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Atopic disease overview in our pediatric population

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Objectives

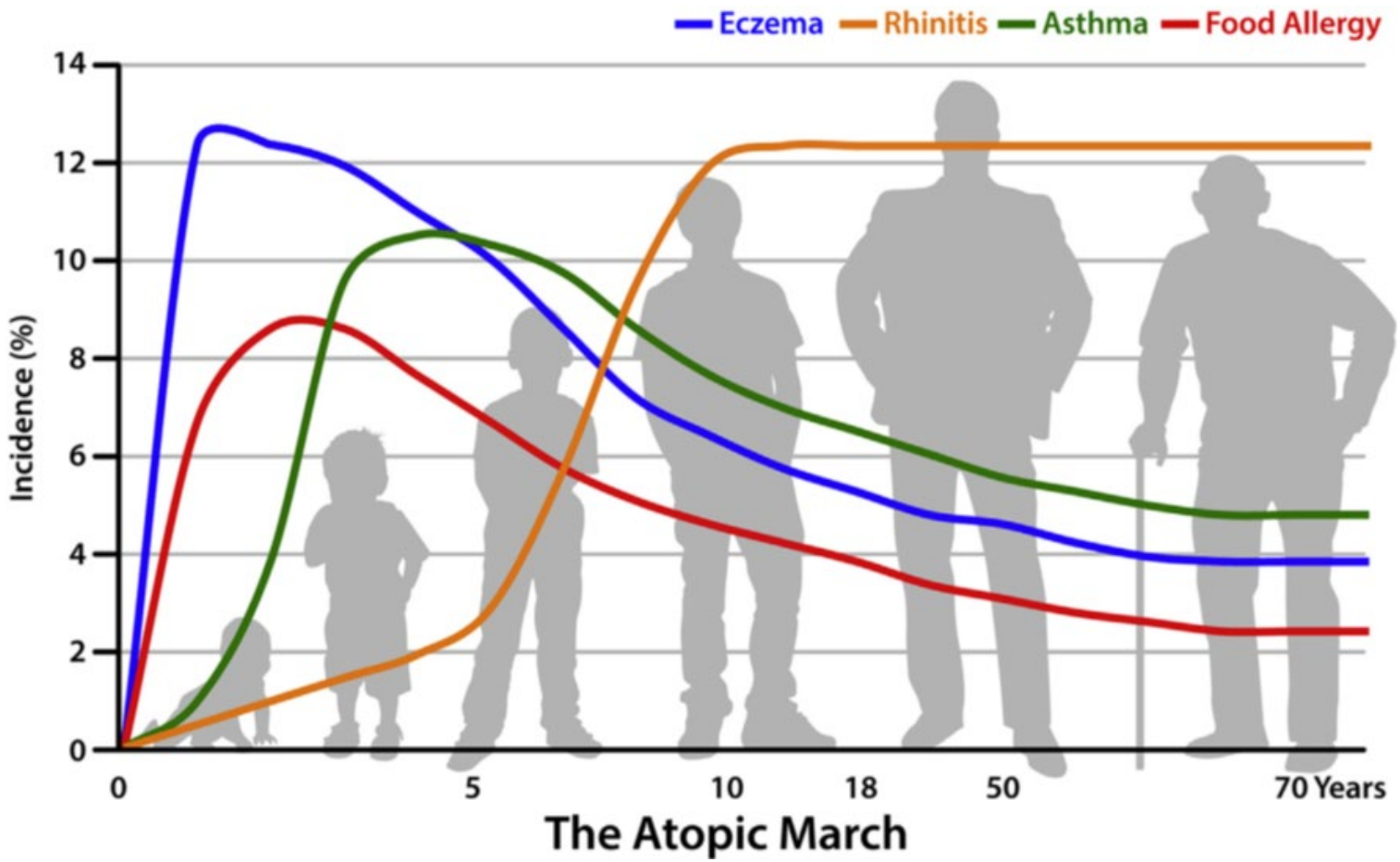
- Understand the clinical connection between various atopic disease
  - Atopic dermatitis
  - Food allergy
  - Asthma
- Understand clinical presentation
- Understand treatment options

Question 1

The most common first disease to present in the atopic march and atopic-multimorbidity is

a. Eczema
b. Food allergy
c. Asthma
d. Allergic rhinitis

Atopic march



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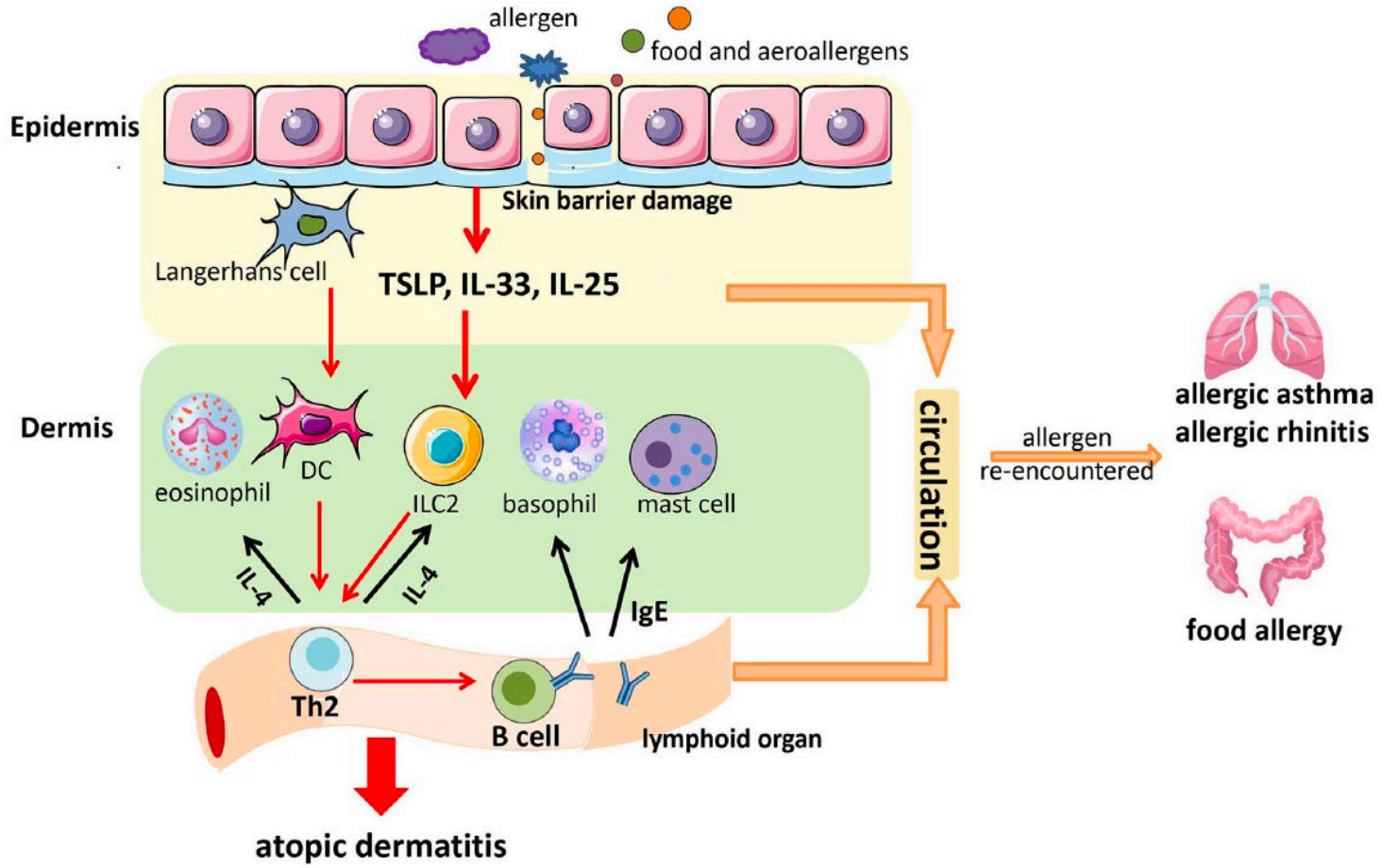
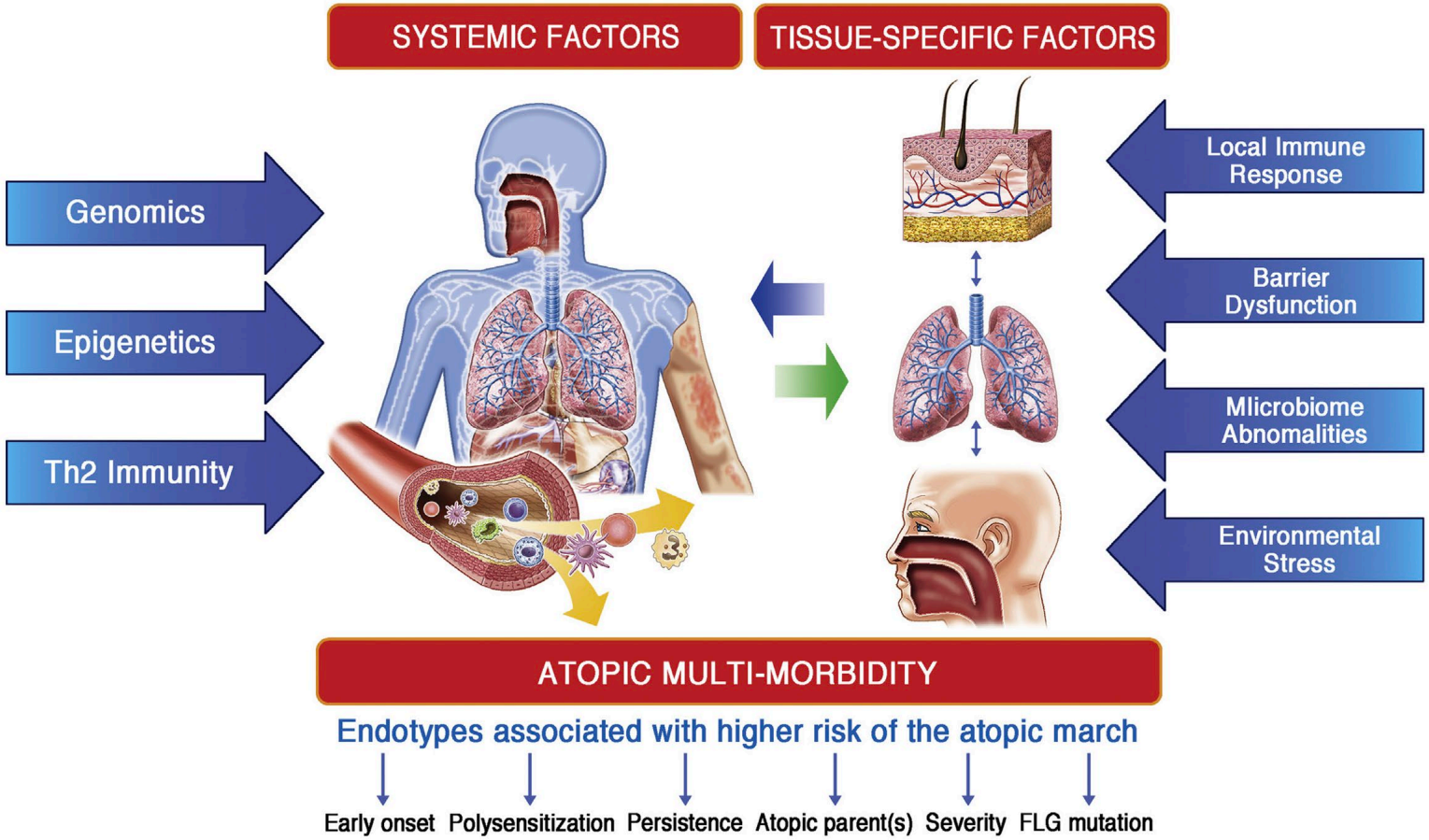
Davidson et al, JACI 2019

