

Hypersensitivity Reactions: An Everyday Occurrence in Pediatric Allergy Clinics

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The explanation of hypersensitivity reactions has long relied on the classification of Gell and Coombs, originally proposed in the 1960s. However, their concepts were predated by other authors by at least 50 years. A 21st century pediatric allergy clinic provides multiple examples of these basic concepts on a daily basis. We review classic and less classic examples of the original criteria, highlight where current disease pathophysiology does not always fit the original model, and provide updated language for common and uncommon immunologically driven hypersensitivity diseases.

Keywords: hypersensitivity, immune, immunity, T cells, B cells, IgE

Introduction

A 21ST CENTURY PEDIATRIC allergy/immunology clinic is still based on ideas and hypotheses from over a century ago.¹ It is virtually every clinic when the premise for a specific hypersensitivity reaction(s) is asked by a clinic learner or is used for patient and parent education purposes. The intent of this review is to present an historical perspective on hypersensitivity reaction classifications, and to update these concepts into modern immunological terminology and understanding.

Format of this review

The basic idea of a hypersensitivity response to a foreign antigen began in the early 20th century and was termed allergy, which was further refined by early observations in hay fever, as summarized by Platts-Mills.¹ All allergic diseases have a vast network of immunological cells, regulatory and effector cells. The current understanding of allergic Gell and Coombs Type 1² reactions as having acute, delayed, and chronic inflammation will serve as a framework.³ The model of early and late reactions after an immunoglobulin E (IgE)-mediated episode became hallmark of the allergic (IgE) process decades ago, but not every allergic disease follows these concepts. The work of Galli et al.³ and Kay⁴ included this concept, and a more recent publication updates its current applicability and immunological correlates.⁵

Each disease presented will have a brief outline, followed by a summary of hypersensitivity classifications. The concept of early and late IgE-mediated responses is included

when applicable.⁵ This review will not include effector cell activity (eg, eosinophils, mast cells).

Hypersensitivity terminology: Historical and current

The classic definition of hypersensitivity reactions was proposed in 1963 by Gell and Coombs,² with a revisit by Rajan.⁶ A review and update of hypersensitivity (allergy) concepts was presented by Kay⁴ and reviewed by Igea.⁷ The allergy conditions seen in pediatric allergy clinics were defined by a Nomenclature Committee for dissemination by the European Academy of Allergology and Clinical Immunology, World Allergy Organization, and American Academy of Allergy, Asthma, and Clinical Immunology.⁸

The original Gell and Coombs² hypersensitivity reactions, with a modification by Rajan⁶ are outlined in Table 1. An expanded concept for the original Gell and Coombs classification was published in 2003 and is included in Table 1.

The Gell–Coombs hypersensitivity reactions were revised using more current understanding of immunology by Kay (Table 2).⁴

A 2015 report by Annunziato et al. synthesized the collective information of innate and adaptive immune responses and proposed a division of innate and adaptive cell-mediated effector pathways into three types (Table 3).⁹ The concept of Type 2 pathophysiology is now a common theme in both scientific and lay press and advertising.

Using current immunological understanding of lymphocyte biology, a newer classification for lymphocyte cell-induced (or cooperative) hypersensitivity is summarized in this study (Table 4) and is used henceforth in this

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TABLE 1. GELL AND COOMBS CLASSIFICATION WITH A MODIFICATION BY RAJAN

	<i>Original Gell and Coombs</i> ²	<i>Rajan update</i> ⁶
Type 1	Hypersensitivity reaction: IgE based (immediate)	Orchestrated by Th2 cells
Type 2	Hypersensitivity reaction: antigen/antibody, complement activation, neutrophils (cytotoxic)	Antibodies to surface antigens of microorganisms, C5a release, polymorphonuclear leukocytes
Type 3	Deposited antigen/antibody, complement, neutrophils (immune complex)	Antibodies complexing with and inactivating circulating viral particles
Type 4	T cells, macrophages, NK cells, leukocytes (delayed: T cell mediated)	CD4 and CD8 cells recognizing MHC antigens presenting viral peptides

IgE, immunoglobulin E; MHC, major histocompatibility complex; NK, natural killer.

