PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

PRESENTATIONS

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Presentations for Friday, June 23, 2023

8:00 am – 8:45 am	**Contact Dermatitis** *Marc Serota, MD*
8:45 am – 9:30 am	**CVID- Evaluation and Management** *Kelli Williams, MD, MPH*
9:30 am – 10:15 am	**Diagnosing and Managing Anaphylaxis in 2023** *Marcus Shaker, MD, MS, FAAP, FAAAAI, FACAAI*
10:45 am – 11:30 am	**Food Protein-Induced Enterocolitis: How common is it?** *Jonathan Spergel, MD, PhD*
11:30 am – 12:15 pm	**Updates in Immunodeficiency** *Kelli Williams, MD, MPH*
12:15 pm – 1:00 pm	**Mayer A. Green Allergy Foundation Memorial Lecture: Eosinophilic Esophagitis: Update on Treatment and Diagnosis** *Jonathan Spergel, MD, PhD*

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Contact Dermatitis

Presented by:

Marc Serota, MD

Friday, June 23, 2023

8:00 a.m. – 8:45 a.m.

Allergic Contact Dermatitis

Marc Serota, MD
FAAD, FAAAAI, FACAAI
Peak Dermatology
Rocky Mountain VA Medical Center

Board Certified:
Dermatology
Allergy/Immunology
Pediatrics

1

Disclosures

- Consultant for Regeneron, Sanofi-Genzyme, Incyte, BMS, Arcutis, Amgen, Dermavant.

2

Objectives

- 1. Review the presentation of allergic contact dermatitis and its mimics.
- 2. Learn the immunology associated with allergic contact dermatitis.
- 3. Discuss the most common allergens encountered in practice.

3

Contact Allergy Principles

- Exposure to a topical allergen.
- Type IV (cell mediated hypersensitivity reaction).
- Should occur with every exposure.
- Timeframe: 48-72 hours.

4

Mechanism

- Contact allergens are low molecular weight (<500 Daltons) chemicals called haptens, which are able to penetrate the stratum corneum barrier of the skin.

- Haptens are not immunogenic by themselves
  - Recognized after binding to a skin protein carrier
  - May be naturally occurring substances such as urushiol (poison ivy), synthetic compounds, dyes, fragrances, drugs, or heavy metal salts.

5

Sensitization Phase

- Initial exposure

- Hapten-protein complex is engulfed and processed by Langerhans cells, which subsequently migrate to the draining lymph nodes where they present the hapten–peptide–MHC complexes to naïve, allergen-specific T cells (priming).

- Clonal expansion of hapten-specific memory/effector T cells, which circulate throughout the body and are subsequently recruited from the circulation into the skin during the elicitation phase.

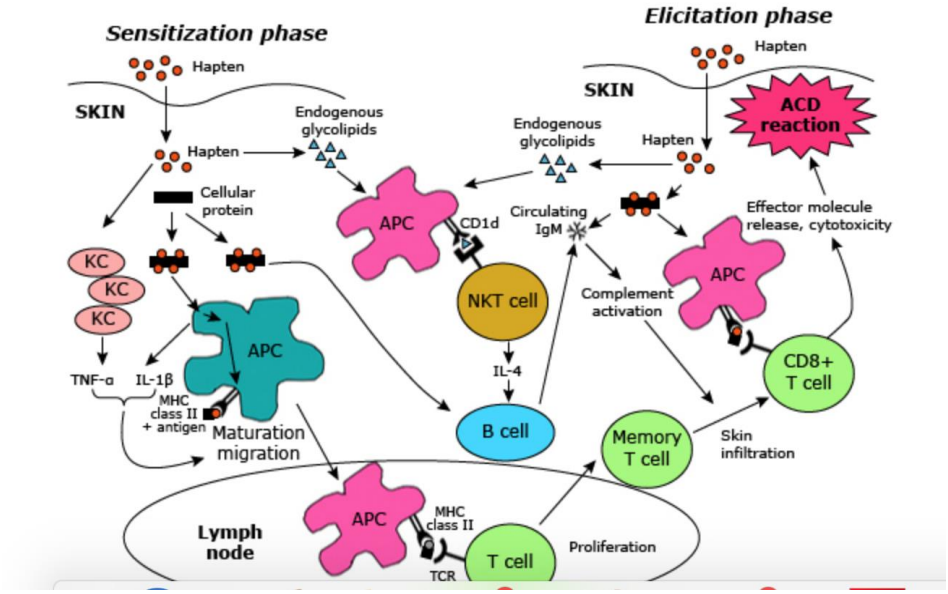
- Hapten-specific T cells are now found in the lymph nodes, in the blood, and in the skin. Upon re-exposure to the same hapten, T cells will be activated and massively recruited in the skin (the elicitation phase).

6

Elicitation Phase

- Haptens enter the epidermis and react with endogenous proteins. The hapten-protein complexes are then taken up by the antigen-presenting cells and presented to the antigen-primed T cells recruited in the epidermis and dermis.
  - Langerhands cells, mast cells, infiltrating macrophages, and keratinocytes .
- CD8+ T-cells induce keratinocyte apoptosis. Release type 1 cytokines, including IFN-gamma and TNF-alpha. Release of chemokines, resulting in a massive recruitment of mononuclear and polymorphonuclear cells and amplification of the inflammatory response.

7



8

Epicutaneous Patch Testing

- Place allergens of concern on skin surface for 48 hours.
- Final read at 72-96 hours.
- Consider re-evaluation at 4-5 days to observe for resolution of irritant reactions and for late reactions and reactions to weaker antigens.

9

T.R.U.E. Test

1 Nickel Sulfate	7 Colophony	13 *p-tert*-Butylphenol Formaldehyde Resin	19 Methyldibromo Glutaronitrile	25 Diazolidinyl Urea	31 Hydrocortisone-17-Butyrate		
2 Wool Alcohols	8 Paraben Mix	14 Epoxy Resin	20 *p*-Phenylenediamine	26 Quinoline Mix	32 Mercaptobenzothiazole		
3 Neomycin Sulfate	9 Negative Control	15 Carba Mix	21 Formaldehyde	27 Tixocortol-21-Pivalate	33 Bacitracin		
4 Potassium Dichromate	10 Balsam of Peru	16 Black Rubber Mix	22 Mercapto Mix	28 Gold Sodium Thiosulfate	34 Parthenolide		
5 Caine Mix	11 Ethylenediamine Dihydrochloride	17 Cl+ Me- Isothiazolinone	23 Thimerosal	29 Imidazolidinyl Urea	35 Disperse Blue 106		
6 Fragrance Mix	12 Cobalt Dichloride	18 Quaternium-15	24 Thiuram Mix	30 Budesonide	36 2-Bromo-2-Nitropropane-1, 3-diol		

10

F.A.L.S.E? What's missing:

- Glutaraldehyde (4.4%)
- Iodopropynyl butylcarbamate(2.6%)
- (Disperse blue 106) (2.3%)
- Dithiomorpholine (2.1%)
- (Sodium thiosulfate) (1.6%)
- Cinnamic aldehyde (1.5%)
- 4-aminoazobenzene (1.0%)
- cocamidopropyl betaine (0.8%)
- N,N-diphenylguanidine (0.8%)

- Total of 17% of missed reactions.

- 427 patients (mean age = 49.8 years) underwent PT.
- 82% were female.
- 54% reported an atopic history.
- The most common occupation was health care worker.
- The top 23 allergens were identified. Of those, 9 allergens were not included in the TT

Mucci et al. What Allergens Would You Miss? Utilization of T.R.U.E.® Test Versus Expanded Patch Test Panels for Allergic Contact Dermatitis. A 5-year, Multi-Center Review from Allergy Practices. JACI abstract VOLUME 129, ISSUE 2, SUPPLEMENT , AB35, FEBRUARY 01, 2012

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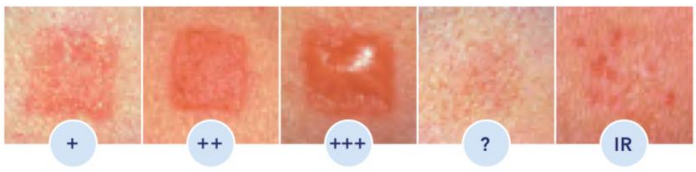


+ Weak Positive Reaction:
non-vesicular with erythema, infiltration, possibly papules

++ Strong Positive Reaction:
vesicular, erythema, infiltration, papules

+++ Extreme Positive Reaction:
bullous or ulcerative reaction

? Doubtful Reaction:
faint macular erythema only

IR Irritant Reaction:
Pustules as well as patchy follicular or homogeneous erythema without infiltrations are usually signs of irritation and do not indicate allergy. Itching is a subjective symptom that is expected to accompany a positive reaction.

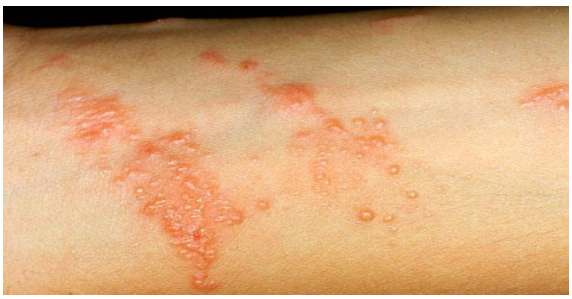
12

Finn Chambers

13

Plant - Toxicodendron

- Anacardiaceae family
- Toxicodendron means "poisonous tree".
  - common or northern poison ivy (*Toxicodendron radicans*),
  - western poison ivy (*Toxicodendron rydbergii*),
  - eastern poison oak (*Toxicodendron toxicarium*),
  - western poison oak (*Toxicodendron diversilobum*)
  - poison sumac (*Toxicodendron vernix*). Toxicodendron means "poisonous tree



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Plant

- Urushiol
  - Found in poison ivy, poison oak, and poison sumac.
  - 50% of people will react to poison ivy in nature
  - 75% will react to patch testing with urushiol.
  - 25 to 40 million Americans require medical treatment after exposure.

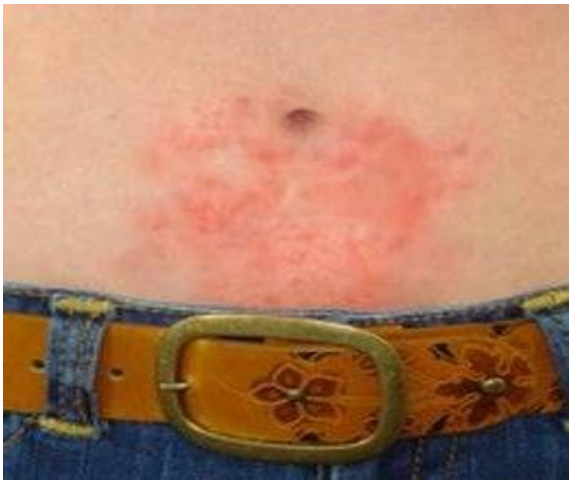
15

Metals

16

Nickel

- Jewelry, belt buckles etc.
- Ingestion of foods in highly allergic: chocolate, nuts, oats, green beans, peas, canned foods
- Implanted metal devices.



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Dimethylglyoxime Test (DMG)

- Few drops of 1% dimethylglyoxime in alcoholic solution and a few drops of 10% ammonium hydroxide solution to a test object and observing for the presence of a red/pink precipitate.

18

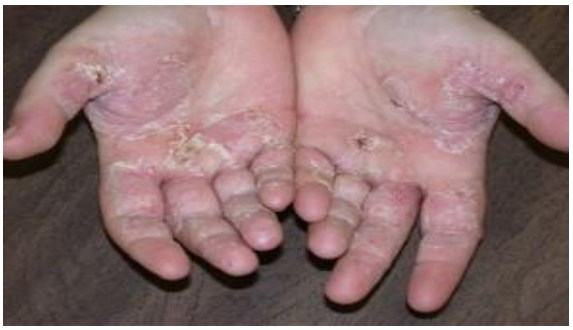
Cobalt

- Metals, cosmetics, especially eye makeup, and blue tattoo pigments.
- Surgical stainless steel and the cobalt-chrome-molybdenum alloys used in orthopedic implants have high cobalt content.
- Spot test
  - Disodium-1-nitroso-2-naphthol-3,6-disulfonate was able to identify cobalt release at 8.3 ppm.
  - Red/pink is positive, yellow (baseline color) is negative.

19

Chromium (potassium dichromate)

- Chromium is used in industry.
- Cement, leather tanning, paints), in various types of stainless steel.
- Green coloring agent in soaps, cosmetics, and tattoo pigments.



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Preservatives

21

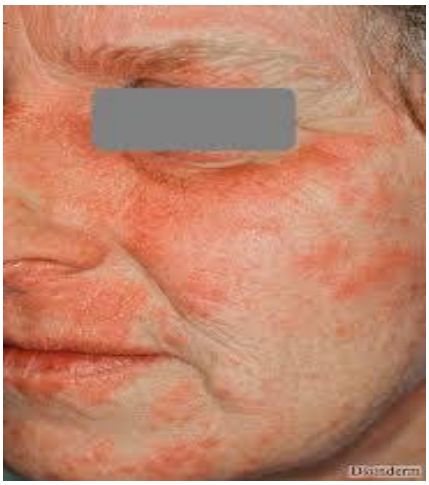
Formaldehyde

- Known human carcinogen.
- Not added to consumer products
- Many chemicals used as preservatives degrade over time and release formaldehyde into the product. Cross-reactions may occur between formaldehyde and all the formaldehyde releasers, which are allergens also in their undegraded state
- Nail polishes, makeup, body washes, deodorants, and shampoos, relaxers (hair straighteners).

22

Isothiazolinones

- Methylchloroisothiazolinone and methylisothiazolinone
  - Rates increasing to around 8% of patch test patients.
  - Wash-off personal care products, such as hair care products and body washes, moisturizing creams/lotions, pr emoistened toilet wipes, and laundry detergents.
  - Both together is called Kanthon CG.



23

Thimerosal

- **Thimerosal**
  - Mercurial antiseptic and antifungal
  - Widely used in the past as a preservative in topical preparations, cosmetics, injectable immunoglobulins, and vaccines.
- **Methylmercury** is the type of mercury found in certain kinds of fish. At high exposure levels methylmercury can be toxic to people.
- Thimerosal contains **ethylmercury**, which is cleared from the human body readily.
- No connection to autism. Hasn't been in vaccines since 2001.

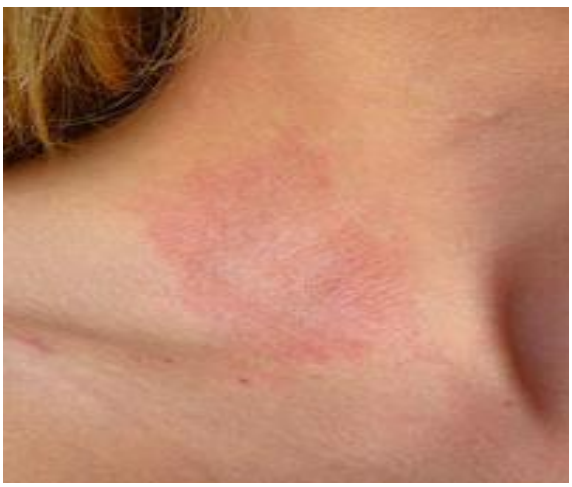
24

Fragrance

25

Fragrance

- Fragrance mix 1
  - cinnamic alcohol, cinnamic aldehyde, hydroxy citronellal, amyl cinnamaldehyde, geraniol, eugenol, isoeugenol, and oakmoss absolute)
- Fragrance mix 2
  - Lyral, Citral, citronellol, farnesol, coumarin, cinnamic aldehyde.
- *Myroxylon pereirae* (balsam of Peru)
- Can have masking agents even in "fragrance free" or unscented".
- Fragrance producers don't have to list specific ingredients.



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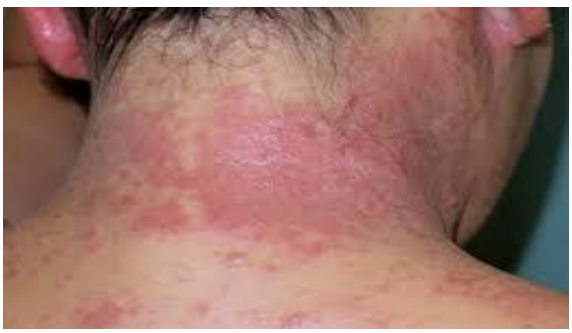
Hair products

27

P-phenylenediamine (PPD)

- Permanent hair dyes/black dye, henna tattoos.
- Also used in black rubbers, photographic developers, fabric dyes, epoxy resin curing agents, oils and greases, and gasoline.



28

Cocamidopropyl betaine

- Surfactant derived from coconut oil and dimethylaminopropylamine.
- "No More Tears" shampoo.
- Foaming agent in many wash-off personal care products.
- Shampoos, body washes, toothpastes), an antistatic agent in conditioners, and an emulsifier in cosmetics.

29

Propylene glycol

- Viscous, colorless, and virtually odorless alcohol.
- Vehicle, humectant (reduces moisture loss), and preservative.
- Topical steroid preparations to increase penetration, deodorant, personal lubricants, conduction gels.
- Can be irritant as well as allergic.

- Propylene glycol free:

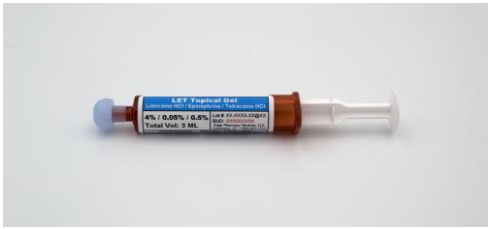
- Low:
- Desonide ointment
- hydrocortisone-17-butyrate lipid cream
- clocortolone cream
- triamcinolone spray

- High:
- halcinonide ointment
- fluocinonide oil
- clobetasol spray

30

Local anesthetics

- Particularly benzoic acid ester group (eg, benzocaine, procaine, tetracaine)
- OTC for itch/pain relief
- May cross react with para-aminobenzoic acid (PABA) derivatives such as p-phenylenediamine and PABA-based sunscreens.
- Local anesthetics from the amide group have lower rates of contact allergy (lidocaine).
- Caine Mix
  - Benzocaine, dibucaine hydrochloride, and tetracaine hydrochloride



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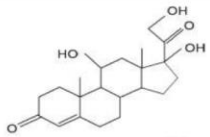
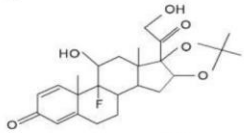
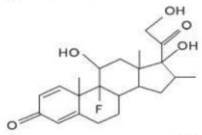
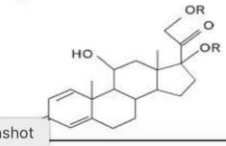
Antibiotics

- Neomycin
  - Often found in “triple antibiotic” or Neosporin.
  - May cross react with gentamicin or tobramycin
- Bacitracin is produced by the Tracey strain of *Bacillus subtilis.*
- Mupirocin does not cross react with bacitracin or neomycin.

32

Topical steroids

Class	Example	Glucocorticoid	Structure
A	Hydrocortisone type without substitution on the D-ring or C17 carbon chain, but including C17 and/or C21 acetate esters.	Hydrocortisone (acetate, succinate, phosphate) Hydrocortisone (acetate, succinate, phosphate) Methylprednisolone acetate (acetate, succinate, phosphate) Prednisolone Prednisolone acetate Tixocortol pivalate	
B	Triamcinolone acetonide type C16,17-*cis*, diol or ketal chain.	Amcinonide Budesonide Desonide Flunisolide Fluocinolone acetonide Fluocinomide Halcinonide Triamcinolone Triamcinolone acetonide	
C	Betamethasone type C16 alkyl substitution.	Betamethasone Desoxymethasone Dexamethasone Paramethasone Flucortolone	
D	Hydrocortisone-17-butyrate type C17 and/or C21 long-chain ester.	Beclomethasone dipropionate (D1) Betamethasone valerate (D1) Betamethasone dipropionate (D1) Clobethasone 17 butyrate (D1) Clobetasol 17 propyonate (D1) Fluticasone, Mometasone and Prednicarbate (D2) Hydrocortisone 17-butirate(D2) Hydrocortisone 17-propionate(D2) Methylprednisolone Aceponate (D2)	

Screenshot

33

Class “C” for contact

- Desoximetasone (Topicort)
- Clocortolone pivalate (Cloderm)

34

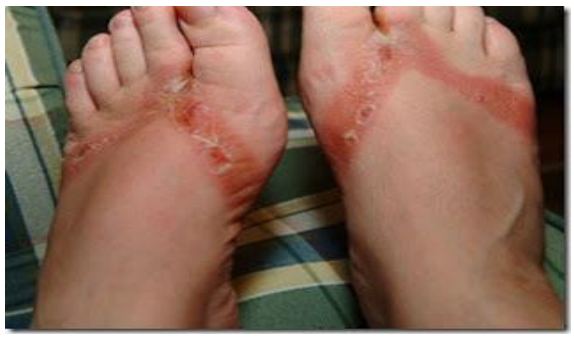
Propolis

- Produced by bees as an adhesive and sealant for small open spaces when building their hives.
- Contains approximately 180 different substances.
- Lip care products.
- May cross react with balsam of Peru, with which it shares more than 20 substances, and fragrances.
- Synthetic beeswax should not cross react.

35

Rubber accelerators

- Chemicals used to speed the polymerization process (vulcanization) in natural latex, synthetic latex, and nonlatex rubber products. T
-
- Thiurams, carbamates, and mercaptobenzothiazoles.
- Thioureas, which are used in the production of neoprene.
- Thiurams most commonly screened are tetramethylthiuram monosulfide, tetramethylthiuram disulfide, tetraethylthiuram disulfide, and dipentamethylene thiuram disulfide.
- Carbamates are commonly tested as a carba mix, which includes 1,3-diphenylguanidine, zinc dibutyl dithiocarbamate, and zinc diethyldithiocarbamate.



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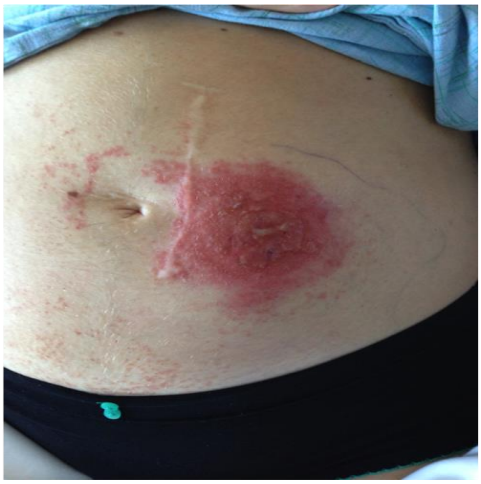
Adhesives

- **Colophony**
  - Rosin is derived from the sap of pine trees.
  - Adhesive bandages, plasticizers, fabrics, asphalt/cements, chewing gum, leather cleaners, photo paper coating, mascaras, and newsprint.
- **Phenol-formaldehyde resins**
  - Neoprene sleeves/braces, wetsuits, glued leather.
- **Epoxy resin**
  - Sporting goods, vehicle parts.



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Acrylates

- Ethyl acrylate and methyl methacrylate
  - Dentures, hearing aids, artificial nail products, dental fillings, glues, and inks.
- Methyl methacrylate
  - component of orthopedic bone cement, medical adhesives, corneal contact lenses, intraocular lenses, and hearing aids.

38

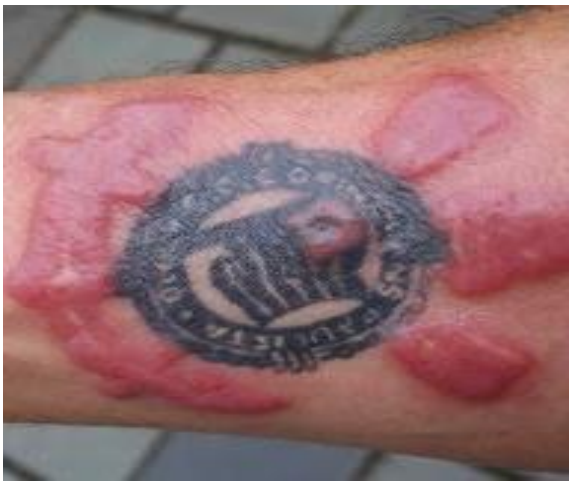
Dyes

- **Disperse blue 106 and 124**
  - Typically involves sites that are in close contact with clothing (axillae, spares vault or thighs) and is worsened by friction and sweating.
  - Disposable diapers.
- **Ethylene urea melamine formaldehyde, dimethylol dihydroxyethyleneurea**
  - Permanent press (prevent wrinkling and shrinkage)

39

Tattoo ink

- Red
  - Mercury sulfide (cinnabar)
  - Ferric hydrate (sienna)
  - Sandalwood
  - Brazilwood
- Black
  - Carbon (india ink)
  - Iron oxide
  - Logwood
- Brown
  - Ferric oxide
- Blue
  - Cobalt aluminate
- Green
  - Chromic oxide
  - Lead chromate
  - Phthalocyanine
- Yellow
  - Cadmium sulfide
- Purple
  - Manganese
  - Aluminum
- White
  - Titanium oxide
  - Zinc oxide



40

Other tattoo reactions

- Skin infection
  - Impetigo
  - Cellulitis
  - HSV
  - Warts
  - Atypical mycobacteria (photo)
  - Serious blood borne (HIV, hepatitis)
- Photo-aggravated
  - Cadmium (yellow)
- Granulomatous
- Lichenoid
- Pseudolymphomatous
  - Plum to red colored nodules and plaques.
- MRI burns from iron oxide (eyebrows)

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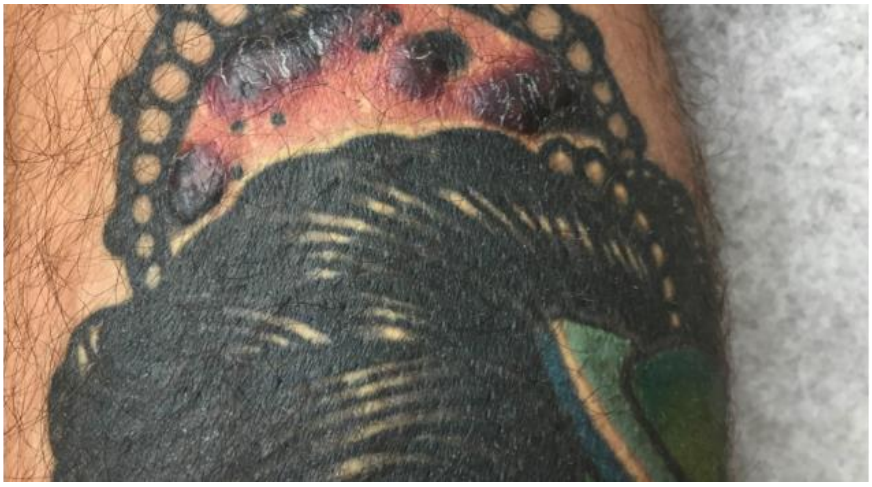
Granulomatous



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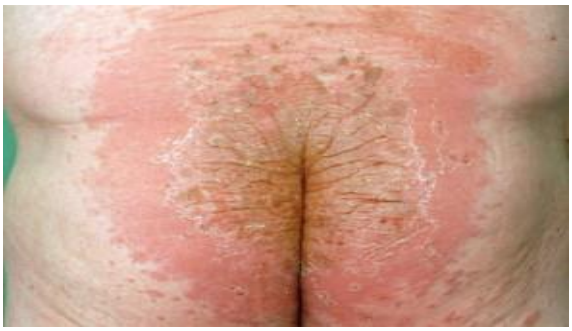
Dimethyl fumarate

- Used for antifungal (preventing mold) properties for furniture or shoes.
- "Sofa dermatitis."
- Saches are stapled to underside of furniture.



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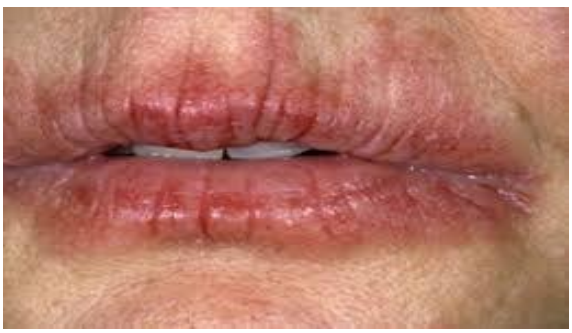
Lanolin

- Wool alcohol.
- Produced by sheep oil glands to repel water.
- Lip products.



