A Review on Allergy and New Updates

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Board Certified Internal Medicine (ABIM)

Board Certified Allergy and Immunology (ABAI)

Outline

- Hypersensitivity types
- Types of allergic diseases
  - Asthma
  - Allergic Rhinitis and Conjunctivitis
  - Food Allergy
    - IgE mediated
    - Non-IgE mediated
  - Adverse Drug Reactions
  - Atopic Dermatitis/Eczema
- Types testing
- Treatment options

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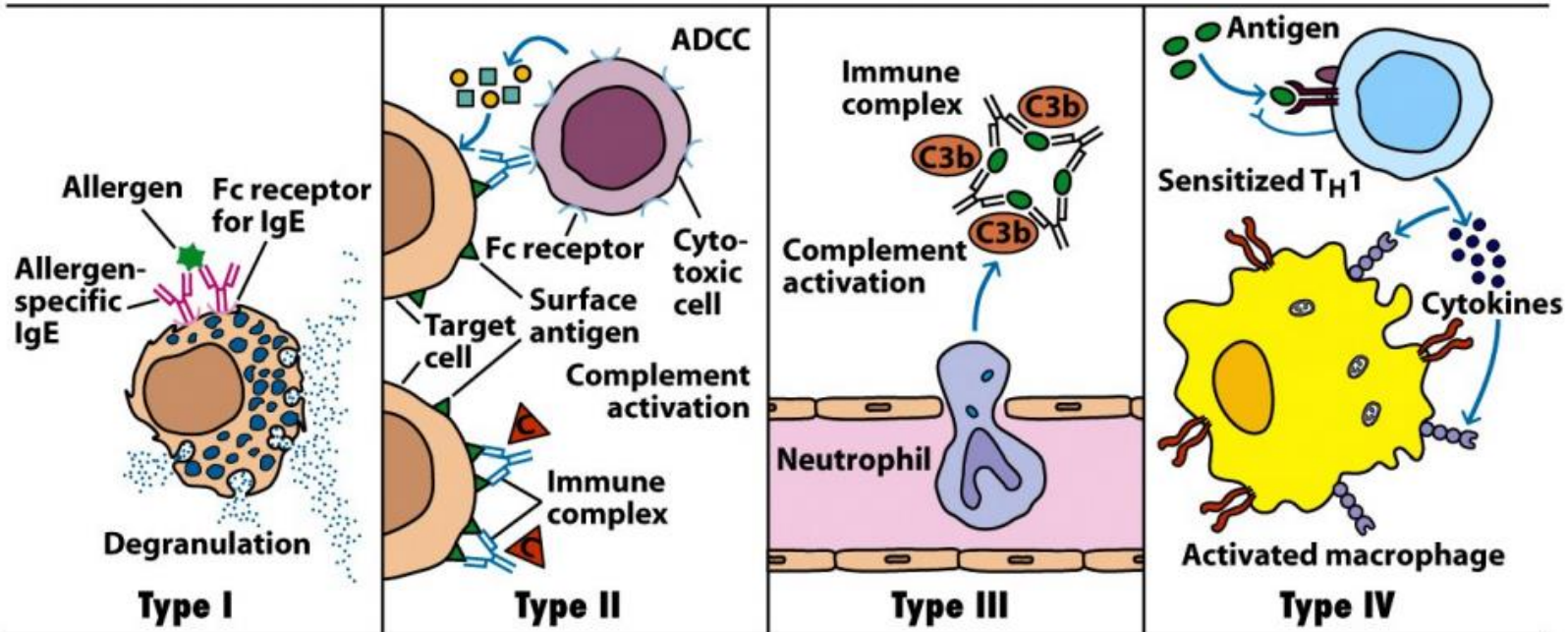
Hypersensitivity reactions

- Type I – IgE Mediated
- Type II – Antibody Mediated Cytotoxic
- Type III – Immune Complex Mediated
- Type IV – Cell Mediated



Type I	Type II	Type III	Type IV
IgE-Mediated Hypersensitivity	IgG- or IgM-Mediated Cytotoxic Hypersensitivity	Immune Complex–Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC.	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.	Sensitized T_H1 cells shown above release cytokines that activate macrophages or T_C cells that mediate direct cellular damage. T_H2 cells and CTLs mediate similar responses.
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.	Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.

Figure 15-1
Kuby IMMUNOLOGY, Sixth Edition

Type I hypersensitivity response

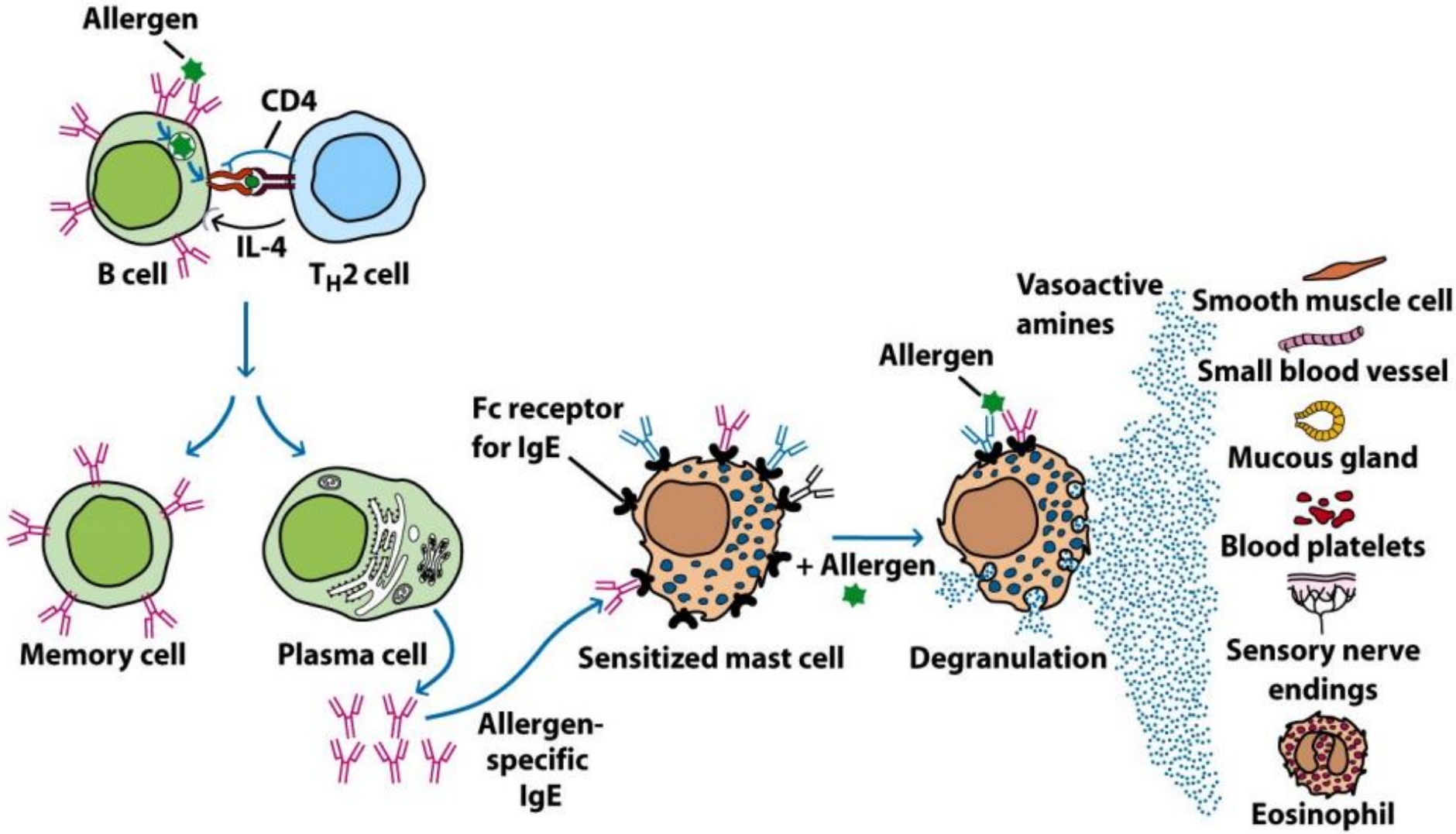


Figure 15-2
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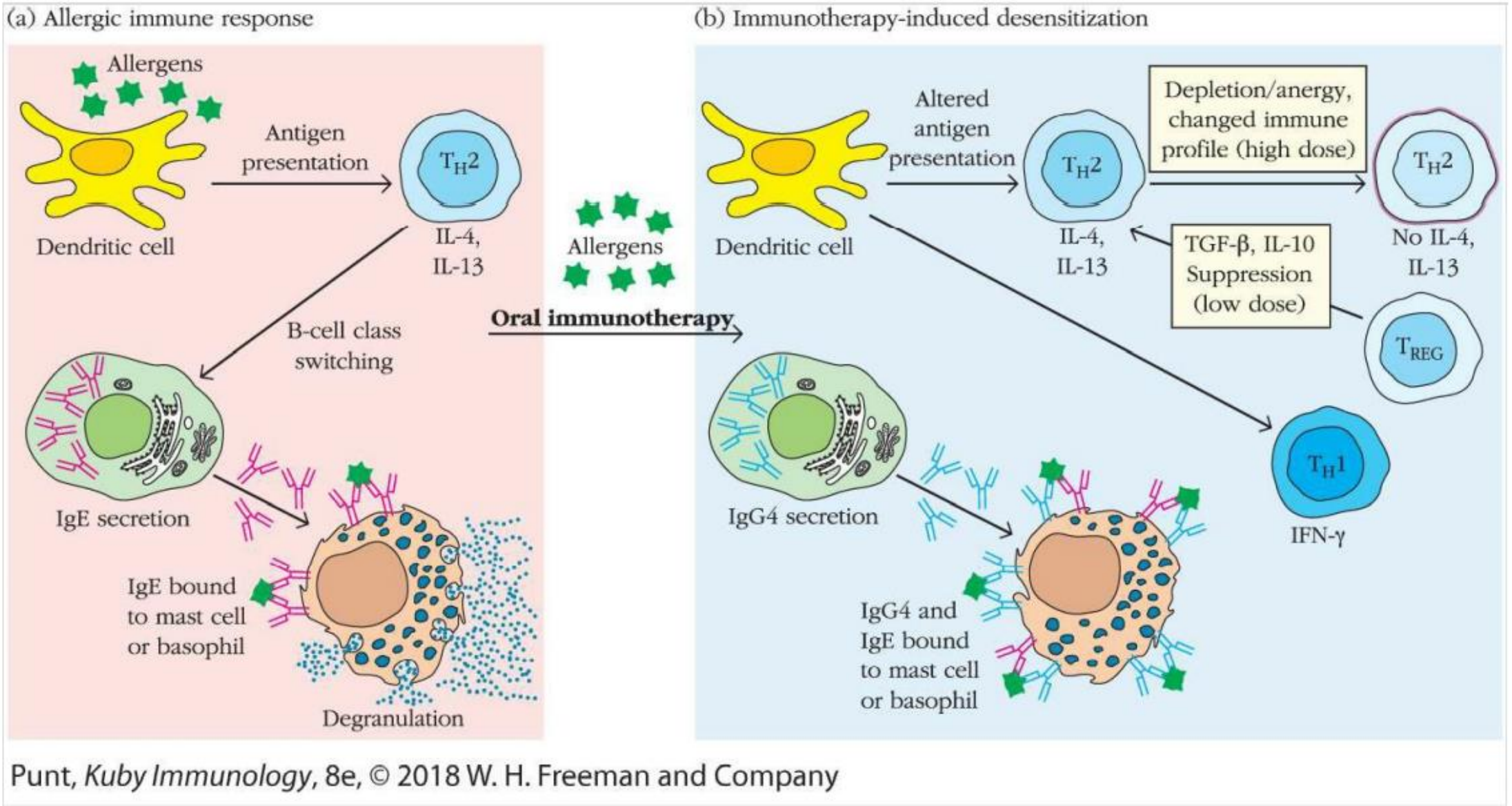
Desensitization of Type 1 Hypersensitivity



Punt, *Kuby Immunology*, 8e, © 2018 W. H. Freeman and Company

Indications for Allergen Immunotherapy

- Moderate-to-severe allergic rhinitis
- Allergic asthma
- Allergic conjunctivitis
- Allergic rhino-conjunctivitis
- Atopic dermatitis
- Immune-mediated and IgE-mediated food allergy
- Insect allergy that causes significant local reaction and anaphylaxis
- Note: Allergen immunotherapy is only indicated when there is evidence of an IgE-mediated reaction that correlates with clinical symptoms. These IgE-mediated reactions can be identified via a blood IgE test or the more preferable skin testing.
- Allergy Immunotherapy - StatPearls - NCBI Bookshelf (nih.gov)

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ASTHMA

- International guidelines are through Global Initiative for Asthma (GINA) and was established by World Health Organization (WHO) which are updated yearly
- Guidelines on asthma in the United States based on expert panel commissioned by the National Asthma Education and Prevention Program (NAEPP) Coordinating Committee (CC), coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health
- Initial EPR was in 1991 and the most recent EPR was in 2007
- In December 2020 an update was finally released and can be found at nhlbi.nih.gov/asthmaguidelines
- Biologics were not addressed in EPR 3 since it would have delayed up date 1-2 more years

PURPOSE

This Clinician's Guide summarizes the *2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group* to help clinicians integrate the new recommendations into clinical care. The full 2020 Report, which is focused on selected topics rather than a complete revision of the 2007 *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3), can be found at **nhlbi.nih.gov/asthmaguidelines.** This summary guide should be used in conjunction with the full report. The Guide is organized by the following topics:

