergens such as house dust mites increases the risk of sensitization to pets such as dogs and rabbits.

There is also conflicting evidence related to exposure to animals in the farms including pets and overall sensitization to any allergen. Some reports show that it is protective while others show an increased risk or no effect. There is also a possibility on evaluation of exposure to pets in children that parents of sick children with allergies avoid pets at home and so cross-sectional studies may show a beneficial effect that children with pets have fewer allergies. Even among adults, only healthy workers continue to work on the farms as compared to people who suffer from allergies and so studies may erroneously observe that fewer people working in farms have allergies (healthy worker effect). One study demonstrated that the protective effect in children living in farms against allergies is not due to exposure to animals but due to drinking unpasteurized milk.

Early Life Factors and Sensitization

The key early life factors that are associated with risk of sensitization are the *family size* (*sib-ship effect*) and the number of older siblings (*birth order effect*). The hypothesis is part of the hygiene hypothesis that states that larger families have higher rates of cross-infection among family members, and infections early in life help immune maturation. Many studies have shown that having a higher number of siblings reduces the risk of sensitization to common aeroallergens. There is also evidence that having a higher number of older siblings reduces the risk of atopy in the child. The hypothesis is again related to the increased frequency of infections in the younger child from their older siblings. Some of the infections shown to have protective effect against sensitization include respiratory, Hepatitis A, measles, and tuberculin reactivity or BCG vaccination. A possibility of a better maternal–fetal interaction in subsequent births toward immune priming in the fetus has been considered but is yet to be proven. This effect of sib-ship size and birth order effect is relevant not only in children but also in adults.

Cigarette Smoking and Sensitization

Cigarette smoking reduces the number of T helper cells and is known to enhance suppressor T cell function. There is conflicting evidence regarding exposure to tobacco smoke and risk for sensitization. Different situations may lead to different outcomes contributing to the confusion. What are the effects of maternal smoking versus paternal smoking on the atopic sensitization in children, prenatal smoking by the mothers and the effect on the fetus, and active smoking by children in adolescence and risk of sensitization? There is still need of studies to answer these questions effectively. The prevailing data from three longitudinal studies suggest that cigarette smoking probably reduces the risk of atopic sensitization both in children and in adults although there are other studies that point to an increased risk. The type of allergen may also matter. Smoking may increase sensitization to house dust mites while reducing sensitization to pets such as cats and dogs. There are many confounders that usually affect interpretation of these studies and it is difficult to design a

JAYPEE BROTHERS

study to answer this question. There is also the possibility that healthy subjects continue to smoke whereas subjects who have developed allergic symptoms avoid smoking and therefore, subjects who smoke may show a lesser degree of sensitization (*healthy bias effect*).

EPIGENETIC MODIFICATIONS

One of the most important aspects that have the current interest of researchers in chronic inflammatory conditions such as development of sensitization leading to the development of allergies and asthma is the role of epigenetic modifications that can activate or silence genes. An individual is born with the allergy genes, but symptoms do not manifest at birth. There are various environmental factors that increase susceptibility to the development of sensitization and clinical disease and these factors help to "switch on" these genes. This hypothesis gained traction with studies on immigrants from South Asian countries to the United Kingdom and the United States, where the children born in the western country had a similar risk to the native Caucasian child.

Some of the common epigenetic factors have been discussed earlier and this section will deal with how these factors regulate gene activation or silencing, which happens through any or all of these—DNA methylation and demethylation, histone acetylation and deacetylation, micro-RNAs (miRNA), and histone methylation. DNA methylation usually leads to silencing of the genes and demethylation leads to transcription of genes. The key enzyme for this is the DNA methyltransferases (DNMT). DNA methylation leading to adverse outcomes is seen due to the epigenetic influences of stress and lifestyle factors on *ADCYAP1R1* gene [(Peripheral blood mononuclear cell (PBMC)], obesity on *CCL5*, *IL2RA*, and *TBX21* genes (PBMC), diesel exhaust particles on genes in CD 4+ cells related to IFNγ, *FOXP3*, and *ACSL3*. DNA methylation leading to good outcomes is related to epigenetic influences of folic acid on *ZFP57* genes (CD4+), farm animals, and rural lifestyles on the following genes: *RAD50* (PBMC), *IL13* (PBMC), *IL4* (PBMC), and *IFN*γ (CD4+). DNA demethylation of Forkhead box 3 protein leads to the differentiation of naïve T cells to T "reg" cells.