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Allergens Of The Year (American Contact Dermatitis Society)

- 2023 - Lanolin
- 2022 – Aluminum
  - Antiperspirants, adjuvants
- 2021 - Acetophenone azine
  - shin pads and footwear containing the foam elastomer ethyl vinyl acetate
- 2020 – Isobornyl Acrylate
  - – adhesive in medical devices such as diabetic pumps.
- 2019 Parabens (Non) Allergen
  - most common preservative but least likely to cause allergic contact dermatitis.
- 2018 – Propylene Glycol
- 2017 – Alkyl Glucoside
  - surfactant in cosemtics.
- 2016 – Cobalt
- 2015 – Formaldehyde
- 2014 – Benzophenones
  - fragrance enhancer (prolongs fragrances
- 2013 – Methylisothiazolinone
- 2012 – Acrylate
- 2011 – Dimethyl fumarate
- 2010 – Neomycin
- 2009 – Mixed dialkyl thiourea
- 2008 – Nickel
- 2007 – Fragrance
- 2006 – p-Phenylenediamine
- 2005 – Corticosteroids
- 2004 – Cocamidopropyl betaine
- 2003 – Bacitracin
- 2002 – Thimerosal (highlighted for not being a significant issue).
- 2001 – Gold
- 2000 – Disperse Blue Dyes

45

Use testing

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Extended Panels

- North American 80
- Bakery series
- Cosmetic series
- Cutaneous adverse drug reaction series
- Corticosteroid series
- Dental materials – patients
- Dental materials – staff
- Dental screening series
- Epoxy series
- European series
- Fragrance series
- Hairdressing series
- Isocyanate series
- International series
- Leg ulcer series
- Acrylate series
- Metal series
- Acrylate nail series
- Acrylate printing series
- Oil and cooling fluid series
- Plastic and glue series
- Plant series
- Rubber additive series
- Shoe series
- Sunscreen series
- Textile colors and finish series

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Top 5 Clinical Pearls

- 1. Contact allergy is not mutually exclusive.
- 2. Avoid vicious cycle: Topical steroid classes and lanolin on the lips.
- 3. “C” for “C”ontact allergy to steroids.
- 4. Be aware of what is commonly tested for and what is not.
- 5. Consider use testing, avoidance and reintroduction.

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

CVID- Evaluation and Management

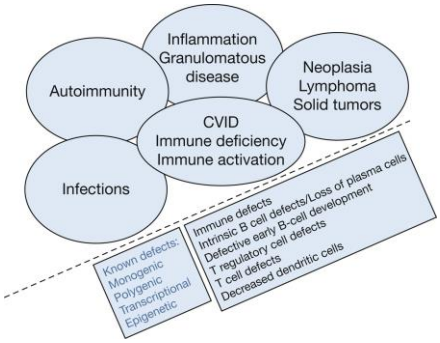
Presented by:

Kelli Williams, MD, MPH

Friday, June 23, 2023

8:45 a.m. – 9:30 a.m.

Diagnosis and Management of CVID



Kelli W. Williams, M.D., M.P.H.
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Disclosures

- Advisory Board/Steering Committee Participant
  - Horizon Therapeutics, Pharming Healthcare, Enzyvant, Pfizer, Kenota Health
- Consultant for GSK (ended)
- Industry Sponsored Clinical Trial Investigator
  - Regeneron (ended), GSK, and ADMA
- *Clinical recommendations are evidence-based and free of commercial bias*

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Learning Objectives

- To know diagnostic criteria for CVID
- To recognize common infectious and non-infectious manifestations of CVID
- To understand key management and surveillance recommendations for CVID patients

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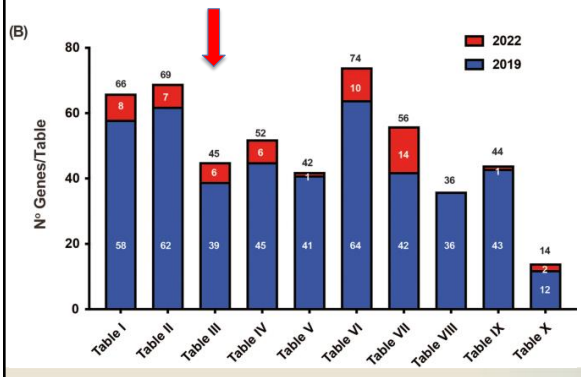
Table III: Predominantly Antibody Deficiencies

IUIS Immunology without Borders
International Union of Immunological Societies

- >50% of all IEIs



I. Combined/T-B deficiencies
II. CID + syndromic features
III. Predominantly antibody
IV. Immune dysregulation
V. Phagocytic defects
VI. Intrinsic or Innate
VII. Autoinflammatory disorders
VIII. Complement deficiency
IX. Bone marrow failure
X. Phenocopies of PID

Tangye et al. *JCI* 2022

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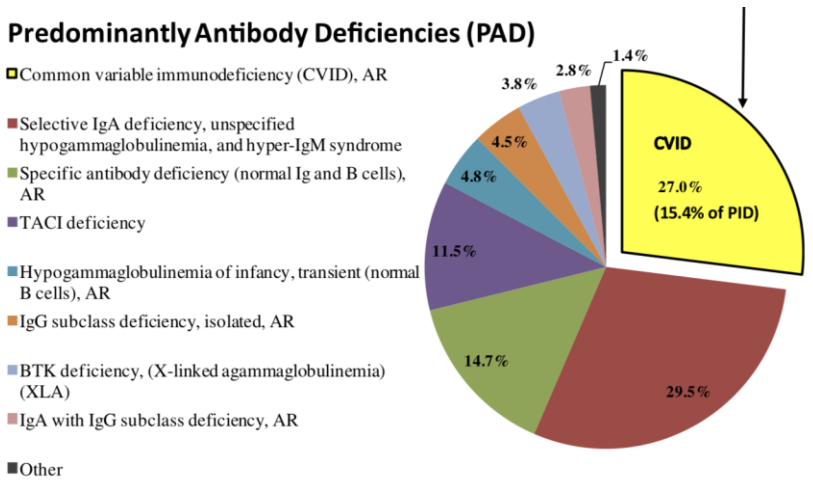
Predominantly Antibody Deficiencies (PAD)



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Gerber WA. *Curr Pediatr Rep* 2019.

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Common Variable Immunodeficiency (CVID)

- CVID is a severe form of primary antibody deficiency that occurs in roughly 1:25,000 persons
- CVID has heterogenous phenotypes and etiologies
- Usually diagnosed in the 3rd decade of life or later
- Usually significant delay between onset of symptoms and diagnosis

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Bonilla et al. *JACI In Practice* 2016.

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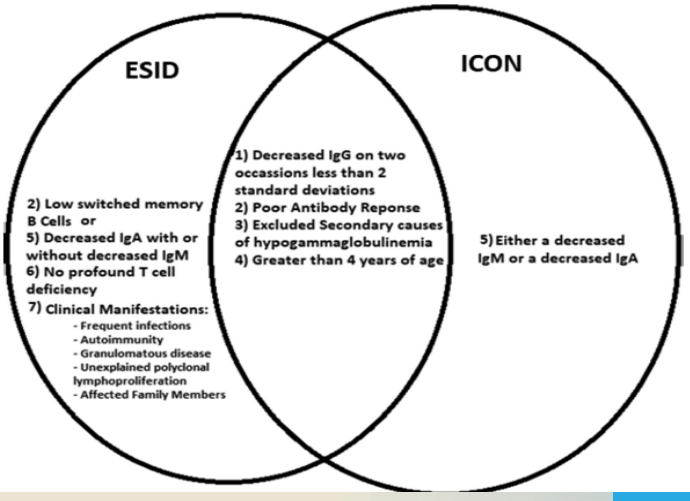
CVID Diagnostic Criteria



Changing What's Possible

Lee et al. *Ann Allergy Asthma Immunol* 2021.

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CVID: ICON 2016 Criteria

- Must have ≥1 clinical manifestation of CVID
  - Infections, autoimmunity, lymphoproliferation
- Must have hypogammaglobulinemia
  - Marked decrease of IgG (at least 2 SD below the mean for age) in at least 2 measurements >3 weeks apart, or IgG <300 mg/dL
- Must have marked decrease in IgA or IgM
- Must have absent isohemagglutinins and/or poor antibody response to vaccines
- Must be ≥4 years of age
- Other causes of hypogam must be excluded

Changing What's Possible

Bonilla et al. *JACI In Practice* 2016.

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ICON 2016 Genetics

- Genetics to investigate monogenetic forms of CVID are NOT required for diagnosis and management in most of the patients
  - Especially those who present with infections only without evidence of immune dysregulation, autoimmunity, malignancy, or other complications
- Specific therapies may be available for some monogenetic forms of CVID

Changing What's Possible

Bonilla et al. *JACI In Practice* 2016.

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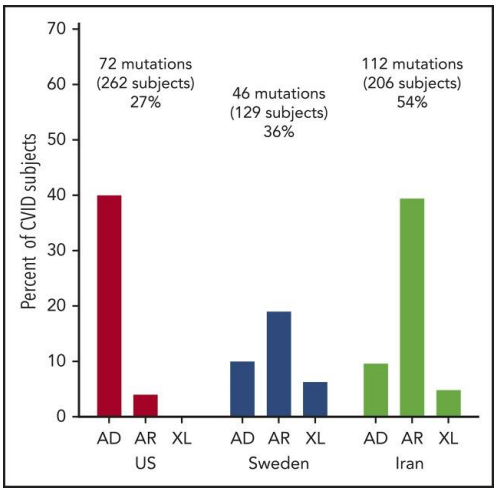
Genetics of CVID



- In the US and Sweden, those with infections only, were less frequently identified to have a genetic cause of their CVID
- In Iran, rates were comparable among those with infections only and non-infectious complications

Changing What's Possible

Abolhassani et al. *Blood* 2020; 135: 656-667.

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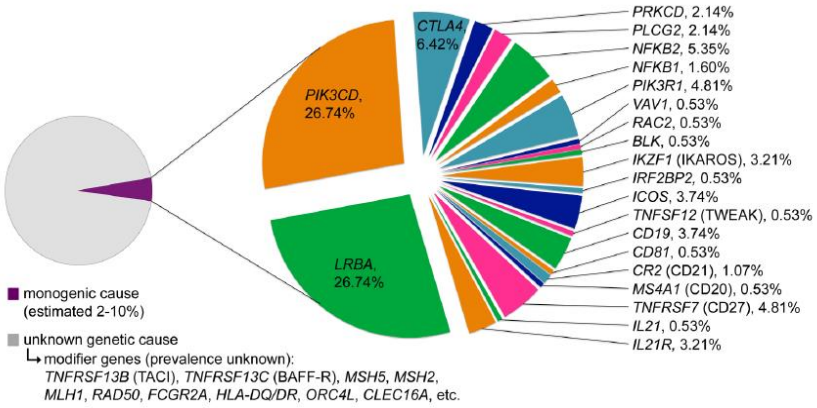
Genetics of CVID



Changing What's Possible

Bogaert et al. *J Med Genet* 2016; 53: 575-590.

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CVID Case

- **HPI: 64 yo Caucasian male referred for hypogammaglobulinemia**

- Pertinent medical history
  - Age 40 – post-viral ITP at age 40, resolved after high dose IVIG
  - Age 43 – Hashimoto's thyroiditis
  - Age 51 – developed lymphadenopathy and ultimately was diagnosed with Burkitt's lymphoma at age 51
    - Treated with R-CHOP
  - Age 52 – Recurrence of lymphadenopathy, found to have granulomatous LN
    - Reactivation of Histoplasmosis
    - Also diagnosed with CVID and started on IVIG q12 wks

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Case

- Pertinent Lab Evaluation (done 12 weeks after IVIG)
  - WBC 5.5k, Hgb 13.6, Plt 164, ANC 2380, ALC 2440
  - IgG 814, IgA 36, IgM 108, IgE <25
  - IgG Diphtheria 0.4, Tetanus 2.4, S. Pneumo 18/23 protective
  - Normal CD3, CD4, CD8, CD19 (281), NK cells
- Close observation

Case

- A year goes by and he remains clinically well, but his IgG is trending down
  - 793 → 574 → 521 → 381 → 289 → 367
  - Now with poor specific antibody production → CVID
  - No infections
- Continued observation
- Develops axillary lymphadenopathy
  - Florid follicular hyperplasia with + EBER
  - Flow not consistent with malignancy
  - PET scan with diffuse hypermetabolic activity within the enlarged spleen, scattered hypermetabolic LNs in the neck, chest and abdomen – some improved, some increased

CVID Complications

Table 2. Summary of complications and incidence*

	Numbers	Percentage
Infections	428	90
Autoimmunity	97	25
Lung impairment	88	24
Gastrointestinal disease	51	14
Malabsorption	31	5
Lymphoid malignancy	36	10
Previous splenectomy	31	8
Granulomatous disease	31	8
Other cancers	21	6

*On the basis of on a cohort of 476 subjects.

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Cunningham-Rundles, C. *Blood* 2010; 116: 7.

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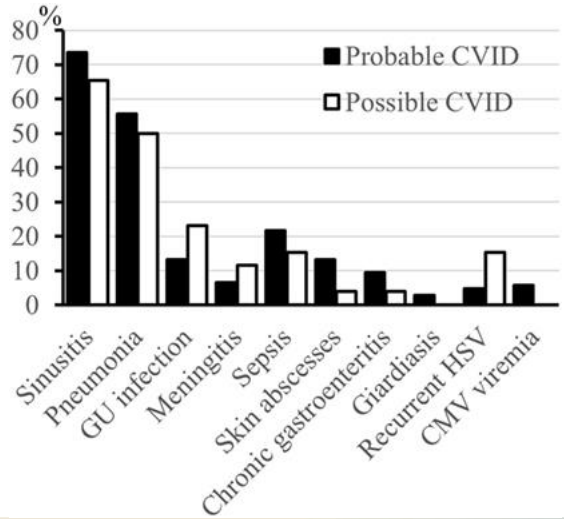
CVID: Infections



Changing What's Possible

Selenius et al. *Frontiers Immunol* 2017.

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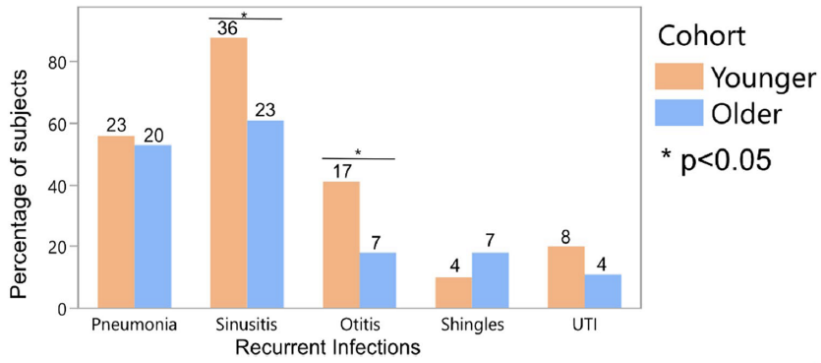
CVID: Infections

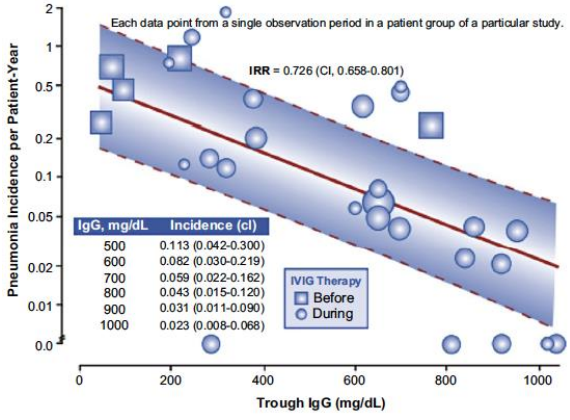


Changing What's Possible

Fortier et al. *J Clin Immunol* 2022.

17

Impact of IgG Trough on Pneumonias

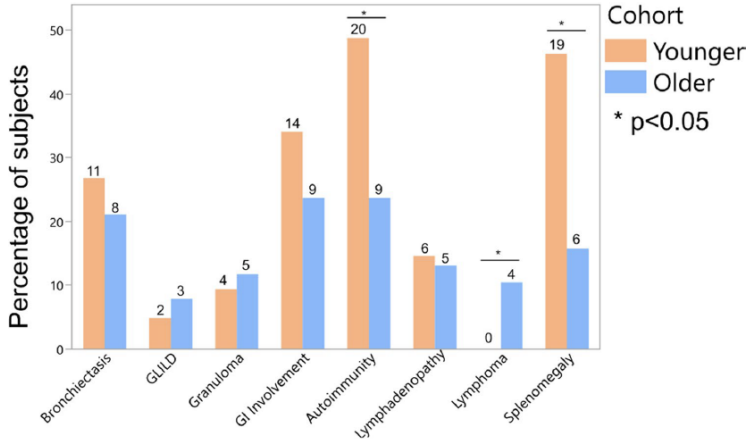


Changing What's Possible

Orange et al. *Clinical Immunol* 2010.

18

CVID: Noninfectious Manifestations



Changing What's Possible

Fortier et al. *J Clin Immunol* 2022.

19

Noninfectious Manifestations

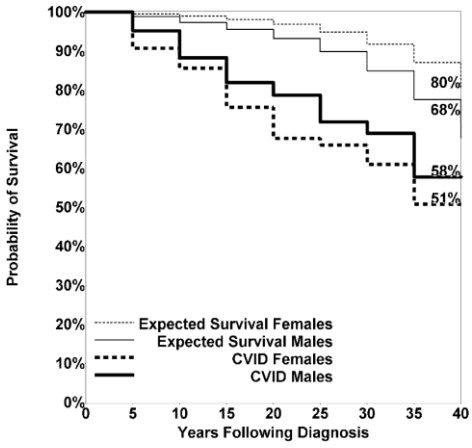
- Occur in > 67% of CVID patients
- May be first and/or only presenting clinical symptom
- Typically not improved by Ig replacement
- For patients on Ig, noninfectious manifestations are the leading cause of morbidity and mortality in CVID

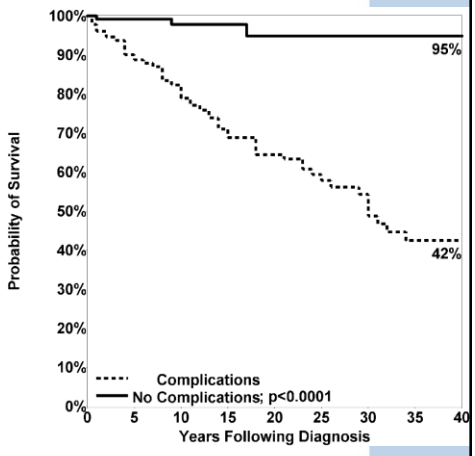
Changing What's Possible

Resnick et al. *Blood* 2012; 119: 1650.

20

CVID Decreases Survival





Changing What's Possible

Resnick et al. *Blood* 2012; 119: 1650.

21

Laboratory Abnormalities in CVID

Table 3
Cluster of Differentiation Markers Within Available B Cell Panels

Lymphocytes	Markers	Relevance to CVID
T cells	CD4	CD4+ or CD8+ T cells may be reduced in CVID, particularly CVIDc.
	CD8	
	CD45RA	Reduction of CD45RA+ naive T cells and increased proportion of CD45RO+ T cells are frequently found in CVIDc.
	CD45RO	
B cells	CD19	CVIDc is typically characterized by low isotype-switched memory B cells (CD19+, CD27+).
	CD27	
	$CD21^{low}$	CVIDc is typically characterized by expansion of $CD21^{low}$ B cells in the blood.

Abbreviation: CVIDc, common variable immunodeficiency with noninfectious complications.

- Reduced class switched memory B cells are a marker of CVID
- $CD21^{low}$ B cells are a marker of autoimmunity and splenomegaly
- Although CVID is generally a humoral immunodeficiency, there is T cell involvement in ~50% of patients

Changing What's Possible

Lee et al. *Ann Allergy Asthma Immunol* 2021.
Bonilla et al. *JACI In Practice* 2016.

22

Autoimmunity in CVID

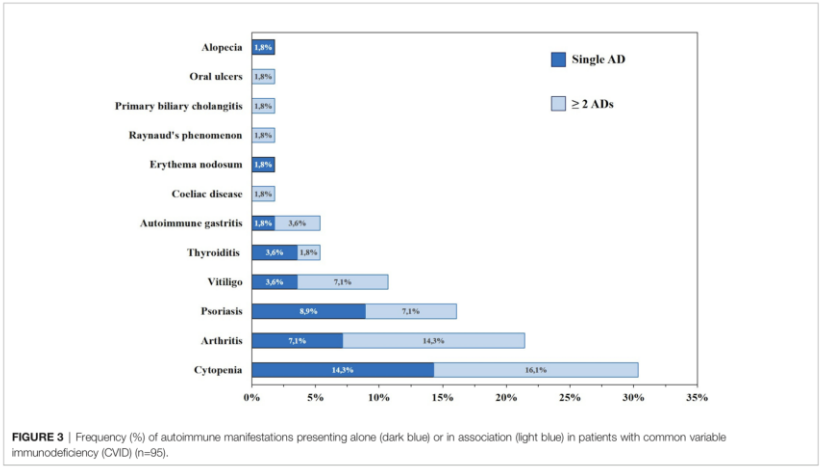


FIGURE 3 | Frequency (%) of autoimmune manifestations presenting alone (dark blue) or in association (light blue) in patients with common variable immunodeficiency (CVID) (n=95).

Changing What's Possible

Mormile et al. *Front Immunol* 2021; 12: 652.

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Autoimmunity in CVID

Autoimmunity	134	28.6
ITP	67	14.2
AIHA	33	7
Evans syndrome	20	4.2
Rheumatoid arthritis	15	3.2
Anti-IgA antibody	7	1.5
Alopecia	5	1.1
Neutropenia, pernicious anemia, anticardiolipin antibody, antiphospholipid syndrome, diabetes mellitus, juvenile rheumatoid arthritis, uveitis, multiple sclerosis, systemic lupus erythematosis, autoimmune thyroid disease, lichen planus, vasculitis, vitiligo, psoriasis	< 5	< 1

- First line treatment for ITP: IVIG + steroids
- Second line treatment for ITP: weekly rituximab (375mg/m2) for 4 weeks

Changing What's Possible

Resnick et al. *Blood* 2012; 119: 1650.

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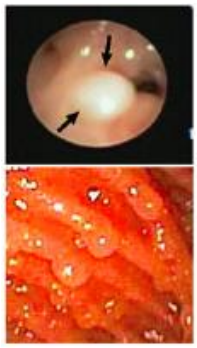
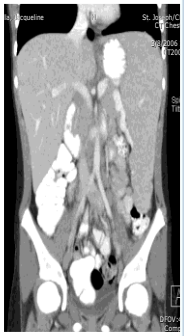
Lymphoproliferation in CVID

- Chronic benign lymphadenopathy, hepatomegaly, splenomegaly, organ-specific lymphoid hyperplasia
- Excisional LN biopsy is

Preferred, not FNA, not

PET-CT





Changing What's Possible

Selenius et al. *Frontiers Immunol* 2017.
Lee et al. *Ann Allergy Asthma Immunol* 2021.

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Granulomas in CVID

- Reported in 8-22% of CVID patients
- Commonly present in the lungs, lymph nodes, spleen, liver, skin, brain, kidney
- Non-caseating granulomas → often diagnosed as sarcoidosis if early in presentation
- Need to biopsy for diagnosis

Changing What's Possible

Bonilla et al. *JACI In Practice* 2016.

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GLILD in CVID

- Granulomatous and lymphocytic interstitial lung disease (GLILD) affects 20% to 30% of patients with CVID
- Patients may develop respiratory symptoms or be ASYMPTOMATIC
- GLILD is associated with increased mortality
- GLILD is associated with the comorbidities of splenomegaly, lymphadenopathy, autoimmune cytopenias, and NRH

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Bonilla et al. *JACI In Practice* 2016.
Verbsky et al. *JACI* 2021.

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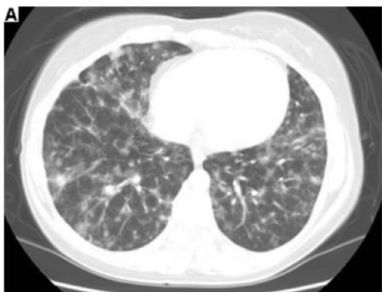
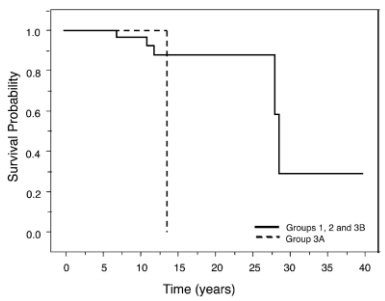
GLILD in CVID





- Diagnosis is surgical lung biopsy (wedge) or transbronchial cryobiopsy
- Stain for T & B cells → peribronchiolar/interstitial lymphocytic infiltration (CD4+ predominance), granulomas, organizing pneumonia

Changing What's Possible

Bates et al. *JACI* 2004.

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PFTs in GLILD

TABLE 4 | Lung function parameters.

	Controls $n = 125$ Median (IQR)	GLILD $n = 47$ Median (IQR)	uILD $n = 26$ Median (IQR)	*p value* (GLILD vs. ctrls)	*p value* (uILD vs. GLILD)	*p value* (uILD vs. ctrls)
FEV1 (% of predicted)	102 (89–111)	88 (72–105)	103 (89–110)	**0.02**	**0.03**	0.94
				0.006	0.15	0.35
FVC (% of predicted)	104 (92–116)	88 (72–103)	104 (93–113)	**<0.001**	**0.01**	0.72
				<0.001	**0.01**	0.40
TLC (% of predicted)	102 (94–108)	87 (75–102)	93 (87–104)	**<0.001**	0.32	**0.03**
				0.001	0.29	**0.05**
DLCO (% of predicted)	83 (75–97)	61 (52–80)	73 (65–86)	**<0.001**	**0.008**	**0.02**
				<0.001	**0.02**	0.07

- Patients with GLILD typically have lower TLC and DLCO
- May also have restrictive pattern on FVL

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Bates et al. *JACI* 2004.
Cinetto et al. *Front Immunol* 2021.

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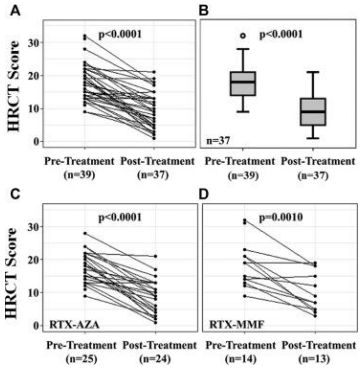
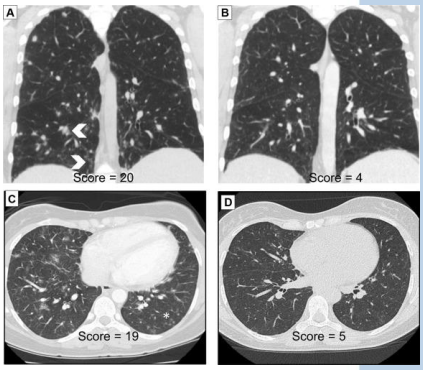
Treatment of GLILD





- Weekly rituximab (375mg/m2) for 4 weeks q6 months for 3-4 courses
- Azathioprine (1-2mg/kg/day) or MMF (250-100mg BID)

Changing What's Possible

Verbsky et al. *JACI* 2021.

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Gastrointestinal Disease in CVID

- Most common symptoms include chronic watery diarrhea, gas, bloating, weight loss
- Can also have chronic norovirus, *giardia*, *Campylobacter*, *C. diff*
- Pathology may show duodenal villous atrophy, intraepithelial lymphocytosis, lymphoid aggregates, crypt distortion, and absent/minimal plasma cells

Changing What's Possible

Agarwal et al. *JACI* 2009; 124: 658.

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Gastrointestinal Disease in CVID

Gastrointestinal disease	73	15.4
Malabsorption	28	5.9
Inflammatory bowel disease (Crohn disease, ulcerative colitis, ulcerative proctitis)	20	4.2
Chronic diarrhea	9	1.9
Idiopathic mucosal inflammation	6	1.3
Nodular lymphoid hyperplasia	5	1.1
Gastrointestinal bleeding, irritable bowel syndrome, partial gastrectomy, diverticulitis, esophagitis	1	< 1

Changing What's Possible

Resnick et al. *Blood* 2012; 119: 1650.

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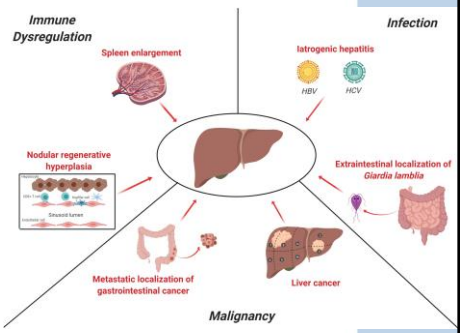
Liver Disease in CVID

- Cirrhosis
- Portal hypertension
- Hepatitis
- Liver granulomas
- Hepatic encephalopathy
- Hepatopulmonary syndrome
- Nodular regenerative hyperplasia

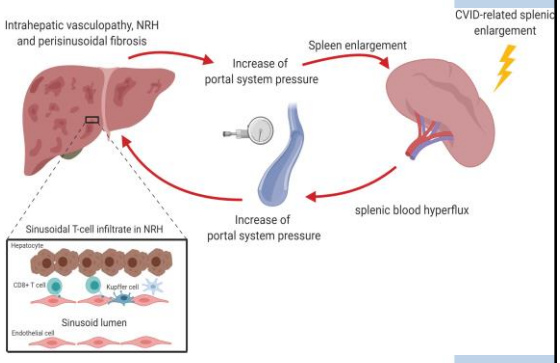


Changing What's Possible

Lee et al. *Ann Allergy Asthma Immunol* 2021.
Resnick et al. *Blood* 2012; 119: 1650.