Intermittent Inhaled Corticosteroids

Long-Acting Muscarinic Antagonists

Indoor Allergen Mitigation

Immunotherapy in the Treatment of Allergic Asthma

Fractional Exhaled Nitric Oxide Testing

Bronchial Thermoplasty

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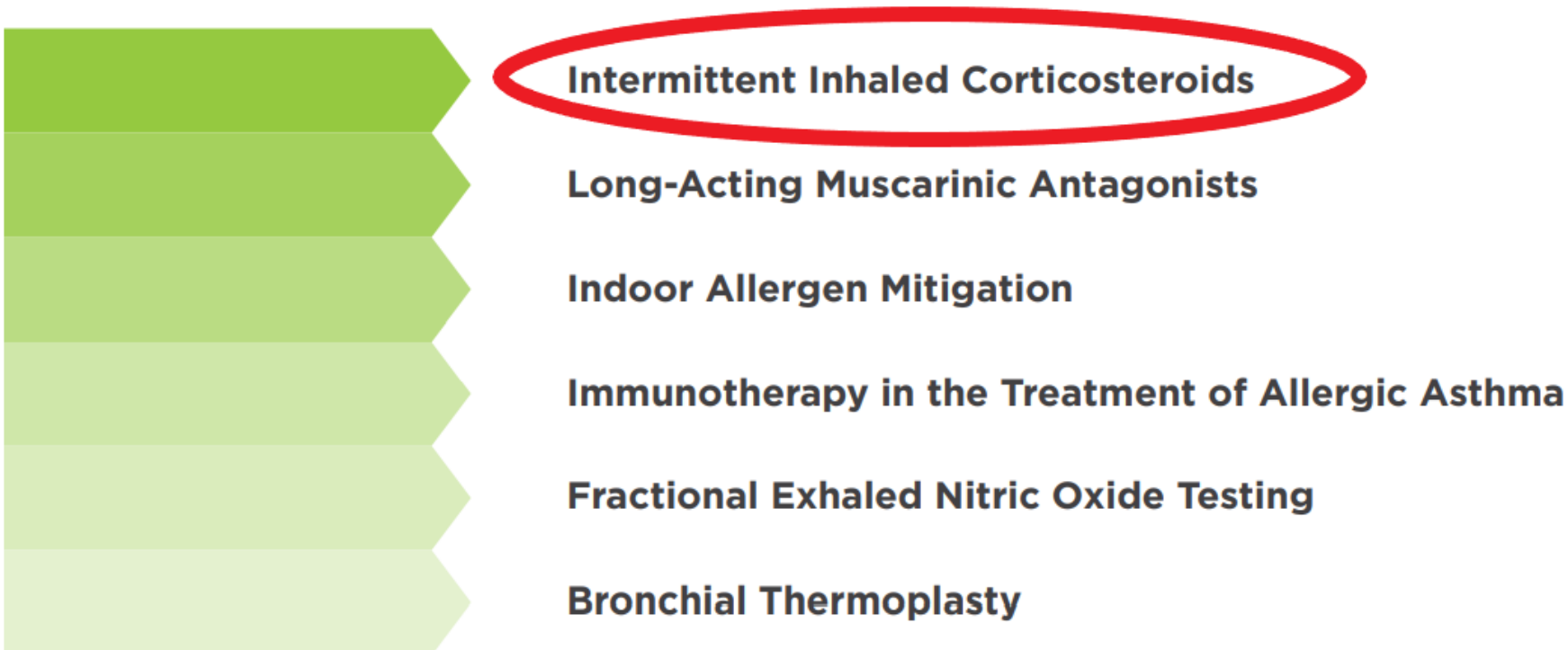

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SINGLE MAINTENANCE AND RELIEVER THERAPY (SMART) IMPLEMENTATION GUIDANCE AND CONSIDERATIONS FOR SHARED DECISION MAKING

- **Target population:** Individuals 4 years and older with a severe exacerbation in the prior year are particularly good candidates for SMART to reduce exacerbations.
- **Who should not receive this treatment:** Do not use ICS-formoterol as reliever therapy in individuals taking ICS-salmeterol as maintenance therapy.
- **Treatment:** Inhaled ICS-formoterol in a single inhaler. This form of therapy has only been studied with formoterol as the long-acting beta$_2$-agonist (LABA).

✓ SMART is appropriate for Step 3 (low-dose ICS) and Step 4 (medium-dose ICS) treatment.

✓ Individuals whose asthma is uncontrolled on maintenance ICS-LABA with SABA as quick-relief therapy should receive the preferred SMART if possible before moving to a higher step of therapy.

✓ ICS-formoterol should be administered as maintenance therapy with 1–2 puffs once or twice daily (depending on age, asthma severity, and ICS dose in the ICS-formoterol preparation) and 1–2 puffs as needed for asthma symptoms.

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Biologics

- Not mentioned in EPR 3 update as it would have prolonged release
- However they are used in multiple disease states
- Anti IL-5 Mepolizumab and Benralizumab
- Anti Ig-E Omalizumab
  - Now approved for nasal polyps
- Anti IL-4 and IL-13 Dupilumab
  - Also approved for atopic dermatitis and nasal polyps

COVID-19 risk and outcomes in adult asthmatic patients treated with biologics or systemic corticosteroids: Nationwide real-world evidence

Yochai Adir, MD, MHA,[a,b] Marc Humbert, MD, PhD,[c,d,e] and Walid Saliba, MD, MPH[b,f] *Haifa, Israel; and*
Le Kremlin-Bicêtre and Le Plessis-Robinson, France

COVID-19 risk and outcomes in adult asthmatic patients treated with biologics or systemic corticosteroids : nationwide real-world evidence in Israel

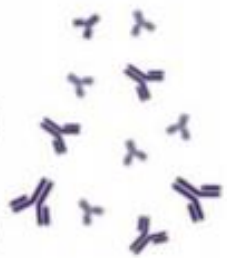
80,602 asthmatics (514 on biologics) were tested with PCR for SARS-CoV-2

8,242 were positive

Patients Previously Treated with Systemic Corticosteroids (n=1358)

Patients on Biologics (n=50)

Increased Risk	COVID-19 Severity	No Increased Risk
Increased Risk	90-days Mortality	No Increased Risk



COVID-19: Coronavirus Diseaese 2019

PCR: Polymerase chain reaction

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

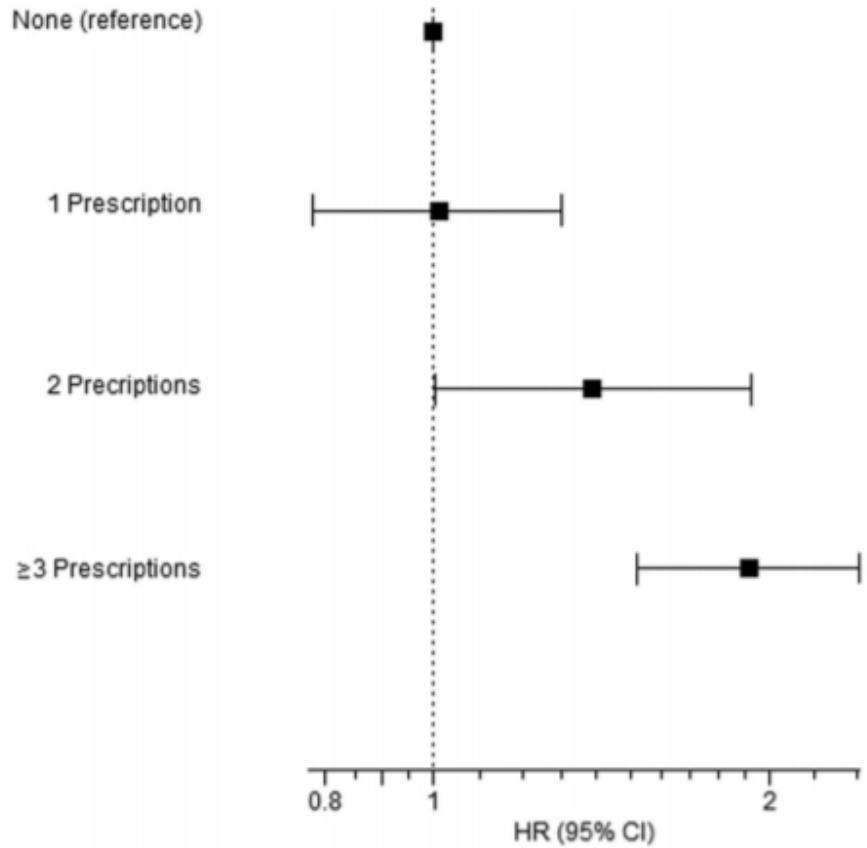


FIG 1. Adjusted* HRs (95% CI) for the association between the number of filled steroid prescriptions in the previous years and the composite of moderate to severe COVID-19 or all-cause mortality within 90 days following PCR date among adult asthmatic patients with positive PCR for SARS-CoV-2 (n = 8242). *Adjusted for age, sex, ethnicity, diabetes, hypertension, ischemic heart disease, obesity, smoking, and biologics use.

TABLE V. Multivariate* analysis for the association between steroids use and the *composite of moderate to severe COVID-19 or all-cause mortality* within 90 d following PCR date among adult asthmatic patients with positive PCR test result for SARS-CoV-2, using different specifications of steroid use (n = 8242)

Variable	Adjusted* HR (95% CI)	*P* value
Steroids use in the previous year		
None	Reference	
Yes	1.38 (1.16-1.64)	<.001
Steroids use in the previous year		
None	Reference	
Recent (≤120 d)	1.76 (1.43-2.17)	<.001
Former (120-365 d)	1.04 (0.82-1.33)	.734
Chronic steroids treatment (≥6 prescriptions in the previous year)		
None	Reference	
Yes	2.07 (1.55-2.76)	<.001
Steroids use in the previous year (no. of filled prescriptions)		
None	Reference	
1 prescription	1.01 (0.78-1.30)	.955
2 prescriptions	1.39 (1.001-1.93)	.049
≥3 prescriptions	1.92 (1.52-2.41)	<.001

Detailed multivariable models are shown in Tables III, E7, E9, and E11.
*Adjusted for age, sex, ethnicity, diabetes, hypertension, ischemic heart disease, obesity, smoking, and biologics use.

https://www.jacionline.org/action/showPdf?pii=S0091-6749%2821%2900938-6

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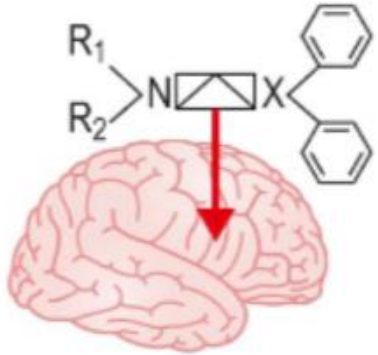
Allergic Rhino conjunctivitis

- Can be cured with allergy desensitization with allergy shots or sublingual
- Topical nasal sprays or antihistamine eye drops more efficacious without adverse effects of oral antihistamines

Dangers of Antihistamines

Potential Adverse Effects of First (Old)-Generation H_1 Antihistamines



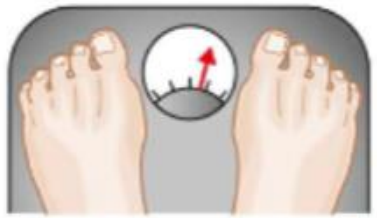
CNS H_1 receptors

↓ Alertness, cognition, learning, memory, and psychomotor performance

↑ Impairment with or without sedation

Muscarinic receptors

↑ Dry mouth
↑ Urinary retention
↑ Sinus tachycardia

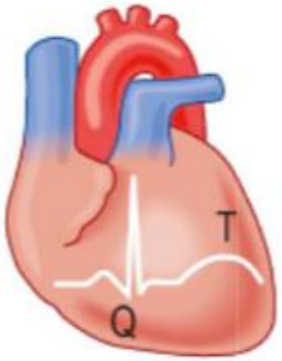


Serotonin receptors

↑ Appetite
↑ Weight gain

α-Adrenergic receptors

↑ Dizziness
↑ Postural hypotension



Cardiac ion channels (I_{Kr}, I_{Na}, and others)

↑ QT interval
↑ Ventricular arrhythmias

Middleton's Allergy 8th Edition

Impairment of H1 antihistamines

Effects of Fexofenadine, Diphenhydramine, and Alcohol on Driving Performance

A Randomized, Placebo-Controlled Trial in the Iowa Driving Simulator

John M. Weiler, MD; John R. Bloomfield, PhD; George G. Woodworth, PhD; Angela R. Grant, BS; Teresa A. Layton, BSN; Timothy L. Brown, MS; David R. McKenzie, MS; Thomas W. Baker, MS; and Ginger S. Watson, PhD

Intervention: One dose of fexofenadine (60 mg), diphenhydramine (50 mg), alcohol (approximately 0.1% blood alcohol concentration), or placebo, given at weekly intervals before participants drove for 1 hour in the Iowa Driving Simulator.