Pathophysiology



Yang, et al. Frontiers in Immunology, 2020

Atopic march versus atopic multimorbidity



Paller et al. JACI 2018

Eczema

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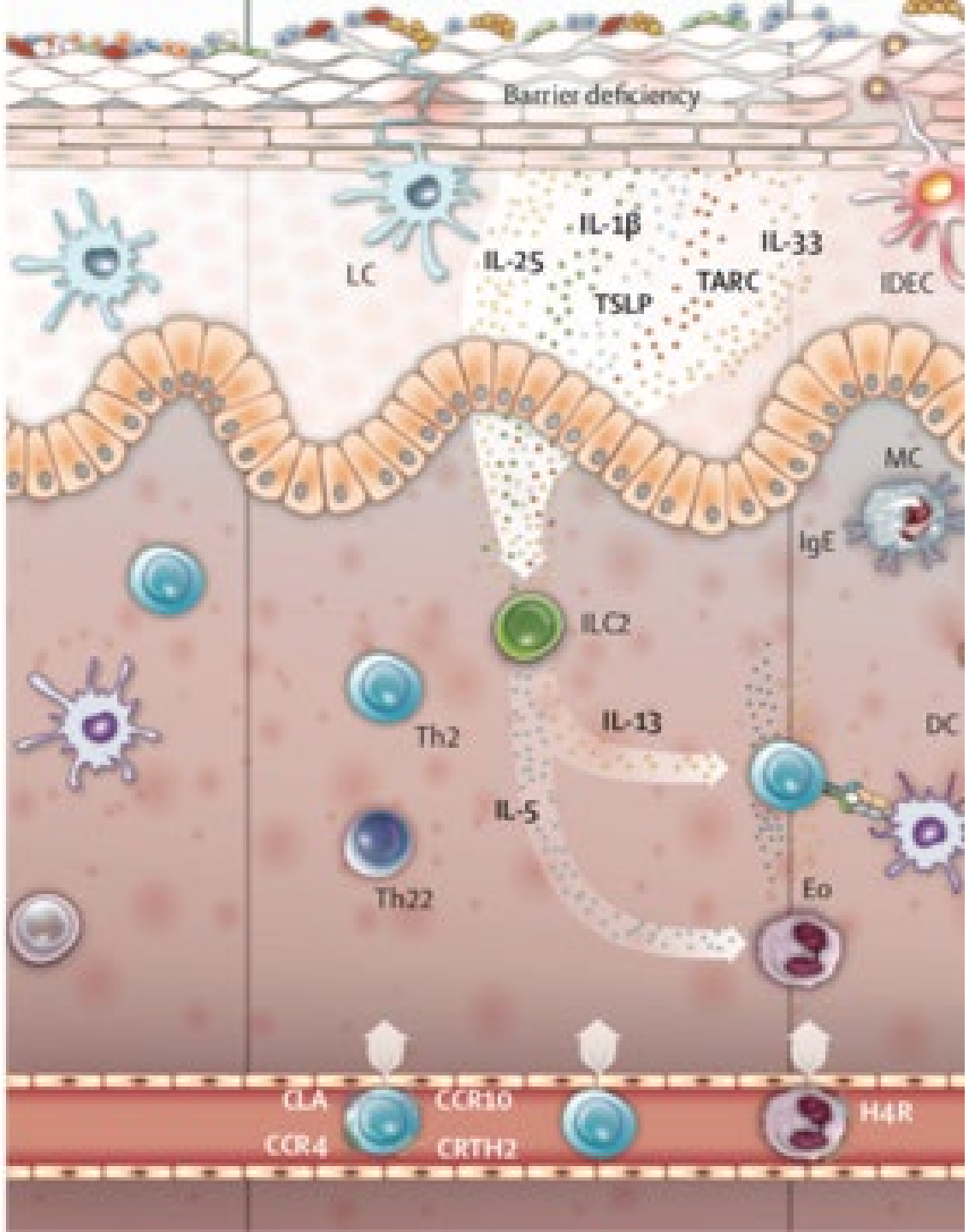
Why it is important

- Atopic dermatitis is the most common inflammatory skin disorder (20%) among infants and children, and known to be an important player in the atopic march
  - Harbinger for food allergy, asthma and allergic rhinitis
- Affects 10% of adults in high-income countries, and increasing prevalence globally
- Difficult to diagnose and treat due to heterogenous clinical presentation
- Has substantial psychosocial impact on patients and families, as well as leading cause of global burden from skin disease



Pathophysiology

- Epidermal barrier dysfunction
  - Increased trans-epidermal water loss and altered lipid composition
  - Multifactorial → genetics and physical scratching
  - Microbial dysbiosis
    - Early life colonization with non-staph is protective vs early *S. aureus* colonization precedes AD
  - downregulate skin barrier genes
  - Keratinocytes that are stressed send proinflammatory signals