NRH in CVID

- Most typical liver involvement in CVID
- Results from intra-hepatic vasculopathy that causes hepatocyte injury and regeneration → nodules compress the sinusoids and portal and central veins

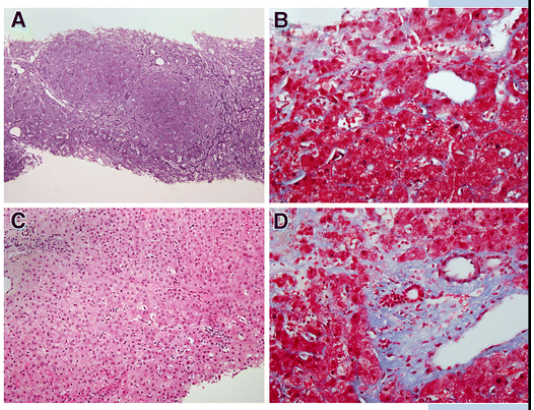


Changing What's Possible

Lee et al. *Ann Allergy Asthma Immunol* 2021.
Pecoraro et al. *Front Immunol* 2020.

NRH in CVID

- Histopathologic diagnosis – you MUST biopsy
- Get reticulin staining to see nodularity
- Alk Phos and GGT are usually increased
- Liver will be stiff on elastography



Changing What's Possible

Fuss et al. *J Clin Immunol* 2013.

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Malignancy in CVID

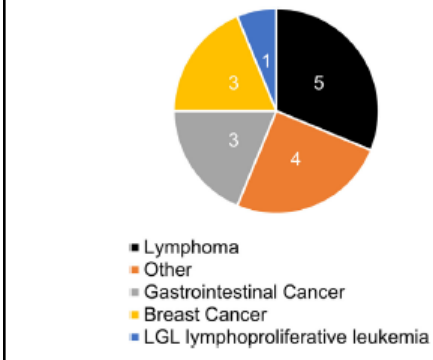

FIGURE 4 | Malignancies (%) in probable CVID patients. Other four cancers include one cervical cancer and one renal carcinoma, one melanoma, and one myeloid sarcoma. LGL, large granular lymphocytic.

- Non-Hodgkins lymphomas are the most common hematologic malignancy in CVID
- Lymphoma is associated with increased mortality

Changing What's Possible

Selenius et al. *Frontiers Immunol* 2017.
Lee et al. *Ann Allergy Asthma Immunol* 2021.

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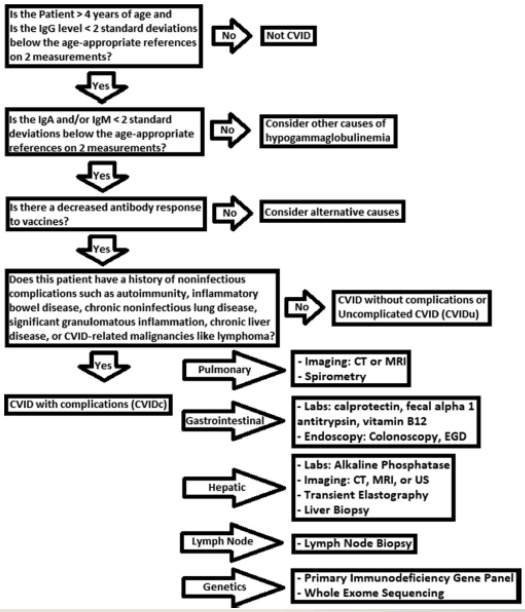

Changing What's Possible

Lee et al. *Ann Allergy Asthma Immunol* 2021.

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Managing CVID

- At baseline evaluation, all should get:
  - CBC with diff, CMP, Serum Immunoglobulins, usually SPEP +/- UPEP
  - HIV PCR, Hep B serologies, Hep C PCR
  - Lymphocyte subsets (T, B, NK)
  - B cell subsets
  - Full spirometry (including diffusion capacity in adults)
  - Chest CT (or MRI)
  - Abdominal imaging (ultrasound or CT)

Changing What's Possible

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Managing CVID

- At least once a year*, all should get:
  - Vital signs including height and weight
  - Physical exam including detailed LN, spleen, liver, and skin exam
  - CBC with diff, CMP, IgG (may want other Igs)
  - Full spirometry (including diffusion capacity in adults)
  - Abdominal imaging (ultrasound)

* If unstable or symptomatic, q3-6 months

Changing What's Possible

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Managing CVID

- As needed, based on symptoms:
  - CXR or repeat Chest CT
  - Referral to subspecialists → commonly GI including hepatology, Heme/Onc, Pulm, Derm, Rheum (Neuro, Endo)
    - Low threshold for colonoscopy, UGI, liver biopsy, LN biopsy
    - Liver elastography
  - PET scan for lymphoproliferation changes
  - Bone densitometry

Changing What's Possible

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Back to Case

Recap: 64 yo M with history of Burkitt's lymphoma s/p rituximab, now with CVID and benign lymphadenopathy

Next Gen Sequencing IEI panel identified:

One Pathogenic variant identified in RAG1. RAG1 is associated with autosomal recessive severe combined immunodeficiency.

Additional Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
RAG1	c.2689C>T (p.Arg897*)	heterozygous	PATHOGENIC
AP3D1	c.2657_2668del (p.Ala886_Pro889del)	heterozygous	Uncertain Significance
CARD11	c.3145-3C>T (Intronic)	heterozygous	Uncertain Significance
DUOX2	c.4273C>G (p.Gln1425Glu)	heterozygous	Uncertain Significance
JAK2	Gain (Exons 23-25)	copy number = 3	Uncertain Significance

Changing What's Possible

41

Back to Case: Hypomorphic RAG1

Additional Laboratory Evaluation:

- TCRvB spectratyping sent with oligoclonal T cells
- TCRVa7.2+ T cells (0.35%) and of TCRVa7.2+CD161+ MAIT cells (0.18%) consistent with values found in RAG mutant patients
- WGS and Sanger Sequencing ordered to look for another RAG1 variant

Changing What's Possible

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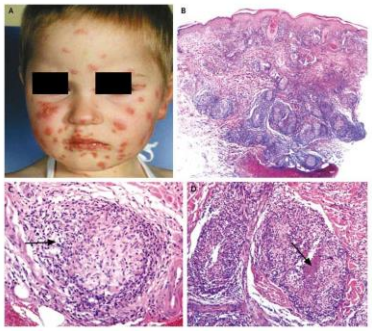
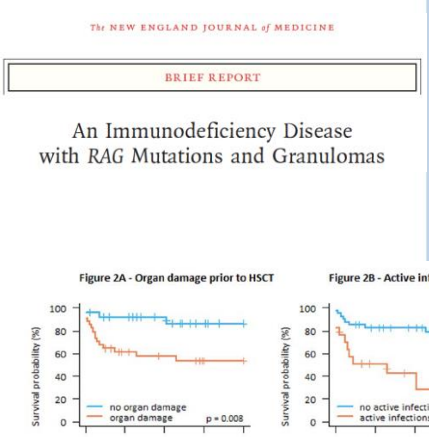
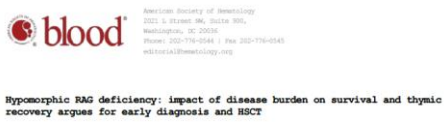
Back to Case: Hypomorphic RAG1







Hypomorphic RAG deficiency: impact of disease burden on survival and thymic recovery argues for early diagnosis and HSCT

Changing What's Possible

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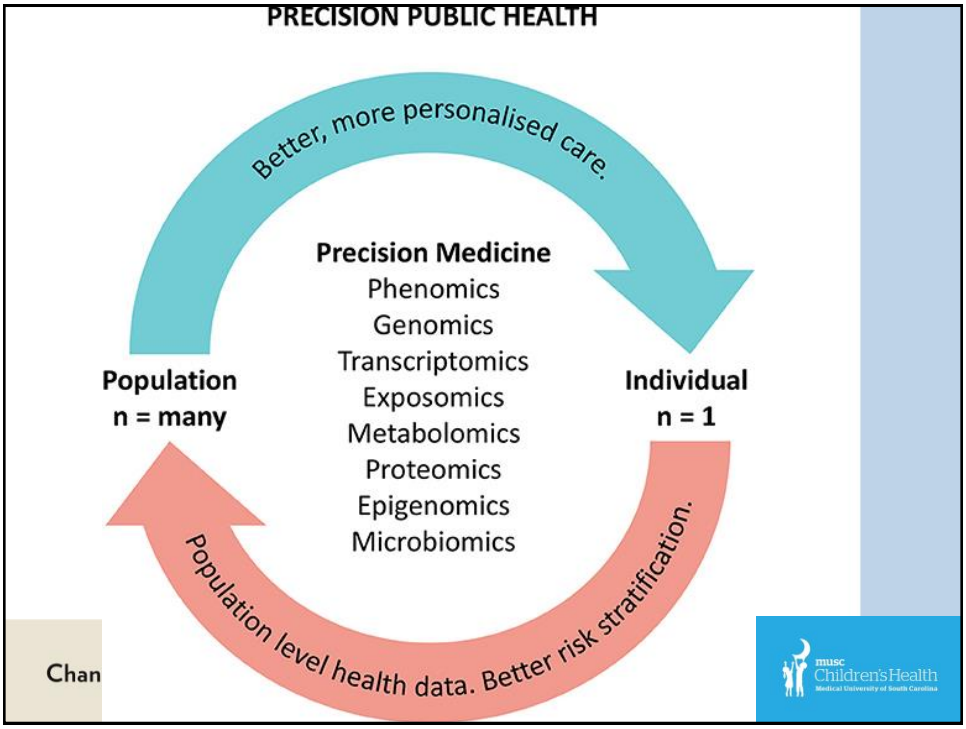

Chan

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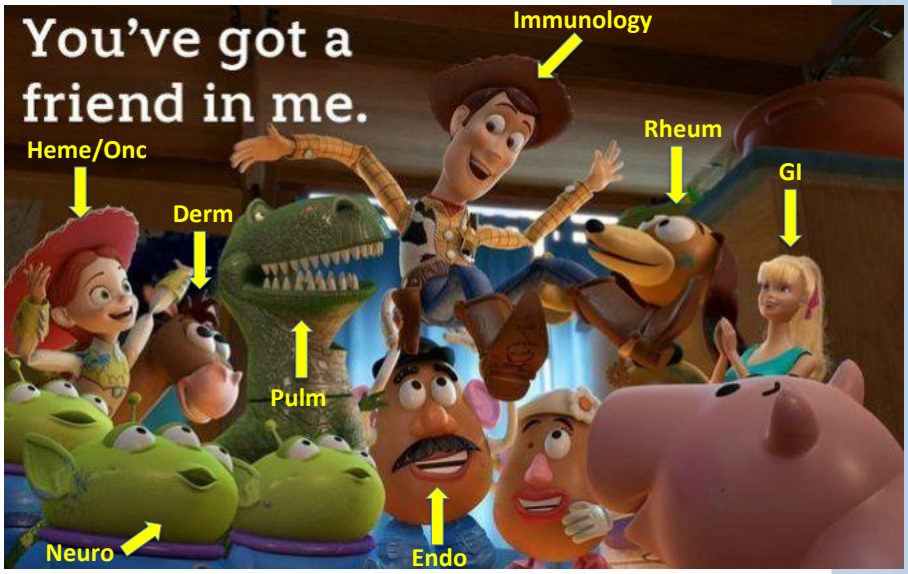
CVID Take Aways

- Let the patient's phenotype guide you
- Infections are easy enough to manage and prevent, but the non-infectious manifestations can be challenging and often will need immunomodulators
- Have a low threshold for ordering genetics
  - Genetics can change your management!



PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Diagnosing and Managing Anaphylaxis in 2023

Presented by:

Marcus Shaker, MD, MS, FAAP, FAAAAI, FACAAI

Friday, June 23, 2023

9:30 a.m. – 10:15 a.m.

Diagnosing and Managing Anaphylaxis in 2023

New Discoveries Meet Time Tested Paradigms of Care

Marcus Shaker, MD, MS
Professor of Pediatric and Medicine
Dartmouth Geisel School of Medicine

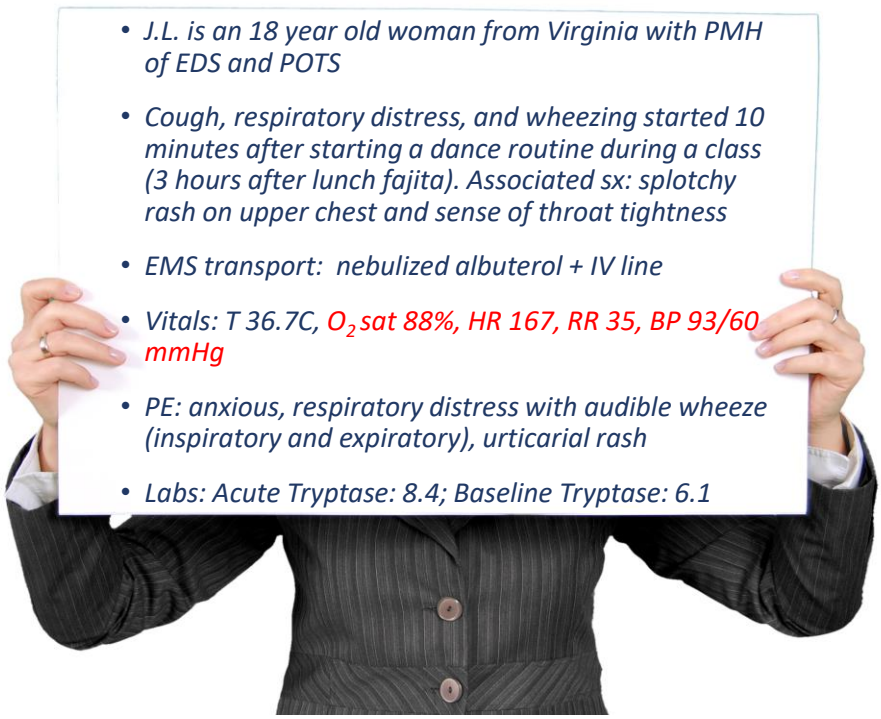
1

Learning Objectives

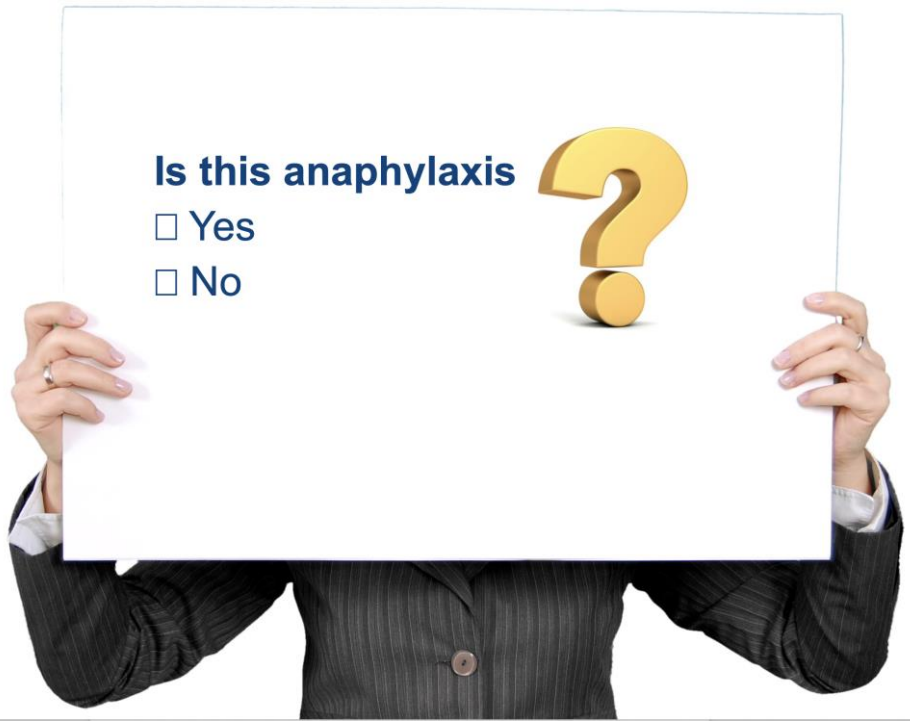
Upon completion of this activity, participants should be able to:

- **Compare and contrast diagnostic criteria for anaphylaxis**
- **Discuss common causes & subsets of anaphylaxis**
- **Formulate an approach to the evaluation of an elevated serum tryptase**
- **Incorporate anaphylaxis management strategies into practice**

2


• J.L. is an 18 year old woman from Virginia with PMH of EDS and POTS
• Cough, respiratory distress, and wheezing started 10 minutes after starting a dance routine during a class (3 hours after lunch fajita). Associated sx: splotchy rash on upper chest and sense of throat tightness
• EMS transport: nebulized albuterol + IV line
• Vitals: T 36.7C, O_2 sat 88%, HR 167, RR 35, BP 93/60 mmHg
• PE: anxious, respiratory distress with audible wheeze (inspiratory and expiratory), urticarial rash
• Labs: Acute Tryptase: 8.4; Baseline Tryptase: 6.1

3

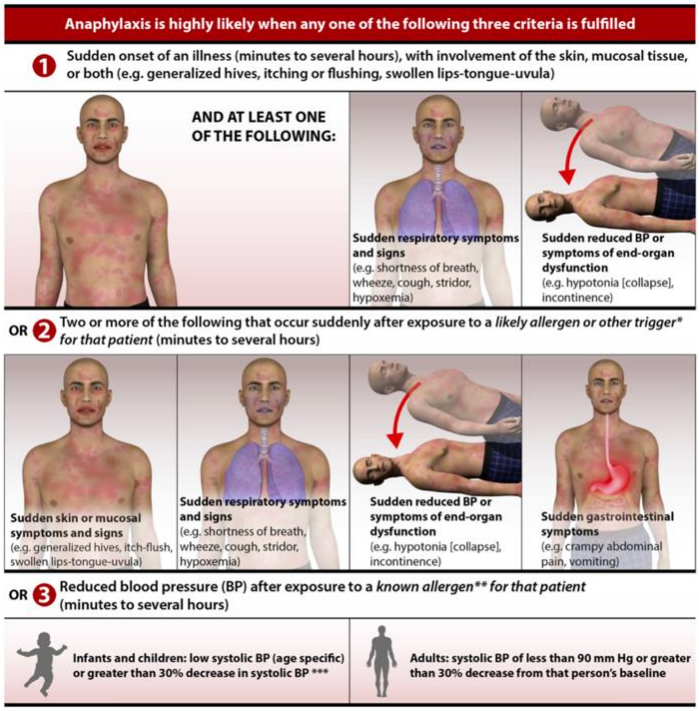

Is this anaphylaxis
☐ Yes
☐ No

4

Anaphylaxis

- An acute, potentially life-threatening systemic allergic reaction
- Diagnostic criteria are not perfect and fulfilling diagnostic criteria are not required for epinephrine use to treat an allergic reaction.
- Lifetime prevalence: 1.6% - 5.1%

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020



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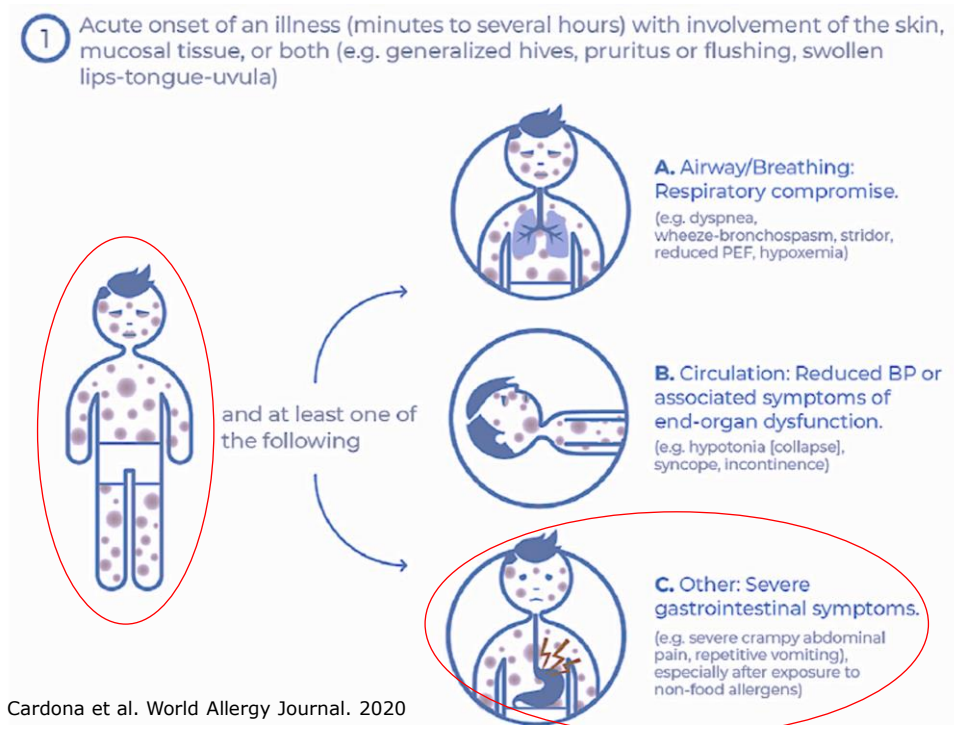
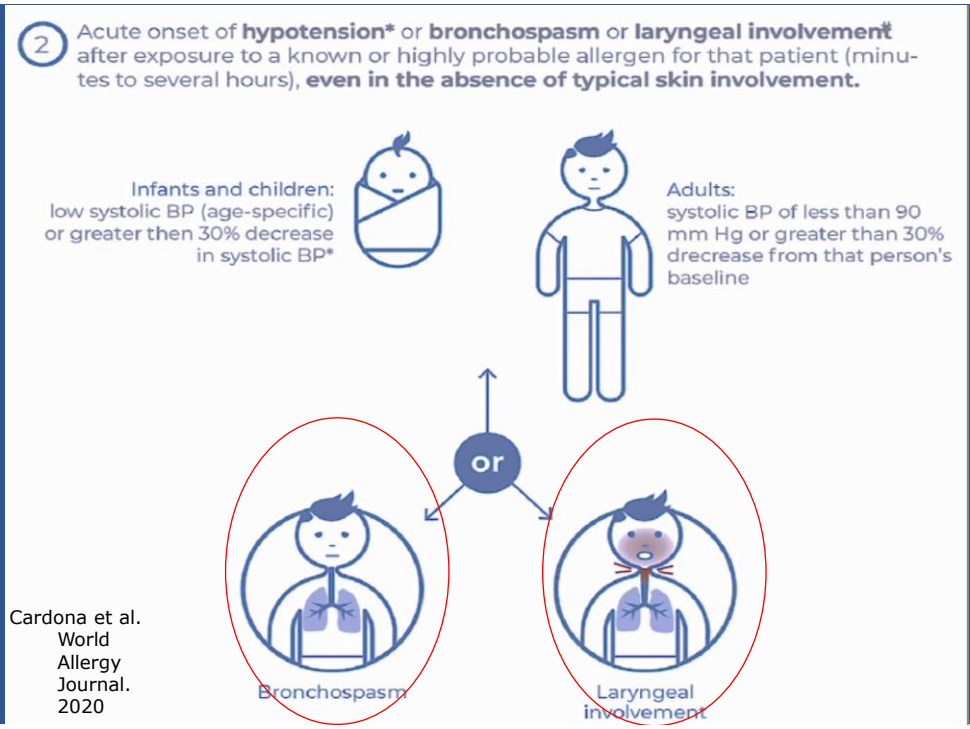


Cardona et al. World Allergy Journal. 2020

6



Cardona et al. World Allergy Journal. 2020

7

Severity of Anaphylaxis –

PMID: 33476673

Severity grading system for acute allergic reactions: A multidisciplinary Delphi study

Check for updates

Timothy E. Dribin, MD,[a,b] David Schnadower, MD, MPH,[a,b] Jonathan M. Spergel, MD, PhD,[c] Ronna L. Campbell, MD, PhD,[d] Marcus Shaker, MD, MSc,[e,f] Mark I. Neuman, MD, MPH,[g,h] Kenneth A. Michelson, MD, MPH,[g,h] Peter S. Capucilli, MD,[i] Carlos A. Camargo, Jr, MD, DrPH,[j] David C. Brousseau, MD, MS,[k] Susan A. Rudders, MD, MS,[h,l] Amal H. Assa'ad, MD,[b,m] Kimberly A. Risma, MD, PhD,[b,m] Mariana Castells, MD, PhD,[n] Lynda C. Schneider, MD,[h,l] Julie Wang, MD,[o] Juhee Lee, MD,[c] Rakesh D. Mistry, MD, MS,[p] David Vyles, DO, MS,[k] Michael Pistiner, MD, MMSc,[q] John K. Witry, MS,[a] Yin Zhang, MS,[r] and Hugh A. Sampson, MD[o]

Cincinnati, Ohio; Philadelphia, Pa; Rochester, Minn; Hanover, NH; Boston, Mass; and Rochester and New York, NY

8

Severity grading system for acute allergic reactions

Grading system application is INDEPENDENT of whether reactions fulfill NIAID/FAAN anaphylaxis diagnostic criteria* (e.g. a reaction can be either Grade 5 anaphylaxis or a Grade 5 non-anaphylactic reaction)

Severity grades**		Clinical criteria (sub-grading system)
Life threatening allergic reactions ↑	5 ANY Severe: *Cardiovascular, Neurologic, Respiratory*	**Cardiovascular**† MILD: *Symptoms* - weak, dizzy, pre-syncope, palpitations, blurred vision; *Infants* - tachycardia not related to other causes such as crying, discomfort, or medications MODERATE: hypotension, syncope (collapse); *Infants* - mottling, cyanosis SEVERE: anaphylactic shock, cardiac arrest; *Infants* - hypotension **Neurologic**† MILD: *Symptoms* - confusion, drowsy, sense of impending doom; *Infants* - persistent and unexplained irritability, inconsolability, crying, or decreased activity MODERATE: GCS (Glasgow Comma Scale; https://www.mdcalc.com/glasgow-coma-scale-score-gcs) 13-14; *Infants* - lethargic SEVERE: GCS <13, seizure; *Infants* - new onset hypotonia **Respiratory** General MILD: *Symptoms* - chest tightness, dyspnea; *Signs* - new onset cough MODERATE: new onset persistent cough, increased WOB, hypoxemia SEVERE: respiratory failure Laryngeal MILD: *Symptoms* - throat tightness or discomfort; *Signs* - voice change; *Infants* - barky or croup like cough, hoarse cry MODERATE: stridor w/o increased WOB SEVERE: stridor with increased WOB (partial or complete upper airway obstruction) Lower airway MILD: wheezing w/o increased WOB MODERATE: wheezing with increased WOB SEVERE: bronchospasm with minimal or no air movement on auscultation AND increased WOB **Mucosal/angioedema** (see Figure E1 in the online repository for example images of mucosal/angioedema severity) MILD: *Symptoms* - mouth tingling, itchy mouth or throat, metallic taste; *Signs* - facial swelling, conjunctival injection, chemosis, nasal congestion, rhinorrhea, throat clearing, lip swelling, mild tongue, soft palate, and/or uvula swelling (anatomical landmarks preserved); *Infants* - tongue thrusting or pulling, repetitive lip, ear or eye rubbing MODERATE: drooling, moderate tongue, soft palate, and/or uvula swelling (anatomical landmarks obscured); *Infants* - marked increase in drooling SEVERE: severe tongue, soft palate, and/or uvula swelling (complete loss of anatomical landmarks) **Skin** Pruritus MILD: *Symptoms* - pruritus, skin discomfort; *Signs* - occasional scratching, localized scratching or excoriations (< 50% body surface area [BSA]) MODERATE: continuous scratching, generalized scratching or excoriations (≥ 50% BSA) Urticaria, rash MILD: localized urticaria (< 50% BSA), localized erythema (< 50% BSA) MODERATE: generalized urticaria (≥ 50% BSA), flushing, generalized erythema (≥ 50% BSA) **Gastrointestinal** MILD: *Symptoms* - nausea, abdominal pain††; *Signs* - 1-2 episodes of emesis or diarrhea; *Infants* - new onset spitting up, hiccups, or back arching MODERATE: *Symptoms* - frequent or continuous nausea or abdominal pain, distressed due to GI symptoms; *Signs* - ≥3 episodes of emesis or diarrhea or 2 of each
	4 ANY Moderate: *Cardiovascular, Neurologic, Respiratory* **OR** Severe: *Mucosal/angioedema*	
	3 ANY Mild: *Cardiovascular, Neurologic, Respiratory*	
	2 2 or more Mild, ANY Moderate: *Skin, Gastrointestinal, Mucosal/angioedema*	
Mild allergic reactions	1 ANY Mild: *Skin, Gastrointestinal, Mucosal/angioedema*	

Terms: *Symptoms*: patient and/or family reported symptoms, not observed by clinicians; ***Signs:*** clinical and/or examination findings; ***Infants*:** signs and symptoms of allergic reactions in infants and young children may overlap with normal behavior. Mild/moderate respiratory, neurologic or CV symptoms may represent increased reaction severity in infants and young children.

Definitions

***Hypotension*:**

Pediatric: systolic BP < 5th percentile for age or < 2 standard deviations below normal for age **or** systolic BP < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 X age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years. Hypotension is a late phase sign in young children; consider use of HR and other CV symptoms in infants. Do not delay management of anaphylaxis for acquisition of BP.