The other important way in which epigenetic changes occur is via the histone modifications, which can be in the form of acetylation, deacetylation, methylation, demethylation, ubiquitination, and phosphorylation. Histones are alkaline proteins that make the DNA compact enough to fit into the cell into compartments called the nucleosomes. Histone acetylation leading to adverse outcomes are seen with epigenetic influences on *PDE4E* (CD4+) and *ACLS3* (CD4+) on exposure to allergens, diesel exhaust on *FOXP3* (CD4+), and the beneficial effects on fish oil due to histone deacetylation on the production of IL6 (macrophages) and TNF (macrophages).

PATHOPHYSIOLOGY

In a genetically susceptible individual, the process of sensitization starts at a certain age, the cause for which remains unknown to date. Why does not the process start earlier or later? What are the sequences of events or exposure that culminates in the initiation of the sensitization? How many critical processes need to happen during the initiation of sensitization that primes the individual to develop IgE antibodies? Is the load of allergen important? Why do some subjects develop sensitization to indoor allergens such as house dust mites and others outdoor

JAYPEE BROTHERS

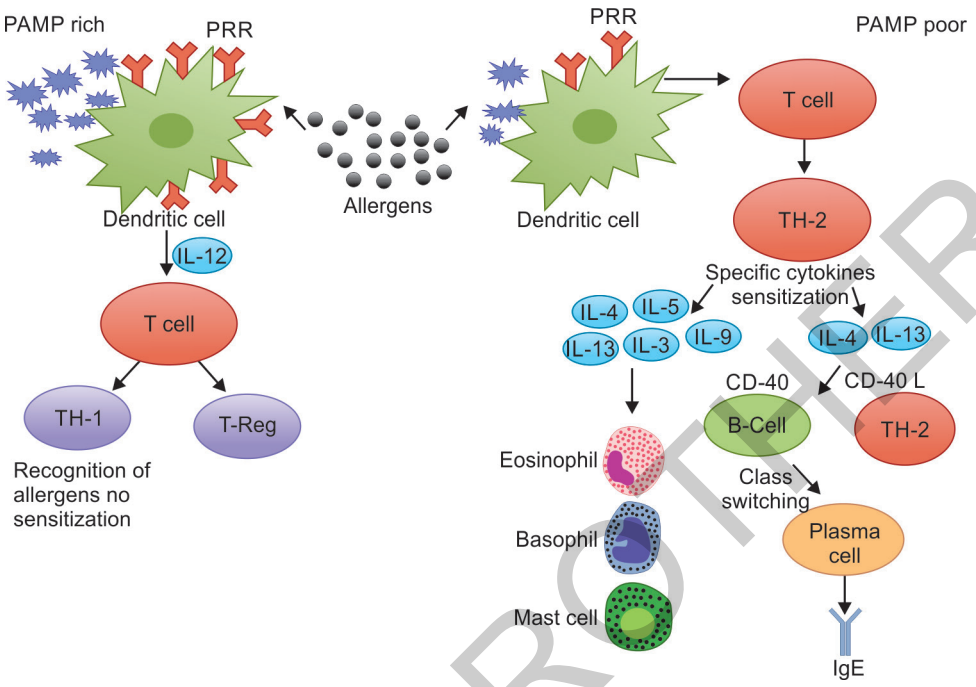

Fig. 2: Key mechanisms involved in the pathogenesis of sensitization. Exposure to allergens in the presence of a pathogen-associated molecular pattern (PAMP)-rich environment with increase in pattern-recognition receptors (PRRs) on the dendritic cells skews the immune system toward the Th1 pathway with absence of sensitization, although there is recognition of the allergens via development of IgM and IgG antibodies. On the other hand, in a PAMP-poor environment, with low number of PRRs on the dendritic cells, there is a skew toward the Th2 pathway with resultant cytokine profile leading to the B cell switch to IgE producing cells and activation of other cells relevant to sensitization and clinical allergy.

allergens such as pollens? A lot remains to be understood. The key mechanisms involved in the pathophysiology of sensitization are depicted in Figure 2.