They concluded participants performed similar when treated with fexofenadine to placebo. Participants who consumed alcohol did well in performing the primary driving task but not the secondary tasks, resulting in poorer overall driving performance. They demonstrated first gen antihistamines like diphenhydramine may have an even greater impact than does alcohol on the complex task of operating an automobile

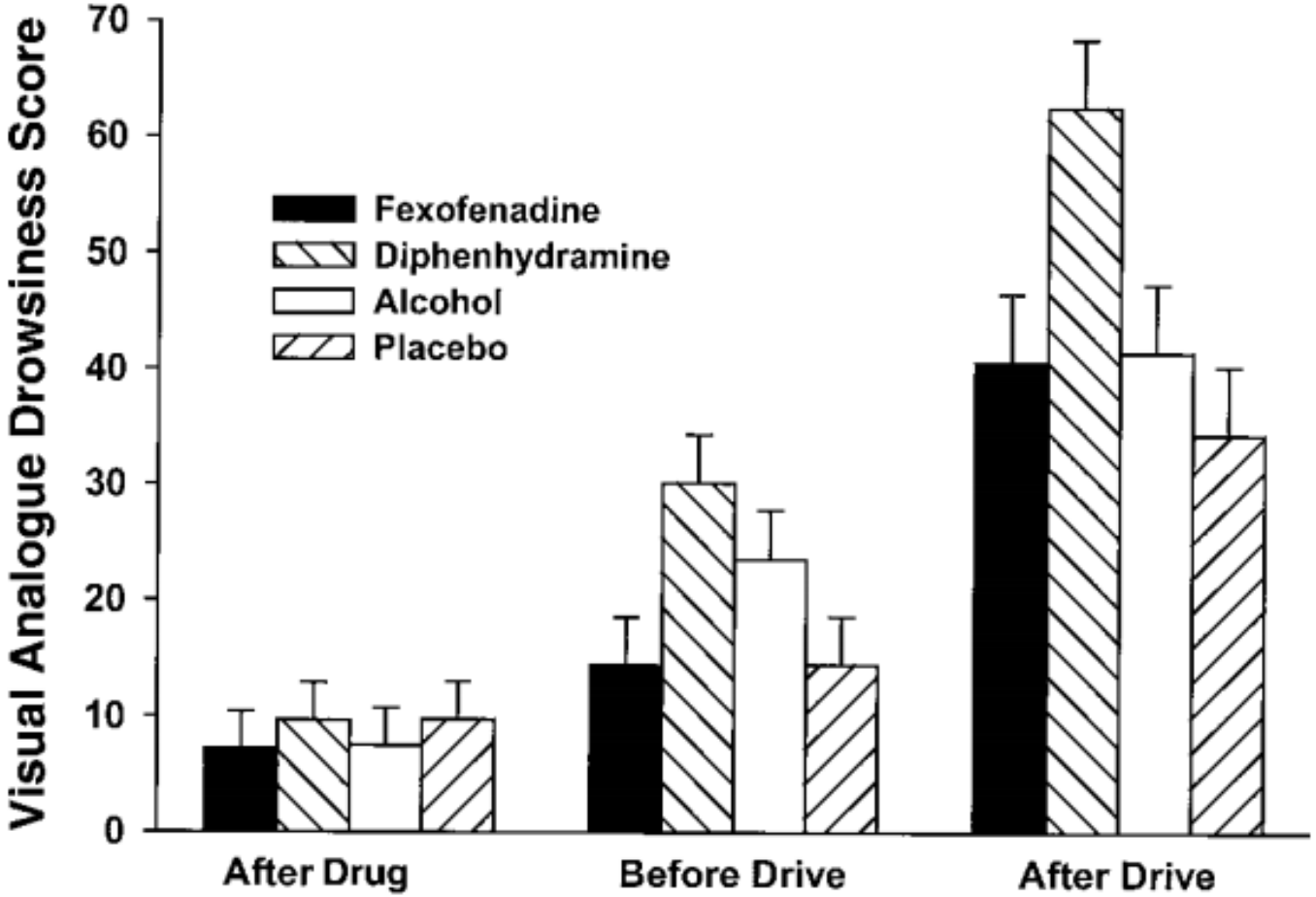


Figure 2. Change from baseline in visual analogue drowsiness scores. Participants rated drowsiness on a scale from "wide awake" to "extremely drowsy," which corresponded to a score of 1 to 100 on a 159-mm scale.

BEERS LIST

Antihistamines		
Anticholinergic antihistamines (A, H): brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexchlorpheniramine, diphenhydramine (oral), doxylamine, hydroxyzine (see CNS section for **meclizine**)	Anticholinergic effects (e.g., confusion, cognitive impairment, delirium, dry mouth, constipation, urinary retention). Elimination reduced in elderly. Tolerance to hypnotic effect.	Diphenhydramine may be appropriate in acute treatment of severe allergic reactions. Of special concern in patients with **dementia**, **cognitive impairment**, **delirium** or **high risk of delirium**, **lower urinary symptoms**, or **BPH** (avoid in men). Avoid combining drugs with anticholinergic effects (risk of cognitive decline). Alternatives: for **allergy**, nasal saline, nasal steroid, 2nd generation antihistamine (e.g., cetirizine, levocetirizine, fexofenadine, loratadine).[16] For **sleep**, consider nonpharmacologic interventions.[5] To help explain these to patients, use our patient education handout, *Strategies for a Good Night's Sleep*. Failing this, consider melatonin.[13]

A = avoid in most elderly (**does not apply to palliative care/hospice patients**)
C = use with caution in elderly
H = High-risk meds in the elderly per CMS Quality Measure (CMS156v1). A Medicare Advantage and Part D display measure. Designated CMS high-risk meds based on 2012 Beers list. (Note: CMS high-risk med trimethobenzamide is no longer included on the Beers list.)

FAA safe list

Type of medication	Commonly found in	Medication or active ingredient generally safe to fly GO	Avoid these medications or ingredients* NO GO	Rationale
Antihistamines	Allergy products Cough/cold products Pain products	Non-sedating products: fexofenadine (Allegra) loratadine (Claritin)	Sedating products: brompheniramine (Dimetapp) cetirizine (Zyrtec) chlorpheniramine (Chlor-Trimeton) **diphenhydramine (Benadryl)** levocetirizine (Xyzal)	Histamines affect not only your allergies, but your sleep wake cycle. Sedating antihistamines can cause drowsiness, impaired thinking and judgement.
	Sleep aid products	Melatonin (not an antihistamine)	**diphenhydramine (such as Zzzquil)**. Same ingredient in Benadryl) Doxylamine (such as Unisom)	"Hang-over effect" morning after safety concern. NOTE: taking melatonin at the wrong time can actually worsen "jet-lag" and cause daytime drowsiness.

[Over the Counter Medications (faa.gov)]

Adverse Food Reactions

- IgE or Immediate Food Allergy
- Oral Allergy Syndrome
- Eosinophilic Esophagitis (EoE)
- Food Protein-Induced Enterocolitis Syndrome (FPIES)

Type I hypersensitivity response

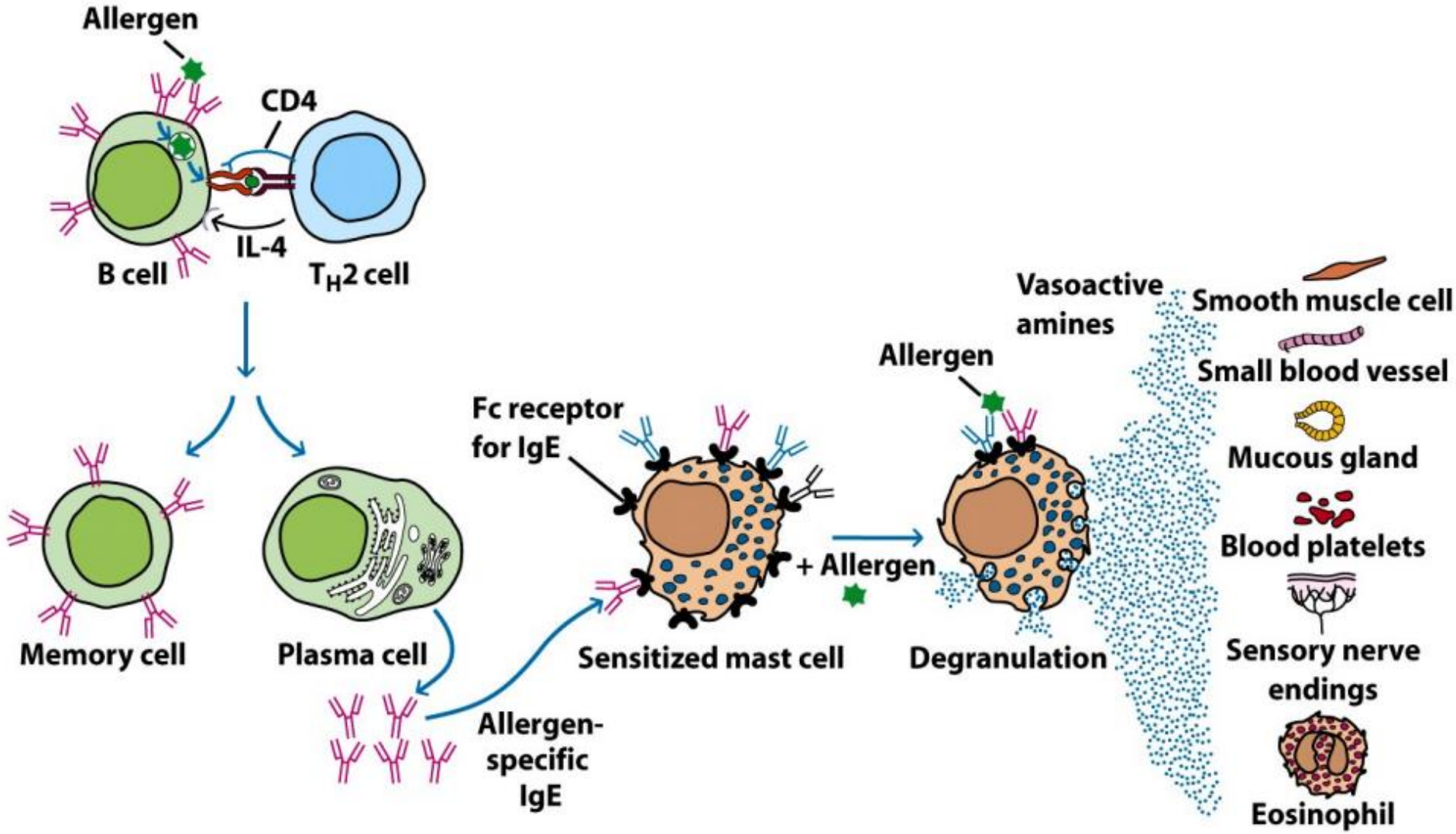


Figure 15-2
Kuby IMMUNOLOGY, Sixth Edition

Adverse Food Reactions

- **IgE or Immediate Food Allergy**
- **Oral Allergy Syndrome**
- Eosinophilic Esophagitis (EoE)
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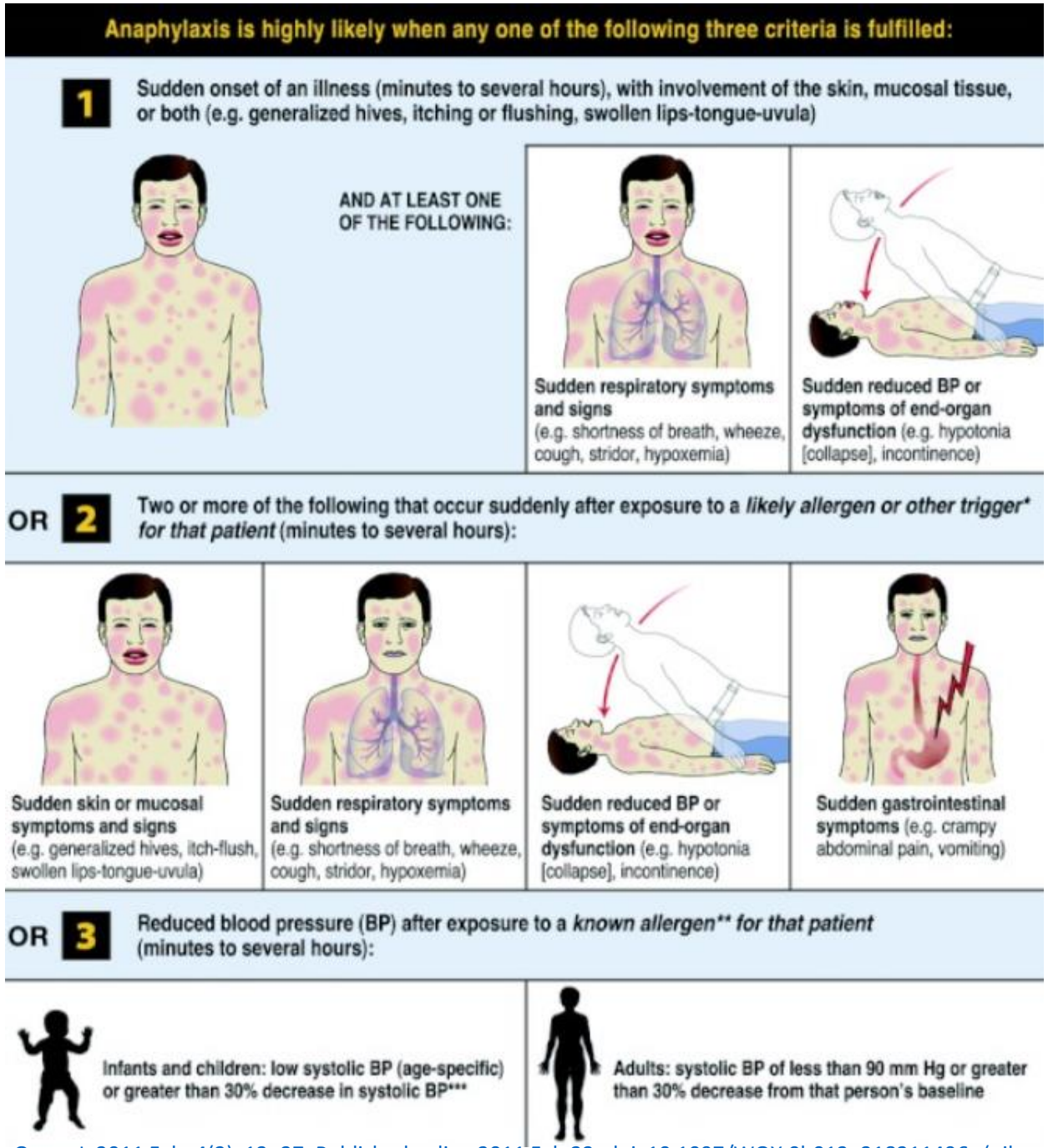
TABLE 15-3 Immune basis for food allergy reactions