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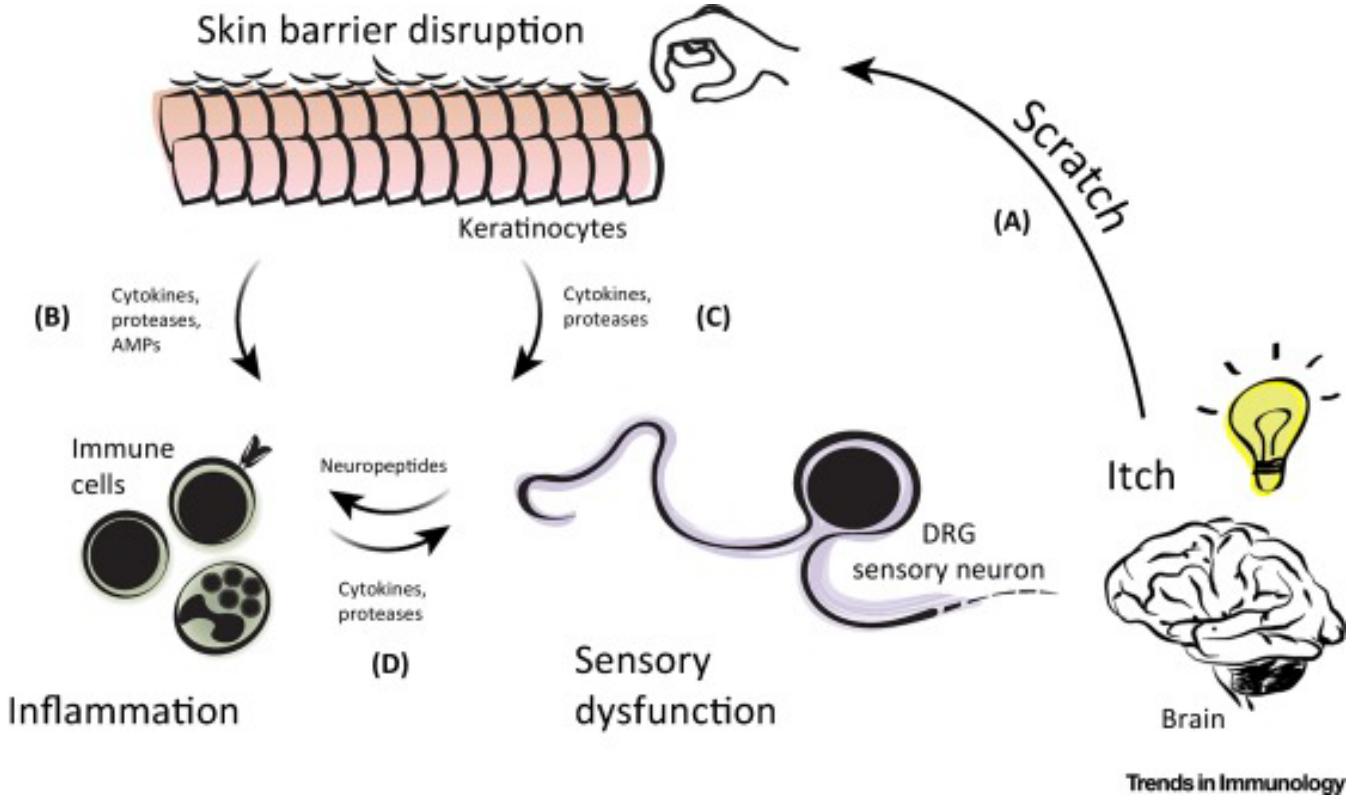
Pathophysiology Continued

- Neuroimmune
  - Itch-scratch cycle
  - Histamine is most studied pruritogen
    - Antihistamines not effective

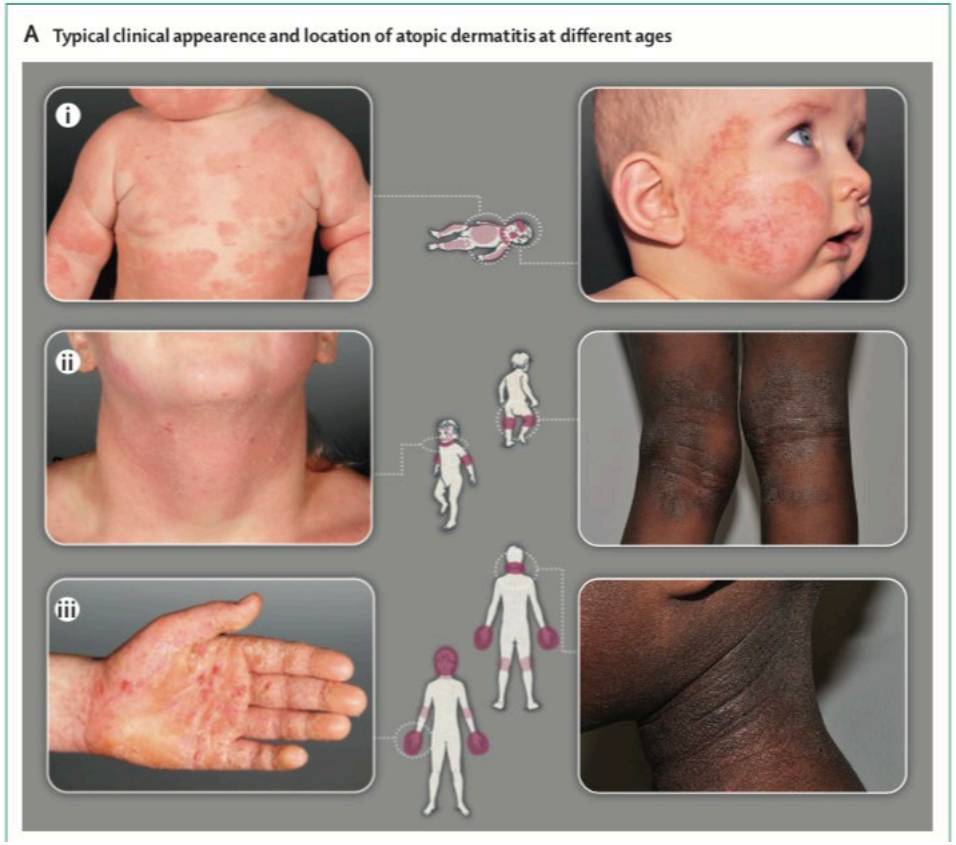
- Allergens and irritants
  - Dust mite has proteases that can eat at skin barrier