ANTIGEN-PRESENTING CELLS

However, once the subject is primed to develop sensitization, the further mechanisms of development of IgE have been understood to some extent. One of the most important cells is the antigen-presenting cell (APC) called the dendritic cells (DCs). The DCs process the allergens and some of the peptides are presented to the naive T lymphocytes in association with MHC II. Exposure to the allergen for sensitization can occur via the inhaled route (most common), ingestion (important for food allergens) or cutaneous. The cross talk between the DCs and the T lymphocytes occurs via the allergen and MHC II complex on the dendritic cell and the T-cell receptor on the T lymphocyte. The response may be different when this cross talk happens in the presence of plenty of pathogen-associated molecular patterns (PAMPs) such as endotoxins versus PAMP-poor environments. The PAMPs influence the cross talk between the APCs and T lymphocytes via the toll-like receptors (TLRs) such as TLR-4. In a PAMP-poor environment, the APCs can divert the differentiation of the

JAYPEE BROTHERS

naive T lymphocyte to an allergen-specific Th2 lymphocyte. This can further lead to secretion of specific cytokines that can lead to class switching of the B lymphocyte. The cross talk between the Th2 lymphocyte and the B-lymphocyte occurs via the binding of CD40 on the B lymphocyte to the CD40 ligand on the Th2 lymphocyte. The other costimulatory molecules include CD80 and CD86. The DCs also produce various cytokines that may be helpful (IL-10) in skewing toward the T regulatory cells that help to develop tolerance. Normally, on exposure to various allergens, an individual produces IgM and IgG antibodies. However, once there is class switching off the B lymphocyte, they produce IgE antibodies. These IgE antibodies bind to high affinity receptors on mast cells and basophils. The other cells that can present the allergen to the Th lymphocytes are macrophages and B-lymphocytes.

CD4 LYMPHOCYTES

CD4 T cells are of different types. There are the effector T lymphocytes, which are further divided depending on the types of cytokines; they release as Th1, Th2, and Th17 cells. Th1 cells release gamma interferon and IL-2 inducing a cell-mediated response. Th2 cells are critical for the development of allergy and the naive T cells under the above influences can differentiate into a Th2 lymphocyte, which produces IL-4 and IL-13 that leads to the class switching of the B lymphocyte, IL-5 leads to activation and recruitment of eosinophils, while IL-9 plays a role in mast cell activation. Th17 cells are important in combating extracellular pathogens and promote neutrophilic inflammation. Besides the effector T lymphocytes, there are memory T cells and T reg cells. Memory T cells can quickly change to effector T cells when required. T reg cells are important regulatory cells maintaining appropriate immune regulation and homeostasis. CD4+, CD25+, FOXP3+, and T reg cells are key in maintaining tolerance to allergens via secretion of IL-10 and TGF-beta. Abnormalities in this cell population of T reg cells lead to the development of sensitization to allergens.

AIRWAY EPITHELIUM

The first barrier to the allergen in the airways is the airway epithelium, which forms a physical, chemical, and immunological barrier. Some of the allergens such as house dust mite antigens are proteases and can alter the physical barrier by affecting the tight junction proteins. The airway epithelium expresses innate immune system receptors such as the pattern-recognition receptors. These can interact with various bacteria, viruses, and fungi and activate immune cells underlying the epithelium such as DCs, T cells, eosinophils, and mast cells. The airway epithelium is damaged on exposure to cigarette smoke and possibly other pollutants as also with certain viral infections. Damage to the airway epithelium allows easy access to the other immune cells in the airways.

TOLL-LIKE RECEPTORS

Toll-like receptors are widely expressed in various cells including the airway epithelial cells, DCs, macrophages, and regulatory T cells. Each of the TLRs can be activated via various microbial products. For example, TLR-4 can be activated by the lipopolysaccharide from the gram-negative bacteria such as endotoxin as well as products from the gram-positive bacteria and viruses such as respiratory syncytial virus.

JAYPEE BROTHERS

Stimulation of TLRs leads to activation of the T regulatory cell and skewing of the Th1/Th2 balance toward Th1.