Disorder	Symptoms	Common triggers	Notes about mechanism
IgE mediated (acute)			
Skin effects: hives (urticaria), itching, angioedema	Redness, swelling triggered by ingestion or skin contact	Multiple foods (e.g., milk, egg, wheat, soy, peanut, tree nuts, shellfish, fish)	Allergen, IgE antibody, and mast cell mediated
Oral allergy	Itchiness, swelling of mouth	Multiple foods	Allergen, IgE antibody, and mast cell mediated. Inhaled pollens may induce IgE that cross-reacts with food proteins
Gastrointestinal effects	Nausea, vomiting, intestinal pain	Multiple foods	Allergen, IgE antibody, and mast cell mediated
Wheezing, asthma, rhinitis	Bronchial constriction, mucus production	Inhalation of aerosolized food proteins	Allergen, IgE antibody, and mast cell mediated
Anaphylaxis	Rapid, multiorgan inflammation that can result in cardiovascular failure	Peanuts, tree nuts, fish, shellfish, milk	Response to systemic distribution of allergen and IgE antibodies
Exercise-induced anaphylaxis	As above, but occurs when one exercises after eating trigger foods	Wheat, shellfish, celery	May be due to changes in gut absorption associated with exercise



PubMed Central, FIGURE 3: World Allergy Organ J. 2011 Feb; 4(2): 13–37. Published online 2011 Feb 23. doi: 10.1097/WOX.0b013e318211496c (nih.gov)

FARE
Food Allergy Research & Education

www.foodallergy.org

For a suspected or active food allergy reaction:

FOR ANY OF THE FOLLOWING SEVERE SYMPTOMS

- **LUNG:** Short of breath, wheezing, repetitive cough
- **HEART:** Pale, blue, faint, weak pulse, dizzy
- **THROAT:** Tight, hoarse, trouble breathing/swallowing
- **MOUTH:** Significant swelling of the tongue and/or lips
- **SKIN:** Many hives over body, widespread redness
- **GUT:** Repetitive vomiting or severe diarrhea
- **OTHER:** Feeling something bad is about to happen, anxiety, confusion

OR MORE THAN ONE MILD SYMPTOM

- **NOSE:** Itchy/runny nose, sneezing
- **MOUTH:** Itchy mouth
- **SKIN:** A few hives, mild itch
- **GUT:** Mild nausea/discomfort

1. **INJECT EPINEPHRINE IMMEDIATELY.**
2. **Call 911.** Request ambulance with epinephrine.

Do not depend on antihistamines. When in doubt, give epinephrine and call 911.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 26, 2015 VOL. 372 NO. 9

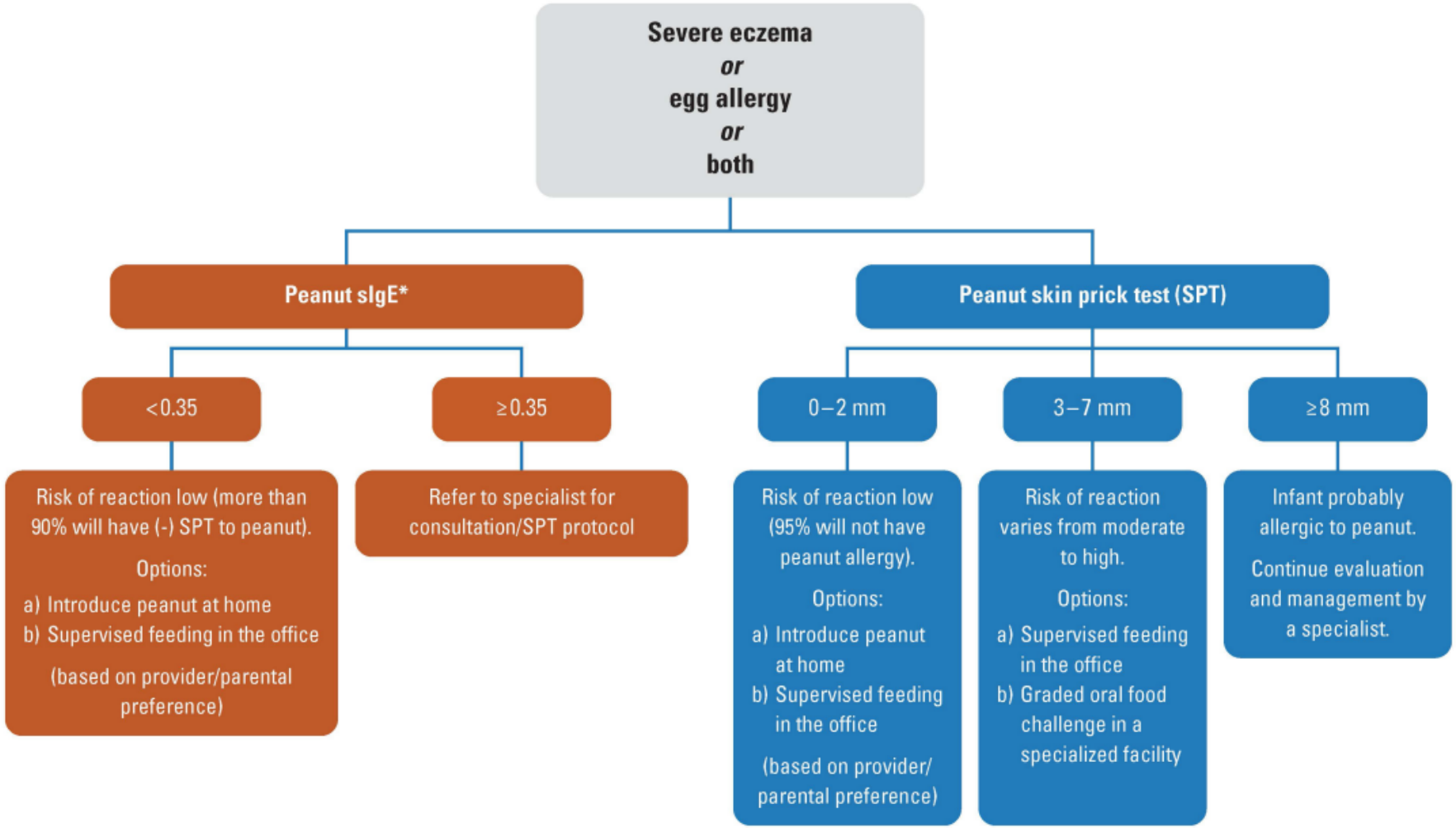
Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D., Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

LEAP Study

- 640 infants age 4 to 11 months old with high risk for peanut allergy based on existing egg allergy or **severe** eczema were enrolled
- 17% of children that avoided peanut developed peanut allergy
- 3% of children that ate peanut developed peanut allergy
- LEAP-On (Persistence of oral tolerance to peanut study) look at the children that initially ate peanut and had them avoid peanut from age 5 to 6 and they were still 74% less likely to have peanut allergy. Thus, tolerance could be long standing

Recommended Approaches for Evaluation of Children With Severe Eczema and/or Egg Allergy Before Peanut Introduction



*To minimize a delay in peanut introduction for children who may test negative, testing for peanut sIgE may be the preferred initial approach in certain healthcare settings. Food allergen panel testing or the addition of sIgE testing for foods other than peanut is not recommended due to poor positive predictive value.

Addendum Gu
the United States: Summary for Clinicians (nih.gov)

Adverse Food Reactions

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- Oral Allergy Syndrome
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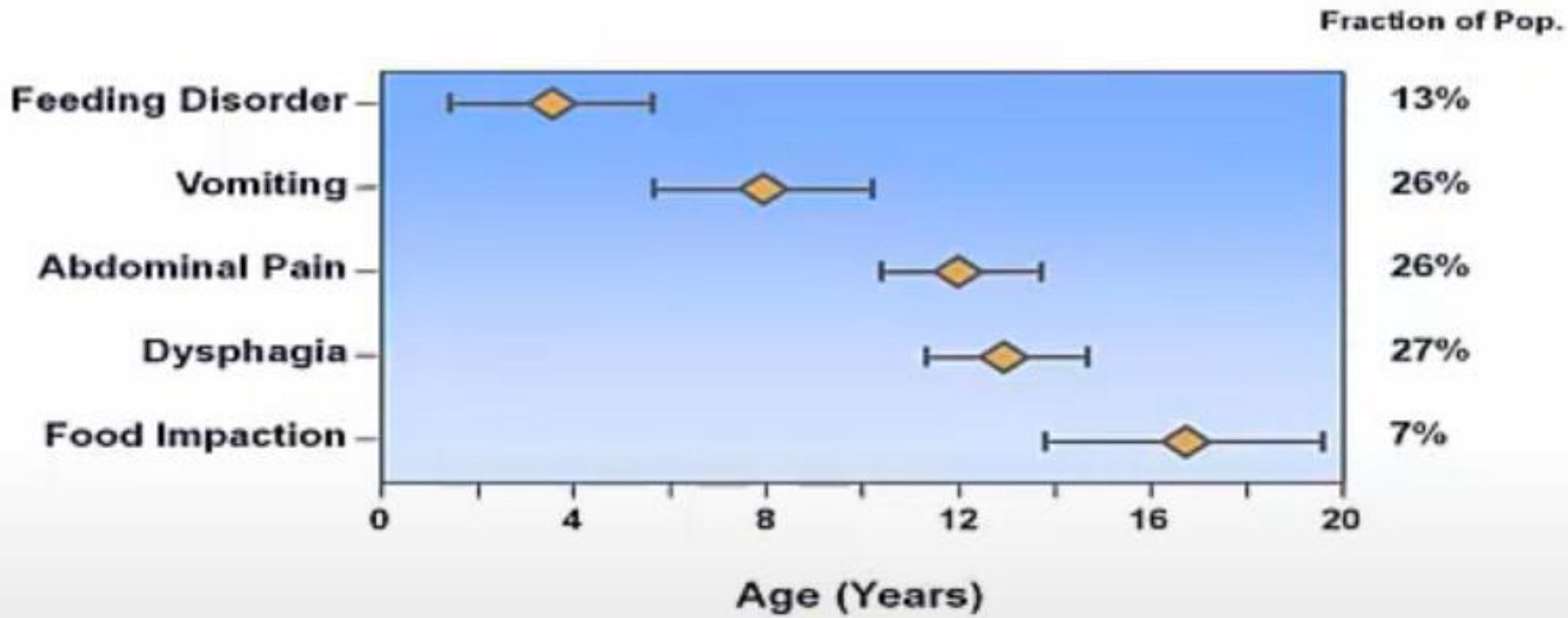
- Food Protein-Induced Enterocolitis Syndrome (FPIES)

Eosinophilic Esophagitis

- Symptoms of esophageal dysfunction
  - Heartburn, food impaction, dysphagia, chest pain/vomiting
  - Atopic diseases increase suspicion
  - EGD findings (trachealization, furrowing, strictures, white papules)
- Eosinophils 15/hpf or more isolated in esophagus
- No other causes for eosinophils in the esophagus
  - Examples like GERD, infectious esophagitis, Achalasia, Hypereosinophilic syndrome, Autoimmune disorders, Vasculitis, Graft vs Host, Drug associated

EoE Presentation by Age



Noel et al. *N Engl J Med.* 2004; 351:940-941.