Adult: estimated or calculated mean arterial pressure (MAP=1/3[systolic BP]+2/3[diastolic BP]) < 65; **or** systolic BP < 90 mm Hg or > 30% decrease from baseline

***Anaphylactic shock*:** anaphylaxis with an IV vasopressor infusion requirement to maintain a MAP ≥ 65 mmHg or systolic BP ≥ 90 mm Hg among adults, and age appropriate BPs among children (see pediatric definitions of hypotension above)

Increased work of breathing (WOB): retractions, use of accessory muscles, nasal flaring or grunting (infants), age defined tachypnea that is not brief or self-resolved

***Hypoxemia*:** SpO2 ≤ 92% on room air

***Respiratory failure*:** impaired oxygenation or ventilation requiring use of non-invasive and/or invasive ventilatory support (bag mask ventilation, high flow nasal cannula, continuous positive airway pressure, bi-level positive airway pressure, mechanical ventilation, extracorporeal membrane oxygenation)

9

Anaphylaxis Subsets

TABLE II. Clinical criteria for diagnosing persistent, refractory, and biphasic anaphylaxis

Persistent anaphylaxis is highly likely when the following criterion is fulfilled*:

Presence of symptoms and/or examination findings that fulfill the 2006 NIAID/FAAN anaphylaxis criteria that persist for at least 4 hours.[1]

Refractory anaphylaxis is highly likely when *both* of the following 2 criteria are fulfilled†:

1. Presence of anaphylaxis following appropriate epinephrine dosing *and* symptom-directed medical management (eg, intravenous fluid bolus for hypotension).
2. The initial reaction must be treated with 3 or more appropriate doses of epinephrine (or initiation of an intravenous epinephrine infusion).‡

Biphasic anaphylaxis is highly likely when *all* of the following 4 criteria are fulfilled§:

1. New /or recurrent symptoms and/or examination findings must fulfill the 2006 NIAID/FAAN anaphylaxis criteria.[1]
2. Initial symptoms and/or examination findings must completely resolve before the onset of new or recurrent symptoms and/or examination findings.
3. There cannot be allergen reexposure before the onset of new or recurrent symptoms and/or examination findings.
4. New or recurrent symptoms and/or examination findings must occur within 1 to 48 hours from complete resolution of initial symptoms and/or examination findings.

Dribin T, Sampson H, Camargo C, et al. Journal of Allergy Clin Immun Pract 2020

10

How Often Does Severe Anaphylaxis Occur? The Cross-Canada Experience

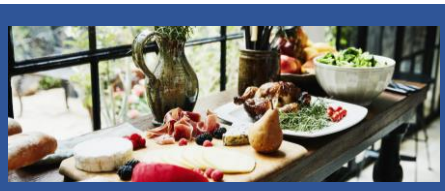
- The 2019 Cross-Canada Anaphylaxis Registry evaluated anaphylaxis cases presenting to ED's in 5 Canadian Provinces over a 6-year period, enrolling 3,498 cases

Anaphylaxis Severity	n = 3,948 (%)
Mild	661 (18.9%)
Moderate	2,594 (74.2%)
Severe	240 (6.9%)

Gabrielli et al. Journal of Allergy and Clinical Immunology In Practice. 2019

11

Anaphylaxis Triggers and Risks



Leading anaphylaxis triggers

- Adults: Medications
  - Antibiotics, NSAIDS, Immunomodulators, Biologics, Anesthetics
- Children/Adolescents: Foods
- All ages: Stinging Insects
- Idiopathic

Risk factors for severe anaphylaxis include

- Cardiovascular disease
- Asthma
- Older age
- Co-morbid conditions
  - Mast cell disorder, beta-blocker use, ACEi use

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020

12

Idiopathic Anaphylaxis (IA)

- Anaphylaxis in the absence of a clear precipitating trigger
  - Up to 1/3 of anaphylaxis
- May affect adults and children, but more commonly adults
- Patients with IA have been reported to have circulating activated T cells and to be responsive to prednisone

TABLE IV. Treatment of IA

Acute	Long-term (preventive)
Epinephrine	H1-antihistamines
H1-antihistamines	Prednisone
Albuterol	Omalizumab
Prednisone	
Intravenous fluids	

Giannetti et al 2017; Gabrielli 2019

13

Original Article

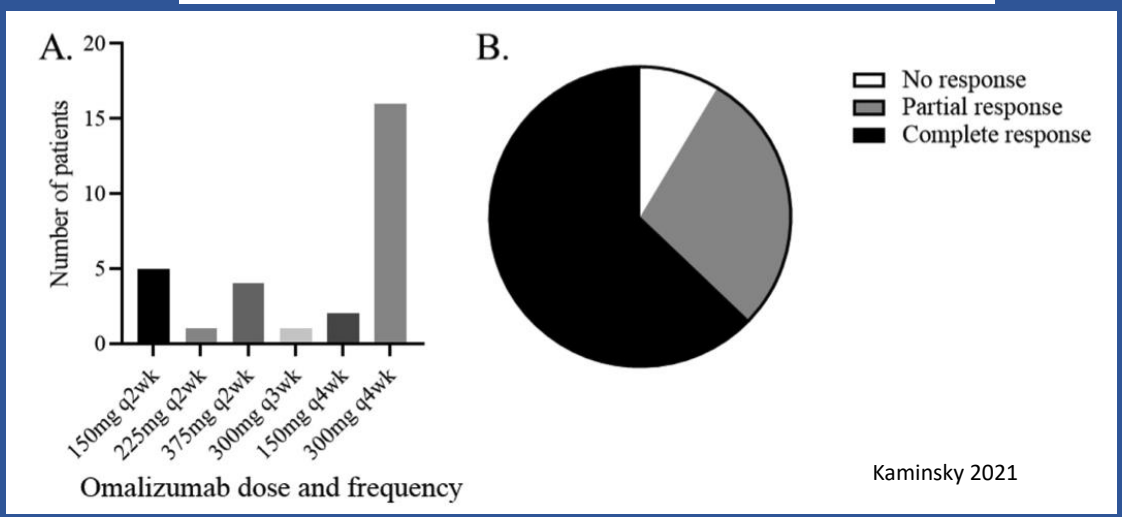
Use of omalizumab for management of idiopathic anaphylaxis

Check for updates

A systematic review and retrospective case series

Lauren W. Kaminsky, MD, PhD*; Kestutis Aukstuolis, DO†,‡; Daniel H. Petroni, MD, PhD†,‡; Taha Al-Shaikhly, MBChB*

* Section of Allergy, Asthma, and Immunology, Department of Medicine, Penn State College of Medicine, Hershey, Pennsylvania
† Northwest Asthma and Allergy Center, Seattle, Washington
‡ Division of Allergy & Infectious Diseases, University of Washington, Seattle, Washington



Kaminsky 2021

14

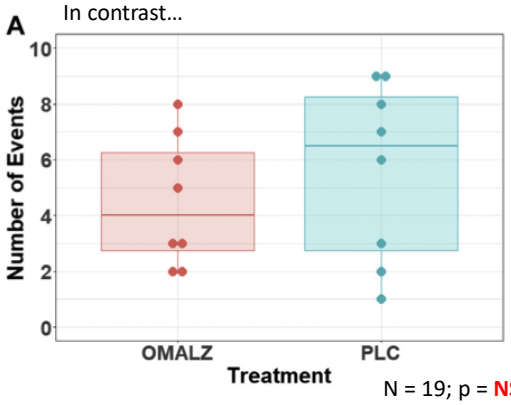
Anaphylaxis, drug allergy, urticaria, and angioedema

A randomized double-blind, placebo-controlled study of omalizumab for idiopathic anaphylaxis

Check for updates

Melody C. Carter, MD,[a] Irina Maric, MD,[b] Erica H. Brittain, PhD,[c] Yun Bai, BS,[a] Keith Lumbard, BS,[d] Hyejeong Bolan, BSN,[a] Daly Cantave, MSN,[e] Linda M. Scott, NP,[a] and Dean D. Metcalfe, MD[a] *Bethesda and Frederick, Md*

In contrast…



N = 19; p = **NS**

Carter JACI 2021

15

Alpha-gal Syndrome

Lone Star Tick

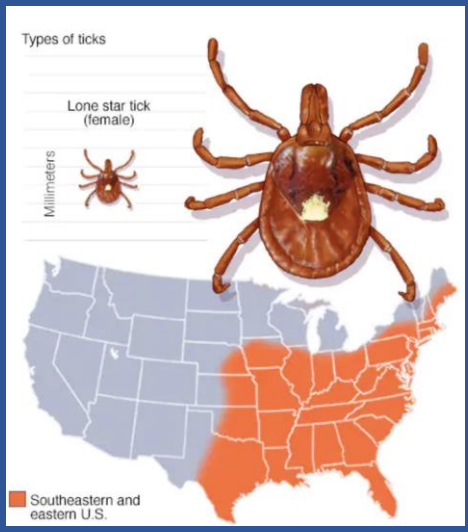
- Sensitization to the carbohydrate moiety galctose-alpha-1,3 galactose
- Symptoms of delayed anaphylaxis to mammalian meats
- Associated with tick bites and alpha gal sensitization
- Type B blood type antigens may be protective
  - Alpha-gal is related to blood group B

https://web.uri.edu/tickencounter/species/lone-star-tick; Hamsten C et al. JACI 2013; Bellamy P et al. JACI IP 2021

16

Alpha-gal Syndrome

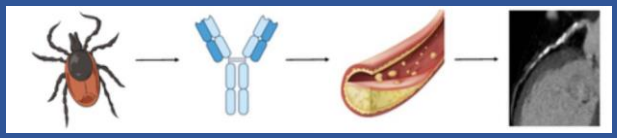
- Certain occupations such as timber harvesting and forestry may increase tick exposure and alpha-gal sensitization
- Geography / travel is an important part of the history
- Many patients may be sensitized without a recognized history of symptoms with eating meat
- Clinical history is key



https://www.mayoclinic.org/tick-species; Hamsten C et al. JACI 2013; Bellamy P et al. JACI IP 2021

17

An unexpected Alpha-gal association



- Alpha-gal sIgE measured in 1056 Australian patients referred for CT coronary angiogram for suspected CAD and 100 patients presenting with STEMI.
- Alpha-gal sensitization associated with:
  - Noncalcified plaque (aOR 1.62, p=0.03)
  - Obstructive CAD (aOR, 2.0, p=0.002)
- Alpha-gal sensitization was 12.8-fold greater in patients with STEMI compared to healthy matched controls and 2.2-fold greater in patients with STEMI compared to stable CAD patients

Caution: Correlation ≠ Causation

Vernon et al. Arterioscler Thromb Vasc Bio 2022

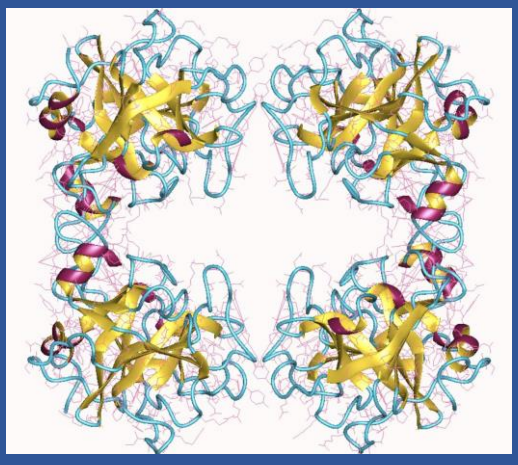
18

What about elevated baseline tryptase?

19

Elevated Baseline Serum Tryptase

- Hereditary alpha tryptasemia
  - 90% of individuals with an elevated tryptase
- Mastocytosis
- Myeloid neoplasms
- Hypereosinophilic syndrome
- Advanced kidney disease



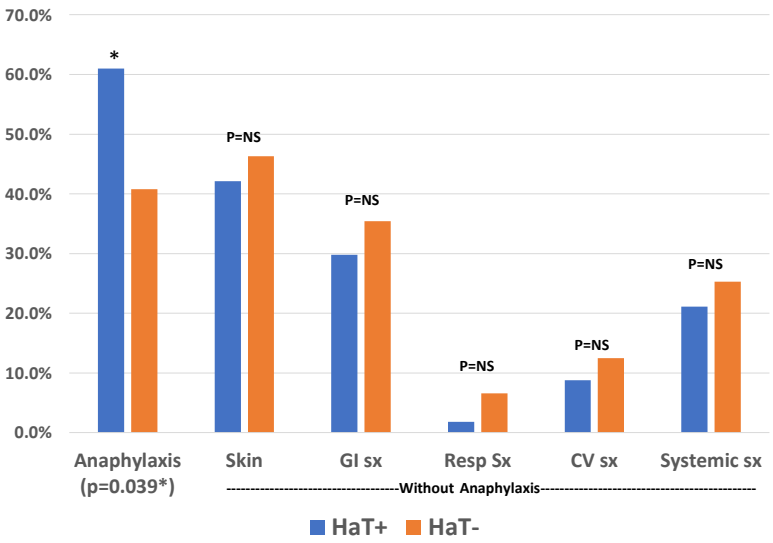
20

Hereditary alpha Tryptasemia (HaT)

- May affect up to 6% of the population
- Increase in baseline tryptase
  - Alpha tryptase copies at TPSAB1 locus
  - Suspect if tryptase > 8 mg/ml
- May increase frequency and severity of allergic reactions
- Variable penetrance

21

Does HaT Cause Non-Anaphylactic Symptoms?



MMAS: monoclonal mast cell activation syndrome

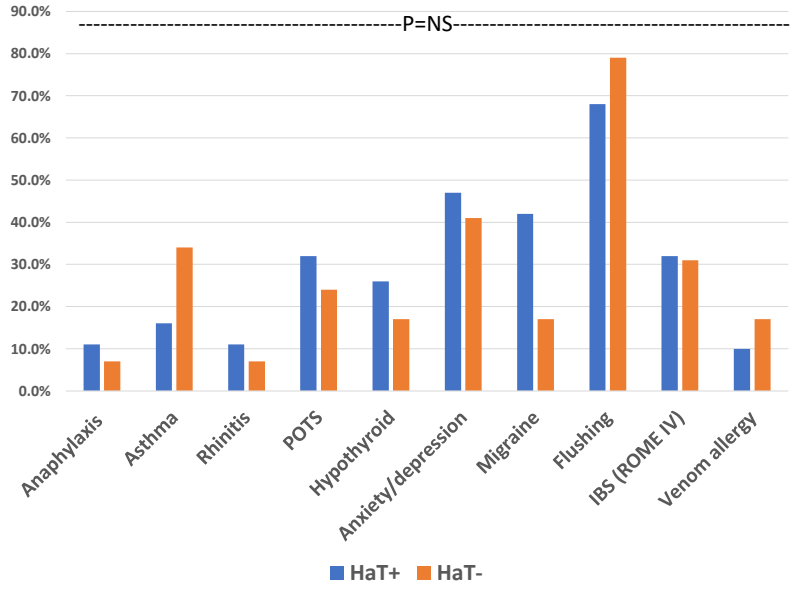
Patients with mastocytosis or MMAS (n=444)

- Multicenter study
- Higher incidence of HaT in patients with mastocytosis(13.3%)
- Apart from anaphylaxis risk for other conditions was not significant elevated

Sordi B et al. JACI 2023

22

Does HaT Cause Non-Anaphylactic Symptoms?



Patients with and without mastocytosis (n=34)

- No significant difference in comorbidities often considered associated with HaT either in patient with or without mastocytosis
- Limitations: small n

Chollet M, Akin C. JACI 2022

23

When is Tryptase Elevated? The Evolving Tryptase Rule

- Classic evidence of mast cell activation:
  - Acute tryptase 20% plus 2ng/ml over baseline
- Validated in perioperative anaphylaxis
  - Sn 98%, Sp 44%
  - PPV 98%, NPV 44%
- Variability limits rule
  - ¼ of individuals may exceed this variability on serial measures
- Alternative thresholds with the ratio of acute to baseline levels
- Ratio 1.685
  - Sn 94.4%, Sp 94.4%
- High vs. Low Clinical Suspicion (Sn 97.5, Sp 97.5)
  - High: 1.374
  - Low: 1.868

2023 Anaphylaxis Parameter; Mateja et al 2022

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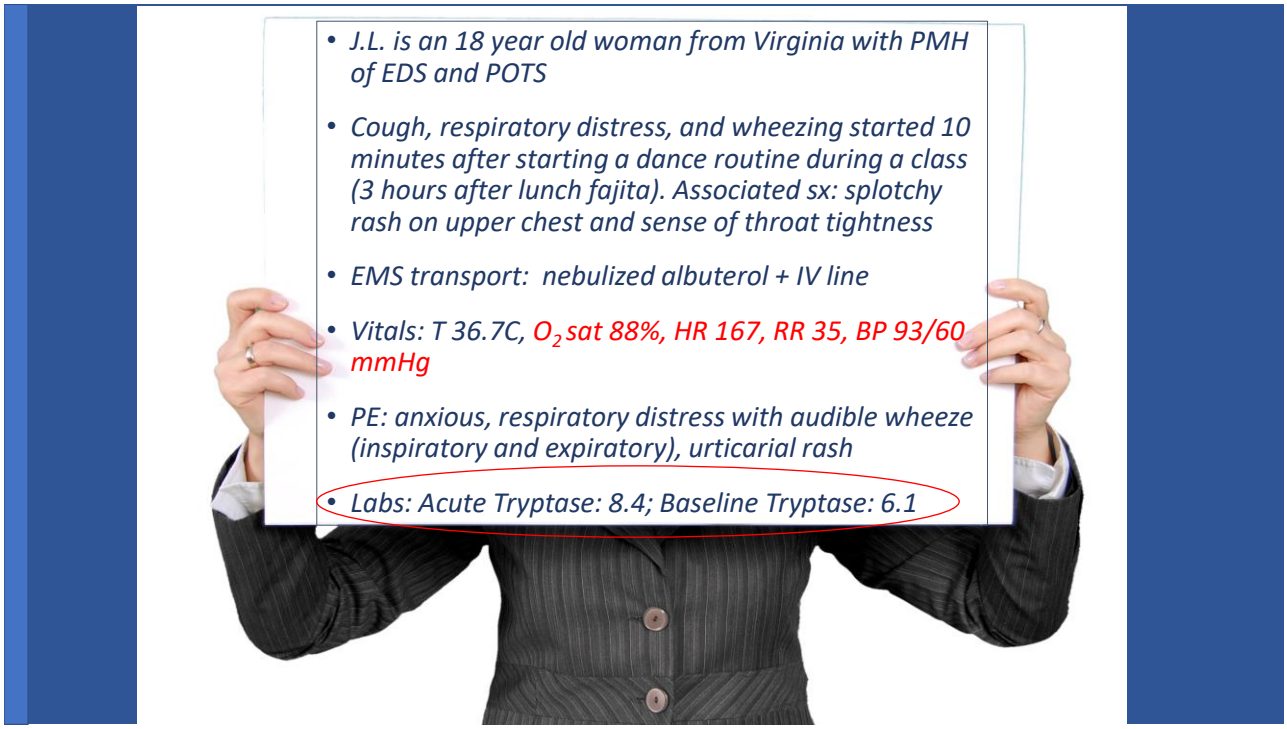

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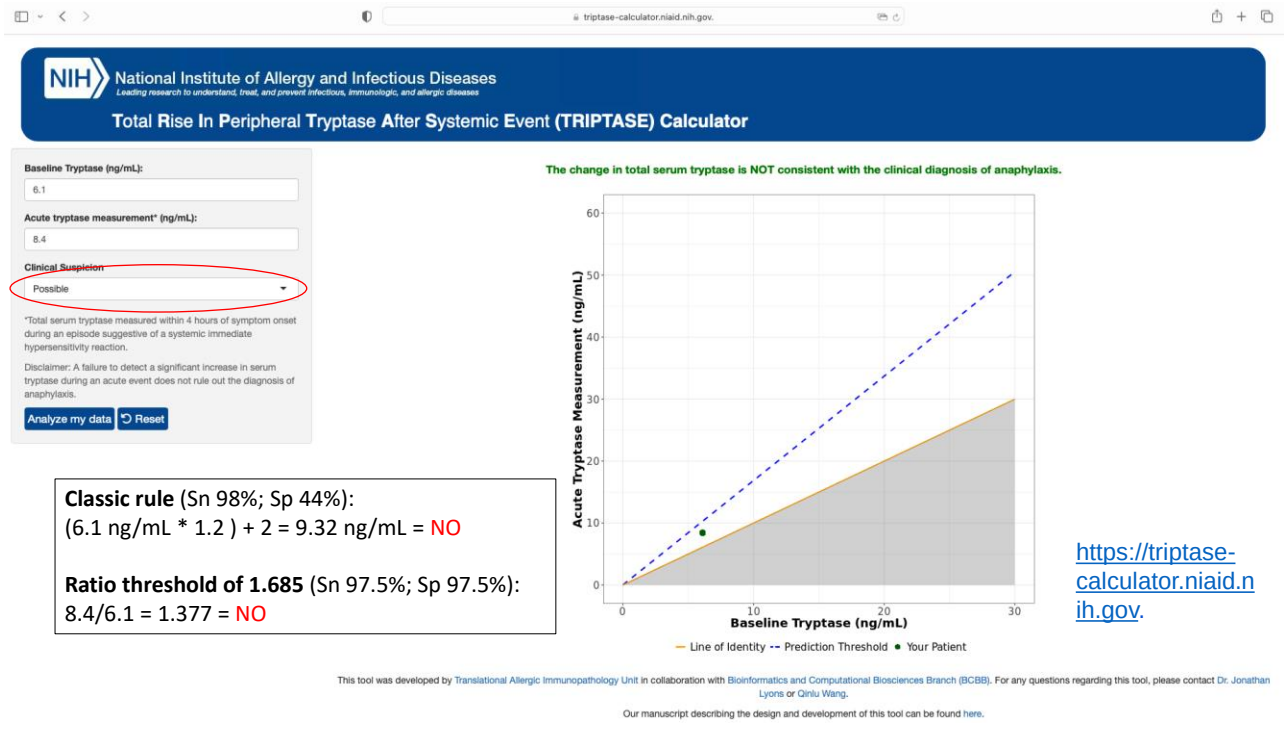
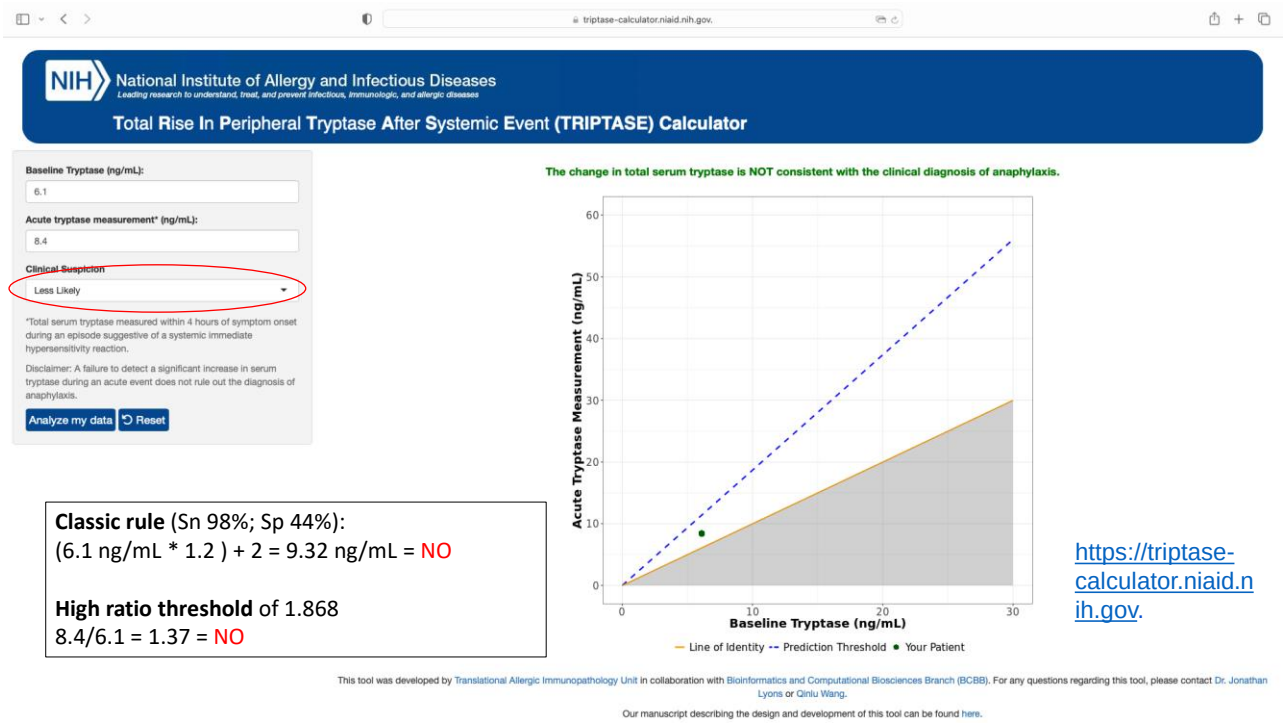


Classic rule (Sn 98%; Sp 44%):
(6.1 ng/mL * 1.2) + 2 = 9.32 ng/mL = NO

Ratio threshold of 1.685 (Sn 97.5%; Sp 97.5%):
8.4/6.1 = 1.377 = NO

https://triptase-calculator.niaid.nih.gov.

26



Classic rule (Sn 98%; Sp 44%):
(6.1 ng/mL * 1.2) + 2 = 9.32 ng/mL = NO

High ratio threshold of 1.868
8.4/6.1 = 1.37 = NO

https://triptase-calculator.niaid.nih.gov.

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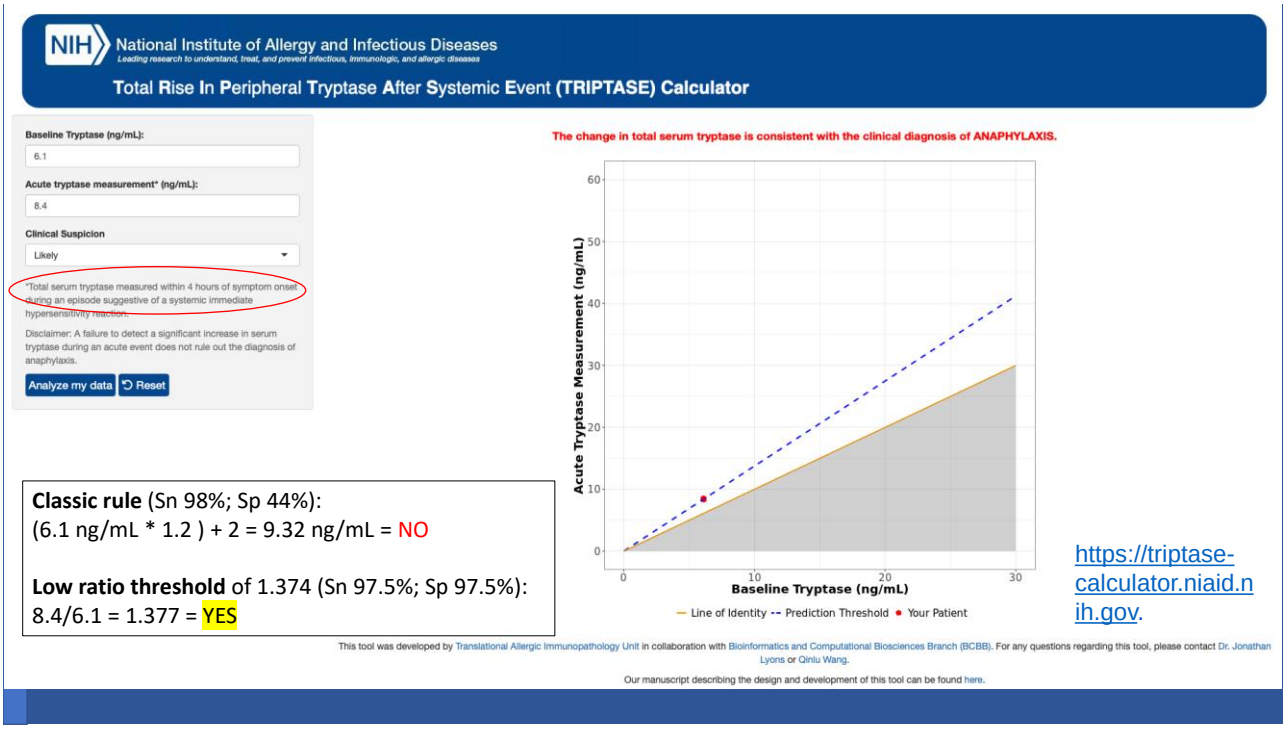

Classic rule (Sn 98%; Sp 44%):
(6.1 ng/mL * 1.2) + 2 = 9.32 ng/mL = NO

Low ratio threshold of 1.374 (Sn 97.5%; Sp 97.5%):
8.4/6.1 = 1.377 = YES

https://triptase-calculator.niaid.nih.gov.