T-REGULATORY CELLS

One of the most important cells that help in the development of tolerance is the T-regulatory cell. The key stimulus for the development of T regulatory cells from naive T cells are the DCs, along with the intestinal epithelial cells (for food tolerance), keratinocytes (for tolerance to contact allergens including food allergens, which are abundantly present in the house dust and the child comes into daily contact), and airway epithelial cells (for aeroallergens). The resident DCs express CD103 and CD11c which are the key drivers for the differentiation of T naive cells into T regulatory cells. These DCs through their enzyme retinaldehyde dehydrogenase 2 converts retinal into retinoic acid (RA) and the same DCs also secrete TGF-beta, both of which are also secreted by the intestinal epithelial cells. In the presence of RA and TGF-beta, naive T cells are differentiated into T regulatory cells that express Forkhead box protein 3, alpha 4 beta 7 integrin, and chemokine receptor 9, which are critical for the development of tolerance.

Sensitization, an intermediate phenotype of clinical allergies such as allergic rhinitis and asthma, is a complex interaction of gene–gene and gene–environment interactions, with significant impact on various epigenetic and metagenetic factors. The diagnosis of sensitization is by identifying specific IgE in the blood via radioallergosorbent test (RAST) or Immunocap or by skin prick tests, which will be discussed in a subsequent chapter. More research is necessary to understand sensitization further and discover mechanisms to delay or prevent its onset, which can further help to delay or prevent clinical allergic diseases.

ACKNOWLEDGMENT

I am thankful to Sangeetha Vishweswaraiah, Research Scholar, Genetics and Genomics Lab, Department of Studies in Zoology, University of Mysore, Karnataka, for her help in designing both the figures in this chapter.

POINTS TO REMEMBER

- Sensitization is an intermediate phenotype and the individual is at high risk to develop allergic disease.
- All allergens that are sensitized are not clinically relevant.
- Genetics, environment, diet, sibship and birth order effects, hygiene hypothesis, smoking and indoor air pollution, pets and microbiome are important determinants of sensitization via epigenetic modifications.
- Antigen presenting cells in a PAMP poor environment can lead to the Th2 deviation of naive T cells.
- Airway epithelium is the first barrier of defense against developing allergic clinical diseases.
- T regulatory cells are critical for the development of tolerance to allergens.

SUGGESTED READING

1. Almqvist C, Garden F, Xuan W, et al. Omega-3 and omega-6 fatty acid exposure from early life does not affect atopy and asthma at age 5 years. J Allergy Clin Immunol. 2007;119(6):1438-44.
2. Barbee RA, Kaltenborn W, Lebowitz MD, et al. Longitudinal changes in allergen skin test reactivity in a community population sample. J Allergy Clin Immunol. 1987;79(1):16-24.
3. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr. 2007;85(3):788-95.