Testing

- Food skin testing does not correlate with the food trigger
- Some data in pediatric population with patch testing to foods
  - Patch testing for foods mainly only available in some EoE clinics
- Subset of patients may benefit with environmental testing and treatment with allergy shots especially with seasonal worsening of symptoms

Treatment options

- PPI maybe effective in about 30% of patients
- Swallowed oral steroids
- Esophageal dilation for stricture
- Diet
  - 2 food elimination diet
    - Milk and wheat
  - 4 food elimination diet
    - Add egg and legumes to elimination aka soy and peanut
  - 6 food elimination diet
    - Add nuts and seafood including fish to elimination

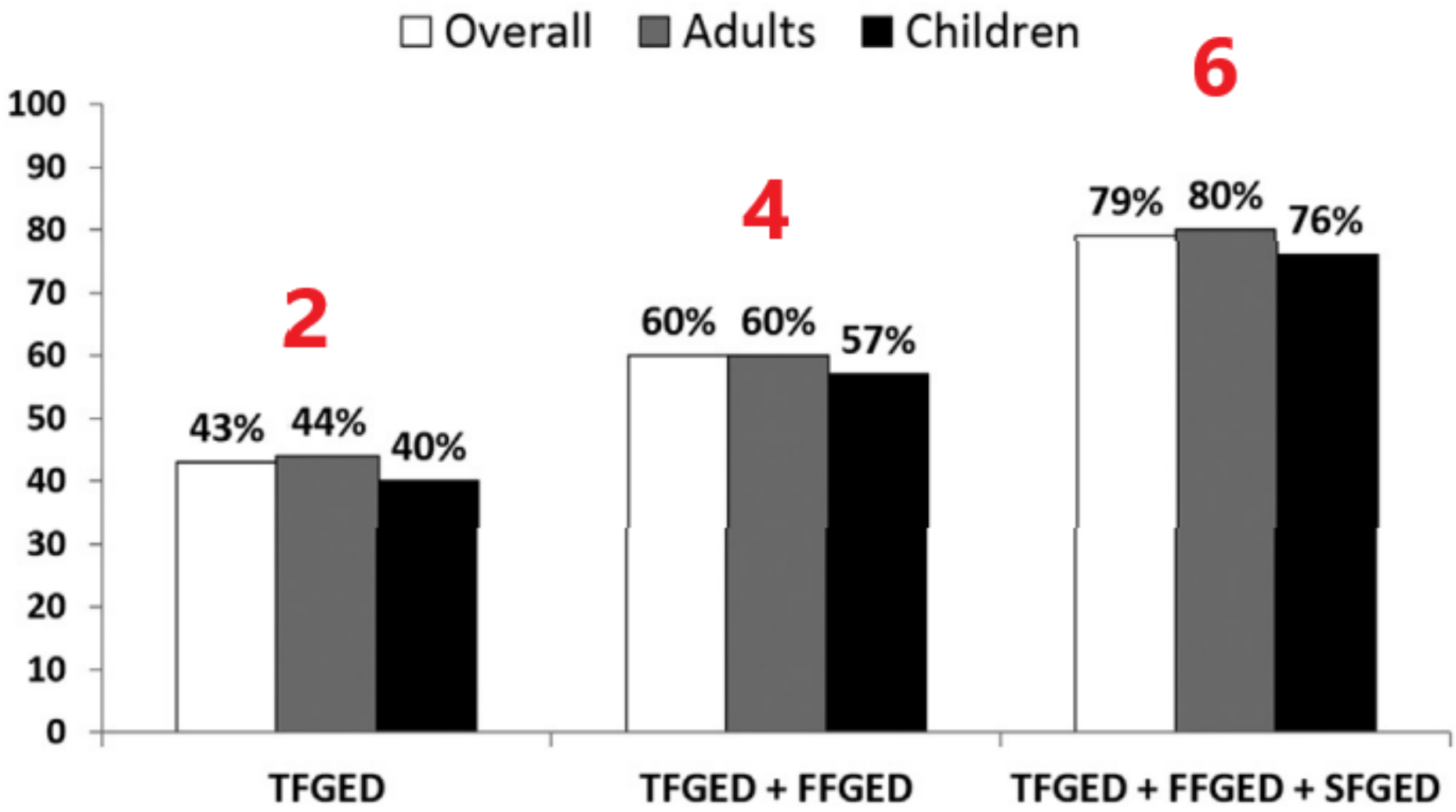


FIG 3. Per-protocol remission rates on a TFGED (56 patients) and after a step-up intervention with an FFGED (10 patients) and an SFGED (7 patients).

Adverse Food Reactions

- IgE or Immediate Food Allergy
- Oral Allergy Syndrome
- Eosinophilic Esophagitis (EoE)
- **Food Protein-Induced Enterocolitis Syndrome (FPIES)**

TABLE IV. Diagnostic criteria for patients presenting with possible FPIES

Acute FPIES

Major criterion:

Vomiting in the 1- to 4-h period after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms

Minor criteria:

1. A second (or more) episode of repetitive vomiting after eating the same suspect food
2. Repetitive vomiting episode 1-4 h after eating a different food
3. Extreme lethargy with any suspected reaction
4. Marked pallor with any suspected reaction
5. Need for emergency department visit with any suspected reaction
6. Need for intravenous fluid support with any suspected reaction
7. Diarrhea in 24 h (usually 5-10 h)
8. Hypotension
9. Hypothermia

The diagnosis of FPIES requires that a patient meets the major criterion and ≥3 minor criteria. If only a single episode has occurred, a diagnostic OFC should be strongly considered to confirm the diagnosis, especially because viral gastroenteritis is so common in this age group. Furthermore, although not a criteria for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours compared with the usual several-day time course of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.

Chronic FPIES

Severe presentation: When the offending food is ingested on a regular basis (eg, infant formula); intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis.

Milder presentation: Lower doses of the problem food (eg, solid foods or food allergens in breast milk) lead to intermittent vomiting and/or diarrhea, usually with poor weight gain/FTT but without dehydration or metabolic acidosis.

The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days after elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 h, diarrhea in 24 h (usually 5-10 h). Without confirmatory challenge, the diagnosis of chronic FPIES remains presumptive.

FPIES

- No testing to find help indicate the food causing the issue
- Most common trigger Milk, Soy, Rice
- Can confirm the caused with oral challenge to the suspected food
- No treatment but avoidance and having a letter for the emergency room about FPIES
- Normally outgrown by age 3 or 4 years old

The FPIES Foundation
www.thefpiesfoundation.org
contact@thefpiesfoundation.org

Dear Doctor (To Whom It May Concern),

My child has a food allergy called Food-Protein Induced Enterocolitis syndrome. This is a type of allergy that usually does not result in typical "allergic" symptoms such as hives or wheezing, but rather with isolated gastrointestinal symptoms.

The foods that this child is avoiding include: _____.

The symptoms of this type of allergic reaction include repetitive vomiting that may not start for a few hours (e.g., 2) following ingestion of the food to which the child is allergic. Even trace amounts can trigger a reaction. There is often diarrhea that starts later (after 6 hours). In some cases (about 20%), the reaction includes lethargy, hypotension, acidemia, and/or methemoglobinemia. The treatment is symptomatic and can include intravenous fluids (e.g. normal saline bolus, hydration) and steroids for significant symptoms. The latter is given because the pathophysiology is that of a T cell response.

Outline

- Hypersensitivity types
- Types of allergic diseases
  - Asthma
  - Allergic Rhinitis and Conjunctivitis
  - Food Allergy
    - IgE mediated
    - Non-IgE mediated
  - **Adverse Drug Reactions**
  - Atopic Dermatitis/Eczema
- Types testing
- Treatment options

ADVERSE DRUG REACTIONS

Drug Reaction	Examples
TYPE A: REACTIONS OCCURRING IN MOST NORMAL PATIENTS GIVEN SUFFICIENT DOSE AND DURATION OF THERAPY	
Overdose	Hepatic failure (acetaminophen)
Side effects	Nausea, headache (with methylxanthines)
Secondary or indirect effects	GI bacterial alteration after antibiotics
Drug interactions	Erythromycin increasing theophylline/digoxin blood levels
TYPE B: DRUG HYPERSENSITIVITY REACTIONS RESTRICTED TO A SMALL SUBSET OF THE GENERAL POPULATION	
Intolerance*	Tinnitus after a single aspirin tablet
Idiosyncrasy† (pharmacogenetics)	G6PD deficiency: anemia after antioxidant drugs
Immunologic drug reactions (allergy)	Anaphylaxis from β-lactam antibiotics

Immunologic Drug Reaction

Drug Reaction	Examples
TYPE A: REACTIONS OCCURRING IN MOST NORMAL PATIENTS GIVEN SUFFICIENT DOSE AND DURATION OF THERAPY	
Overdose	Hepatic failure (acetaminophen)
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TYPE B: DRUG HYPERSENSITIVITY REACTIONS RESTRICTED TO A SMALL SUBSET OF THE GENERAL POPULATION	
Intolerance*	Tinnitus after a single aspirin tablet
Idiosyncrasy† (pharmacogenetics)	G6PD deficiency: anemia after antioxidant drugs
Immunologic drug reactions (allergy)	Anaphylaxis from β-lactam antibiotics

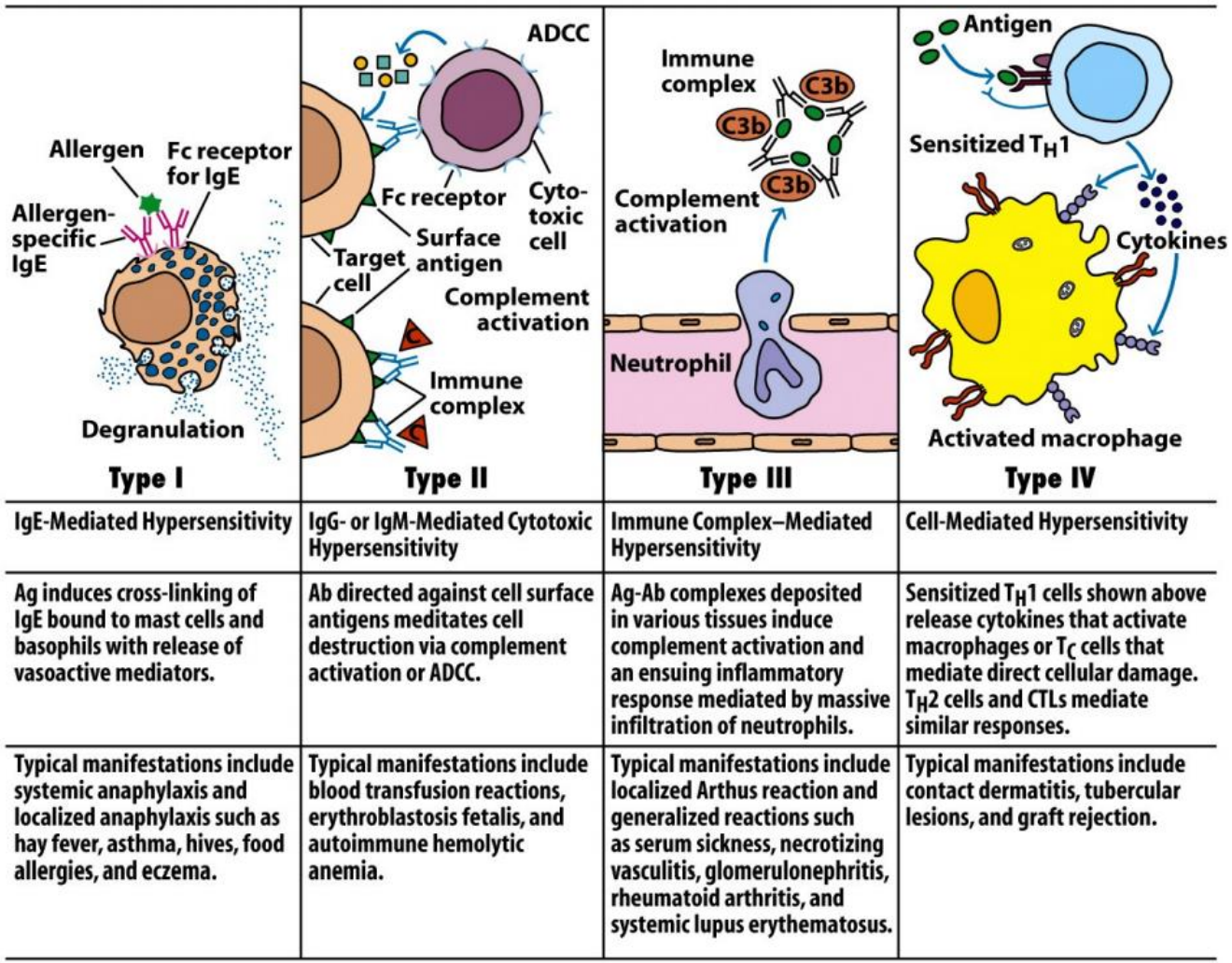
Drug Reactions

Gell-Coombs Classification	Mechanism	Examples of Adverse Penicillin Reactions
I	Anaphylactic (IgE-mediated)	Acute anaphylaxis Urticaria
II	Complement-dependent cytolysis (IgG/IgM)	Hemolytic anemias Thrombocytopenia
III	Immune complex damage	Serum sickness Drug fever Some cutaneous eruptions and vasculitis
IV	Delayed or cellular hypersensitivity	Contact dermatitis Morbilliform eruptions SJS/TEN Hepatitis