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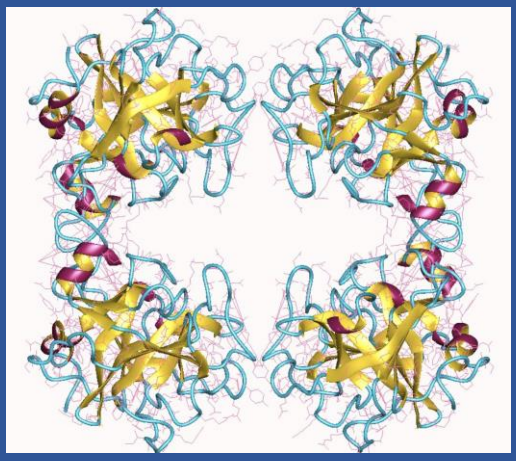
Elevated Baseline Serum Tryptase

- Hereditary alpha tryptasemia
  - 90% of individuals with an elevated tryptase
  - Each TPSAB1 replication increases basal serum tryptase by approximately 9 ng/ml
- **Mastocytosis**
- Myeloid neoplasms
- Hypereosinophilic syndrome
- Advanced kidney disease



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Baseline Tryptase Elevations: REMA & NICAS

Score ≥ 2 suggestive of clonal mast cell disease

2023 Anaphylaxis Parameter

Variable		REMA score	NICAS score
Gender	Male	+1	+1
	Female	-1	-1
Clinical Symptoms During Attack	Absence of urticaria and angioedema	+1	--
	Presence of urticaria and/or angioedema	-2	--
	Presyncope or syncope	+3	
	Absence of angioedema	--	+1
	Flushing	--	-1
	Urticaria	--	+1
	Syncope	--	+3
Tryptase	< 15 ng/mL	-1	--
	>25 ng/ml	+2	---
	< 11.4 ng/mL	--	-1
	> 11.4 ng/mL	--	+3
Allele-specific PCR (D816V)	Negative	--	-1
	Positive	--	+3

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Baseline Tryptase Elevations

TPSAB1 copy number can be used to interpret the baseline tryptase level

Additional TPSAB1 copy number	Basal serum tryptase (ng/mL), median (range)	Upper 95% predictive interval	Upper limit using (basal serum tryptase) / 1+copy equation
0	4.1 (0 - 10.4)	11.4	20
1	13.6 (6.5 - 33.9)	36.2	40
2	22.5 (10.5 - 39.5)	62.2	60
3	27.3 (23.4 - 40)	88.8	80
4	37 (25.5 - 62.7)	115.9	100
6	87 (N/A)	171.2	140
10	133 (110 - 156)	285.1	220

Lyons 2022

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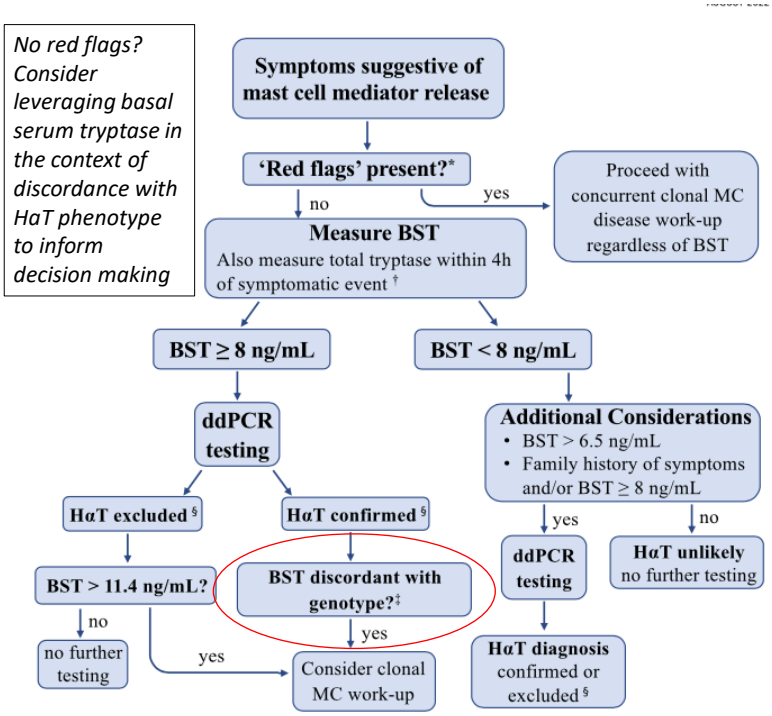
No red flags? Consider leveraging basal serum tryptase in the context of discordance with HαT phenotype to inform decision making



Red flags may include but are not limited to hepatosplenomegaly, lymphadenopathy, CBC anomalies (thrombocytopenia, anemia, polycythemia, neutrophilia, eosinophilia with AEC > 1500), severe and/or recurrent anaphylaxis (in particular idiopathic or Hymenoptera), urticaria pigmentosa, premature fracture

Lyons 2022

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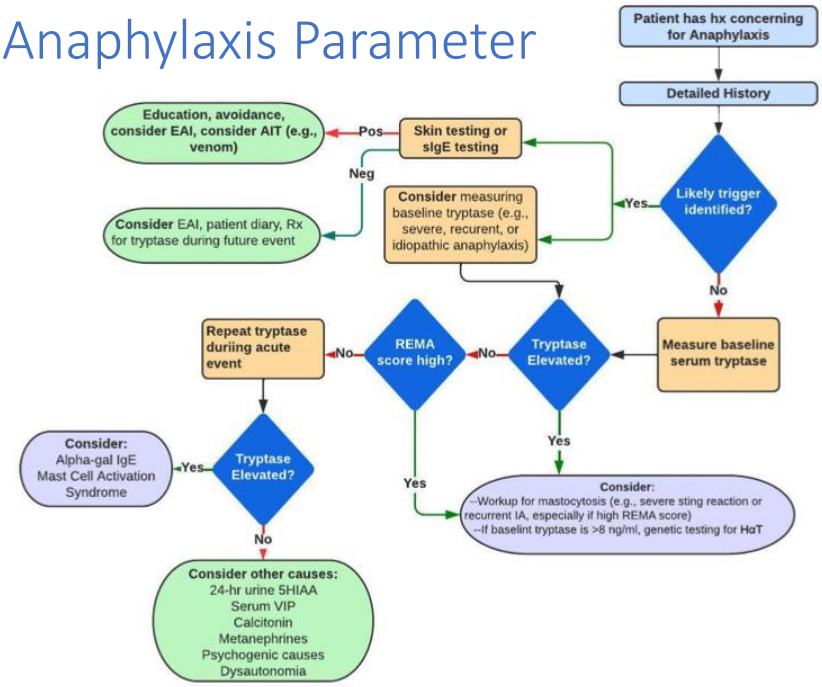
2023 Anaphylaxis Parameter



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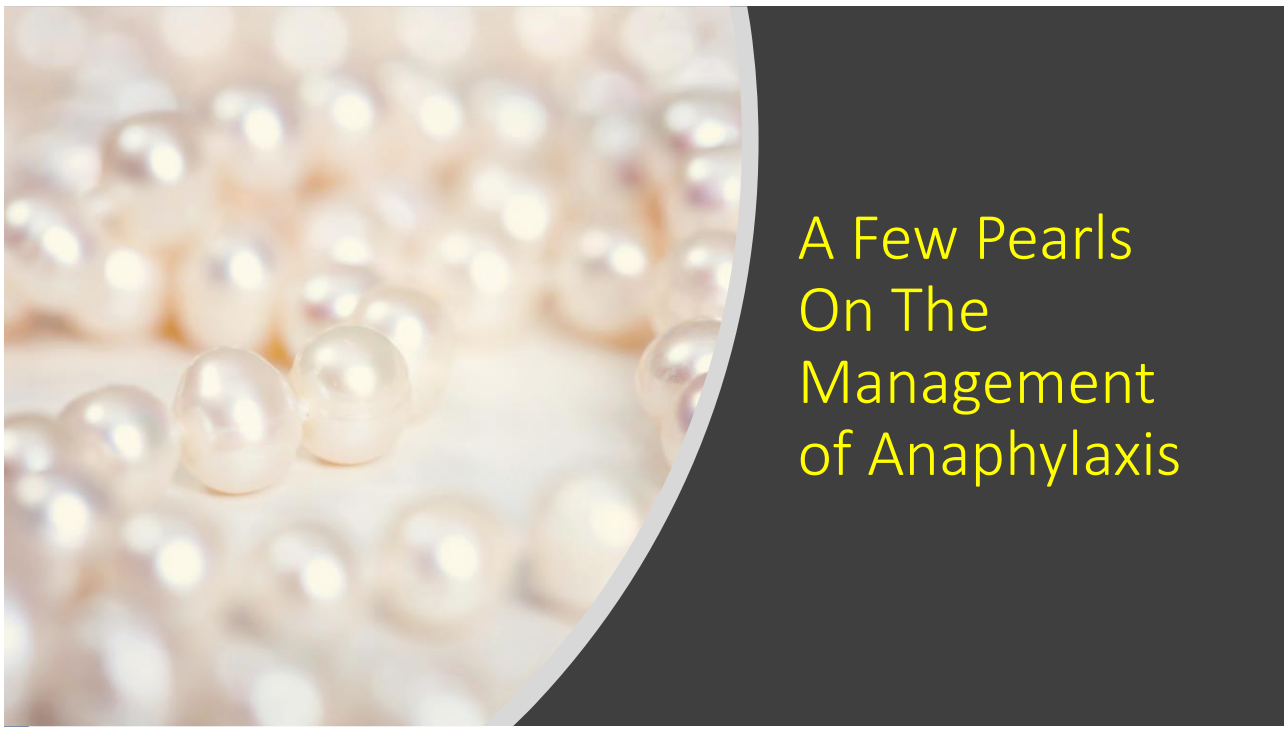

34

Practice parameter

Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis

- Topics were selected in coordination with the AAAAI and ACAAI
- Topics were selected because there was a critical need to inform practice in two major domains:
  - (1) To identify risk factors for biphasic anaphylaxis (to inform management, preparedness, and education), and
  - (2) To understand if giving patients glucocorticoids and/or antihistamines prevents anaphylaxis.

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020

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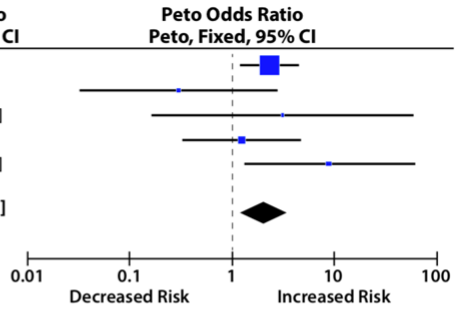
Severe anaphylaxis

A

Study or Subgroup	Biphasic Events	Biphasic Total	No Biphasic Events	No Biphasic Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brown 2013	22	49	72	266	66.0%	2.34 [1.20, 4.54]
Confino-Cohen 2010	0	11	11	120	5.9%	0.31 [0.03, 2.82]
Lee 2000	6	6	90	99	3.4%	3.16 [0.17, 59.06]
Manuyakorn 2015	12	15	47	62	16.6%	1.26 [0.34, 4.73]
Vezir 2013	4	5	28	91	8.1%	8.96 [1.34, 59.87]
Total (95% CI)		**86**		**638**	**100%**	**2.11 [1.23, 3.61]**
Total Events	44		248			

Heterogeneity: Chi² = 5.88, df = 4 (P = 0.21); I² = 32%
Test for overall effect Z = 2.70 (P = 0.007)

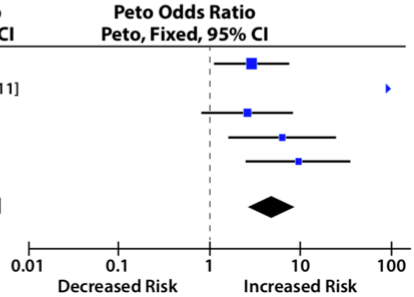


> 1 dose of epinephrine

B

Study or Subgroup	Biphasic Events	Biphasic Total	No Biphasic Events	No Biphasic Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Alqurashi 2015	10	71	27	413	37.2%	2.91 [1.13, 7.49]
Inoue 2013	2	2	1	59	0.8%	9.56E8 [1.49E6, 6.13E11]
Lee 2017	6	36	73	836	24.7%	2.62 [0.82, 8.36]
Mehr 2009	7	12	21	95	18.0%	6.41 [1.65, 24.96]
Scranton 2009	9	14	8	46	19.2%	9.69 [2.60, 36.14]
Total (95% CI)		**135**		**1449**	**100%**	**4.82 [2.70, 8.58]**
Total Events	34		130			

Heterogeneity: Chi² = 36.98, df = 4 (P < 0.00001); I² = 89%
Test for overall effect Z = 5.33 (P < 0.00001)



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Biphasic Anaphylaxis
Additional Outcomes with statistically significant effect size

Risk Factors	Odds Ratio (CI)	Evidence Certainty	Heterogeneity
Wide pulse pressures	2.11 (1.32, 3.37)	Very low	Low
Drug as trigger in pts <18 yrs.	2.35 (0.16, 4.65)	Very low	Moderate
Unknown trigger	1.63 (1.13, 2.33)	Very low	Moderate
Cutaneous symptoms	2.54 (1.25, 5.15)	Very low	Low

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020

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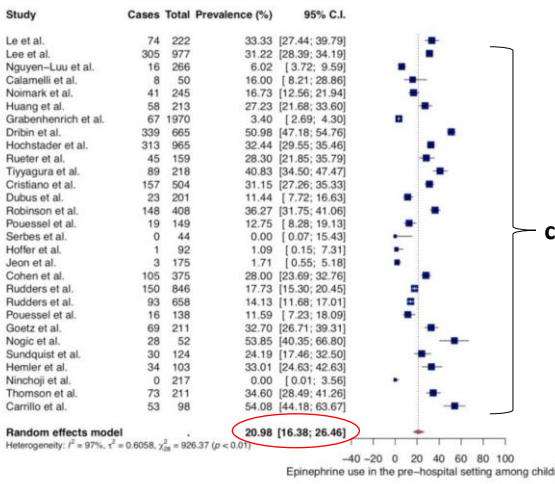
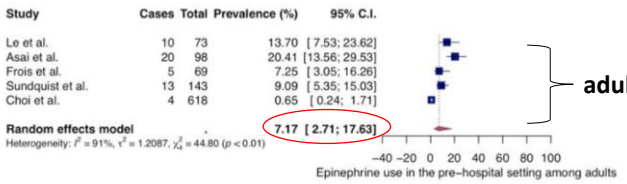
Pre-hospital Epinephrine



children

30 min epi delay: OR 3.39 for biphasic rxn



adults

Miles, Ratnarajah, Gabrielli, Abrams, et al. JACI IP 2021

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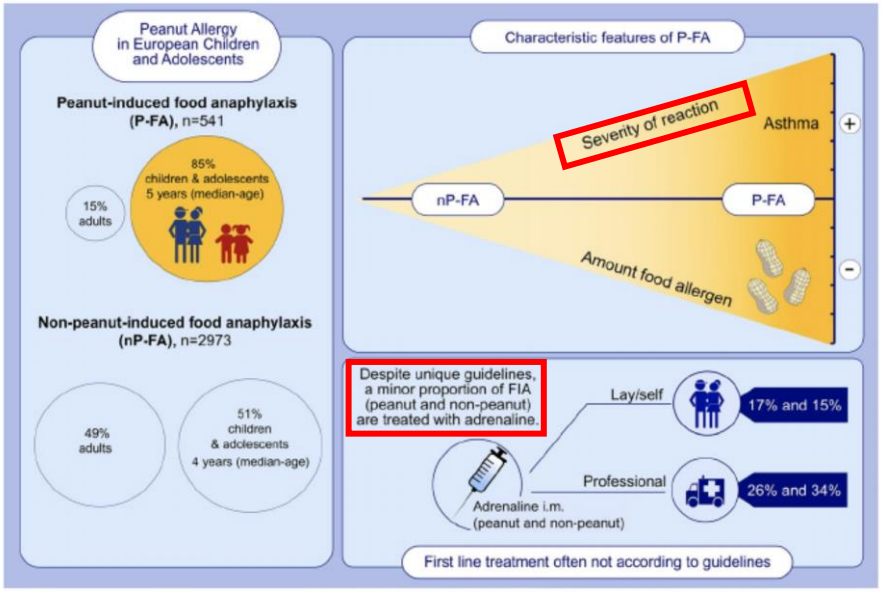
European Anaphylaxis Registry

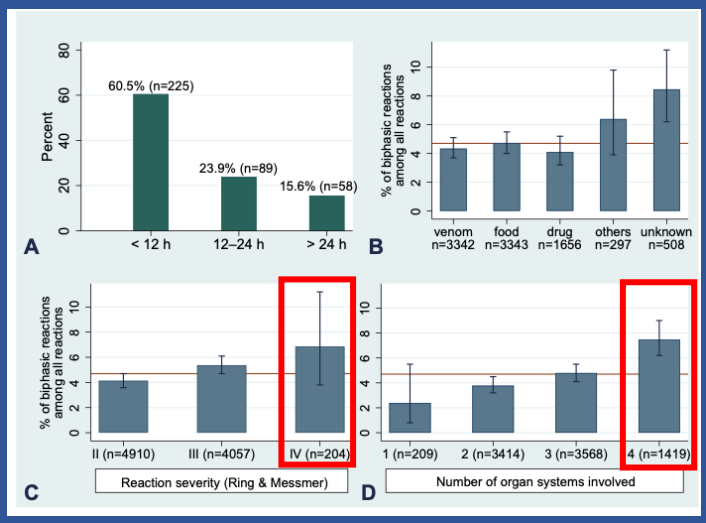


Maris et al. Allergy 2021

39

International Anaphylaxis Registry: Biphasic Risks

- Reaction severity
- Multi-organ involvement
- Peanut or tree nut
- Unknown elicitor
- Exercise as a co-factor
- Chronic urticaria
- Delay in initial symptoms
- Antihistamine treatment



Kraft et al. JACI IP Nov-Dec 2020

40

Biphasic Anaphylaxis Risk Factors

Question 1	Recommendation 1: **The guideline suggests that a clinician incorporate severity of anaphylaxis presentation and/or the administration of more than one dose of epinephrine for the treatment of initial anaphylaxis as a guide to determining a patient's risk for developing biphasic anaphylaxis**
	Recommendation 2: **The guideline suggests in favor of extended clinical observation in a setting capable of managing anaphylaxis (to detect a biphasic reaction) for patients with resolved severe anaphylaxis and/or those who need more than one dose of epinephrine**

Conditional Recommendations; Very Low Certainty Evidence

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020

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Antihistamines and glucocorticoids are commonly used to prevent biphasic anaphylaxis, but do they work?

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The Cross-Canada Experience

- Prehospital treatment with epinephrine (aOR 0.23, 95% CI 0.14-0.38) and antihistamine (aOR, 0.61; 95% CI 0.44-0.85) decreased the likelihood of multiple epinephrine doses in the ED
- However, prehospital treatment with corticosteroids increased risk of ICU or hospital admission (aOR, 2.84, 95% CI, 1.55-6.97).

Gabrielli et al. Journal of Allergy and Clinical Immunology In Practice. 2019

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International Anaphylaxis Registry: Biphasic Risks

TABLE E8. Impact of the first-line treatment of the reaction on a biphasic course

	OR for occurrence of biphasic reactions	95% CI	*P* value
(A) Multivariate analysis (n = 7328)*			
Treatment			
Adrenaline	0.91	[0.71-1.16]	.44
Corticosteroids	1	[0.76-1.31]	.996
Antihistamines	1.52	[1.14-2.02]	**.005**
Severity grade III+IV vs II	1.35	[1.09-1.68]	**.006**
(B) Multivariate analysis (n = 7111)†			
Treatment‡			
Antihistamines only (n = 676)	1.99	[1.17-3.39]	**.011**
Corticosteroids only (n = 539)	1.14	[0.62-2.12]	.66
Adrenaline only (n = 328)	1.12	[0.55-2.26]	.76
Antihistamines + corticosteroids (n = 3187)	1.6	[1.01-2.54]	**.047**
Antihistamines + adrenaline (n = 124)	0.22	[0.03-1.63]	.14
Corticosteroids + adrenaline (n = 291)	1.05	[0.5-2.22]	.89
Antihistamines + corticosteroids + adrenaline (n = 1349)	1.58	[0.96-2.59]	.07
Severity grade III + IV vs II	1.34	[1.08-1.67]	**.008**

Kraft et al. JACI IP Nov-Dec 2020

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2020 Anaphylaxis GRADE Guideline

Question 1	**What risk factors should clinicians take into consideration in determining the likelihood of biphasic anaphylaxis?**
Question 2	**Should antihistamines and/or glucocorticoids be used to prevent biphasic anaphylaxis?**
Question 3	**Should antihistamine and/or glucocorticoid premedication be used to prevent index hypersensitivity/infusion reactions to chemotherapy?**
Question 4	**Should antihistamine and/or glucocorticoid premedication be used to prevent recurrent hypersensitivity reactions to radiocontrast media?**
Question 5	**Should antihistamine and/or glucocorticoid premedication be used to prevent anaphylactic reactions to allergen immunotherapy or other agents?**

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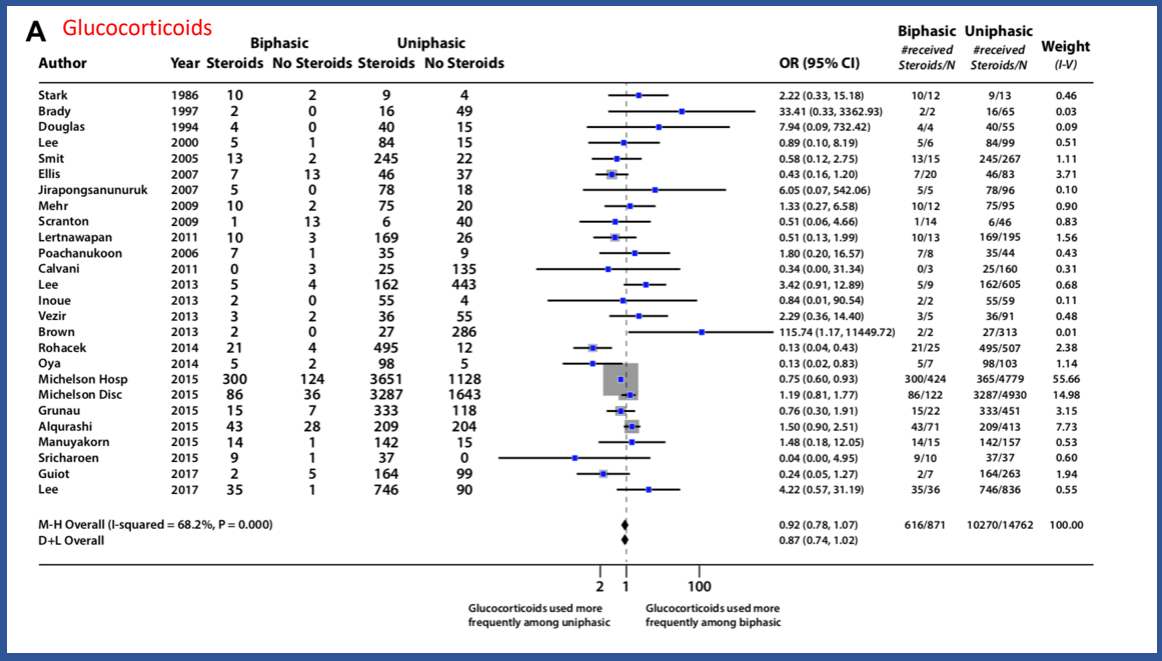
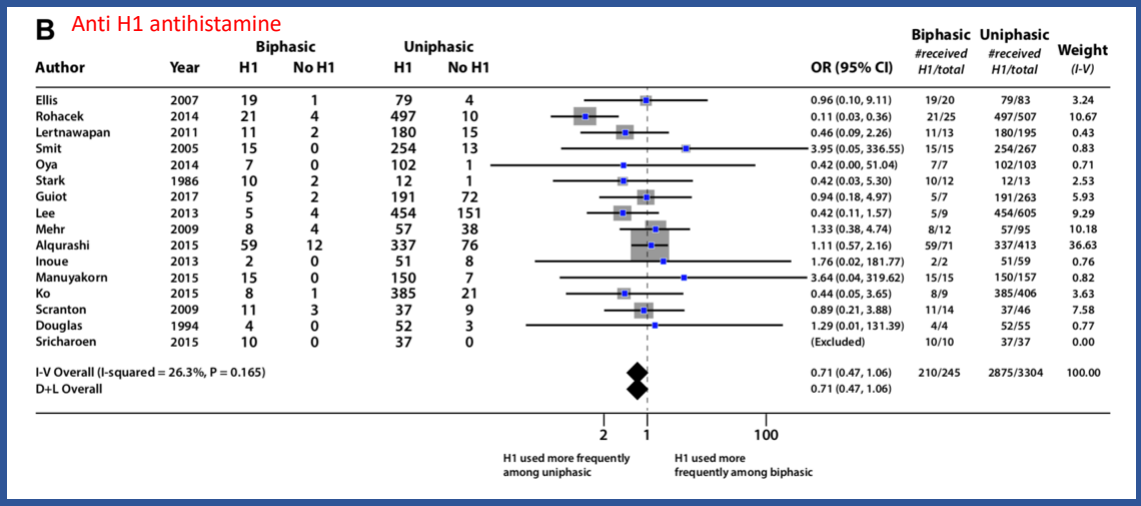


46

B Anti H1 antihistamine



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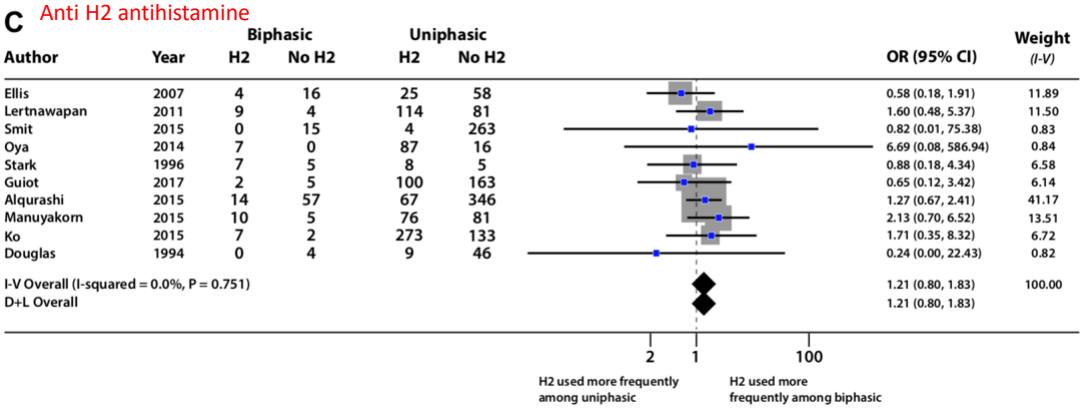
C Anti H2 antihistamine



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Supplemental Therapies to Prevent Anaphylaxis

Question 2	Recommendation: **The guideline suggests against glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis**

Conditional Recommendations; Very Low Certainty Evidence

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020

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American Academy of Allergy Asthma & Immunology

American College of Allergy, Asthma & Immunology

Coming Attractions

2023 Anaphylaxis Parameter

JOINT TASK FORCE ON PRACTICE PARAMETERS JTF PP

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Key Messages

- Despite slight variations in details, anaphylaxis criteria are more alike than different
- New understanding of the pathophysiology of mast cell release is informing our approach to anaphylaxis risk
- History is key when evaluating both HaT and the alpha gal syndrome; some cases of anaphylaxis remain idiopathic

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Key Messages

- Epinephrine is the first line pharmacotherapy for uniphasic and biphasic anaphylaxis
- Severe anaphylaxis and multiple epinephrine doses increase biphasic risk
- Using antihistamines and/or glucocorticoids to prevent anaphylaxis is a low value practice, in general

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Food Protein-Induced Enterocolitis: How common is it?

Presented by:

Jonathan Spergel, MD, PhD

Friday, June 23, 2023

10:45 a.m. – 11:30 a.m.

FPIES: How Common is it? What Foods are involved?

Jonathan M. Spergel, MD, PhD
The Children's Hospital of Philadelphia
Perelman School of Medicine at Univ. of Pennsylvania

Children's Hospital of Philadelphia

1

Disclosures

Jonathan M. Spergel, MD, PhD

Grants: NIH, FARE, Regeneron/Sanofi, Bristol-Myers-Squib

Consultant: Regeneron/Sanofi, Readysetfood, Novartis,

DSMB: Alladapt, NIAID

Royalities: Uptodate

None related to the talk

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2

2

FPIES

Definition by NIAID Guidelines

"FPIES is a non-IgE-mediated disorder that usually occurs in young infants. Symptoms include chronic vomiting, diarrhea, and failure to gain weight or height. When the allergenic food is removed from the infant's diet, symptoms disappear. Milk and soy protein are the most common causes, but some studies report reactions to rice, oat, or other cereal grains. A similar condition also has been reported in adults, most often related to eating crustacean shellfish."

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3

Boyce et al. *J Allergy Clin Immunol.* 2010; 126:S1-58.

3

Early Reported Cases-Powell

In 1978, 9 infants aged 4 to 27 days presented acutely ill and dehydrated (8/9)

- Reacted to milk and soy

Follow up oral challenges at 5 ½ months

- 14/18 positive challenges
  - 10/14 had vomiting
  - 14/14 had diarrhea (blood, WBC, eosinophils, carbohydrate in stool)
  - PMN rise peaked at 6 hours

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Powell, *J Pediatrics* 1978; 93: 553-560.

4

Diagnosis

- Clinical Diagnosis
- Skin Testing or Specific IgE Negative >90%
- Biopsy are not routine

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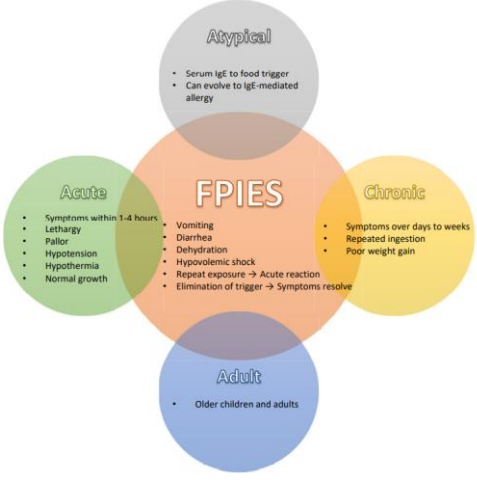
5

FPIES subtypes and overlay



Adult FPIES Defining features	• Older age of onset: adolescents and adults • Symptoms of vomiting, diarrhea, and severe abdominal pain that develops 1-4 h after food ingestion • Common triggers: shellfish, dairy, wheat, egg • Hypothermia, lethargy, pallor, weakness, dizziness, blurred vision, and loss of consciousness have been reported at presentation and during oral food challenge
Atypical FPIES Defining features	• Development of food-specific IgE to identified FPIES trigger • Protracted course with symptom resolution at an older age • IgE-mediated allergic reactions to FPIES food trigger can develop

Hoffmann NV, et al. Ann Allergy Asthma Immunol 2021;126: 498-505.