JAYPEE BROTHERS

4. Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr. 2007;85(3):853-9.
5. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol. 2005;115(6):1109-17; quiz 1118.
6. Dunstan JA, Mori TA, Barden A, et al. Maternal fish oil supplementation in pregnancy reduces interleukin-13 levels in cord blood of infants at high risk of atopy. Clin Exp Allergy. 2003;33(4):442-8.
7. Fitzsimon N, Fallon U, O'Mahony D, et al. Mothers' dietary patterns during pregnancy and risk of asthma symptoms in children at 3 years. Ir Med J. 2007;100(8):27-32.
8. Glick-Bauer M, Yeh MC. The health advantage of a vegan diet: exploring the gut microbiota connection. Nutrients. 2014;6(11):4822-38.
9. Hancox RJ, Welch D, Poulton R, et al. Cigarette smoking and allergic sensitization: a 32-year population-based cohort study. J Allergy Clin Immunol. 2008;121(1):38-42.e33.
10. Janse JJ, Wong GW, Potts J, et al. The association between foodborne and orofecal pathogens and allergic sensitisation—EuroPrevall study. Pediatr Allergy Immunol. 2014;25(3):250-6.
11. Johansson-Lindbom B, Borrebaeck CA. Germinal center B cells constitute a predominant physiological source of IL-4: implication for Th2 development in vivo. J Immunol. 2002;168(7):3165-72.
12. Kalliomaki M, Antoine JM, Herz U, et al. Guidance for substantiating the evidence for beneficial effects of probiotics: prevention and management of allergic diseases by probiotics. J Nutr. 2010;140(3):713S-21S.
13. Linneberg A, Nielsen NH, Madsen F, et al. Smoking and the development of allergic sensitization to aeroallergens in adults: a prospective population-based study. The Copenhagen Allergy Study. Allergy. 2001;56(4):328-32.
14. Liu AH. Innate microbial sensors and their relevance to allergy. J Allergy Clin Immunol. 2008;122(5):846-58; quiz 858-60.
15. Mahesh PA, Kummeling I, Amrutha DH, et al. Effect of area of residence on patterns of aeroallergen sensitization in atopic patients. Am J Rhinol Allergy. 2010;24(5):e98-103.
16. Mandhane PJ, Sears MR, Poulton R, et al. Cats and dogs and the risk of atopy in childhood and adulthood. J Allergy Clin Immunol. 2009;124(4):745-50.e744.
17. Marks GB, Mihrshahi S, Kemp AS, et al. Prevention of asthma during the first 5 years of life: a randomized controlled trial. J Allergy Clin Immunol. 2006;118(1):53-61.
18. Marsh DG, Hsu SH, Roebber M, et al. HLA-Dw2: a genetic marker for human immune response to short ragweed pollen allergen Ra5. I. Response resulting primarily from natural antigenic exposure. J Exp Med. 1982;155(5):1439-51.
19. Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. Nat Immunol. 2011;12(1):5-9.
20. Matheson MC, Dharmage SC, Abramson MJ, et al. Early-life risk factors and incidence of rhinitis: results from the European Community Respiratory Health Study—an international population-based cohort study. J Allergy Clin Immunol. 2011;128(4):816-23, e815.
21. Matricardi PM, Franzinelli F, Franco A, et al. Sibship size, birth order, and atopy in 11,371 Italian young men. J Allergy Clin Immunol. 1998;101(4 Pt 1):439-44.
22. Min YG. The pathophysiology, diagnosis and treatment of allergic rhinitis. Allergy Asthma Immunol Res. 2010;2(2):65-76.
23. Nickel R, Wahn U, Hizawa N, et al. Evidence for linkage of chromosome 12q15-q24.1 markers to high total serum IgE concentrations in children of the German Multicenter Allergy Study. Genomics. 1997;46(1):159-62.
24. Nwaru BI, Ahonen S, Kaila M, et al. Maternal diet during pregnancy and allergic sensitization in the offspring by 5 yrs of age: a prospective cohort study. Pediatr Allergy Immunol. 2010;21(1 Pt 1):29-37.
25. Palm NW, Rosenstein RK, Medzhitov R. Allergic host defences. Nature. 2012;484(7395):465-72.

JAYPEE BROTHERS

26. Park YB, Mo EK, Lee JY, et al. Association between pet ownership and the sensitization to pet allergens in adults with various allergic diseases. Allergy Asthma Immunol Res. 2013; 5(5):295-300.
27. Piippo-Savolainen E, Remes S, Korppi M. Does early exposure or sensitization to inhalant allergens predict asthma in wheezing infants? A 20-year follow-up. Allergy Asthma Proc. 2007;28(4):454-61.
28. Rhodes HL, Sporik R, Thomas P, et al. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. J Allergy Clin Immunol. 2001;108(5):720-5.
29. Rosenkranz RR, Rosenkranz SK, Neessen KJ. Dietary factors associated with lifetime asthma or hayfever diagnosis in Australian middle-aged and older adults: a cross-sectional study. Nutr J. 2012;11:84.
30. Sausenthaler S, Koletzko S, Schaaf B, et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2y of age. Am J Clin Nutr. 2007;85(2):530-7.
31. Schafer T, Meyer T, Ring J, et al. Worm infestation and the negative association with eczema (atopic/nonatopic) and allergic sensitization. Allergy. 2005;60(8):1014-20.
32. Steinke JW, Borish L, Rosenwasser LJ. 5. Genetics of hypersensitivity. J Allergy Clin Immunol. 2003;111(Suppl 2):S495-501.
33. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259-60.
34. Strachan DP, Cook DG. Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. Thorax. 1998;53(2):117-23.
35. Sunyer J, Jarvis D, Pekkanen J, et al. Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. J Allergy Clin Immunol. 2004;114(5): 1033-9.
36. Svanes C, Jarvis D, Chinn S, et al. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. J Allergy Clin Immunol. 1999;103(3 Pt 1):415-20.
37. van Ree R, Hummelshoj L, Plantinga M, et al. Allergic sensitization: host-immune factors. Clin Transl Allergy. 2014;4(1):12.
38. Viswanathan RK, Mathur SK. Role of allergen sensitization in older adults. Curr Allergy Asthma Rep. 2011;11(5):427-33.
39. von Bubnoff D, Geiger E, Bieber T. Antigen-presenting cells in allergy. J Allergy Clin Immunol. 2001;108(3):329-39.
40. Warm K, Lindberg A, Lundback B, et al. Increase in sensitization to common airborne allergens among adults–two population-based studies 15 years apart. Allergy Asthma Clin Immunol. 2013;9(1):20.