Mack, *Trends in Immunology* 2018

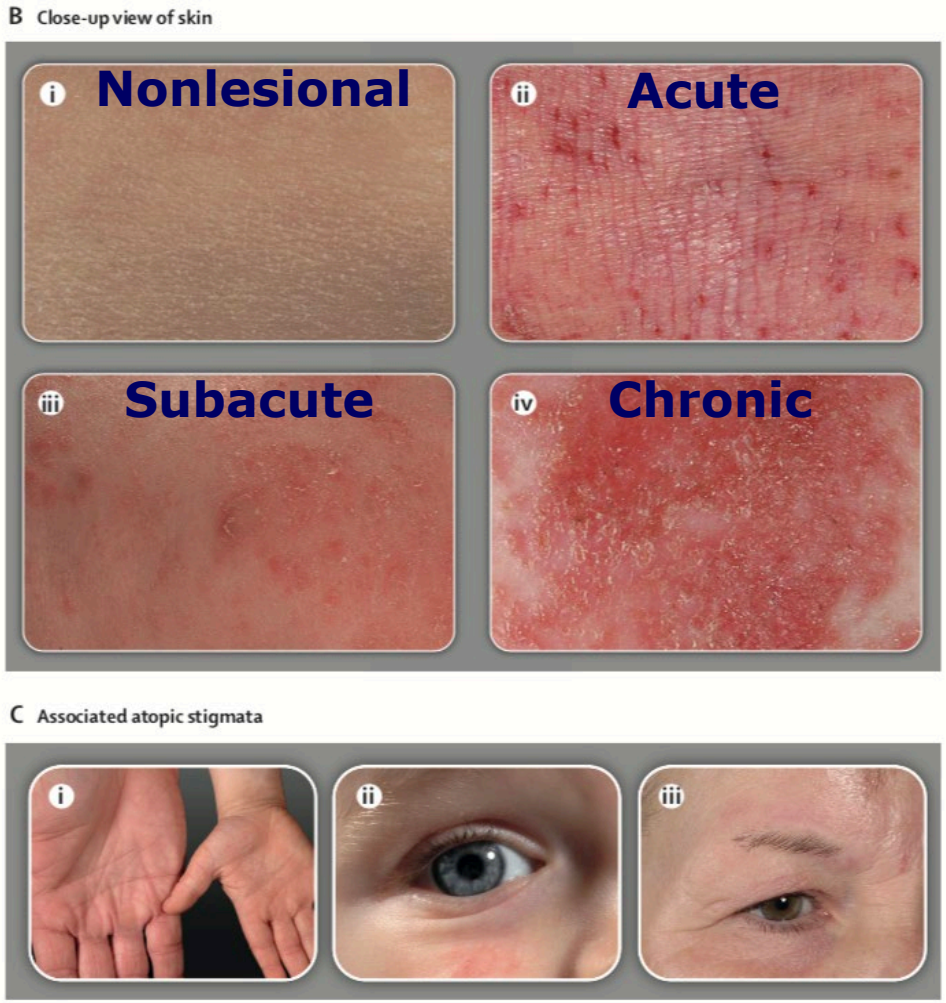
Eczematous lesions - Distribution

- 0-2 years: poorly defined erythema and edema, vesicles, excoriations that are diffuse
  - commonly face, cheeks and trunk (diaper sparing)
- >2 years: localized, paler erythema, xerosis, flexor lichenification



Eczematous lesions - characterization

- Chronicity
- Papulation, excoriation
- Atopic status
- Persistent AD
  - Predictors: asthma, allergic rhinitis, non-white
- Associated signs:
  - Hyper-linearity of palms and soles (*FLG* mutation)
  - Dennie-Morgan infraorbital folds
  - cycling of legs, thinning of hair on posterior scalp, erythematous chin, "clubbing of toes"



Differential diagnosis – not all eczema is just eczema

TABLE II. Differential diagnosis in patients with severe AD

Differential category	Diagnostic examples
Congenital disorders	Netherton syndrome
Chronic dermatoses	Seborrheic dermatitis
	Contact dermatitis (allergic or irritant)
	Nummular eczema
	Psoriasis (erythrodermic and inverse)
Infections and infestations	Scabies
	HIV-associated dermatitis
Malignancy	Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome)
Immunodeficiencies	Wiskott-Aldrich syndrome
	Severe combined immunodeficiency
	Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome
	HIES
	Dedicator of cytokinesis 8 mutation-associated immunodeficiency
Metabolic disorders	Zinc deficiency
Proliferative disorders	Letterer-Siwe disease

Question 2

Treatment for eczema includes all but the following:

a. Moisturization
b. Topical steroids
c. Food avoidance
d. Bathing

Nonpharmacologic treatment

- Food avoidance is NOT recommended and not a known trigger for eczema flares

- Moisturizers
  - Emollients (glycol, glyceral stearate, soy sterol) → soften skin
    - Cetaphil → Cerave → Vanicream
  - Occlusive (petrolatum, dimethicone, mineral oil) → decrease water loss from evaporation
  - Petrolatum: upregulates antimicrobial peptide, innate immune genes and key epidermal barrier differentiation markers
  - Aquaphor can cause lanolin hypersensitivity rash
  - Best when used in conjunction with bath

- Bathing
  - Act of bathing is beneficial
  - Soak and seal: 10-15 min bath followed by immediate moisturizer and medication (2-3 min) daily
  - Cleansers: neutral pH, fragrance free

Nonpharmcologic treatment continued

- Bleach baths
  - Reduce skin inflammation and decrease S. aureus colonization
  - Recent studies question this but patients do report improvement
  - Baby bath: 1 tbsp Chlorox in full bath. Let sit for 10 minutes before soaking baby
  - Full bath: ¼ - ½ cup bleach in full bath.
  - Ensure rinsing off after bath

- Wet wrap therapy
  - After soaking bath, wetted bandage or pajamas is applied over a layer of topical steroid or emollient, followed by dry layer
  - Use cautiously: can cause rashes (folliculitis)

Pharmacological treatment

- Topical steroids
  - Reduce proinflammatory cytokines, interfere with antigen processing, reduce activity of immune effector cells and S. aureus
  - Potency:
    - Low: class VI-VII
      - Safe for everywhere including face, skin folds, groin
  - Withdrawal: can cause burning/stinging, erythema

- Topical calcineurin inhibitor
  - Moderate-to-severe AD for age 2 and up
  - Black box warning for malignancy → based on trials with oral agents for solid organ transplant pt
  - Better side effect profile than topical steroids

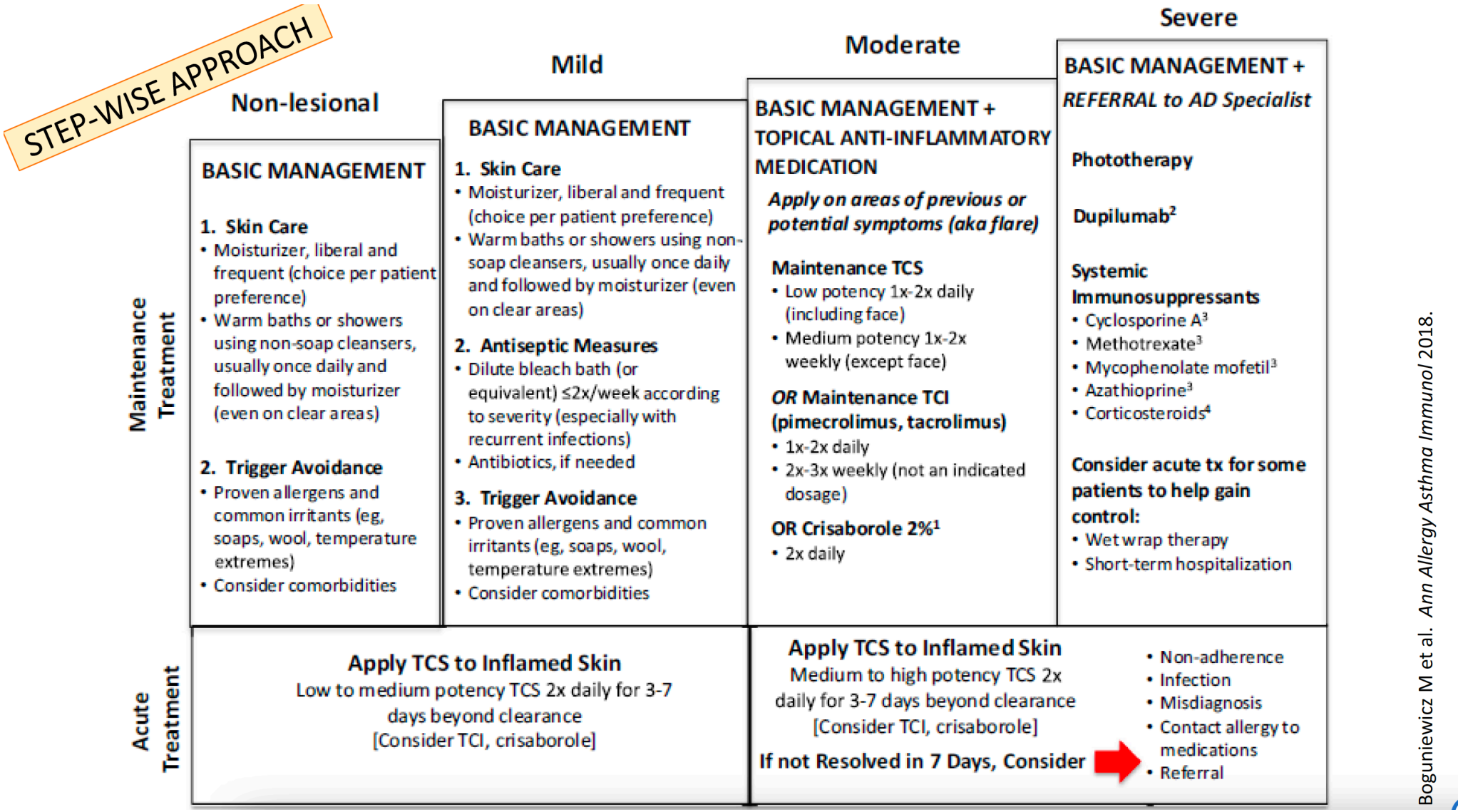
Systemic therapy options

- Dupilumab (age 6 months and up)
  - 75% improvement in EASI at week 16
  - Side effect: conjunctivitis
    - Seen in only trials for AD, not asthma or polyposis