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Laboratory Features

Acute	Chronic
• Elevated white count (neutrophil predominance) • Thrombocytosis • Methemoglobinemia • Fecal leukocytes and eosinophils • Increased carbohydrates in stool	• Anemia • Hypoalbuminemia • Elevated white count • Metabolic acidosis • Methemoglobinemia • Stool reducing substances

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Sicherer. *J Allergy Clin Immunol.* 2005;115(1):149-156

7

Epidemiology

- Unclear due to misdiagnosis or underdiagnosis
- Spain: 0.79%
- Israel: 0.34%
- Australia: 0.16%
- Japan 1%
- United States
  - Birth Cohort
    - Massachusetts 1%
  - EMR Cohort: 0.14%

Katz et al, *J Allergy Clin Immunol.* 2011; 127(3):647-53.; Mehr et al, *Pediatrics* 2009;123:e459-464.
Su et al, Allegy 2023; Prattico et al. Int. Arch Of Allergy Immunol 2023

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Differential Diagnosis

- Acute
  - IgE mediated reaction
  - Food Poisoning
  - Acute Abdomen
  - Sepsis
- Chronic or multiple foods
  - Severe GERD
  - IBD
  - Metabolic disease
  - Carbohydrate deficiency
  - Anatomical Issues
    - Tethered cord
    - Malrotation

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9

Associated Atopic Conditions

Table 2
Atopic Comorbidities in Patients With Food Protein-Induced Enterocolitis Syndrome

Country	IgE-mediated food allergy (%)	Atopic dermatitis (%)	Allergic rhinitis (%)	Asthma (%)
Australia[25]	16	42	3	3
Italy[17,44]	10	9-19	NA	NA
Israel[21]	18	NA	NA	NA
Korea[40]	0	NA	NA	NA
Spain[26,34]	2.3-15.7	NA	NA	NA
US children[33]	65	9.2	32.6	25.2
US adults[33]	42.5	22.3	31.1	37.4
Philadelphia, Pennsylvania, United States[15,27]	19-23.8	20.6-34	28	17-26.6
New York City, New York, United States[23]	39	57	38	25
Houston, Texas, United States[38]	5	46	19	7

Abbreviations: IgE, immunoglobulin E; NA, not available.

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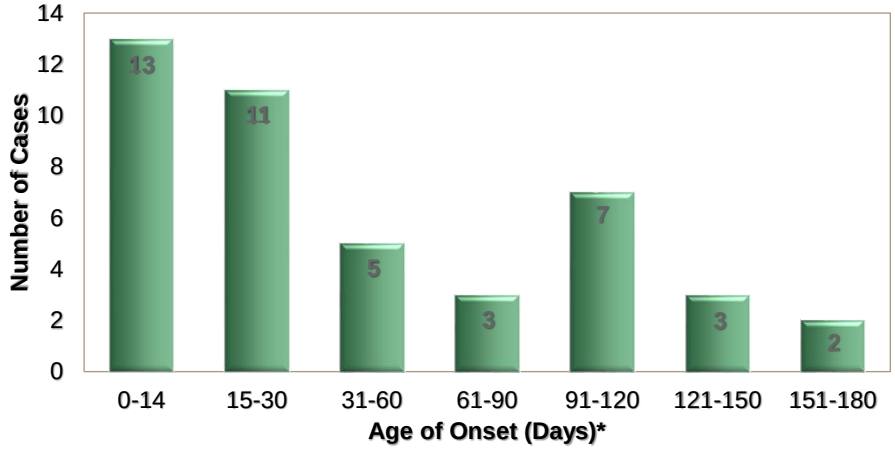
Age of Onset



*Age distribution for the onset of FPIES. All patients had FPIES before the age of 180 days
Katz, et al, *J Allergy Clin Immunol.* 2011; 127(3):647-53.

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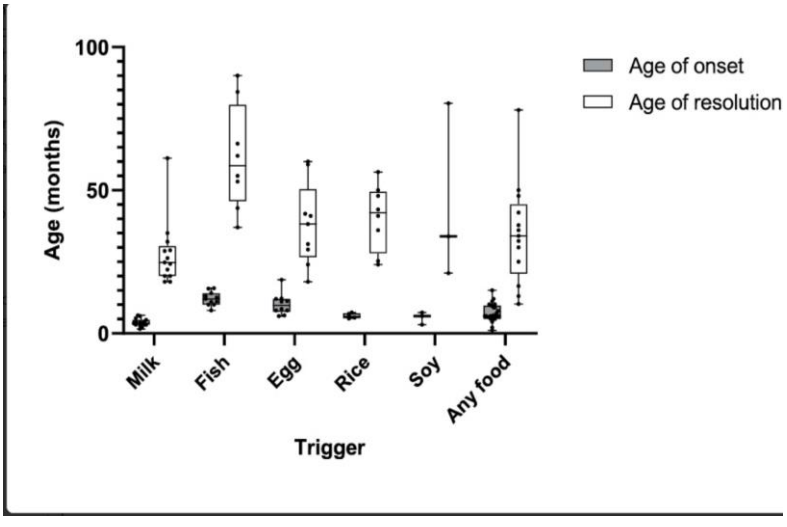
11

Natural History



Prattico et al. Int Arch Allergy Immunol 2023

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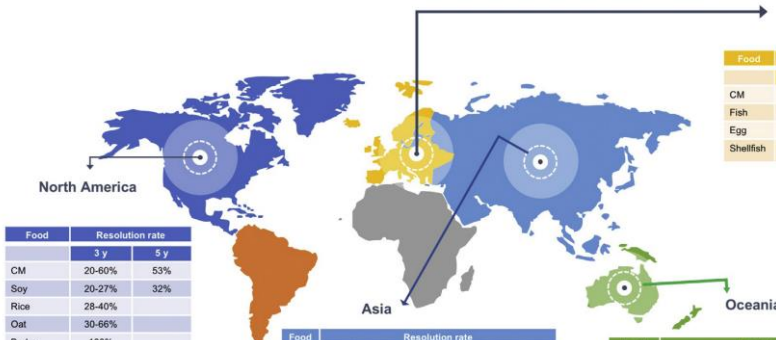
Rates of resolution



Food	Resolution rate			
	2 y	3 y	4 y	5 y
CM	50-63%		75%	
Fish			25-60%	75%
Egg		50%		100%
Shellfish		20%	25%	19-75%

Food	Resolution rate		
	3 y	5 y	
CM	20-60%	53%	
Soy	20-27%	32%	
Rice	28-40%		
Oat	30-66%		
Barley	100%		
Poultry		50%	
Vegetables	67%		

Food	Resolution rate					
	6 m	8 m	10 m	1 y	2 y	3 y
CM	27%	42%	64%	50%	89%	94%
Soy	75%	91%	92%			

Food	Resolution rate				
	1 y	2 y	3 y	4 y	5 y
CM	12%	56%	88%	96%	96%
Rice	0%	63%	80-87%	100%	
Egg	0%	12.5-50%	12.5%	12.5%	27%
Shellfish	0%	25%	25%	25%	25%
Soy			83%		

Bird JA, et al. Annals Allergy, Asthma, Immunol 2021; 126:506-515.

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Adult Onset FPIES

- Age on onset: 40's
- Symptoms: abdominal pain, diarrhea (more than vomiting)
- Neutrophilic shift on challenge
- Shellfish and fish
  - Some reports to milk and egg
- 20-40% developed tolerance in 18 months

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Graham and Coubet J Allergy Clin Immunol In Practice 2022

14

Potential Risk factors for FPIES

- Japanese national cohort of 100,000 pregnancies
- Occurred 0.6-1.6%
- Egg and milk
- 81% had only one food
- Prenatal Antibiotics might be risk factor
- C-section is not risk factor

Yamamoto-Handa et al. Clin Exp Allergy 2023

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What Foods Cause FPIES

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Australia: 16 Year Experience

- 35 children with 66 episodes
  - Highly referred population; pediatricians handle most cases without referral
  - Mean age 5.5 months
  - 29 reacted to 1 food; 6 to 2 foods
  - 14 rice, 12 soy, 7 milk, 2 meats, 2 oats, 1 fish, 3 fruits & vegetables
- 100% vomiting, 85% lethargy, 67% pallor, 24% diarrhea

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Mehr *Pediatrics* 2009;123:e459-464.

17

FPIES-UK Experience[1]

- 437 children
- 25% with symptoms at 8 years of age
- Milk, egg, soy and wheat most common

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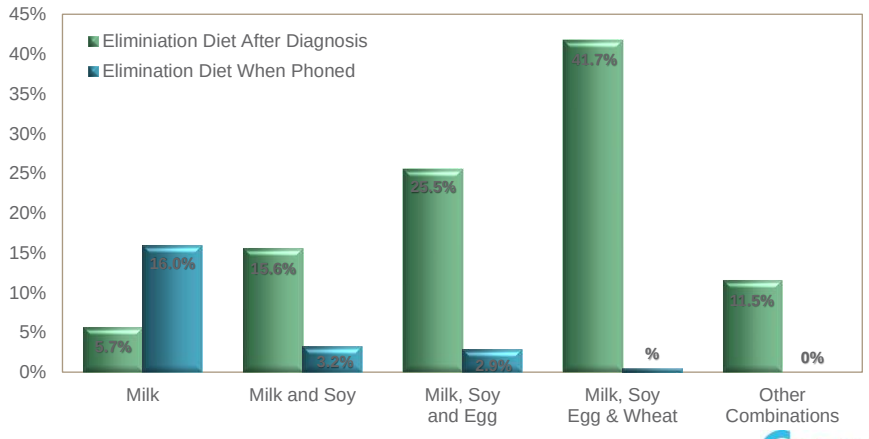
Meyer et al. *World Allergy Organ J* 2013; 6:13-22.

18

What Foods?

Fig. 2 Elimination diets suggested by clinicians at diagnosis and foods still eliminated at follow-up phone call in 2009.



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CHOP Experience

N=380

Milk	38%
Soy	24%
Rice	9%
Oat	8%
Wheat	7%

- Average 2.55 Foods
- No gender or racial predisposition

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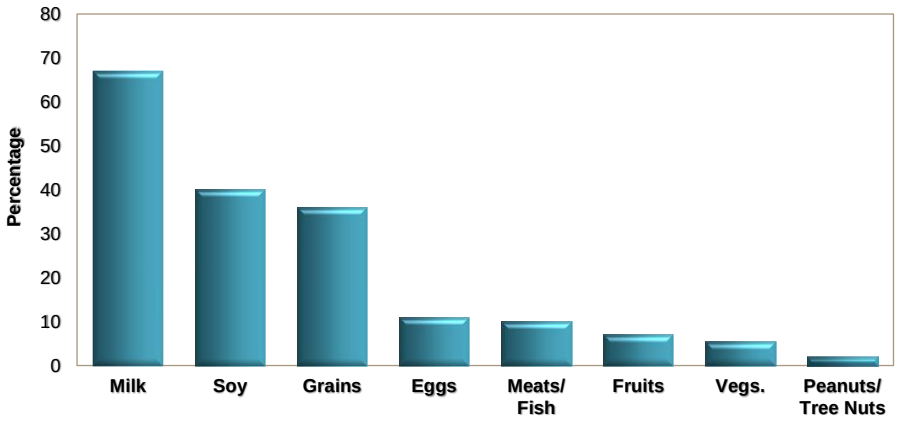
Ruffner et al, *J Allergy Clin Immunol:* In Practice 2013; 1:343-349.

20

Foods That Trigger FPIES



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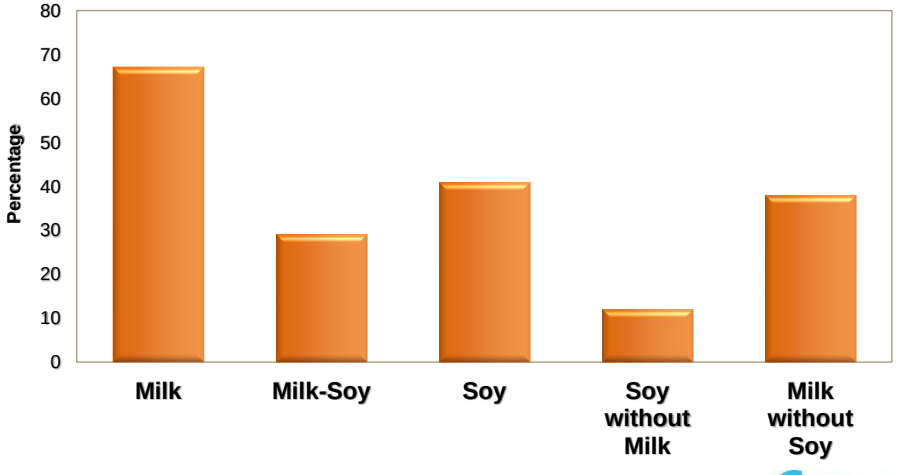
Ruffner et al, *J Allergy Clin Immunol:* In Practice 2013; 1:343-349.

21

Milk to Other Foods



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Ruffner et al, *J Allergy Clin Immunol:* In Practice 2013; 1:343-349.

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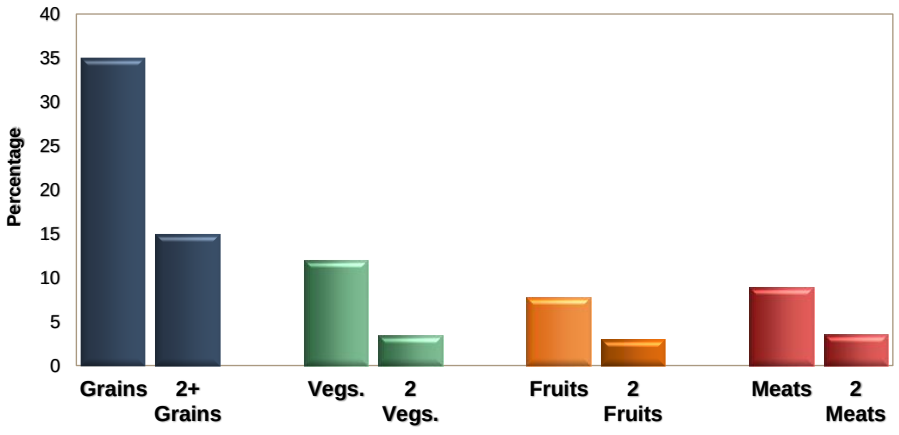
Cross Reactivity



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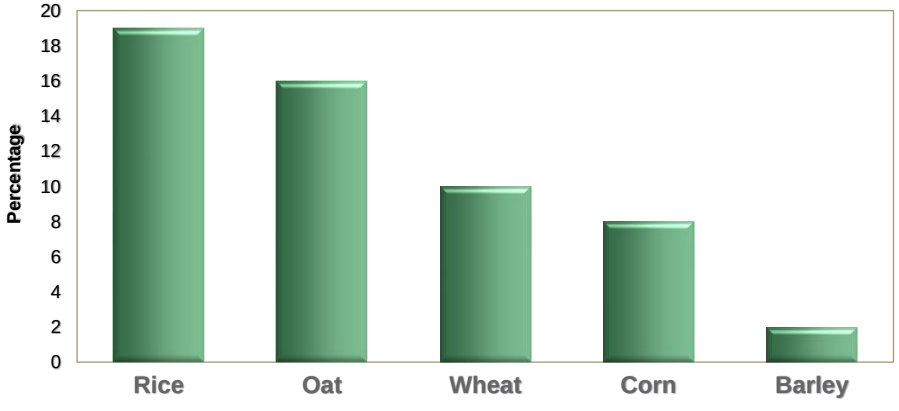
Ruffner et al, *J Allergy Clin Immunol:* In Practice 2013; 1:343-349.

23

Grains That Trigger FPIES



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Ruffner et al, *J Allergy Clin Immunol:* In Practice 2013; 1:343-349.

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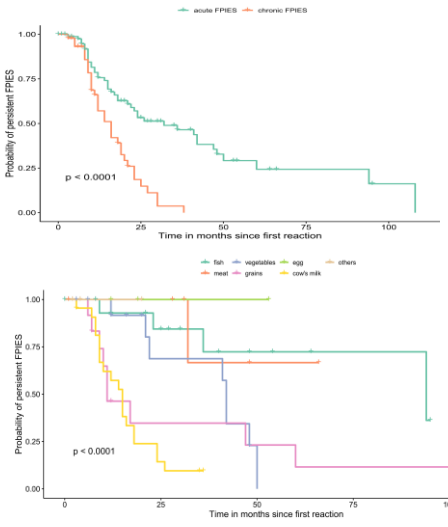
FPIES in Germany

- 142 children
- 84% only to one food
- IgE sensitization in 14% but only 2 had IgE symptoms
- Milk was most common



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Lange et al, J Allergy Clin Immunol 2021

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Most Commons Foods Worldwide

Country/Region	Most common triggers (%)		
Australia	Rice (45.0)	CM (31.5)	Egg (12.0)
Chile	CM (58.1)	Vegetables[a] (37.1)	Rice (22.6)
France	CM (45.5)	Fish (17.0)	Egg (13.5)
Germany	CM (28.0)	Fish (27/0)	Vegetables[b] (24.0)
Greece	Fish (44.4)	CM (40.4)	Egg (6.0)
Italy	CM (38.8)	Fish (10.7)	Egg (6.0)
Japan	Egg (42.0)	CM (23.0)	Soy (11.0)
Spain	Fish (39.3)	CM (35.9)	Egg (10.3)
Sweden	CM (26.0)	Fish (25.0)	Oat (22.0)
East Mediterranean	CM (47.8)	Egg (36.0)	Fish (26.9)
UK	CM (35.0)	Fish (14.5)	Egg (14.5)
USA	CM (39.1)	Grains (28.4)	Soy (24.9)

[a] Includes carrot, squash, potato, tomato, zucchini, chard, spinach, lettuce, broccoli, and cauliflower. [b] Includes potato, pumpkin, carrot, sweet potato, turnip, cabbage, soy, mushroom, courgette, cauliflower, and green bean.

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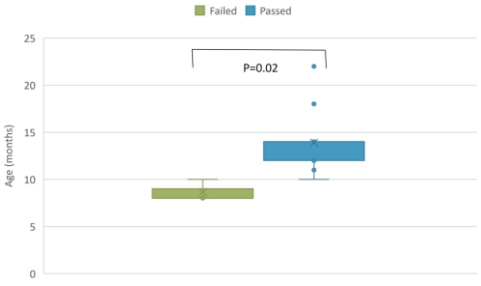
Baked Milk FPIES

- 9/11 patients tolerated baked milk that reacted to raw milk
  - Confirmed by food challenges to baked milk
  - Challenge from 1-11 months after reaction to raw milk



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Faitelson et al, *J Allergy Clin Immunol:* In Practice 2023

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Pathogenesis

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Pathophysiology: Role of TNFα

- Degree of expression increased in patients with villous atrophy
- Was not seen in control patients

Fig. 6 TNFα expression in both epithelium and mononuclear cells in the lamina propria.

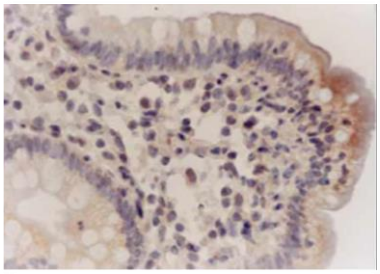
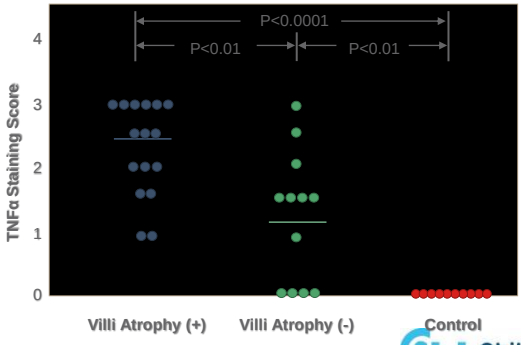


Fig. 7 Mucosa TNFα expression is significantly higher in patients with villous atrophy than in patients without villous atrophy and control subjects.



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Chung, et al. *JACI* 2002;109:150-4.

29

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Mucosal Finding

- From mucosal biopsy:
  - ↑TNF-a
  - ↓TGF-b receptor
- From serum:
  - ↑ IL-10
  - ↑ IP-10 (CXCL-10)
  - ↓ Latent TGF-b produced by PBMCs in response to food protein
- Colonoscopic findings:
  - Decreased vascularity, friability, ulceration
- Upper endoscopic findings:
  - Gastric edema, erythema and mucosal friability and erosion among vomiting and failure to-thrive infants

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Su et al. Ann Allergy Immunol 2021

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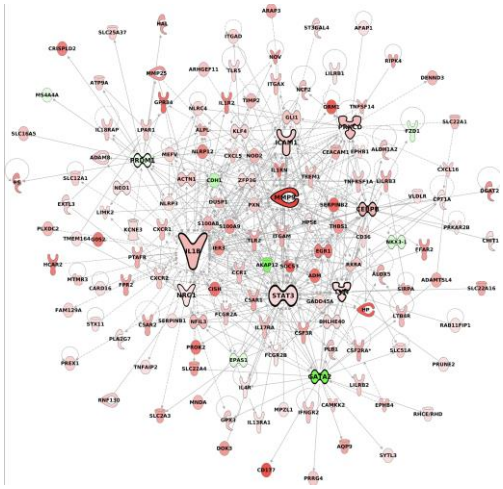
Unbiased Gene Expression:

- Examined pre/post OFC samples
  - 198 upregulated genes after OFC
  - RNA sequencing on the samples
  - TNF, LPS, CSF 2 and 3, IL-13, CEBPA, *IL1B*, IL-6, *TGFB1*, and *IFNG*



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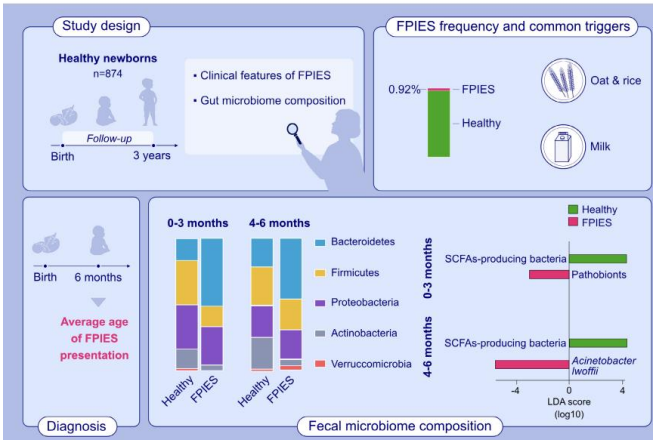
Mehr et al J. Allergy Clin Immunol 2019

31

Pathogenesis: Dysbosis

- Microbiome
  - In a pilot study, there was dysbiosis with less Bifidobacterium and increased bacteroides fragilis (Su et al, Allergy 2023)
  - 8 children with FPIES



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Su et al, Allegy 2023

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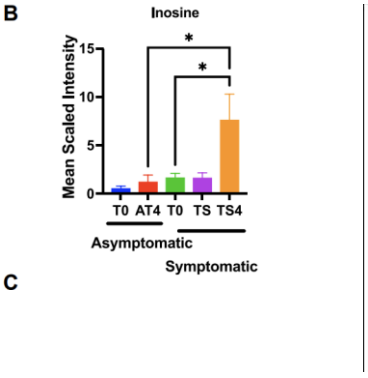
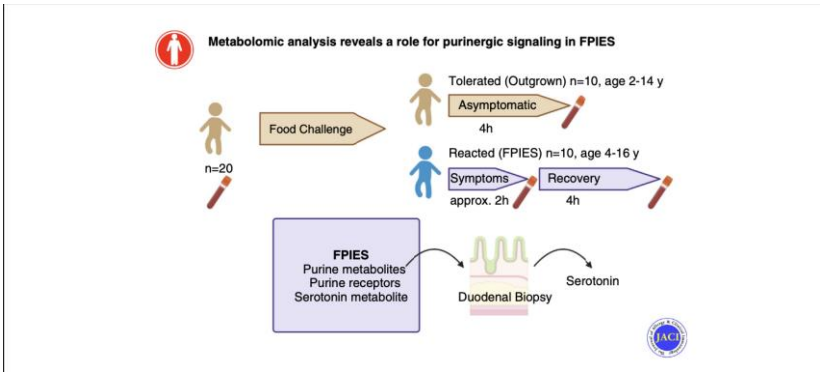
Pathogenesis

- Increase in Serotonin and adenosine





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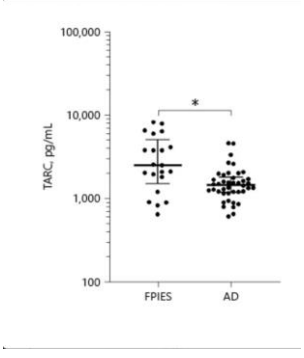
Lorenzo-Ojalvo et al, J Allergy Clin Immunol 2023

33

Role of TARC

- Elevated in patients during FPIES food challenge but not IgE food challenge
- Higher levels than AD



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Makita et al. Pediatr Allergy Immunol 2022; Makita et al Int Arch Allergy Immunol 2022

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Cytokine Expression in CD3+ Cells

- DBPCFC to rice in an 8 month old
- Measured intracellular T cell expression of IL4 (CD4), IL10 (Treg), and IFNγ (CD8) pre and post challenge during an acute challenge and when tolerance developed 6 months later
- Did not find rise in absolute neutrophil or platelet counts

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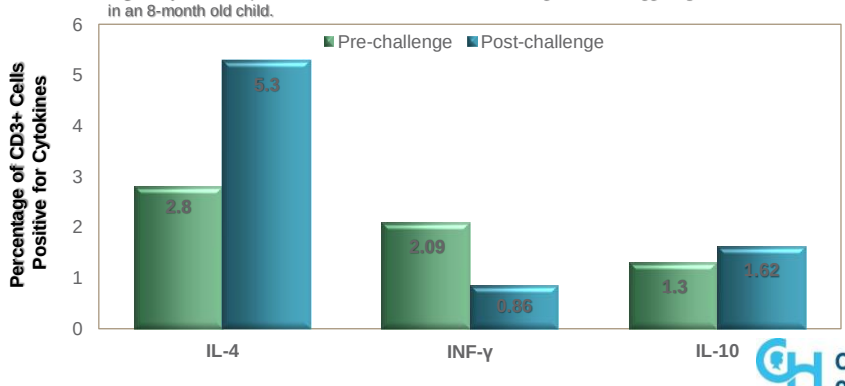
Mori et al. *Clin and Devt. Immunology* 2009.

35

Cytokine Expression in CD3+ Cells: Positive Food Challenge

- Increase in IL4 and decrease in IFN-γ, no change with IL-10
- One thought is that there is a skewing of T cells toward Th2 skewing

Fig. 1 Cytokines expression levels before and after a challenge with rice triggering a FPIES attack in an 8-month old child.



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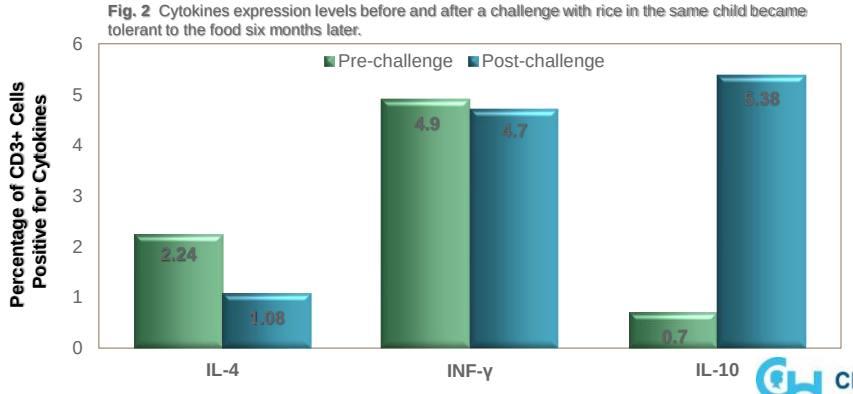
Mori et al. *Clin and Devt. Immunology* 2009.

36

Cytokine Expression in CD3+ Cells: Tolerance Developed

- After 6 months, tolerance developed
- Increase IL10 expression, decreased IL4 response
- IL10 plays important role in regulating Th1 and Th2 cells



Mori et al. *Clin and Devt. Immunology* 2009.

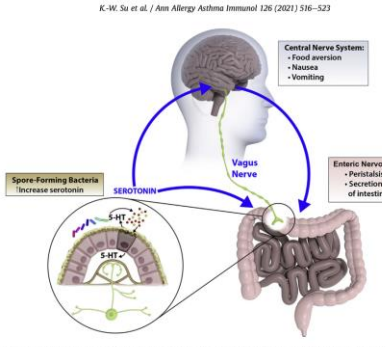


Figure 1. Serotonin might be the key mediator participating in the FPIES and non-IgE–mediated food allergic diseases. Intestinal dysbiosis increased the production of serotonin in the enterochromaffin cells or sensory enteroendocrine cells. Serotonin then affects the peristalsis in the intestine and induced nausea, vomiting, and food aversion in the central nervous system. 5-HT, 5-hydroxytryptamine; FPIES, food protein–induced enterocolitis syndrome; IgE, immunoglobulin E.