Ig, Immunoglobulin; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

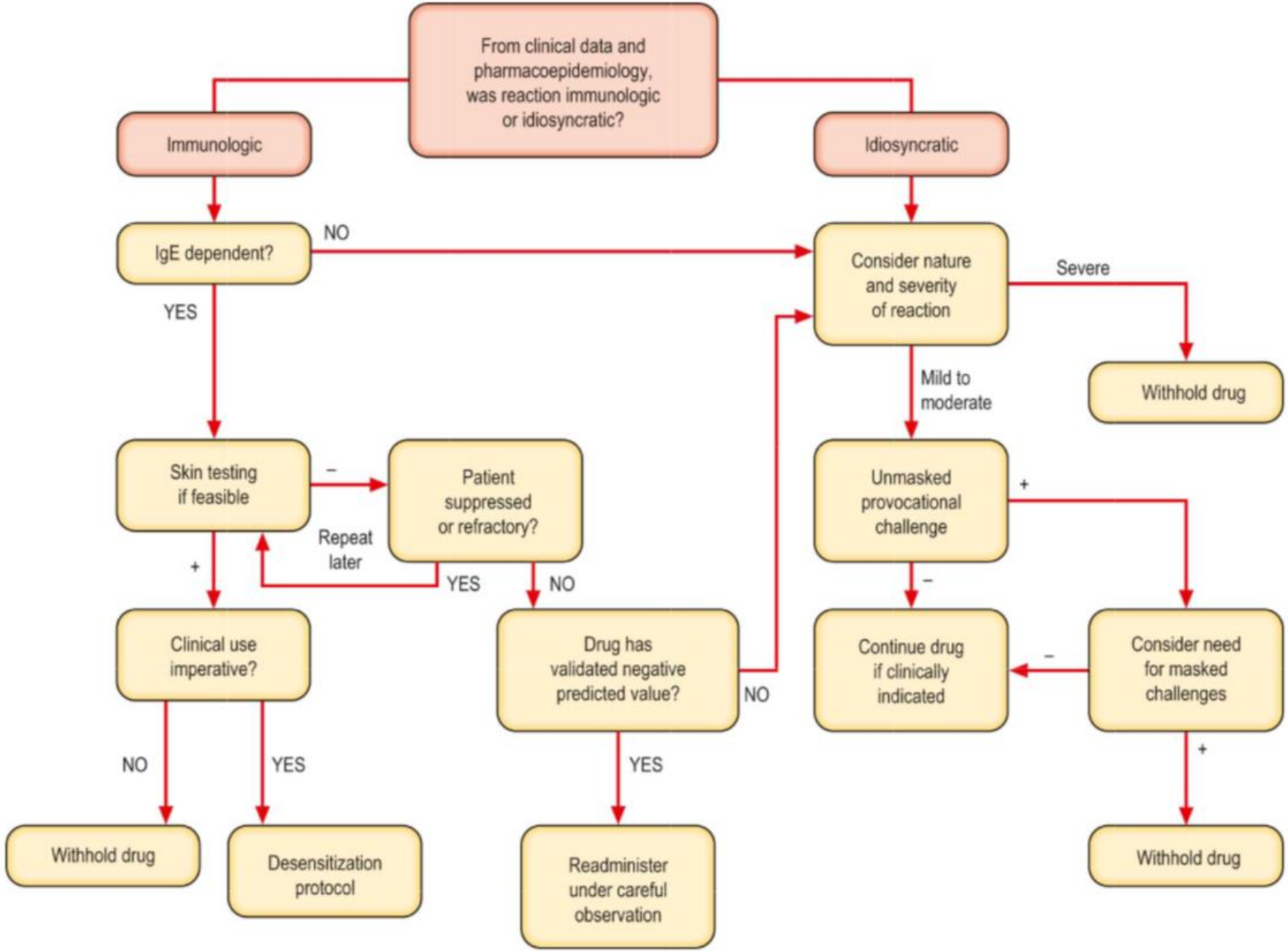
Examples of Adverse Penicillin Reactions

1	Acute anaphylaxis Urticaria
2	Hemolytic anemias Thrombocytopenia
3	Serum sickness Drug fever Some cutaneous eruptions and vasculitis
4	Contact dermatitis Morbilliform eruptions SJS/TEN Hepatitis

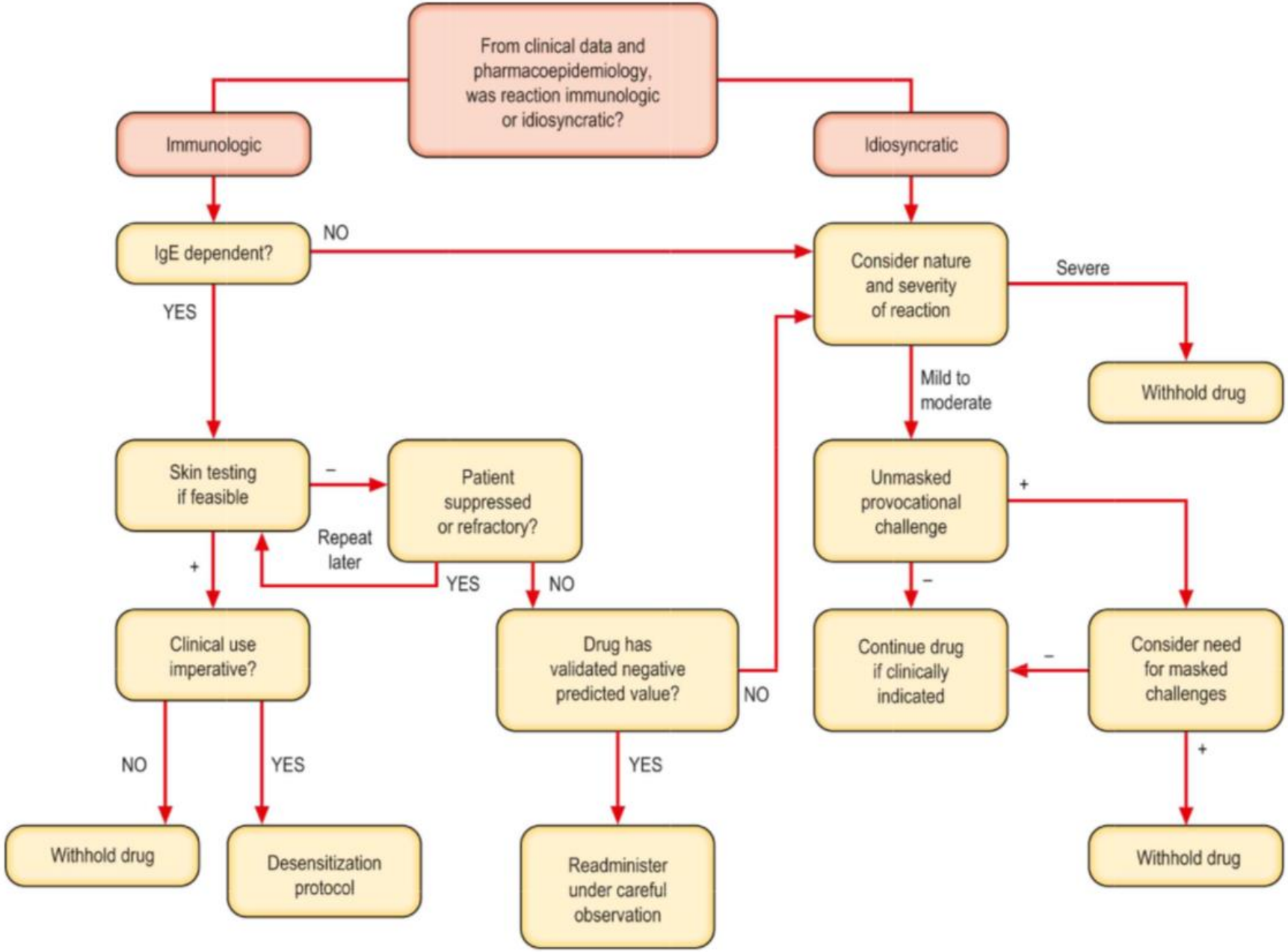


Type I	Type II	Type III	Type IV
IgE-Mediated Hypersensitivity	IgG- or IgM-Mediated Cytotoxic Hypersensitivity	Immune Complex–Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces cross-linking of IgE bound to mast cells and basophils with release of vasoactive mediators.	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC.	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils.	Sensitized T_H1 cells shown above release cytokines that activate macrophages or T_C cells that mediate direct cellular damage. T_H2 cells and CTLs mediate similar responses.
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema.	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia.	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus.	Typical manifestations include contact dermatitis, tubercular lesions, and graft rejection.

Figure 15-1
Kuby IMMUNOLOGY, Sixth Edition


From clinical data and pharmacoepidemiology, was reaction immunologic or idiosyncratic?
Immunologic
Idiosyncratic
IgE dependent?
NO
YES
Consider nature and severity of reaction
Severe
Withhold drug
Mild to moderate
Skin testing if feasible
–
Patient suppressed or refractory?
Repeat later
YES
NO
+
Unmasked provocational challenge
+
–
Clinical use imperative?
Drug has validated negative predicted value?
NO
Continue drug if clinically indicated
–
Consider need for masked challenges
+
NO
YES
YES
Withhold drug
Desensitization protocol
Readminister under careful observation
Withhold drug

Examples of Adverse Penicillin Reactions	
1	Acute anaphylaxis Urticaria
2	Hemolytic anemias Thrombocytopenia
3	Serum sickness Drug fever Some cutaneous eruptions and vasculitis
4	Contact dermatitis Morbilliform eruptions SJS/TEN Hepatitis



Examples of Adverse Penicillin Reactions

1	Acute anaphylaxis Urticaria
2	Hemolytic anemias Thrombocytopenia
3	Serum sickness Drug fever Some cutaneous eruptions and vasculitis
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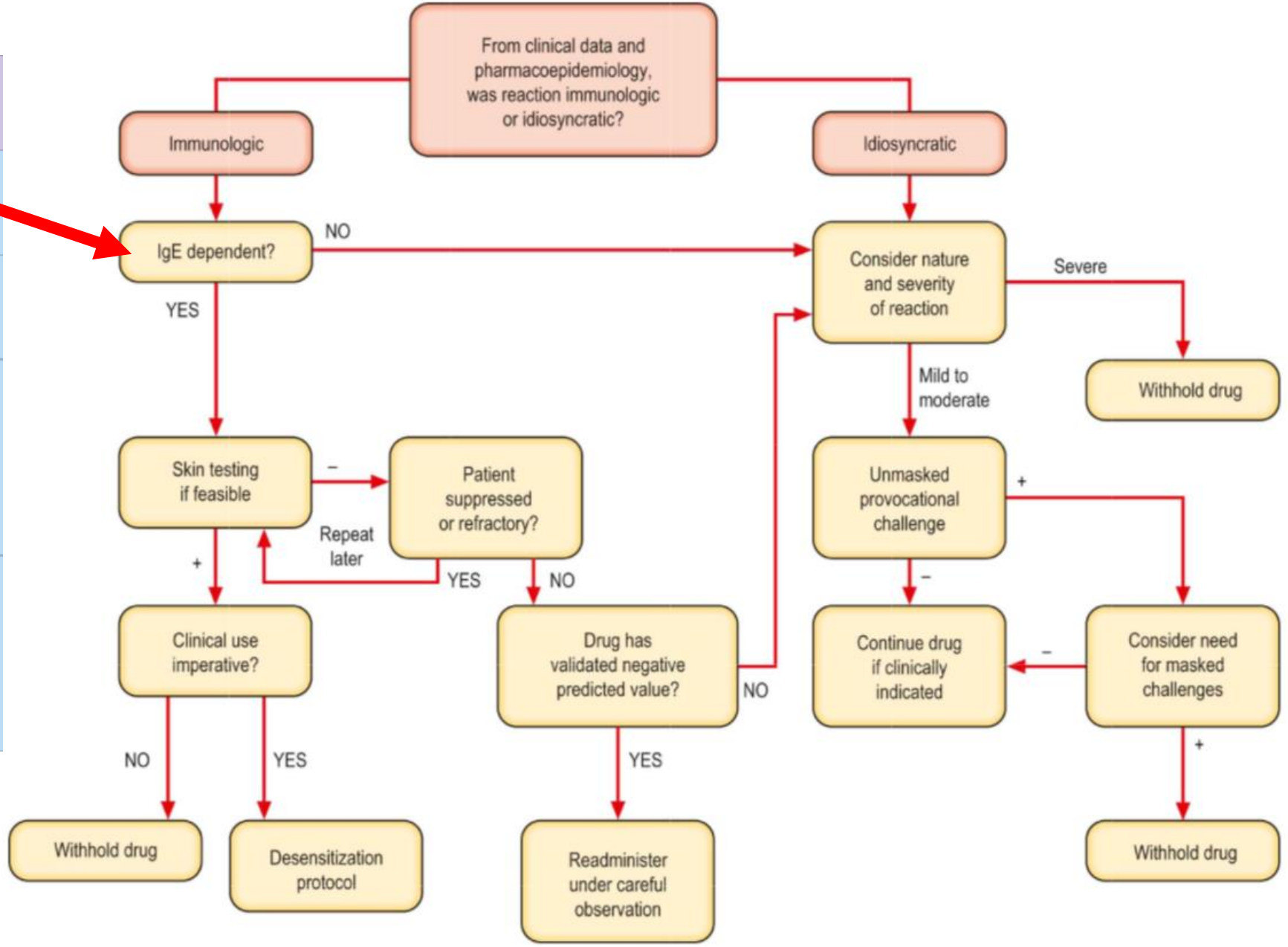


Penicillin Allergy

- About 90% of these patients are not truly allergic and could safely receive ß-lactam antibiotics
- Patients are often treated unnecessarily with an alternate broad spectrum antibiotic, which could increase costs and contribute to the development and spread of multiple drug-resistant bacteria.
- Immediate allergic reactions to cephalosporins is lower compared to penicillin
- Cross-reactivity among cephalosporins is lower compared to cross-reactivity between penicillin and cephalosporins.