- Phototherapy
  - Caution with those on topical calcineurin inhibitor
  - Not approved in children younger than 12 years
  - Side effect: stinging, reactivation of herpes infection

- Immunosuppressive agents

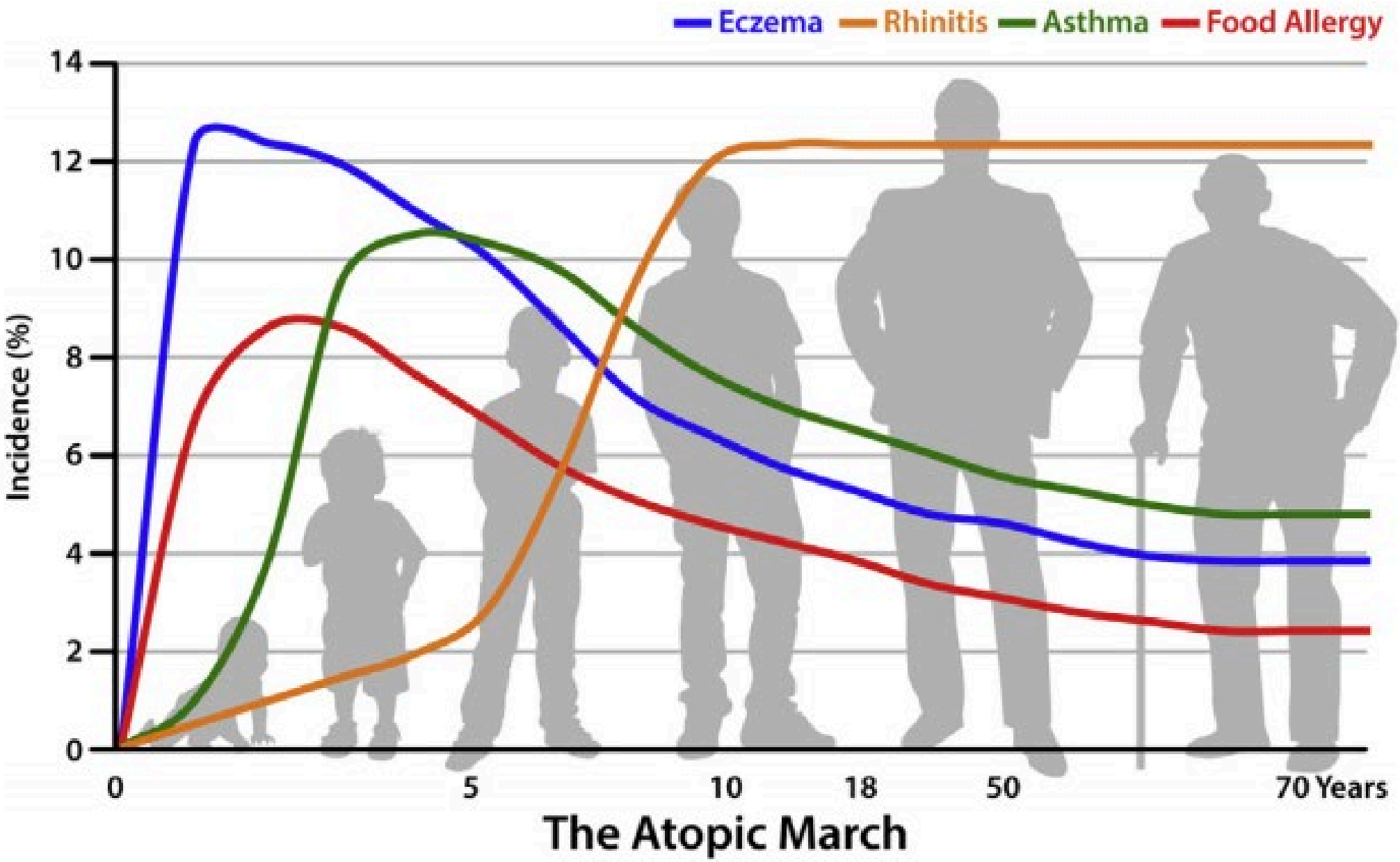
Step-wise Approach



Boguniewicz M et al. *Ann Allergy Asthma Immunol* 2018.

AD Prevention

- Two pilot trials suggested daily emollient applications from birth may prevent AD in high-risk infants
  - First-degree relative with AD, asthma or allergic rhinitis
  - Emollients with ceramide and amino acids
- Failed to show benefits in larger, multicenter trials
- UK study showed that frequent emollient use multiple times per day is associated with increased food allergy
  - Flawed due to use of olive oil as moisturizer



The Atopic March

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Food allergy

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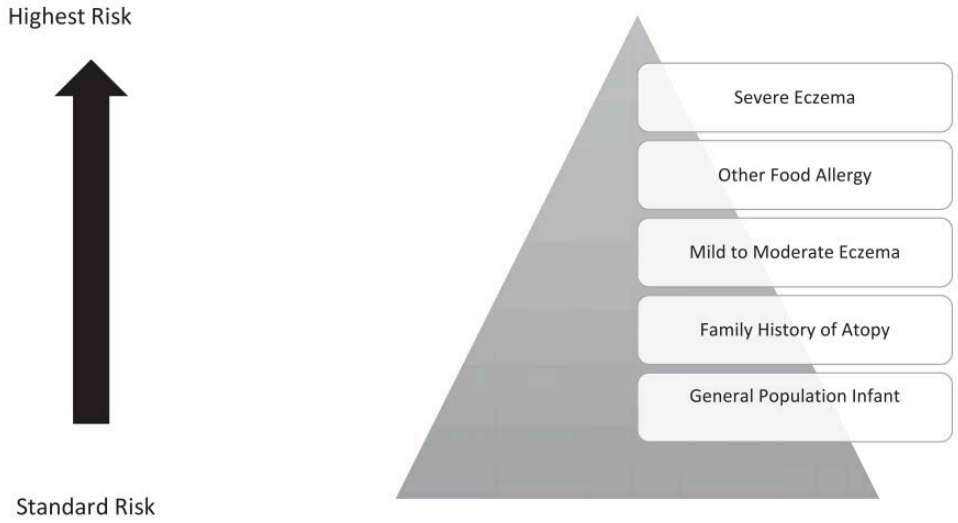
Question 3

We recommend avoidance of highly allergenic foods until a child is 1 year of age

a. True
b. False

Overview

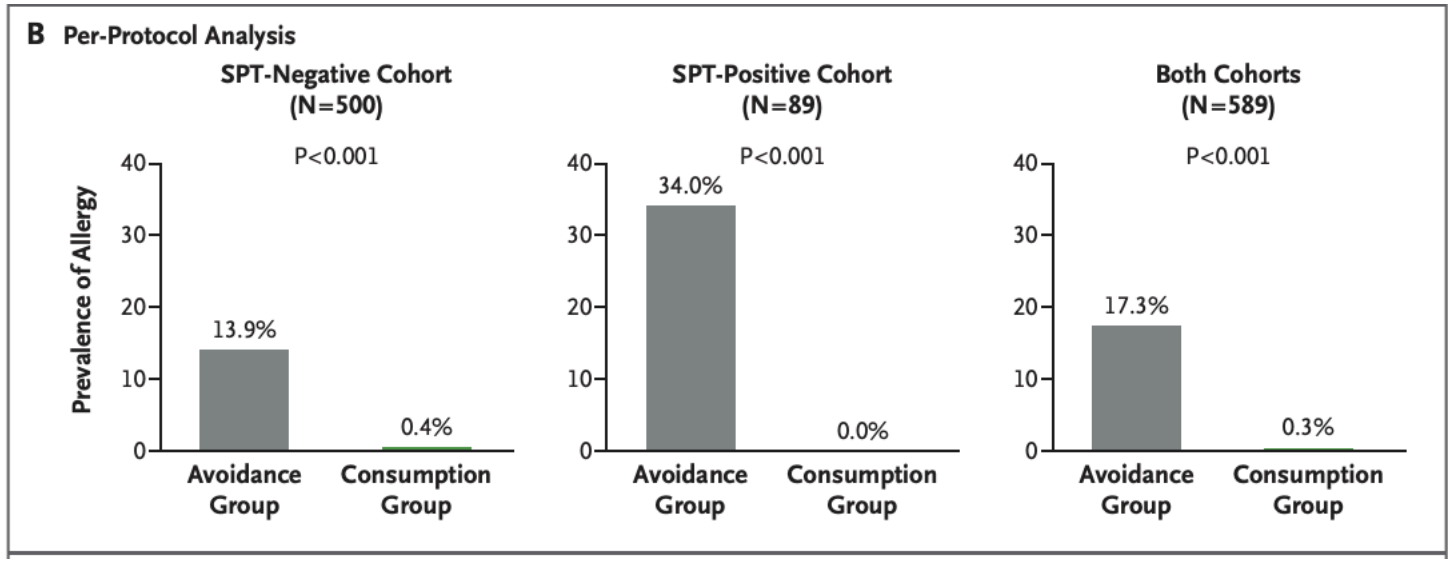
- One-third of infants with moderate-to-severe AD have food allergy
- Cow's milk, hen's egg, peanut, wheat, soy, nuts, and fish are responsible for >90% of food allergy in children
- Early introduction (4-6 months) can prevent onset of food allergy