TABLE 2. KAY CLASSIFICATION

Type 1	Immediate-type (IgE dependent) or anaphylactic hypersensitivity
Type 2a	Cytolytic or cytotoxic reactions
Type 2b	B cell-stimulating reactions involving altered cell function
Type 3	Arthus type, immune complex
Type 4 (Th1)	Classic delayed hypersensitivity
Type 4 (Th2)	Cell-mediated eosinophilic hypersensitivity, and chronic allergic inflammation
Type 4 cytotoxic	Tissue injury by cytotoxic T lymphocytes

Kay.⁴

discussion.^{10–12} This, in part, overlaps with the cell-mediated effector immunity classification (Table 3).⁹

Finally, a recent review of drug allergy provides a modified Gell–Coombs reaction which is most applicable for drug sensitivity.¹³ Its specifics will be discussed under drug allergy.

Allergic Rhinoconjunctivitis

As the most straightforward form of hypersensitivity, acute allergic rhinoconjunctivitis, with eye itching and swelling and a sneezing attack after cat exposure, epitomizes the classic Type 1 Gell and Coombs hypersensitivity (Table 5).² Chronic allergen exposure can generate both allergic acute (early) and delayed (late) responses; however, chronic allergic rhinitis has inflammatory responses beyond the Type 1 Gell–Coombs hypersensitivity pattern,⁵ and Kay's Type 4 (Th2) provides a partial explanation.⁴

Food Allergy (Immediate and Anaphylaxis)

The ingestion (or skin contact) with an allergic food may induce local or widespread hives, and/or the ingestion of food can cause respiratory, cardiac, and vascular responses, even death (Table 6).^{14,15} In most situations the effect of a food allergy is immediate but the complexity of food anaphylaxis may include a prolonged or a dual-phase (biphasic) response.¹⁶ The pathophysiology of prolonged and biphasic

appears to involve a small subset of patients with no clear immunological disadvantage.¹⁶ The avoidance of a Type 1 food exclusively revolves around a total or significant reduction in the food ingestion.¹⁷ The lack of an allergic (or anaphylactic) response in an individual with circulating food IgE but tolerance to the food also has immunological underpinnings, including immunoglobulin G (IgG) antibodies, and T regulatory cells.^{1,15}

Atopic Dermatitis

The explanation of hypersensitivity in atopic dermatitis is complex.¹⁸ Atopic dermatitis is often an early manifestation of the atopic march in children.¹⁹ Descriptions of cytokine pattern in blood and nonlesional and lesional skin in children provides guidance for the hypersensitivity pattern(s) seen in this pediatric allergic process.²⁰

Becoming more common in atopic dermatitis is using classifications based using phenotype and endotype descriptions.²⁰ An older, and a clinically defined concept, is allergic and non-allergic (intrinsic versus extrinsic) atopic dermatitis.^{18,20,21} This division is defined by negative or positive allergy testing (environmental and/or food), although the atopic dermatitis is rarely changed by the avoidance of the allergen(s) identified.

Whether immunological endotypic differences truly occur between pediatric allergic and nonallergic atopic dermatitis phenotypes deserves further evaluation.

Adolescent and adult-onset atopic dermatitis may also have immunological distinctions (endotypes) from pediatric onset.²⁰ Even Asian atopic dermatitis differences are noted, and also black versus nonblack ethnicity.²⁰ The epidermal dysfunction likely has separate immunological variability in atopic dermatitis, but will not be the subject of the discussion.^{21,22}

Clinicians do not generally discuss acute atopic dermatitis other than in the context of an acute worsening superimposed on chronic atopic dermatitis, and the causes are multifactorial (eg, infection). In Table 7 the acute phase is included, but is underemphasized clinically, as it could be

TABLE 3. CELL-MEDIATED EFFECTOR IMMUNITY

Type 1	CD4+ T _H 1 cells, CD8+ T _C 1 cells, group 1 ILCs, NK cells
Type 2	CD4+ T _H 2 cells, CD8+ T _C 2 cells, group 2 ILCs
Type 3	CD4+ T _H 17 cells, CD8+ T _C 17 cells, group 3 ILCs

Annunziato et al.⁹
ILCs, innate lymphoid cells.