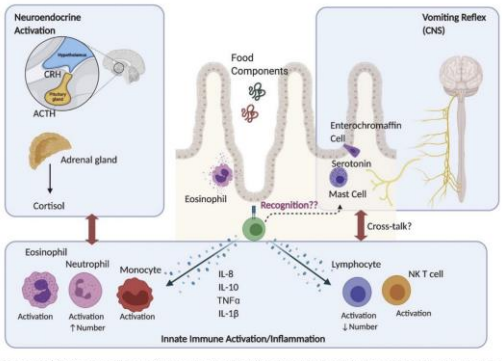


Figure 1. The pathophysiology of FPIES. Ingestion of the specific triggering food in FPIES leads to activation of 3 systems: the neural pathway leading to vomiting, the innate immune system, and the neuroendocrine system. The mechanism of recognition of foods and the involvement of the immune system in symptoms remain poorly understood. Figure created with BioRender (BioRender, Toronto, Canada). ACTH, adrenocorticotropic hormone; CNS, central nervous system; CRH, corticotrophin-releasing hormone; FPIES, food protein–induced enterocolitis syndrome; IL, interleukin; NK, natural killer; TNFα, tumor necrosis factor α.

M.C. Berin / Ann Allergy Asthma Immunol 126 (2021) 478–481

Treatment of Reactions

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Treatment of Acute Reaction

Ondanestron

- John Hopkins
  - 5 consecutive patients responded with 10-30 minutes after medications
  - Patients reacted 2 hours after ingestion
  - All had IV fluids
  - Did not respond to oral
  - No control group

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Holbrook et al, *J Allergy Clin Immunol.* 2013; 132(5):1219-1220.

40

Treatment of Acute Reaction

- Intravenous fluid boluses
- Supportive care
- Epinephrine does NOT help
- Ondansetron (works on serotonin pathway)

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FPIES Challenge Update

- 1-3 doses
  - Lower dose: 1/3 serving dose
- IV vs no IV

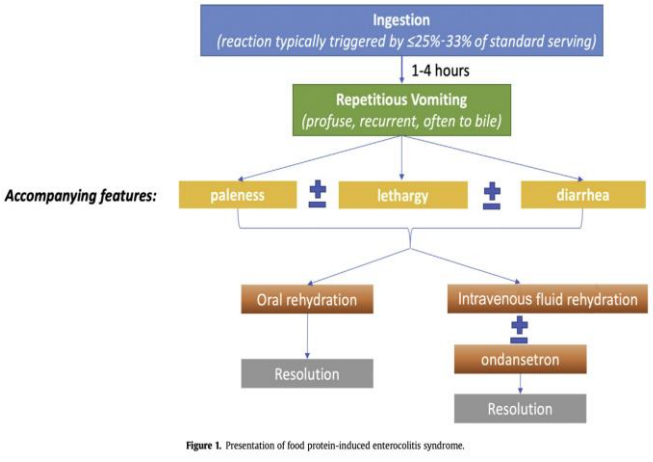

Figure 1. Presentation of food protein-induced enterocolitis syndrome.

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Conclusion

- FPIES is a non-IgE mediated disease
- Presents in infancy in most cases
- Symptoms – vomiting, hypotension
- Most common foods – milk and soy
- Outgrown – 3 yr (but can last into adulthood)

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Updates in Immunodeficiency

Presented by:

Kelli Williams, MD, MPH

Friday, June 23, 2023

11:30 a.m. – 12:15 p.m.

Clinical Updates in Immunodeficiency

Kelli W. Williams, M.D., M.P.H.
williamske@musc.edu

Changing What's Possible

musc Children's Health Medical University of South Carolina

1

Disclosures

- Advisory Board/Steering Committee Participant
  - Horizon Therapeutics, Pharming Healthcare, Enzyvant, Pfizer, Kenota Health
- Consultant for GSK (ended)
- Industry Sponsored Clinical Trial Investigator
  - Regeneron (ended), GSK, and ADMA

- *Off-label use of immunomodulators will be discussed*
- *Clinical recommendations are evidence-based and free of commercial bias*

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Learning Objectives

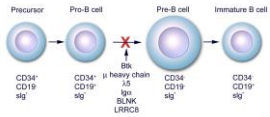
- To describe how the clinical presentation of immunodeficiency has evolved and expanded in the last 10 years
- To identify key clinical red flags concerning for possible inborn error of immunity (IEI)
- To discuss the importance of identifying a genetic cause and how this can impact medical management

From PID to IEI?

- Inborn errors of immunity (IEI – formerly called primary immunodeficiencies or PI, PID or PIDD) are a group of rare, inborn disorders of the immune system that result from:
  - Absent or reduced number of immune cells
  - Absent or reduced function of immune cells
- Increased risk for recurrent or severe infections
- Increased risk for autoimmunity, lymphoproliferation and hyperinflammation (e.g. PIRD)

The Early Years

- 1952: 1st described case of primary immunodeficiency
  - 9 month old boy found to have recurrent pneumonia, URIs, and ear infections
  - No detectable serum immunoglobulins
  - Treated with IM immunoglobulin therapy
- 1993: BTK gene defect identified as causative



X-Linked Agammaglobulinemia (XLA)

Changing What's Possible

Bruton O. *Pediatrics* 1952.
Vetrie et al. *Nature* 1993; 361: 226.

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The Early Years

- 1971: "Bubble Boy" was born
- Prior brother died at age 7 months from severe infection, later found to have X-SCID
- Precautions taken early, lived in bubble 12 years until transplanted

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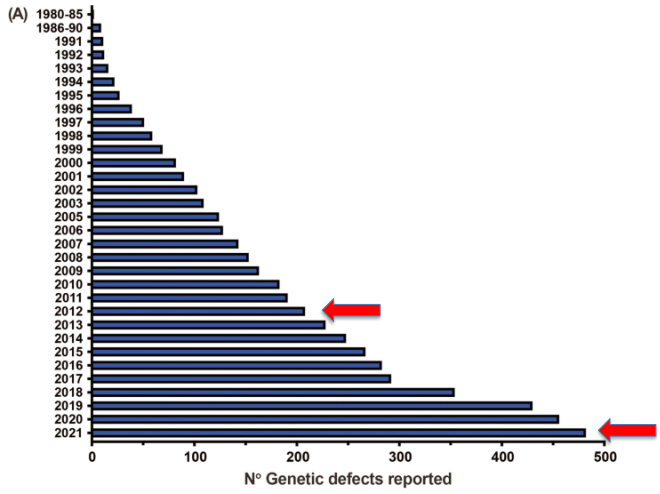
The Story of David, IDF

6

IEI Over the Years



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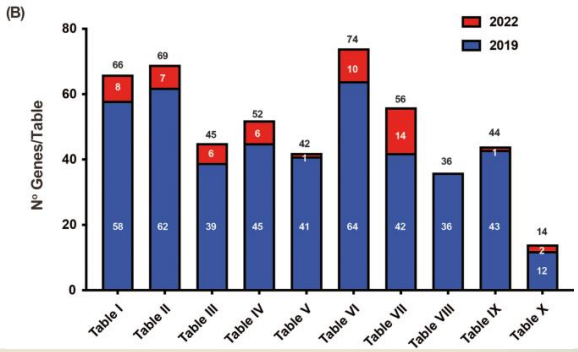
Tangye et al. *JCI* 2022; available online.

7

Frequency & Distribution of IEIs

- Incidence: 1/700-1,000,000 (2:1, ♂:♀)
- Distribution



I. Combined/T-B deficiencies

II. CID + syndromic features

III. Predominantly antibody

IV. Immune dysregulation

V. Phagocytic defects

VI. Intrinsic or Innate

VII. Autoinflammatory disorders

VIII. Complement deficiency

IX. Bone marrow failure

X. Phenocopies of PID

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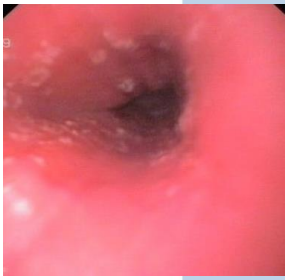
Tangye et al. *JCI* 2022

8

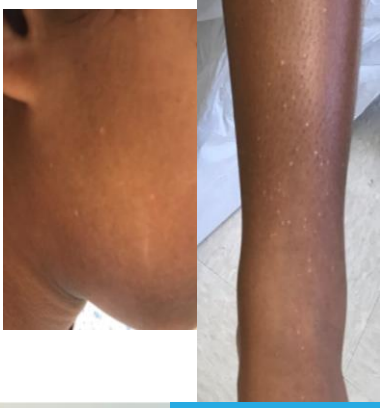
Case 1

- 7 year old African American female with recurrent “oral ulcers”
  - Seen in dental clinic for ulcers, which were swabbed and + *C. albicans*
  - By age 9 she was seen by ID and GI for recurrent oral and esophageal candidiasis
  - Responsive to fluconazole, but recurrences q3 months for the last 2 years
  - EGD showed gastritis, esophagitis with ulcerations and candidiasis



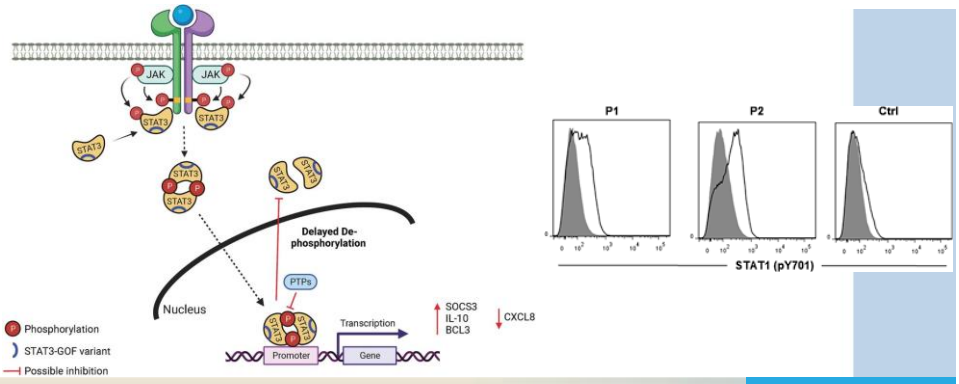
Case 1

- History of recurrent & difficult to treat thrush in infancy
- History of chronic ear infections starting at age 6 months, 2 sets of tubes
- History of recurrent and prolonged URIs, 10 day hospitalization for RSV at age 18 months
- History of Hashimoto’s thyroiditis since age 4
- 1 CXR proven pneumonia
- 2 year history of diffuse flat warts



JEM Journal of Experimental Medicine

Gain-of-function human *STAT1* mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis



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Clinical Phenotype in STAT1 GOF

- Chronic mucocutaneous candidiasis
- Disseminated Coccidioidomycosis or Histoplasmosis
- Recurrent sinopulmonary infections
- Systemic or atypical viral infections
  - HSV, VZV, then CMV, EBV, HPV, molluscum
- Significant autoimmunity starting in childhood
  - Thyroid, T1DM, cytopenias, vitiligo, alopecia, SLE
- Cerebral aneurysms

Vinh et al. *Blood* 2010; 115: 1519.

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Case 2

- HPI: 20 year old female presented to PCP clinic with flare of her psoriasis and is noted to have moderate cervical lymphadenopathy
  - ITP diagnosed at age 4 after presenting with petechiae and large hematoma after a fall
    - Ongoing recurrences of ITP despite IVIG, Rho(D), IVIG + steroids
    - Bone marrow evaluation not concerning for malignancy
  - Diagnosed with autoimmune hemolytic anemia, intermittent neutropenia, and T cell lymphopenia at age 8
  - Found to have IgA deficiency at age 9
  - Developed chronic abdominal pain and bloody diarrhea at age 10, diagnosed as IBS
  - Diagnosed with psoriasis at age 14

Case 2

- Immune evaluation identified low IgG, low IgA, normal IgM, CD4 lymphopenia, inverted CD4/CD8 ratio, decreased class switched memory B cells
- ALPS flow not suggestive
- Colon biopsies showed colitis, crypt apoptosis, absence of goblet cells
- Bone marrow repeated and no evidence of malignancy
- Cytogenetics reassuring
- Bone Marrow Failure gene panel negative

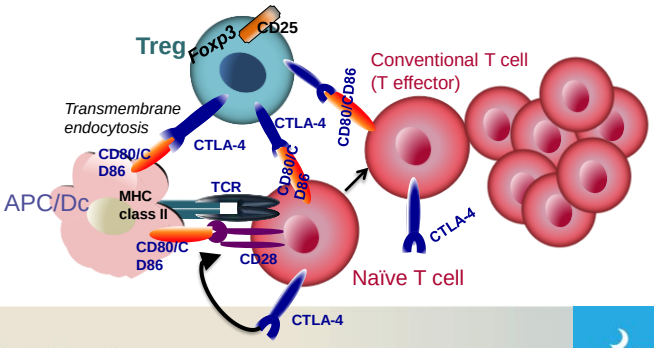
Case 2

- Pertinent family history
  - Father has lung and GI lymphocytic, CVID, splenomegaly, and cytopenias
  - Two older sisters with autoimmune thyroiditis
  - One sister with chronic sinusitis
  - Younger brother with recurrent ear infections s/p tube placement and chronic diarrhea (diagnosed as celiac disease based on pathology)

IMMUNODEFICIENCY

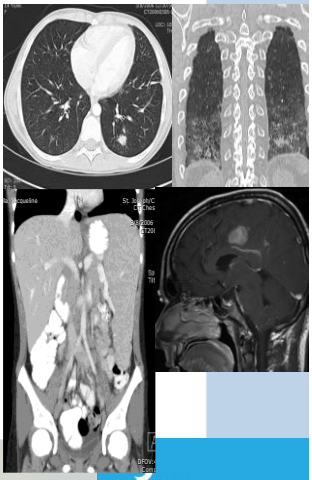
Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4

Hye Sun Kuehn,[1*] Weiming Ouyang,[2*] Bernice Lo,[3,4*] Elissa K. Deenick,[5,6] Julie E. Niemela,[1] Danielle T. Avery,[5] Jean-Nicolas Schickel,[7] Dat Q. Tran,[8] Jennifer Stoddard,[1] Yu Zhang,[4,9] David M. Frucht,[2] Bogdan Dumitriu,[10] Phillip Scheinberg,[10] Les R. Folio,[11] Cathleen A. Frein,[12] Susan Price,[3,4] Christopher Koh,[13] Theo Heller,[13] Christine M. Seroogy,[14] Anna Huttenlocher,[14,15] V. Koneti Rao,[3,4] Helen C. Su,[4,9] David Kleiner,[16] Luigi D. Notarangelo,[17] Yajesh Rampertaap,[18] Kenneth N. Olivier,[18] Joshua McElwee,[19] Jason Hughes,[19] Stefania Pittaluga,[16] Joao B. Oliveira,[20] Eric Meffre,[7] Thomas A. Fleisher,[1†] Steven M. Holland,[4,18] Michael J. Lenardo,[3,4†] Stuart G. Tangye,[5,6] Gulbu Uzel[18†]



Heterozygous Germline Mutations in *CTLA-4* Cause Autoimmunity, Immune Dysregulation and Lymphoproliferation by Haploinsufficiency

- Brain and pulmonary lymphocytic infiltrates and/or nodules
- GI enteropathy
- Hepatosplenomegaly
- Lymphadenopathy
- Recurrent sinopulmonary infections
- Recurrent *C. diff* infection
- Susceptibility to viral infections, EBV, warts



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Schubert et al. *Nature Medicine* 2014; 20: 1410. Schwab et al. *JACI* 2018; 142: 1932.

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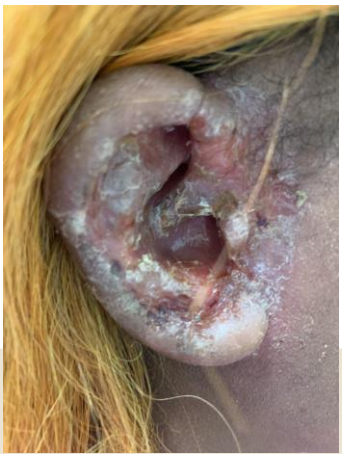
Case 3

- HPI: 19 yo girl presented with refractory ear eczema, chronic otitis externa and poor wound healing



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Case 3

- **Other pertinent medical history**
  - Diagnosed as CGD carrier at age 13
    - Missense mutation of C→T in exon 9 of the CYBB gene (T362I)
  - Recurrent skin abscesses & lymphadenitis starting at age 15
  - Eczema started at age 15
    - Patch test + nickel
    - Treated with topical steroids, prednisone and countless antibiotics
    - Treated with dupilumab
  - Open breast wounds by age 15
    - Treated with prednisone and adalimumab
  - Chronic otitis externa started at age 18

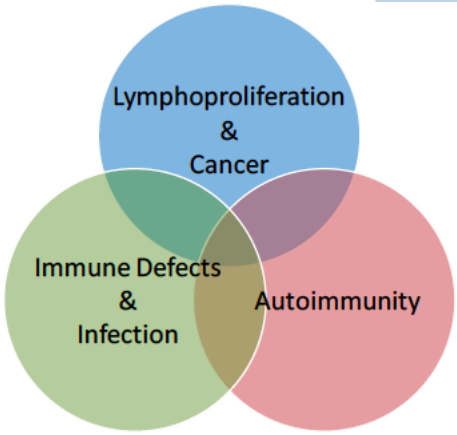
What is a PIRD?

- Primary immune regulatory disorders (PIRD) are a group of rare, inborn disorders of the immune system that result in manifestations of immune-mediated pathology, namely:
  - Affecting initiation of inflammation (e.g. inflammasomopathies)
  - Control of self-reactivity (e.g. IPEX, CTLA4, LRBA)
  - Strength of immune activation (e.g. HLH)

Chan et al. *Front Immunol* 2020; 11: Article 239.

Clinical Manifestations of Immune Dysregulation

- Altered regulation of the immune response
- Often results from dysregulated self-tolerance
- Clinical features include:
  - Lymphoproliferation, autoimmunity, hyperinflammation, increased susceptibility to infection and malignancy
- Often presents with organ-specific autoimmunity



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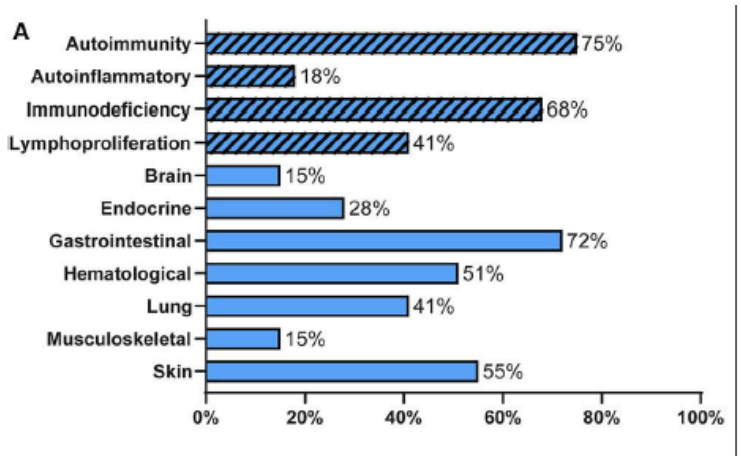
Organ Specific Autoimmunity in PIRD



Chan et al. *Front Immunol* 2020; 11: Article 239.

Chan et al. *Front Immunol* 2020; 11: Article 239.

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	PIDD	PIRD
Age of Onset	Bimodal (young children, late adulthood)	Early (first condition commonly diagnosed by age 2)
Primary Clinical Manifestations	-Infections (recurrent, severe, opportunistic) -May develop autoimmunity with time	-Autoimmunity (multiple disorders, early) -Autoinflammation -Benign lymphadenopathy (marked, diffuse) -May have infections but not a prominent feature
Main Treatments	-Antimicrobials -Immunoglobulin replacement -Chronic immunosuppression (e.g. steroids, targeted biologics) -HSCT or Gene Therapy	-Immunomodulation and/or immunosuppression (e.g. steroids, targeted biologics) -HSCT or Gene Therapy

Infectious Manifestations of IEI

- Recurrent bacterial sinopulmonary infections
- Recurrent, severe or deep seated pyogenic bacterial infections
- Recurrent fungal infections (e.g. oral thrush, esophagitis, vaginal, nail, skin)
- Opportunistic and live viral vaccine-related infections (e.g. Rubella skin granulomas)
- Diffuse cutaneous viral infections (e.g. warts, Herpes simplex, Molluscum, Varicella)
- Susceptibility to unusual or atypical pathogens (e.g. *Burkholderia, Aspergillus, Mycobacterium*)
- HSV encephalitis
- Recurrent *Neisseria* meningitis
- Persistent CMV or EBV viremia

Non-Infectious Manifestations of IEI

- Autoimmunity (e.g. early onset, cytopenias, multiple forms of organ-specific autoimmunity)
- Autoinflammation (e.g. recurrent fevers +/- rashes, arthralgias, abdominal pain, oral ulcers)
- Lymphoproliferation (e.g. lymphadenopathy, hepatomegaly, splenomegaly)
- Inflammatory bowel disease (e.g. early onset, treatment refractory)
- Interstitial lung disease or non-CF related bronchiectasis
- Severe or refractory atopic dermatitis (+/- markedly elevated IgE, hypereosinophilia)
- Failure to thrive
- Malignancy (e.g. leukemia, lymphomas)

Laboratory Evaluation of PIDD

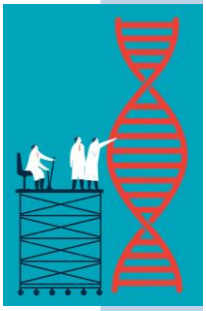
Category	Examples	Diagnostic lab test
Humoral defect	Selective IgA Deficiency, X-linked agammaglobulinemia, Combined Variable Immune Deficiency	-CBC, serum immunoglobulins and lymphocyte flow cytometry -Vaccine titers (S. pneumo, tetanus, diphtheria
Cellular defect	DiGeorge Syndrome, Wiskott-Aldrich Syndrome	-CBC and lymphocyte flow cytometry → LOOK AT ALC -Antigen & mitogen proliferation
Combined defect	Severe combined immunodeficiency, Ataxia-Telangiectasia	-Send all of the above (humoral and cellular defects) **NOW TREC ON NBS**
Phagocytic disorders	Chronic granulomatous disease, Leukocyte Adhesion Deficiency	-CBC → LOOK AT WBC, ANC -Flow cytometry (DHR, CD18/CD11b)
Complement deficiency	C1q/r/s, C2-C9 deficiency	-CH50 -AH50, Factor H,B,I,D, Properdin

Laboratory Findings in PIRD

Category	Examples	Common Lab Findings
PIRD	STAT3 GOF, LRBA, CTLA4, APDS, ITCH deficiency, BACH2	-Low or Normal IgG -Occasionally elevated IgM -Occasionally elevated IgE -Impaired specific antibody production (vaccine response) -Lymphocytes usually normal -Decreased class switched memory B cells -Inverted CD4/CD8 -Increased T cell activation markers (HLA-DR, CD38, CD69) -Elevated sIL2R -Varying Treg numbers & function

Genomic Concepts in Immunity

- ~10-12% of human coding genes are involved in the immune system
- That translates into ~2400 genes linked to immune function
  - Adaptive immunity involves ~700 genes
  - Innate immunity involves ~1700 genes
- To date, there are now >500 monogenetic diseases of the immune system
  - Most pathogenic variants cause loss of function
  - Now several genes with either loss or gain of function
  - Growing list of digenic diseases

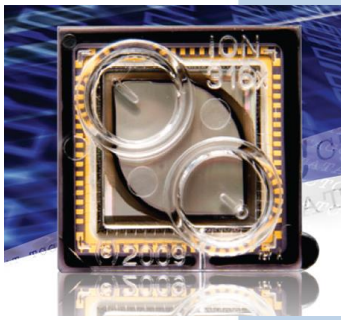


Why Reach a Genetic Diagnosis?

- Establishes a definitive diagnosis
- Provides a prediction of disease severity
- Identifies patients at higher risk for malignancy and thus closer surveillance
- Provides opportunity to screen for others at risk patients and provide family counseling
- Increases understanding of a specific disorder and genetic mechanisms involved
- Can identify new potential therapeutic targets
- Can improve survival and outcomes

Beyond One Gene: NGS

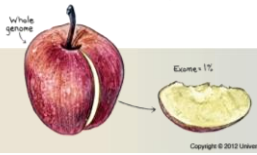
- Next generation sequencing (NGS)
  - Targeted panel of genes
  - High throughput
  - Lower cost than sanger sequencing
  - Nonbiased evaluation
  - Cost effective



***Generally speaking, this is often first line for IEI genetic evaluations

Beyond One Gene: WES, WGS

- Whole exome sequencing (WES)
  - Evaluates all and only exons
  - Intermediate to high coverage and depth
  - Estimated to pick up a<50% of disease causing mutations
  - Moderate cost
- Whole genome sequencing (WGS)
  - Evaluates all coding and noncoding base pairs
  - Low to intermediate coverage
  - High cost

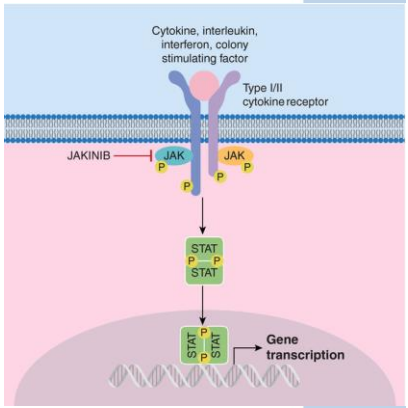


Current Treatment Options

- TREAT and PREVENT INFECTIONS
- Humoral deficiency or dysfunction
  - Prophylactic antibiotics
  - Immunoglobulin replacement (IV, SC)
- Cellular deficiency or dysfunction
  - Prophylactic antibiotics
- Immune dysregulation
  - Immunomodulators or immunosuppressants
- When applicable, hematopoetic stem cell transplant or gene therapy

Back to Case 1: STAT1 GOF

- **Recap: 7 yo F with chronic mucocutaneous candidiasis (CMC), diffuse flat warts, oral ulcers, Hashimoto's thyroiditis**



- Started on daily fluconazole with complete resolution of CMC
- Now on ruxolitinib with reduced warts, controlled autoimmunity

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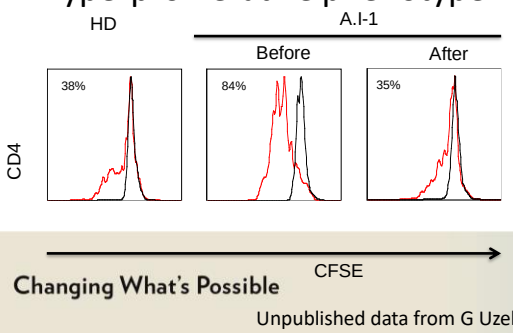
Back to Case 2: CTLA-4

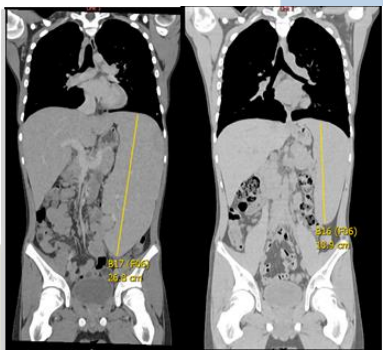
- **Recap: 30 yo F with psoriasis, lymphadenopathy, and autoimmuno cytopenias**
- Abatacept is a soluble fusion protein on the extracellular domain of CTLA-4
- In the lab, abatacept rescues *ex vivo* T cell hyperproliferative phenotype



Unpublished data from G Uzel

Pre- Tx

4 months of Tx



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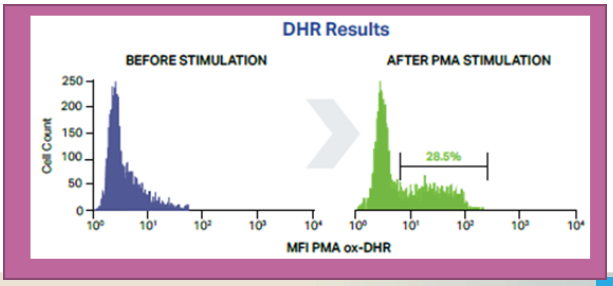
Back to Case 3: CGD

Recap: 19 yo F with poor wound healing, ear eczema, chronic otitis externa

- Skin biopsy showed deep non-necrotizing granulomatous inflammation
- DHR: 28.7% PMA ox-DHR; MFI 10.78



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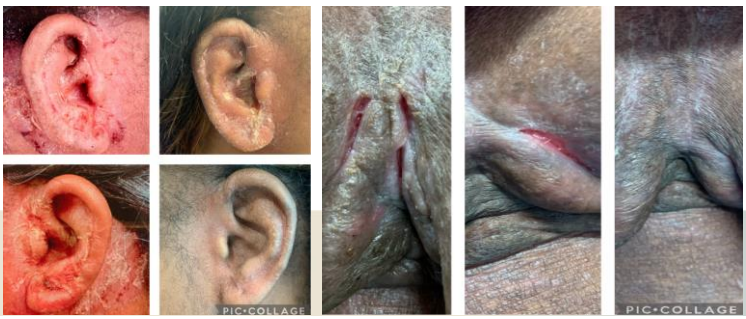
Back to Case 3: CGD

- Started on triple therapy with trimethoprim-sulfamethoxazole, Itraconazole, and interferon gamma-1b
- Since starting this regimen, no abscesses, no lymphadenitis, chronic otitis externa, improved wound healing



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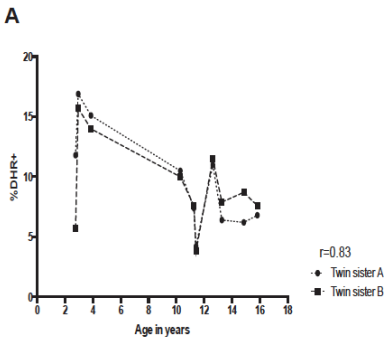
X-Linked CGD Carriers Can Change Over Time



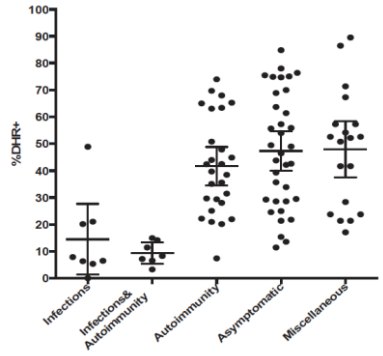


FIG 2. Clinical features by %DHR$^+$ values. %DHR$^+$ values according to clinical manifestations are shown, and values are presented as means with 95% CIs.