Fleischer et al, JACI, Jan 2021

LEAP study

87% risk reduction in peanut allergy in infants who introduce peanut at 4-6 months



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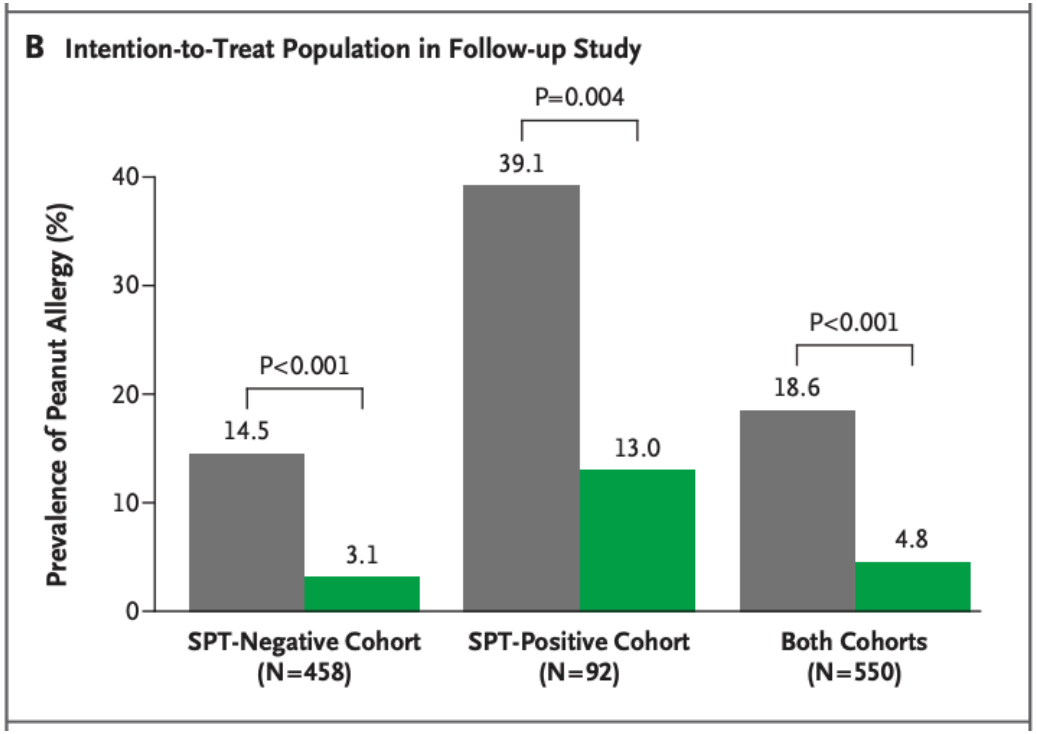
Du Toit et al, NEJM, 2015

LEAP-ON

In infants who introduce peanut early, a 12-month avoidance of peanut is NOT associated with increased risk of peanut allergy



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Du Toit et al, NEJM, 2017

Which infants do we recommend early introduction?

- Consensus approach for primary food allergy prevention:
  - Introduce peanut-containing products to all infants, **irrespective of their relative risk of developing peanut allergy**, starting around 6 months of life, though not before 4 months of life.
  - Introduction can occur at home when the infant is developmentally ready for complementary food introduction, but not before the infant demonstrates developmental readiness with eating a few other common starter foods.

Early introduction – consensus statement

- When we perform allergy testing
  - Testing is not perfect and only as good as our history – eczema infants are more likely to have falsely elevated sIgE and SPT
  - Recommend to not perform allergy panels due to this
  - Refer patients for testing when appropriate
    - Screening peanut/tree-nut skin or sIgE testing and/or in-office introduction is not required for early introduction
    - remains an option to consider for families that prefer to not introduce peanut at home; this decision is preference-sensitive and should be made taking into account current evidence and family preferences.
  - For those that are positive, we recommend in office challenge dependent on results

- Reserve specific testing for severe eczema infants
  - Shared decision making with family
    - Moderate eczema: Will test for peanut if family feels uncomfortable

Early introduction guidelines

- What about other foods?
  - Early infant diversity is associated with decrease in prevalence of other food allergies
  - Encourage diverse diet as preferred by family preference
  - Do not recommend allergy testing prior to food introduction except as noted

TABLE VII. General discussion points for parents and caregivers regarding early introduction of allergenic foods

Concept of early introduction • Primary care providers should implement talking points surrounding early introduction into all well-child visits, beginning at birth and repeated at age 2, 4, 6, and 9 mo. • Allergists seeing infants for conditions such as atopic dermatitis should discuss concepts surrounding early introduction with families. • Obstetricians can introduce these concepts with expecting parents to help them increase awareness and understanding.
Benefits of early introduction • Medical providers who discuss timing and method of solid food introduction should include discussion of the benefits of incorporating allergenic foods into the diet. • Medical providers should also discuss that early introduction has not been associated with increased harm or risk for food allergy development.
Risk stratification • Medical providers should identify infants at highest risk to develop food allergies and discuss that risk, along with benefits of early introduction, with families. • Medical providers should help parents of infants at low risk to develop food allergy understand that special precautions are not necessary surrounding the early introduction of allergenic foods and encourage them to diversify their infant's diet.
Testing • Medical providers should understand and discuss the pitfalls associated with overuse and misinterpretation of food sIgE tests. • When deemed appropriate, medical providers should discuss the role of IgE testing before introduction of foods as a method to determine whether the food will be introduced at home or under supervision in the office setting. • Medical providers should discuss with families that food sIgE testing in an infant who has never ingested a food is not diagnostic for food allergy and should not be used as a routine screening test.

How about other foods?

- Tree nuts
  - Mixed nut butter with purees
- Egg
  - Scrambled egg white
- Wheat
  - Cream of wheat, wheat puffs

- Important:
  - once introduced, peanut should be kept in diet at least 3 times per week (bag of bambas a week) until 5 years of age
  - Mixed nut butter should be done at least once a week
  - Other foods: 1-3 times per week minimum

How do we prevent food allergies?

- Early introduction
- Milk
  - Formula within the first 3 days of life has increased risk of milk allergy if avoided later on
  - Giving one feed with formula (minimum an ounce) prevented milk allergy in infants
- Breastfeeding
  - Beneficial but conflicting data on preventing food allergies
- Early emollient use: conflicting data
  - Creams (Cerave, Vanicream) and petrolatum over ointments (Aquaphor)
    - Lanolin sensitivity
- Formula choice
  - We do not recommend extensively hydrolyzed formulas over cow's milk formula if needing to supplement

FPIES

- Food protein-induced enterocolitis
  - Severe vomiting, diarrhea 1-4 hours after ingestion of a food
  - Common foods: cow's milk, soy
    - Avoidance: rechallenge 1.5-2 years from last reaction
  - Can have both IgE-mediated and FPIES allergy to same food