TABLE 4. LYMPHOCYTE SUBSETS

<i>Lymphocyte type</i>	<i>Predominate functions</i>
B cell	IgG, IgM, IgA, IgE, IgD production
Th1 (T _H 1)	Cellular immune functions
Th2 (T _H 2)	Parasitic and allergic responses (has different subsets)
Th9 (T _H 9)	Parasitic and allergic responses
Th17 (T _H 17)	Protection in fungal and bacterial infections and proinflammation
Th22 (T _H 22)	Effect nonhematopoietic cells, skin, GI, and tissue inflammation
T follicular helper cells (T _{FH})	Antibody synthesis augmentation (has different subsets)
Innate lymphoid cell ILC1	Less defined
Innate lymphoid cell ILC2	Increase allergic inflammation, antiparasitic protection
Innate lymphoid cell ILC3	Less defined

Geginat et al.,¹⁰ Caza and Landas,¹¹ and Pasha et al.¹²

TABLE 5. PEDIATRIC ALLERGIC RHINITIS

	<i>Acute</i>	<i>Late</i>	<i>Chronic</i>
Gell and Coombs	Type 1		
Rajan	Type 1		
Kay	Type 1	Type 4 Th2	Type 4 Th2
Cell-mediated effector	Type 2	Type 2	Type 2
Lymphocyte subsets	B cell (IgE), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2	B cell (IgE), Th2 (T _H 2), Th9 (T _H 9), ILC2	Th2 (T _H 2), Th9 (T _H 9), ILC2

TABLE 6. PEDIATRIC FOOD ANAPHYLAXIS

	<i>Acute</i>	<i>Prolonged/biphasic</i>
Gell and Coombs	Type 1	Type 1
Rajan	Type 1	Type 1
Kay	Type 1	Type 1
Cell-mediated effector	Type 2	Type 2
Lymphocyte subsets	B cell (IgE), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2	B cell (IgE), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2

TABLE 7. PEDIATRIC ATOPIC DERMATITIS

	<i>Acute</i>	<i>Chronic</i>
Gell and Coombs	Type 1	
Rajan	Type 1	
Kay	Type 1	Type 4 Th2
Cell-mediated effector	Type 2	Type 2
Lymphocyte subsets	B cell (IgE), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2, Th22 (T _H 22), Th17 (T _H 17)	B cell (IgE), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2, Th22 (T _H 22), Th17 (T _H 17), with? Th1 (T _H 1)

allergen triggered (eg, post-food ingestion). The late-phase concept of IgE reactions is removed for atopic dermatitis hypersensitivity classifications, as it melds with chronic inflammation, and is rarely considered.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) has provided some variances on the standard understanding of the allergic diseases²³: (1) a rare patient may have near immediate esophageal symptoms after a specific food ingestion, which may or may not have a concomitant positive allergy test (sensitized); (2) the majority of pediatric EoE patients have positive food allergic testing (sensitization) but the positive food is not necessarily the culprit food; (3) food can cause a delayed patch test response, even when the allergy test was

negative; (4) and IgG4 has been suggested to play a role.²⁴ With regard to IgG4, the high occurrence of positive IgG4 that occurs in normal immunological tolerance brings pause to the role of IgG4 in EoE.²⁴ (5) Finally, the indolent development of a clinicopathologically verified EoE suggests minimal immediacy of the Gell–Coombs Type 1 response, whereas the chronicity (immunologically) echoes an atopic dermatitis and/or asthmatic persistence (Table 8).^{23,25}

Pediatric Eosinophilic Gastrointestinal Diseases

Pediatric Eosinophilic Gastrointestinal diseases (gastric, duodenal, remainder of small bowel, cecum, colon) are uncommon allergic diseases (Table 9).²⁶ They may occur with EoE, but most often they develop alone or in combination(s).²⁶ As they are most often indolently presenting

TABLE 8. EOSINOPHILIC ESOPHAGITIS

	+ Allergy test	+ Patch/ -Allergy test	Chronic
Gell and Coombs	Type 1		
Rajan	Type 1		
Kay	Type 1		Type 4 Th2
Cell-mediated effector	Type 2		Type 2
Lymphocyte subsets	B cell (IgE), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2, Th22 (T _H 22), Th17 (T _H 17)	B cell (IgG4)? Th2 (T _H 2)?	B cell (IgE, IgG4), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2, Th22 (T _H 22), Th17 (T _H 17), with? Th1 (T _H 1)

diseases,²⁶ an acute-phase reaction is rarely a component; and continued disease could be compared with chronic EoE, although there is evidence that EoE and eosinophilic gastritis are not of the same genetic pathway.²⁷

Pediatric Asthma

An example of using modern hypersensitivity concepts to explain asthma is a recent article on phenotypes and endotypes of adult asthma (Table 10).²⁸ They use cluster analysis studies to divide adult asthma in different phenotypes, and use immunological data to further characterize endotypic features.²⁸ A recent study used adult asthmatics that had a pediatric onset to define the cellular census of their disease.²⁹ These types of reports are the basis of redefining asthma in modern immunological constructs and continues to define this common but complex disease. The pediatric-onset adult asthmatics are presented in this study in a limited format as a foundation for the future of pediatric asthma typing.²⁹