THE FACTS ABOUT PENICILLIN ALLERGY: A REVIEW (nih.gov)

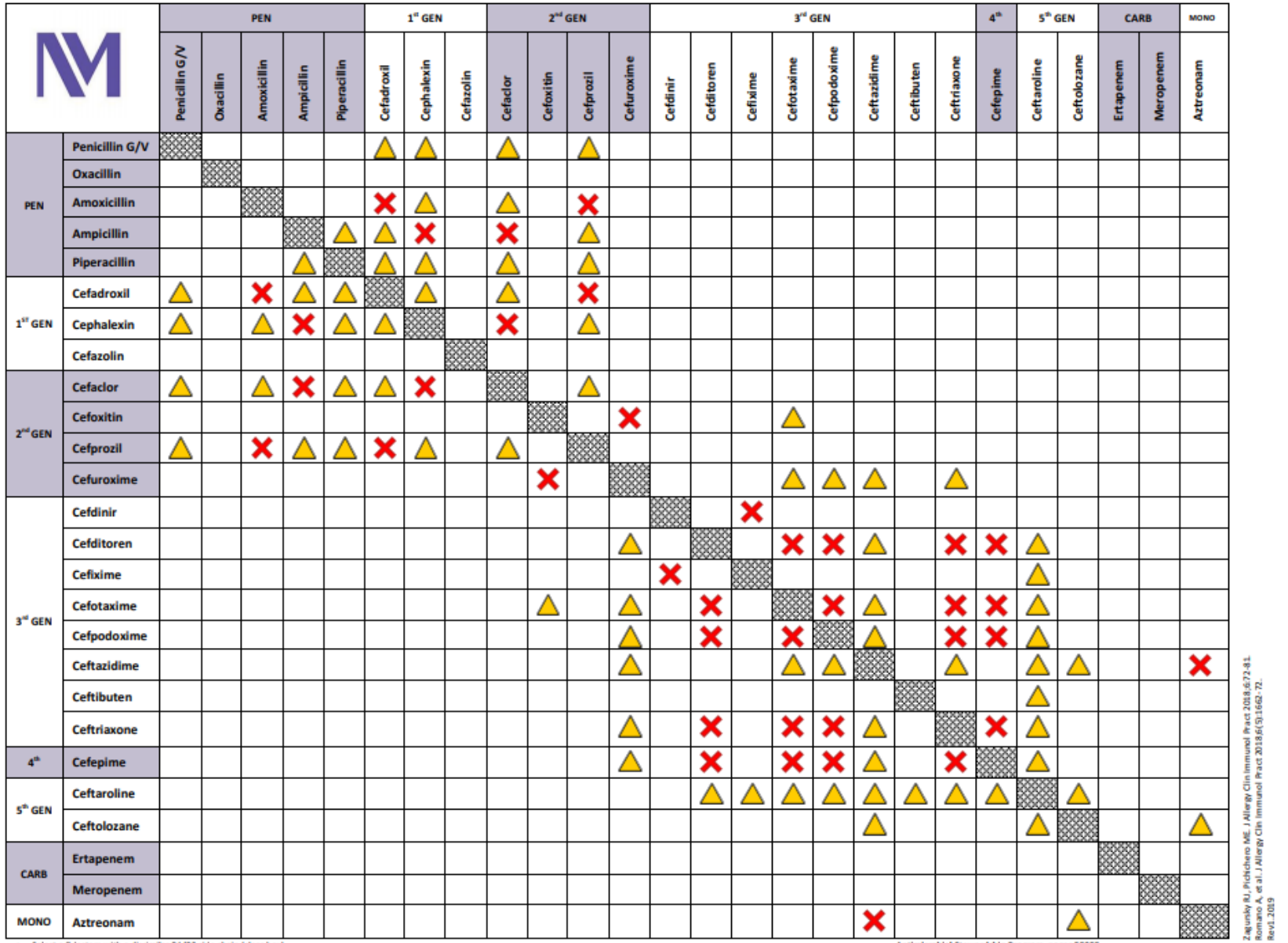
Table 2: Beta-Lactam Cross-Reactivity in Penicillin Allergic Patients

Drug Class and Available Formulary Agents	Estimated Cross-Reactivity[3,7]	Recommendations for Challenge in Penicillin Allergic Patients
1st Generation Cephalosporin (cefazolin, cephalexin)	1.9 – 7.9%	• Results are influenced by two large trials conducted when early cephalosporin agents were contaminated with penicillin • Inconsistent definitions of allergic reaction resulting in overestimation of cross-reactivity • Patients allergic to ampicillin should avoid cephalosporins with identical R-group side chains (cephalexin and cefaclor[NF])
2nd Generation Cephalosporin (cefuroxime, cefoxitin)	1.9%	• Patients allergic to penicillin G should avoid using cephalosporins with identical R-group side chains (cefoxitin) • Patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cefadroxil[NF] and cefprozil[NF])
3rd Generation Cephalosporin (ceftriaxone, ceftazidime)	0.7%	• Generally considered safe
Advanced (4th/5th) Generation Cephalosporin (cefepime, ceftolozane-tazobactam, ceftaroline[NF])	N/A	• Minimal data available • Generally considered safe
Carbapenem (meropenem, ertapenem)	1%	• Risk profile similar to general population (no increased risk of reaction)
Monobactam (aztreonam)	< 1%	• Cross-reactivity is highly unlikely • Patients allergic to ceftazidime should avoid aztreonam due to side chain similarity

NF = non-formulary at Nebraska Medicine

penicillin-allergy-guidance.pdf (unmc.edu)

Northwestern Medicine β-Lactam Cross-reactivity Side-Chain Chart



- Select a β-lactam with a dissimilar R1/R2 side chain (clear box)
- The R1 side chain is the major factor for cross-reactivity due to antibody recognition between cephalosporins and penicillins.
- Cross-reactivity with cefazolin or carbapenems is very unlikely
- Cross-reactivity with monobactam (aztreonam) is absent, with the exception of ceftazidime
- Independent hypersensitivity reactions (HSR) not related to a cross-reaction due to antibody recognition may occur (e.g. oxacillin: often non-IgE-mediated HSR - maculopapular rash, acute interstitial nephritis, and immune-mediated hepatitis

Antimicrobial Stewardship Program, pager 55955

= AVOID
Cross-reaction likely
Identical R1 or R2 side chain

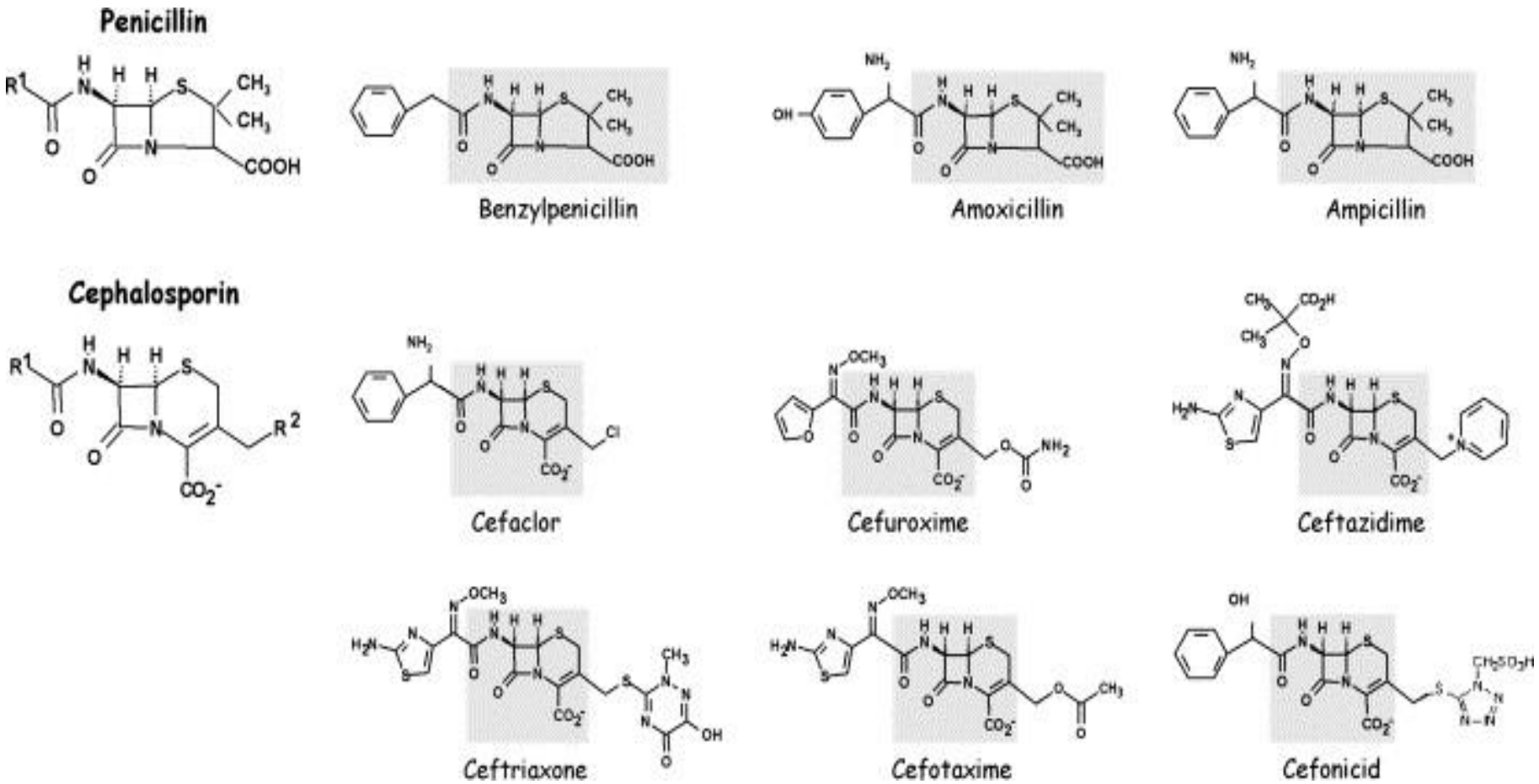
= CAUTION
Cross-reaction less likely
Similar R1 or R2 side chain

= SUGGEST
Cross-reaction least likely
Dissimilar R1 or R2 side chain

Zagursky RJ, Pichichero ME. J Allergy Clin Immunol Pract 2018;6:72-81.
Romano A, et al. J Allergy Clin Immunol Pract 2018;6(5):1662-72.
Rev1.2019

[Microsoft Word - CROSS RXN (GRADED CHALLENGE) FINAL_1.23.19.docx (nm.org)]

Structure



Journal of Allergy and Clinical Immunology 2006 117404-410DOI: (10.1016/j.jaci.2005.10.032)

Vaccine Allergy

- Immunoglobulin E–Mediated Reactions to Vaccine Constituents Other Than the Immunizing Agent like gelatin, egg, yeast
- COVID vaccine suspected PEG or Polysorbate thus skin testing is available
- The CDC has provided the following differentiation:
  - **Contraindication:** Persons with a known (**diagnosed**) allergy to PEG or polysorbate have a contraindication to vaccination.
  - **Precaution:** Persons with a reaction to a vaccine or injectable therapy that contains multiple components, one of which is PEG, another mRNA vaccine component or polysorbate, but in whom it is unknown which component elicited the immediate allergic reaction have a precaution (counseling, 30-minute observation).

COVID Vaccine

- Individuals with a history of food, pet, insect, venom, environmental or latex allergies are able to proceed with vaccination with a standard 15 minute observation period.
  - Vial stoppers of mRNA vaccines are not made with natural rubber latex
  - The mRNA vaccines do not contain egg or gelatin
- Those with a history of severe allergic reaction (e.g. anaphylaxis) to an injectable medication should use caution when receiving the vaccine and follow a 30-minute observation period.
- Results of safety monitoring from VAERS and V-safe after one month of vaccinations show over 90% of reactions were non-serious. Anaphylaxis rates (4.5 per million doses) remain in range of other vaccines.

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  - **Atopic Dermatitis/Eczema**
- Types testing
- Treatment options

Atopic Dermatitis

- Breakdown of skin barrier genetically thus immune system reacts with staph and also outdoor allergens or irritants
- Superinfections common with fungal, bacterial or even viral (eczema herpeticum)
- Staph causes IL31 release which does cause pruritus possible biologics being developed to block IL31
- Can be triggers by environmental allergies thus efficacy with allergy shots especially with dust mites
- Multiple avenues for treatment and Dupilamab anti IL4 and IL13 is now approved for 2 and older