TABLE IX. Empiric guidelines for selecting weaning foods in infants with FPIES

Ages and stages	Lower-risk foods*	Moderate-risk foods*	Higher-risk foods*
4-6 mo (as per AAP, CoN)	Vegetables		
If developmentally appropriate and safe and nutritious foods are available: ● Begin with smooth, thin purees and progress to thicker purees ● Choose foods that are high in iron ● Add vegetables and fruits	Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
6 mo (as per WHO)	Fruits		
Complementary feeding should begin no later than 6 mo of age: ● In the breast-fed infant, high-iron foods or supplemental iron (1 mg/kg/d) are suggested by 6 mo of age ● Continue to expand variety of fruits, vegetables, legumes, grains, meats, and other foods as tolerated.	Blueberries, strawberries, plum, watermelon, peach, avocado	Apple, pear, orange	Banana
8 mo of age or when developmentally appropriate:	High-iron foods		
● Offer soft-cooked and bite-and-dissolve textures from around 8 mo of age or as tolerated by infant.	Lamb, fortified quinoa cereal, millet	Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Higher-iron foods: fortified, infant rice and oat cereals
12 mo of age or when developmentally appropriate:	Other		
● Offer modified tolerated foods from the family: table-chopped meats, soft cooked vegetables, grains, and fruits	Tree nuts and seed butters* (sesame, sunflower, etc.) *Thinned with water or infant puree for appropriate infant texture and to prevent choking	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

This table should be considered in the context of the following notes:
A. Exclusive breast-feeding until 4 to 6 months of age and continuing breast-feeding through the first year of life or longer as long as mutually desired by both mother and child (Baker RD, Greer FR, Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics 2010;126:1040-50).
B. If an infant tolerates a variety of early foods, subsequent introduction can be more liberal. Additionally, tolerance to one food in a food group (green pea) is considered a favorable prognostic indicator for tolerance of other foods from the same group (legumes; Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J Allergy Clin Immunol 2005;115:149-56).
AAP, CoN, American Academy of Pediatrics, Committee on Nutrition; *WHO*, World Health Organization.
*Risk assessment is based on the clinical experience and published reports of FPIES triggers.

FPIES letter

International FPIES Association (I-FPIES)
319 Richmond Avenue
Point Pleasant Beach, NJ 08742

www.fpies.org
contact@fpies.org

Date

Re:(Patient's Name)
(Date of Birth)

Dear Doctor (To Whom It May Concern),

_____ has a food allergy called Food Protein-Induced Enterocolitis Syndrome (FPIES). This is a type of allergy that usually does not result in typical "allergic" symptoms such as hives or wheezing, but rather isolated gastrointestinal symptoms.

The symptoms of this type of allergic reaction include repetitive vomiting that may not start for a few hours (e.g., two hours) 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 (~20%), the reaction includes hypotension and lethargy. The treatment is symptomatic and can include intravenous fluids (e.g., normal saline bolus, hydration) and steroids (e.g., Solumedrol 1-2 mg/kg) for significant symptoms. The latter is given because the pathophysiology is that of a T-cell response.

This information is being given so that this could be considered in the differential diagnosis for this patient in event of symptoms. Of course, this illness does not preclude the possibility of other illness (e.g., infection) or even other types of allergic reactions leading to symptoms, so it is up to the evaluating physician to consider all possibilities. Similarly, the treating physician is encouraged to pursue any other treatments deemed necessary (e.g., symptomatic such as epinephrine for shock, antibiotics for presumed infections, etc.).

Sincerely,

Asthma

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Overview -Asthma

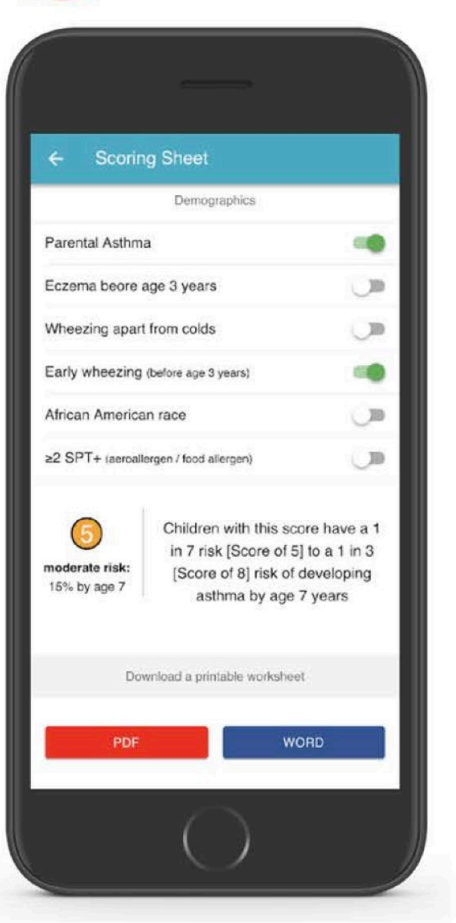
- Pediatric presentation
  - Cough
  - Worsening with activity
  - Wheezing with viral illnesses

- Important to treat early on as repeated exacerbations can cause abnormal lung growth seen in adulthood

Asthma phenotypes in children

- Preschool asthma
  - Intermittent symptoms with viral illnesses
  - Early infection with rhinovirus is associated with increased risk of asthma
- Early onset allergic asthma (genetic predisposition)
  - Allergic sensitization to environmental allergens
- Pollution-induced
  - Diesel exhaust particles not only flare asthma but also contribute to development of it in childhood
    - Cause sensitization to aeroallergens by making allergen more allergenic
- Obesity-related asthma
  - Physical but also immunologic
  - Obesity causes CD4+ T cells to skew towards a Th1 phenotype vs Th2 → making them steroid unresponsive

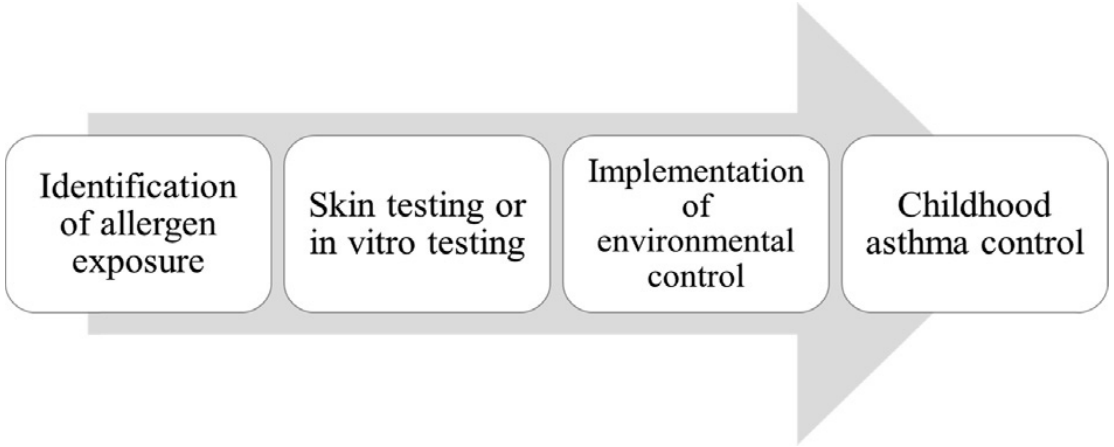
Pediatric Asthma Risk Score



PARS

PARS Score	Risk of Asthma by age 7 years	Interpretation
0-4	3%-11%	LOW RISK
5-8	15%-32%	MODERATE RISK
9-14	40%-79%	HIGH RISK

Co-morbidities to manage: Allergic rhinitis



- Role of allergic rhinitis
  - Allergen contributed asthma exacerbations can benefit from allergen immunotherapy
  - Early start of allergen immunotherapy shown to prevent asthma onset in children

TABLE II. Exposures in indoor environment that affect asthma[20]

Allergens
Dust mites
Furry pets
• Cats
• Dogs
• Others
Rodents
• Mice
• Rats
Cockroach
Dampness and mold
Pollutants
Particulate matter
Secondhand smoke
Ozone
Sulfur dioxide
Nitrogen dioxide

Environmental controls

- Pollutants
  - AQI: highest concentration 11am-8pm
- School
  - US EPA created Indoor Air Quality tools that aim to improve environmental conditions (ventilation, clutter that collect dust, infestation and animal dander)
  - Key partnership between school and family

AQI Basics for Ozone and Particle Pollution

Daily AQI Color	Levels of Concern	Values of Index	Description of Air Quality
Green	Good	0 to 50	Air quality is satisfactory, and air pollution poses little or no risk.
Yellow	Moderate	51 to 100	Air quality is acceptable. However, there may be a risk for some people, particularly those who are unusually sensitive to air pollution.
Orange	Unhealthy for Sensitive Groups	101 to 150	Members of sensitive groups may experience health effects. The general public is less likely to be affected.
Red	Unhealthy	151 to 200	Some members of the general public may experience health effects; members of sensitive groups may experience more serious health effects.
Purple	Very Unhealthy	201 to 300	Health alert: The risk of health effects is increased for everyone.
Maroon	Hazardous	301 and higher	Health warning of emergency conditions: everyone is more likely to be affected.