The diagnosis of asthma does not have a gold standard and the fact that many children wheeze, and many of those have multiple episodes, complicates the big picture. In fact, large studies have looked solely of epidemiology of wheezing, with attempts to tie these wheezing phenotypes to asthma.^{30,31} The remainder of this section will focus specifically on pediatric asthma, as it is currently understood.³²

Pediatric asthma phenotyping has not advanced as has its adult counterparts, largely based on the invasiveness of obtaining bronchial samples. Some early conceptualization of pediatric asthma phenotyping has occurred, using existing populations and clinical data³³; and a recent review on childhood asthma outlines the complexity of pediatric asthma phenotyping.³⁴

TABLE 9. EOSINOPHILIC GASTROINTESTINAL DISEASES

	Acute (±skin test)	Chronic*
Gell and Coombs	Type 1	
Rajan	Type 1	
Kay	Type 1	Type 4 Th2
Cell-mediated effector	Type 2	Type 2
Lymphocyte subsets	B cell (IgE), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2, Th22 (T _H 22), Th17 (T _H 17)	B cell (IgE, IgG4), T _{FH} , Th2 (T _H 2), Th9 (T _H 9), ILC2, Th22 (T _H 22), Th17 (T _H 17), with? Th1 (T _H 1)

Since the majority of children with asthma have allergic (extrinsic) asthma, the hypersensitivity classification of this phenotype has been historically defined,³⁵ with recent definitional updating.^{33,34} In the allergic (extrinsic) phenotype, an immediate wheeze might result from cat allergy, resulting in wheezing, and then (sometimes) a late response.^{5,35} This allergic phase superimposes upon the chronic asthmatic state and enhances the phenomenon of native bronchial hyperresponsiveness.⁵ The allergic (extrinsic) phenotype often has nonallergic aggravation, including viral illness, exercise, or irritants (Table 11).³⁵

A recent large population study identified genes on the 17q chromosome in pediatric asthma to be a significant signal, but adult asthma was not significantly linked to this locus.³⁶ An editorial about the study labeled adult asthma as “less active Type 2 immunity” with either “eosinophilic or neutrophilic” involvement.³⁷ An editorial reviewing the work of Schleich et al.,³⁸ which investigated the volatile gas exhalate of asthmatics, stated there “is a need for type 2 and increasingly nontype 2 asthma.” inflammatory profiling.³⁹

A separate clinically recognized pediatric asthmatic phenotype revolves solely around nonallergic triggering, largely viral illness.³⁵ For the sake of this discussion, IgE mediation is nonexistent, and conventional allergic testing is negative, and nitric oxide is not elevated. However, this phenotype could be divided by the presence of eosinophilic or noneosinophilic lavage cytology. It is probable this pediatric nonallergic phenotype is several distinct phenotypes, but studies are limited, although starting to emerge, but usually limited to “refractory/chronic” patients (Table 12).⁴⁰ This recent report of lavage data in therapy-resistant children suggest there are several less typical pediatric phenotypes and also provides a summary of existing reports of phenotypic differentiation that has been published.⁴⁰ Data in adults often characterize less or (non-) Type 2 asthma.²⁸ Pediatric data are moving in the direction of phenotyping, but is limited by age and invasiveness of tissue sampling.

Obesity in pediatric asthma may be an additional (sub-) phenotype; as there is suggestion that a separate inflammatory process accompanies the obesity.^{41,42}

TABLE 10. ADULT ASTHMA (CHILDHOOD ONSET)

	Chronic asthma state ²⁹
Lymphocyte subsets	Th2 (T _H 2) (2 subsets), ILC2, B cells (not elevated but present: Th1 (T _H 1) and Th17 (T _H 17). T _{FH} not discussed

TABLE 11. ALLERGIC (EXTRINSIC) PEDIATRIC ASTHMA

	<i>Acute phase</i>	<i>Late phase</i>	<i>Chronic</i>
Gell and Coombs	Type 1		
Rajan	Type 1		
Kay	Type 1	Type 4 Th2	Type 4 Th2
Cell-mediated effector	Type 2	Type 2	Type 2
Lymphocyte subsets	B cell (IgE), T _{FH} , Th2 (T _{H2}), Th9 (T _{H9}), ILC2	B cell (IgE), Th2 (T _{H2}), Th9 (T _{H9}), ILC2	Th2 (T _{H2}), Th9 (T _{H9}), ILC2