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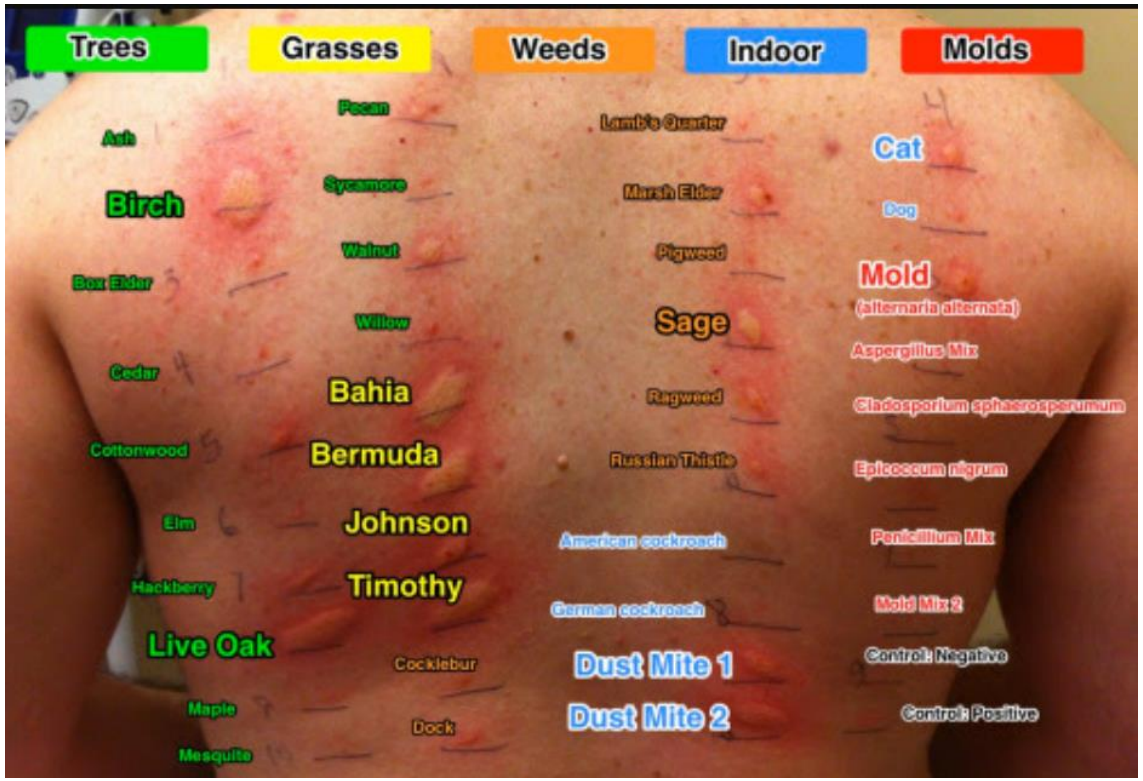
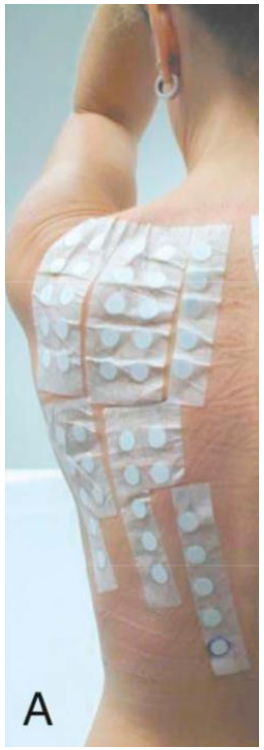
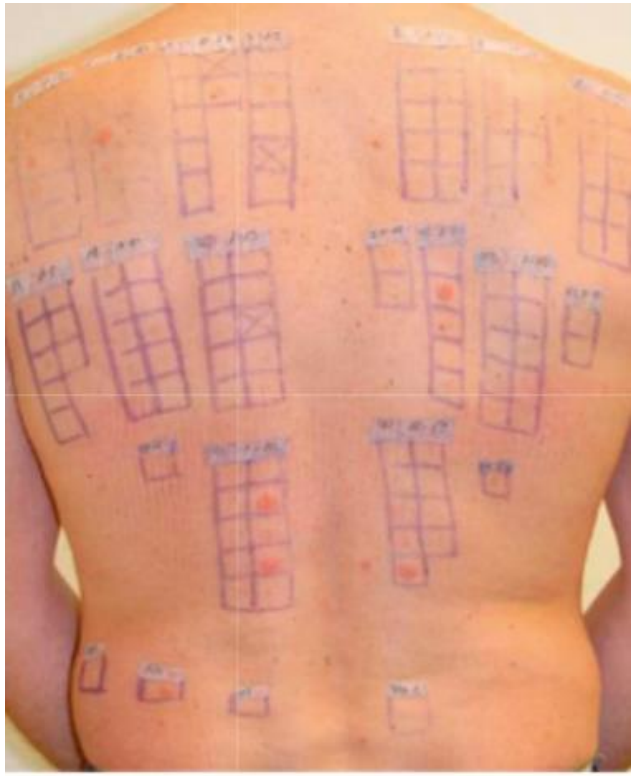
Types of Testing

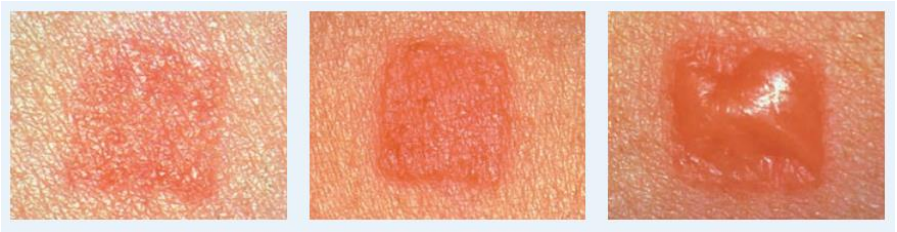
Type 1 Hypersensitivity



Type IV Hypersensitivity







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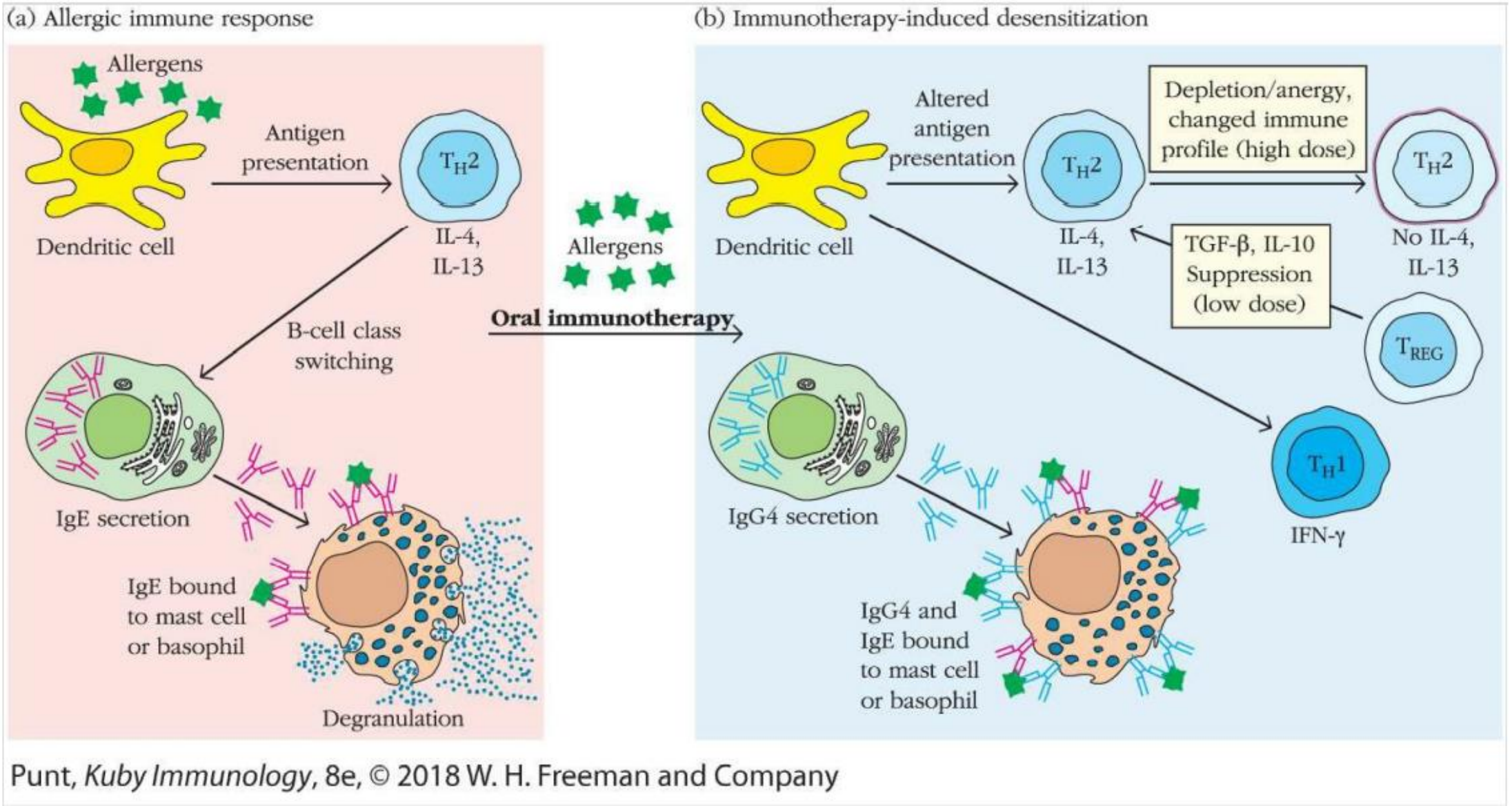
- **Treatment options**

Desensitization of Type 1 Hypersensitivity



Punt, *Kuby Immunology*, 8e, © 2018 W. H. Freeman and Company

Types Desensitization

- Cure only for IgE mediated or Type 1 hypersensitivity reactions
- Immunotherapy either sublingual or subcutaneous desensitizes environmental allergies that trigger nasal or eye symptoms, eczema and asthma
- Drug desensitization have protocols with increased doing of the medication till the final dose
- New and recently FDA approved palforzia small doses of peanut to help protect against anaphylaxis
  - Multiple regiments but not FDA being done currently

Signs of Immunodeficiency for Children

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of Primary Immunodeficiency.

Signs of Immunodeficiency in Adults

1. Two or more new ear infections within 1 year.
2. Two or more sinus infections within 1 year w/o allergies
3. One pneumonia per year for more than 1 year
4. Chronic diarrhea with weight loss
5. Repeat viral infections like (colds, herpes, warts)
6. Recurrent need for intravenous antibiotics to clear infections
7. Recurrent deep abscesses in skin or internal organs
8. Persistent thrush in mouth or fungal infection on skin
9. Infection with normally harmless tuberculosis-like bacteria
10. A family history of Primary Immunodeficiency.

You have a 6 yo male with moderate persistent asthma who follows up with his mother. He is currently on Flovent (Fluticasone) 110 mcg 2 puffs twice daily with a spacer. He needs his albuterol maybe once or twice a month but denies any nighttime symptoms or any oral steroids this last year. His mother notes she is concerned about the effect of steroids on his height and wonders if there is any other options for him besides his current maintenance inhaler.

What is/are possible treatment options to decrease total steroid exposure based on the new updated EPR-3?

A) Allergy evaluation for possible environmental testing
B) Changing maintenance inhaler from Flovent (Fluticasone) 110 mcg to 44 mcg
C) Changing to SMART therapy
D) Changing his maintenance inhaler to a LAMA like Tiotropium
E) A and C
F) All of the above

What is/are possible treatment options to decrease total steroid exposure based on the new updated EPR-3?

A) Allergy evaluation for possible environmental testing
B) Changing maintenance inhaler from Flovent (Fluticasone) 110 mcg to 44 mcg
C) Changing to SMART therapy
D) Changing his maintenance inhaler to a LAMA like Tiotropium
E) A and C
F) All of the above

After discussing some of the options with his mother she is interested in doing SMART therapy which of the following inhalers would be an acceptable choice?

A) Asmanex (Mometasone) 100 mcg
B) Advair (Fluticasone/Salmeterol) 230/21 mcg
C) Spiriva Respimat (Tiotropium) 2.5 mcg
D) Dulera (Mometasone/Formoterol) 100/4.5 mcg
E) None of the above
F) All of the above

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C) Spiriva Respimat (Tiotropium) 2.5 mcg
D) Dulera (Mometasone/Formoterol) 100/4.5 mcg
E) None of the above
F) All of the above

After discussing some of the options with his mother, they decided to get an allergy evaluation and was found to have positive testing to multiple allergens. What are possible options per EPR 3 update for his asthma with this information?

A) Start Sublingual Immunotherapy aka allergy drops
B) Start Subcutaneous Immunotherapy or allergy shots
C) Doing indoor mitigation of his allergens like dust mite precautions
D) B and C
E) None of the above
F) All of the above

After discussing some of the options with his mother, they decided to get an allergy evaluation and was found to have positive testing to multiple allergens. What are possible options per EPR 3 update for his asthma with this information?

A) Start Sublingual Immunotherapy aka allergy drops
B) Start Subcutaneous Immunotherapy or allergy shots
C) Doing indoor mitigation of his allergens like dust mite precautions
D) B and C
E) None of the above
F) All of the above

You have a 65 yo male who has some mild cognitive impairment and BPH. He is not interested in allergy evaluation or doing anything like allergy shots at this time. He is just on tamsulosin to help with his BPH. He notes his nose is always running and he is congested. He does not want to use nasal sprays. What is the safest medication for him to use.

A) Start Diphenhydramine 25 mg every 4-6 hrs as need

B) Start Chlorphenamine 4 mg every 4-6 hrs as needed

C) Start Phenylephrine 10 mg daily as needed

D) Start Fexofenadine 180 mg daily as needed

You have a 65 yo male who has some mild cognitive impairment and BPH. He is not interested in allergy evaluation or doing anything like allergy shots at this time. He is just on tamsulosin to help with his BPH. He notes his nose is always running and he is congested. He does not want to use nasal sprays. What is the safest medication for him to use.

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You have a 6 month old male with severe eczema. His mother started to introduce solid foods and wonders about starting peanuts.

A) Hold peanut products as it is a highly allergic food

B) Note there is no link with eczema and food allergy and introduce peanut

C) Ask about egg allergy and if he tolerates egg then introduce peanut

D) Get blood testing for peanut

E) Refer to an allergy specialist

F) D and E

G) All of the above

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E) Refer to an allergy specialist

F) D and E

G) All of the above

You have 4 year old male with confirmed peanut allergy. He carries his epipen and has avoided peanut at home. However, his mother and father are concerned with him starting Kindergarten. They ask if there is anything they can do to help prevent severe reactions with peanut.

A) Tell them there is no other FDA approved options but avoidance

B) Note that must kids out grow peanut allergy by age 3 and to not worry

C) Tell them there is oral desensitization with peanut flour called palforzia

D) None of the above

You have 4 year old male with confirmed peanut allergy. He carries his epipen and has avoided peanut at home. However, his mother and father are concerned with him starting Kindergarten. They ask if there is anything they can do to help prevent severe reactions with peanut.

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C) Tell them there is oral desensitization with peanut flour called palforzia

D) None of the above