Pharmacologic management

Shown to decrease oral prednisone use

Figure I.b: Stepwise Approach for Management of Asthma in Individuals Ages 0–4 Years

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 0–4 Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA and At the start of RTI: Add short course daily ICS▲	Daily low-dose ICS and PRN SABA	Daily medium-dose ICS and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily montelukast* or Cromolyn,* and PRN SABA		Daily medium-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast*+ oral systemic corticosteroid and PRN SABA
			For children age 4 years only, see Step 3 and Step 4 on Management of Persistent Asthma in Individuals Ages 5–11 Years diagram.			

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 4–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 3 or higher is required. Consider consultation at Step 2.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist; RTI, respiratory tract infection; PRN, as needed

▲ Updated based on the 2020 guidelines.

* Cromolyn and montelukast were not considered for this update and/or have limited availability for use in the United States. The FDA issued a Boxed Warning for montelukast in March 2020.

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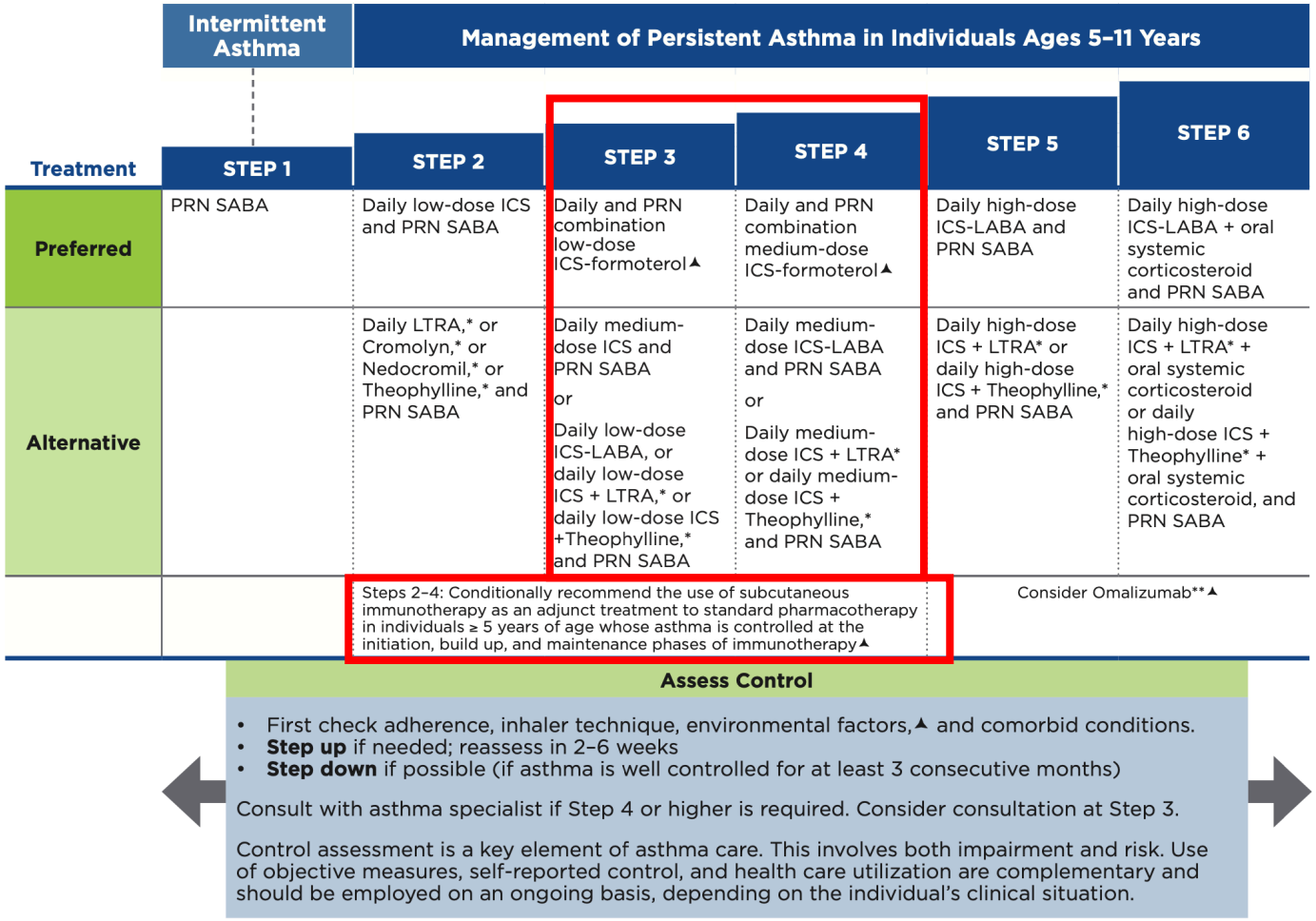
Step 3&4: use ICS/LABA 1-2 puffs as needed up to maximum 8 puffs per day maintenance and rescue (36mcg)

Figure I.c: Stepwise Approach for Management of Asthma in Individuals Ages 5–11 Years



Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including montelukast, and Theophylline were not considered in this update and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

** Omalizumab is the only asthma biologic currently FDA-approved for this age range.

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Stepwise Approach for Ages 12 years and older

Step 3&4: use ICS/LABA 1-2 puffs as needed up to maximum 12 puffs per day maintenance and rescue (54 mcg)

Figure I.d: Stepwise Approach for Management of Asthma in Individuals Ages 12 Years and Older

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

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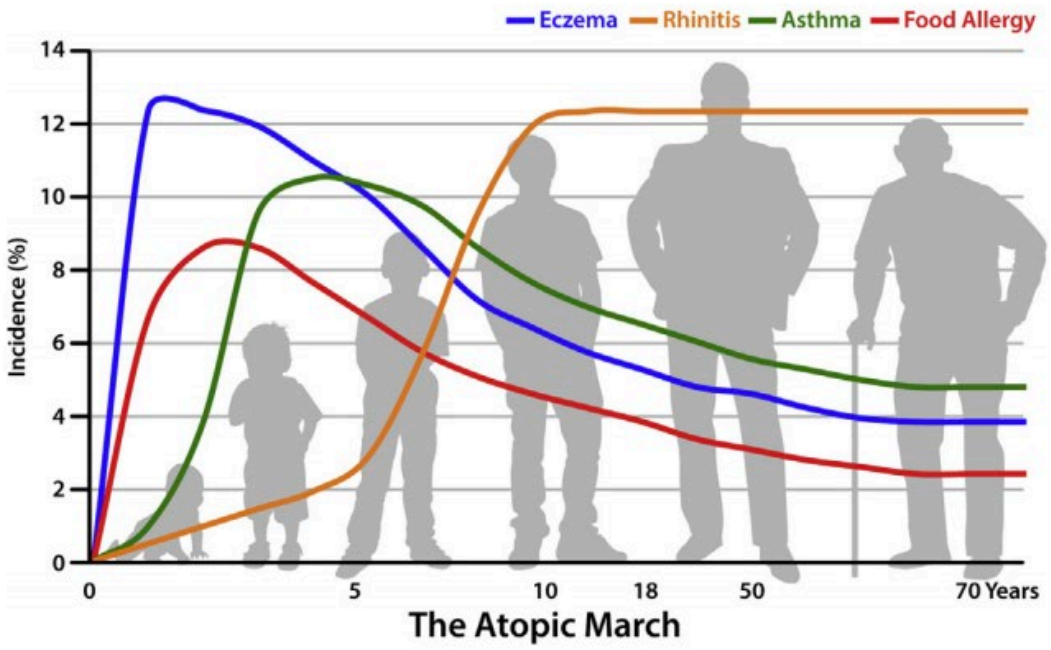
SMART therapy

- Removal of black box warning on ICS/LABA
  - Studies showed use of LABA with ICS does not have an increased risk of cardiac-related deaths with use
  - Previous studies showing risk was with LABA use alone
- Use as rescue linked to quicker control and resolution of exacerbations

Conclusion



- AD, food allergy, asthma are co-morbid conditions that work along similar immune pathways
- Treatment of one is connected to treatment of others
- Important to consider on managing care

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