TABLE 12. NONALLERGIC (INTRINSIC) PEDIATRIC ASTHMA

	<i>Acute wheeze</i>	<i>Chronic</i>
Gell and Coombs		
Rajan		
Kay		Type 4 Th2
Cell-mediated effector		Type 2 (when eosinophilic)
Lymphocyte subsets	Th2 (T _{H2}), Th9 (T _{H9}), ILC2	Th2 (T _{H2}), Th9 (T _{H9}), ILC2

Chronic Urticaria in Children

Cutting across a huge swath of mast cell hyperreactivity situations with or without clear-cut immunological contributions, chronic urticaria is a common pediatric condition (Table 13).^{43,44} Diverting from the previous tabular form of hypersensitivity explanation(s) the potential explanations are listed below in a more general fashion, although the etiologies are in agreement with recent reviews (Table 13).^{43–45} Pediatric chronic hives remains enigmatic.⁴⁶

Food Protein Enterocolitis Syndrome

An uncommon, but now more recognized, non-IgE food-induced syndrome, Food Protein Enterocolitis Syndrome

(FPIES) is accepted as a complex immunopathological process. Several recent publications provide information in this regard.^{47,48}

The clinical presentation has been summarized in international guidelines.⁴⁹ FPIES is almost universally outgrown in children, but adult initiation can occur.⁵⁰

The majority of the information has been gathered during passed and failed rechallenges for target food(s). The results suggest a large and diverse pathway, with upstream regulatory cytokines and chemokines.^{47,48} The innate immune response to specific antigen (food) is a paramount component, but the profile of upregulated modulators are part of T and B cell pathway activation.^{47,48}

For the purpose of this review, hypersensitivity reaction classifications are inapplicable to explain FPIES.

TABLE 13. PEDIATRIC HIVES

Primary suspected cause for Hives	Basic Immunological Potentials Beyond the Mast Cell
Food	B cell (IgE)
Medication	B cell, T cell
Physical (inducible) urticaria	
Infection	B cell (IgE-parasites); IgG (bacteria, virus with complement)
Autoimmune	B cell (IgG)
Spontaneous chronic urticaria	Unknown

TABLE 14. DRUG REACTIONS

	<i>Explanation</i>	<i>Clinical presentation</i>	<i>Common drug</i>
Type 1	IgE	Allergic	β-lactams
Type 2	IgG, cell or matrix-associated antigen	Hemolytic anemia thrombocytopenia	β-lactams, sulfa, rifampin,
Type 3	IgG, complement	Serum sickness, arthus reaction, vasculitis	β-lactams, sulfa, minocycline
Type 4a	INF-γ, TNF-α, TH ₁ cells	TB skin test, contact dermatitis	
Type 4b	IL-5, IL-4, IL-13, TH ₂ cells	Drug rash with eosinophilia and systemic symptoms	
Type 4c	Perforin/granzyme B	Steven–Johnson syndrome/Toxic toxic epidermal necrolysis, bullous exanthema and fixed drug reactions, hepatitis	
Type 4d	IL-8, CG-CSF (T cell)	Acute generalized exanthematous pustulosis	β-lactams

Khan et al.¹³

CG-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; INF, interferon; TNF, tumor necrosis factor.

Antibiotic/Drug Allergy

Untoward responses to drugs, utilized for therapeutic reasons, are not uncommon in pediatric clinics. The vast majority occur during or immediately after antibiotic therapy. The concern is most often dermatological, (ie, hives) which occur while on an antibiotic for an infection, often with an accompanying fever.

A recent review of cephalosporin allergy presented a modified Gell and Coombs hypersensitivity schematic that is pertinent to drug allergy, and is thus presented in this study.¹³ This classification was drawn from previous reviews,^{51,52} but schematized by Khan.¹³ It has applicability for antibiotic and nonantibiotic drugs, and overlaps conceptually with another publication of drug allergy (Table 14).⁵³

Summary

Pediatric Allergy and Immunology clinics are the primary referral pathway for a wide collection of immediate and chronic conditions. Familiar to most primary care providers, their suddenness/severity coupled with nonresolution often directs them to specialty care.

As reviewed in this study, the explanation of a hypersensitivity reaction may be straightforward and easily explained (peanut allergy), or may have complex or multiple pathways (asthma, atopic dermatitis). The pathophysiology of hypersensitivity reactions has become complicated, and their immunology explanations are advancing. This review was an attempt to advance the Gell–Coombs language and explanation into modern immunological phraseology.

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