JAYPEE BROTHERS

for detailed information on pediatric books, visit our website www.jaypeebrothers.com, for detailed information on pediatr

MANUAL OF PEDIATRIC ALLERGY

The first ever comprehensive book on pediatric allergy in India came into the hands of clinicians in the year 2015 and was well received. To update ourselves with the newer developments following ongoing research globally in the field of Allergy, Asthma and Clinical immunology, the author with his added clinical experience, has come out with the second edition of the *Manual of Pediatric Allergy*. Some chapters are newly included, while some others are extensively discussed upon. This elaborate and improvised second edition will help the practicing pediatricians, postgraduates and allergists, as a desktop ready-reckoner in their office practice, in the management of allergic diseases in children.

Major K Nagaraju MD DCH DAP DAA FAGE FIAP FAIMS FICMCH FICAAI FACI is currently working as Professor of Pediatrics, Division of Allergy and Clinical Immunology at Saveetha Medical College and Hospital, Chennai, Tamil Nadu, India. He is the course Director for Fellowship in Allergy and Clinical Immunology, which is affiliated to Saveetha University, Chennai. He is the Senior Consultant Pediatric Allergist, Apollo Children's Hospital, Chennai.

He is instrumental in the formation of Indian Academy of Pediatrics (IAP) Allergy and Applied Immunology Chapter, which is registered as Pediatric Allergy Association of India in Chennai. He is the founder Secretary General of this association. At present, he is holding Immediate Past President post of this Chapter. He founded VN Allergy and Asthma Research Center at Chennai, a Center of International standards. In this center, he is treating all types of allergies including drug allergies. Recognizing his good work in Pediatric Allergy, Vasanthi Charitable Organization honored him with Vaidya Ratna award at Nellore, Andhra Pradesh.

He is instrumental in training a hundred and more pediatricians in the field of Pediatric Allergy, Asthma and Clinical Immunology. He regularly conducts allergy testing workshops and Allergen-specific Immunotherapy workshops. He has presented several papers in national and international conferences. He has several publications to his credit. For his good work in Allergy and Clinical immunology, Indian College of Allergy, Asthma and Applied Immunology, awarded him fellowship (FICAAI). He has also received fellowship award from Fellowship of Indian Academy of Pediatrics (FIAP). The Saveetha University has conferred a fellowship for his contribution in the Field of Allergy and Clinical Immunology (FACI).

With special interest in pediatric allergy, he underwent training in allergy in national and international centers. He is the first pediatrician from India to qualify in Pediatric Allergy and Clinical Immunology examination conducted by the European Academy of Allergy and Clinical Immunology (EAACI).

From a grass root worker of IAP, he rose to President of IAP, Tamil Nadu and Executive Board Member of central IAP for 4 terms 2010, 2011, 2018 and 2019. He is instrumental in developing a module on Allergic Rhinitis in 2019, which is named as CARE Module (Childhood Allergic Rhinitis Expertise Module). He has a key role in developing ARCTM (Allergic Rhinitis Comorbidities Training Module) and ADEX (Airway Disease Education and Expertise) modules.

He is one of the most sought after speakers in many conferences, CMEs or workshops related to Allergy, Asthma and Immunology. He is a pioneer in Allergen-specific immunotherapy and has made this mode of therapy popular among the pediatricians. His work on Food Dependent exercise-induced anaphylaxis was well appreciated in EAACI. His special interests are sublingual immunotherapy, specific oral tolerance induction (foods) and drug allergies. He has widely traveled across the country, training the pediatricians, ENT specialists and pulmonologists interested in the field of allergy.

He has conducted several awareness programs on allergy and asthma for the school children, parents and various professionals. He has conducted several free camps, emphasizing on preventive aspects of allergy, through various social service organizations. These awareness programs and free camps speak volumes about his passion and commitment in the field of allergy and asthma.

He has also done several programs for the public through audiovisual and print media at various places.

Available at all medical bookstores
or buy online at www.jaypeebrothers.com



JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
PEDIATRICS