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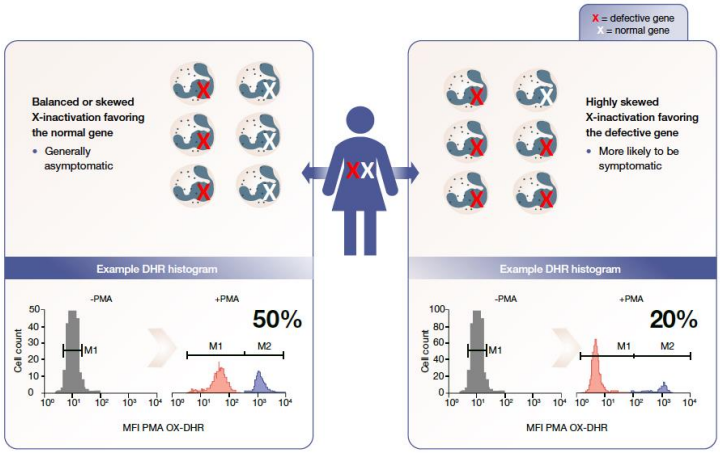
Marciano et al. *JACI* 2018; 141: 365-371.

X-Linked CGD Carriers Can Change Over Time



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Genetics Can Change Medical Management!

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TABLE 3 Example of targeted therapies for patients with genetically defined primary immune regulatory disorders

Condition	Gene	Targeted therapy
IPEX	*FOXP3*	Tacrolimus Cyclosporin Sirolimus
STAT1 GOF	*STAT1*	Ruxolitinib (JAK 1/2 inhibitor) Sirolimus
STAT3 GOF	*STAT3*	Tocilizumab (IL-6 receptor blocker) Siltuximab (IL-6 blocker) Ruxolitinib (JAK 1/2 inhibitor)
LRBA deficiency	*LRBA*	Abatacept Sirolimus Hydroxychloroquine
CTLA4 haploinsufficiency	*CTLA4*	Sirolimus Abatacept
APDS	PIK3CD PIK3R1	Sirolimus Leniolisib (PI3K inhibitor)
XIAP and NLRC4	BIRC4 NLRC4	IL-18 binding protein
Primary HLH	PRF, UNC13 D STX11, STXBP2	Emapalumab (IFN-γ blocking antibody) Ruxolitinib (JAK 1/2 inhibitor)

Genetics Allow for our Practice of Precision Medicine

Chandrakasan et al. *Pediat Blood Cancer* 2019.

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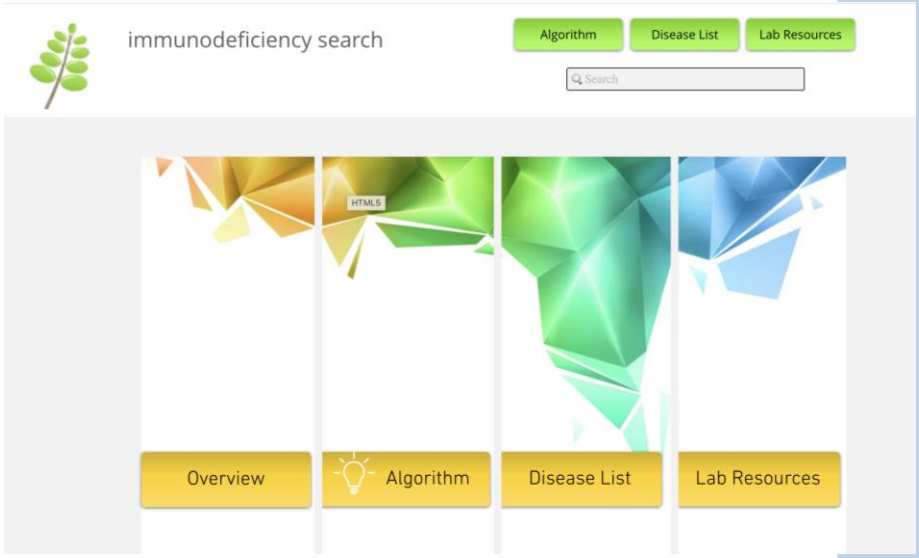
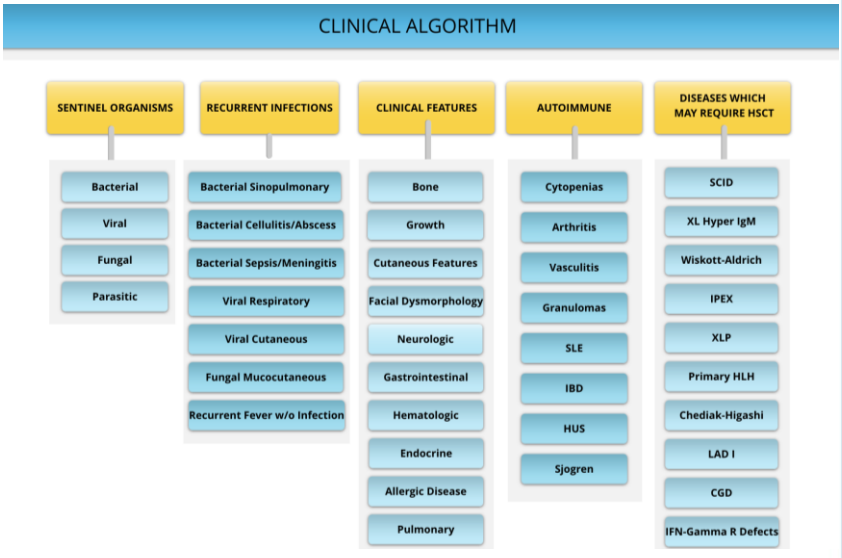


Changing What's Possible https://www.immunodeficiencysearch.com/



Changing What's Possible https://www.immunodeficiencysearch.com/

There's an App for That!

Clinical Immunology Red Flags & When to Refer

- Severe infections with common pathogens
  - Deep tissue infections (empyema, meningitis)
  - Unusual sites of infection (liver or brain abscess)
- Opportunistic infections
  - Mycobacterial infections
  - Live virus vaccine associated illnesses
- Chronic diarrhea with FTT, VEO-IBD or refractory enteropathy
- Severe atopic disease
- Early onset autoimmune disease(s)
- Difficult to manage lymphocytic infiltrates

They're out there

williamske@musc.edu

PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Mayer A. Green Allergy Foundation Memorial Lecture: Eosinophilic Esophagitis: Update on Treatment and Diagnosis

Presented by:

Jonathan Spergel, MD, PhD

Friday, June 23, 2023

12:15 p.m. – 1:00 p.m.

EoE: Diagnosis and treatment updates

Jonathan M. Spergel, MD, PhD
Perelman School of Medicine, University of Pennsylvania
Children's Hospital of Philadelphia
Philadelphia, PA
spergel@chop.edu

Children's Hospital of Philadelphia

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Learning Objectives

- *Describe symptoms of Eosinophilic Esophagitis*
- *Review evidence-based treatments for Eosinophilic Esophagitis*
- *Identify monitoring of EoE patients*

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Disclosures

- Speaker: Medscape (WedMD)
- Grants: Sanofi, Regeneron, Novartis, Astra-Zeneca, Celegene/BMS, FARE, NIH
- Consultant: Regeneron/Sanofi, Ready Set Food, Novartis,
- Royalties: Uptodate

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2011 Consensus Report

- Panel of 33 physicians (6 months)
- Conceptual Definition
  - *"Eosinophilic esophagitis represents a chronic, immune/antigen mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation"*
- Pediatric and Adult EoE likely the same disease

Liacouras et al, J Allergy Clin Immunol 2011

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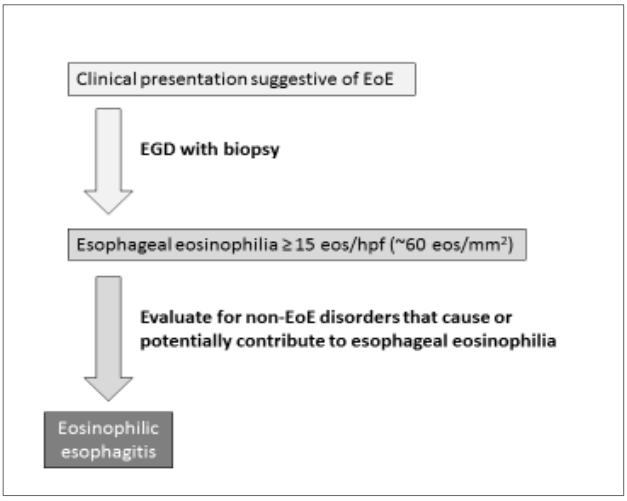
AGREE Conference: 3rd Revision for Diagnostic Criteria for EoE

- Nearly identical transcriptome in the biopsy
  - Difference in K+ channel protein
- 50% of esophageal eosinophilia respond to PPI
- 2 case reports of patients with PPI-REE also responding to diet
- High dose PPI has anti-inflammatory effects acting on Stat-6
- But, some patients do not respond to diet, swallowed CS and respond to high dose PPI



Dellon et al Gastro 2018

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Symptoms of EoE

EoE Clinical Features

- Symptoms vary by age
- Symptoms may be intermittent
- Male> Female
- Untreated Disease may progress to fibrosis

EoE patient	Common Symptoms
Infant	**Food refusal, FTT**, feeding intolerances/aversions, reflux
Children	**Vomiting, dysphagia, abdominal pain**, heartburn, regurgitation, feeding refusal/feeding aversions
Adult	**Dysphagia, food impaction**, heartburn, reflux

Furuta et al, *Gastroenterology* 2007
Spergel et al *J Pediatr Gastroenterol Nutr* 2009

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EoE and Other Atopic Disease

(what to do-Look for EoE in our atopic patients)

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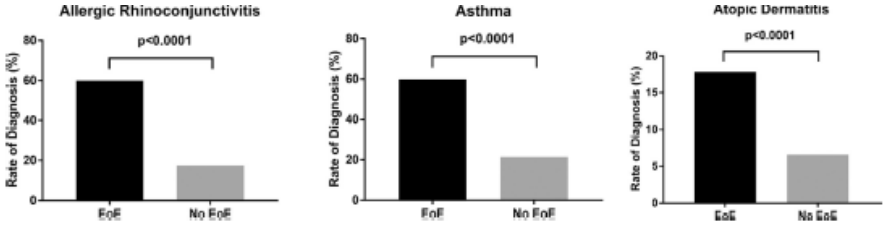
EoE Comorbidities-Pediatrics

	EoE N (%)	No EoE N (%)	*P* value
N Total	428	455,720	
Race			
White	311 (72.7)	238,368 (52.3)	<.001
Black	68 (15.9)	134,037 (29.4)	<.001
Asian/Pacific Islander	15 (3.5)	15,979 (3.5)	>.99
Other	5 (1.2)	5,571 (1.2)	>.99
Unknown	29 (6.8)	61,765 (13.6)	<.001
Ethnicity			
Non-Hispanic	405 (94.6)	430,611 (94.5)	>.99
Hispanic	23 (5.4)	25,109 (5.5)	>.99
Sex			
Male	307 (71.7)	231,264 (50.7)	<.001
Female	121 (28.3)	224,456 (49.3)	<.001



Capucilli et al, Ann Allergy Asthma Immunol 2018

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EoE related disease-Adult Cohort

Demographic Characteristics of the Study Cohorot

Characteristic	No. (%) of patients (N = 950)
Sex	
Male	611 (64)
Female	339 (36)
Race	
African American	69 (7)
Asian	20 (2)
White	842 (89)
Other or unknown	19 (2)
Ethnicity	
Hispanic	24 (3)
Non-Hispanic	926 (97)

Table 3
Comorbid Conditions

Condition	EoE cohort, % (N = 950)	UPHS prevalence, % (N = 3,617,345)
Asthma	36	3.7
Allergic rhinitis	70	3.5
Atopic dermatitis	14	2.8
Food allergy	24	0.49
Pollen food allergy syndrome	34	0.07
Drug allergy	30	0.42
Latex allergy	3	0.1
Anaphylaxis	16	0.24
Autoimmune disease	9[a]	4[a]
Psychiatric disease	21[a]	8[a]

Abbreviations: EoE, eosinophilic esophagitis; UPHS, University of Pennsylvania Health Systems.
[a]Total of each type or subtypes listed in Table 4 and Table 5.

Autoimmune Comorbidities

Comorbidity	EoE cohort, No. (%) (N = 950)	UPHS prevalence, No. (%) (N = 3,617,345)
Celiac disease	19 (2)	4,156 (0.11)
IBD	19 (2)	21,096 (0.58)
Crohn disease	14 (1.47)	9,642 (0.27)
UC	5 (0.53)	11,454 (0.31)
Psoriasis	12 (1.26)	20,708 (0.57)
AI thyroiditis	10 (1.05)	8,880 (0.25)
SLE	10 (1.05)	14,530 (0.40)
Vitiligo	5 (0.53)	9,954 (0.28)
Type 1 diabetes	3 (0.32)	18,573 (0.51)
Graves disease	2 (0.21)	16,542 (0.46)
Dermatomyositis	2 (0.21)	1,245 (0.03)
Scleroderma	2 (0.21)	1,366 (0.04)

Abbreviations: AI, autoimmune; EoE, eosinophilic esophagitis; IBD, inflammatory bowel disease; SLE, systemic lupus erythematosus; UC, ulcerative colitis; UPHS, University of Pennsylvania Health Systems.

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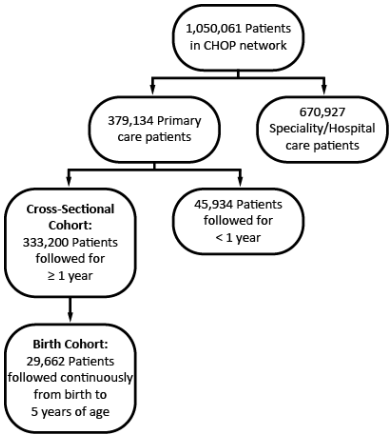
Leigh and Spergel, Ann Allergy Asthma Immunol 2018

9

CHOP Examination of the Atopic March



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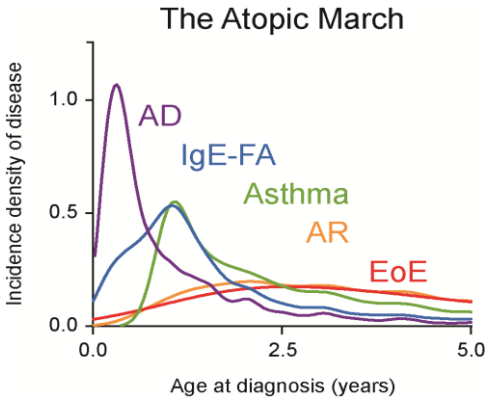
Hill et al, BMC 2016

10

What about EoE?



Primary Diagnosis	Secondary Diagnosis: AD	IgE-FA	Asthma	EoE	AR
AD	-	2.5	1.5	3.2	1.7
IgE-FA		-	1.5	9.1	1.6
Asthma			-	1.9	1.6
EoE				-	2.1
AR					-

Hill, Spergel JACI

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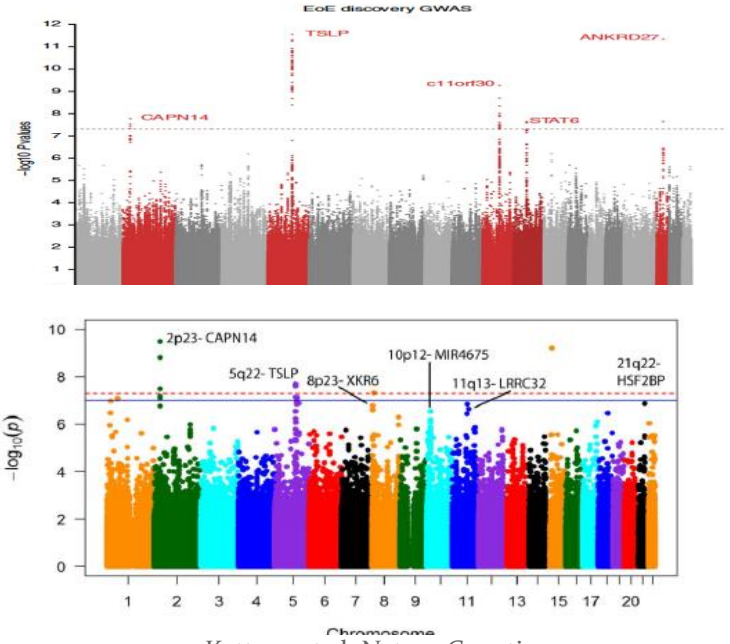

Kattyan et al. Nature Genetics 2014
Sleiman *et al*, Nature Commun 2014

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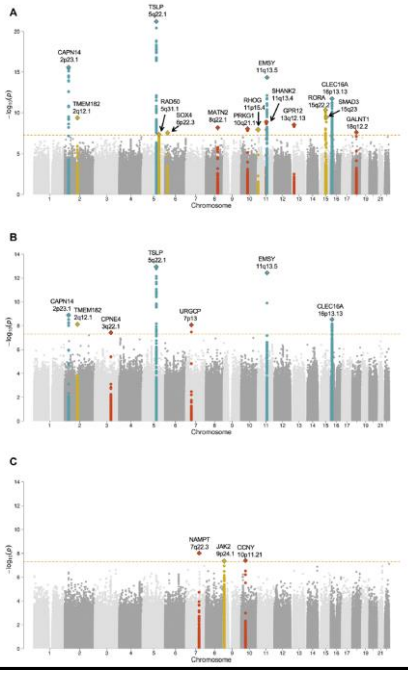

- Examined 4 EoE cohorts
  - 1930 cases, 13,634 controls
- 11 new loci
- 5 common allergic loci
- Most significant MATN2

Chang et al, J Allergy Clin Immunol 2021

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New Genes previous disease and function

Previous identified Diseases

- **SMAD3**- Fibrosis, IBD
- **TMEM**-allergic rhinitis, eczema
- RoRA-immune function, associated with Eos count, atopic disease
- **5q31**-IL3,4,5 loci
- **MATN2** role in mRNA stability, affect T cell differentiation
- **GPR12**-GED, eosinophilia
- **CPNE4**-GERD
- **Sox4**-allergic alveolitis
- **CCNY**-Esophageal disease, eosinophilia
- **Jak2**-IBD, eosinophilia
- **URGCP**-asthma, IBD

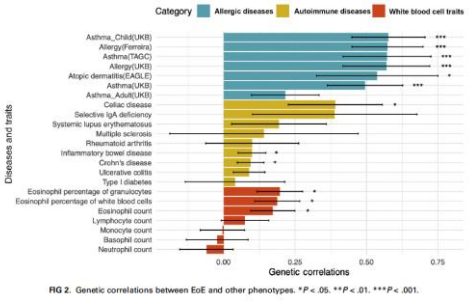

FIG 2. Genetic correlations between EoE and other phenotypes. *P < .05. **P < .01. ***P < .001.

Chang et al, J Allergy Clin Immunol 2021

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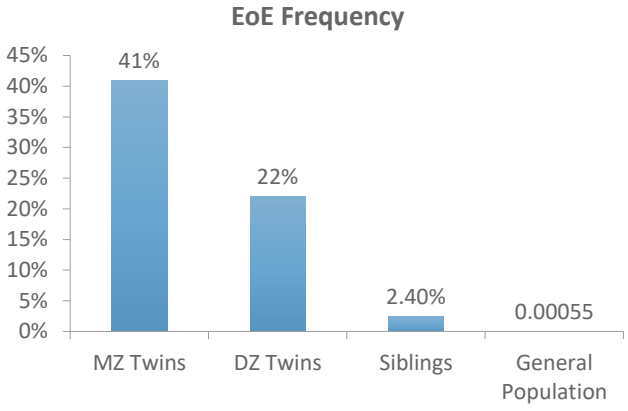
Environmental/Genetic Factors



Alexander et al. J Allergy Clin Immunol 2014

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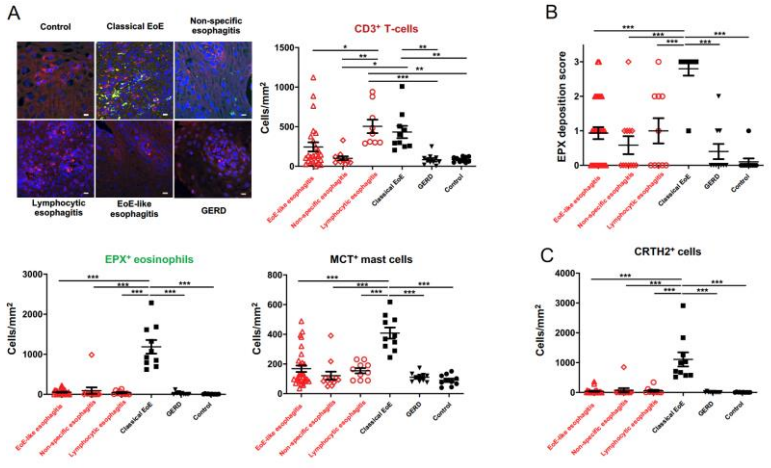
Role of T cells



Guenter et al, Allergy 2022

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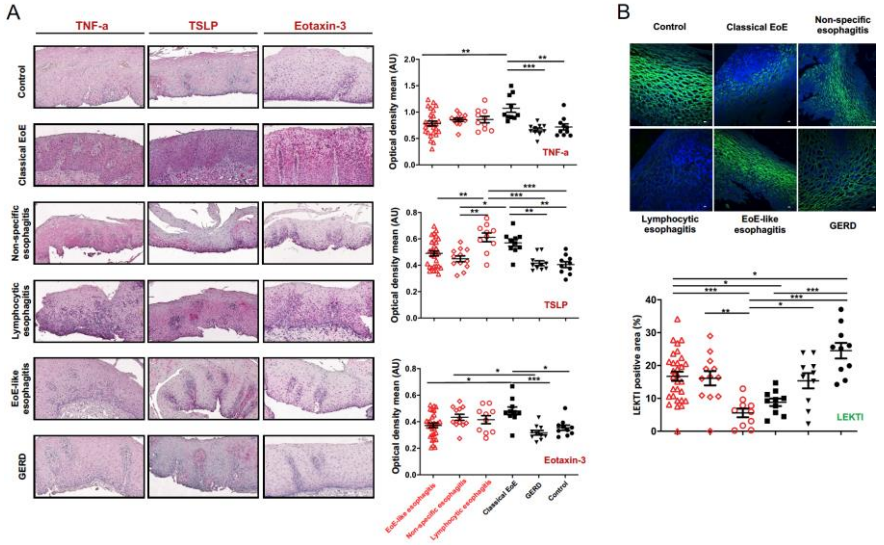
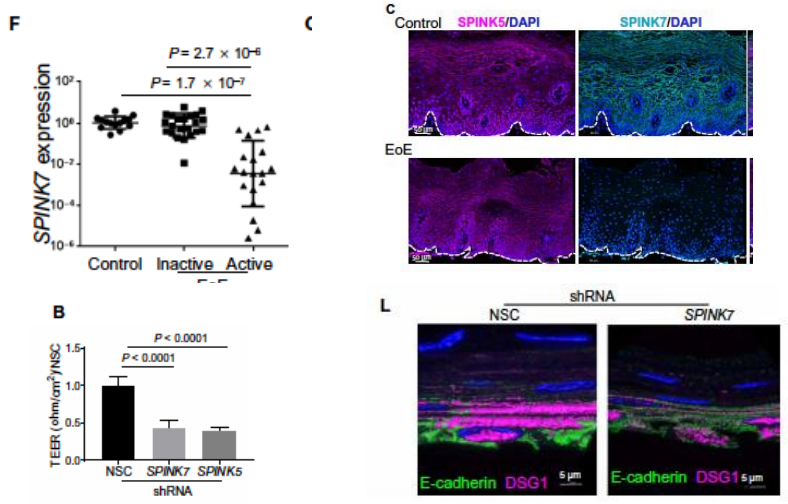
Cytokine



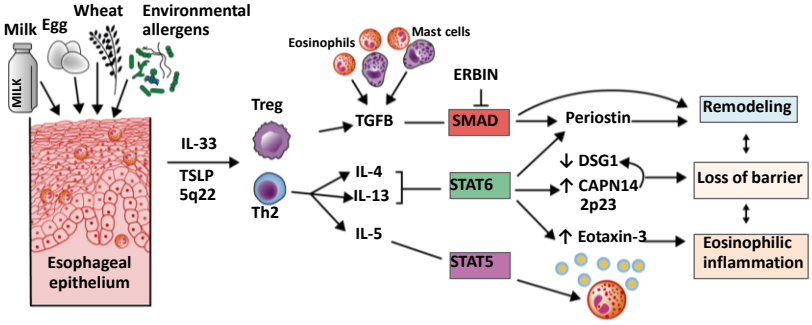
Guenter et al, Allergy 2022

Decrease in SPINK7 leads to barrier dysfunction



Azouz…Rothenberg Sci. Transl Med 2018

Summary EoE Pathophysiology



1. O'Shea KM et al. *Gastroenterology*. 2018;154:333-345.

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Treatment Options

- EoE diagnosis
- Educate family on options

- Nutrition therapy
  - **Elimination diet**
  - **Combination** Elimination diet with elemental supplementation
  - **Elemental diet**
- Pharmacologic therapy
  - **Combination of diet and steroids**
  - **Steroids** Topical or systemic
  - **Biologics**
- Dilation

No disease-modifying treatment or therapeutic option available

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Cianferoni A, Spergel J. *Clin Rev Allergy Immunol.* 2016;50(2):159-174.

20

Budesonide Orodispensible tablets

- Approved in EU in 2018
- 1st trial
  - 88 adults

Any TEAE	37 (62.7)	12 (41.1)
Severe TEAE	0 (0)	1 (3.4)
Esophageal food impaction	0 (0)	1 (3.4)
TEAE related to study drug	23 (39.0)	1 (3.4)
Serious AEs	0 (0)	0 (0)
TEAE leading to withdrawal from the study	0 (0)	1 (3.4)
Esophageal food impaction of severe intensity requiring endoscopic intervention	0 (0)	1 (3.4)
TEAEs by occurring in ≥2 patients in any treatment group		
Gastrointestinal disorders	10 (16.9)	3 (10.3)
Gastroesophageal reflux disease	3 (5.1)	0 (0)
Nausea	2 (3.4)	0 (0)
Infections and infestations	21 (35.6)	6 (20.7)
Suspected local fungal infection,[a] thereof:	14 (23.7)	0 (0)

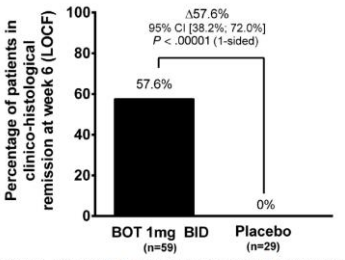

Figure 1. Primary study end point in EoE patients treated with BOT or placebo in the 6-week DB phase. Clinico-histologic remission was defined as achieving both histologic remission (peak eosinophil count <16 eos/mm^2 hpf; equivalent to <5 eos/hpf) at week 6 (LOCF) and clinical remission (symptoms severity of ≤2 points on 0–10 NRS for dysphagia and a severity of ≤2 points on 0–10 NRS for odynophagia on each day in the week before week 6 (LOCF) (1-sided Fisher's exact test). Patients who experienced food impaction needing endoscopic intervention, needed a dilation during the study, or withdrew prematurely were assessed as treatment failure. BID, twice daily; CI, confidence interval; LOCF, last observation carried forward.

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Lucendo et al, Gastro 2019

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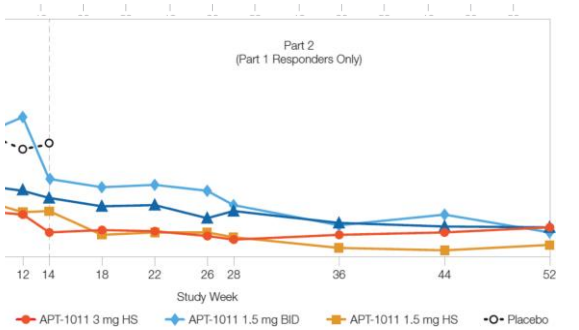
TEAE category	Double-blind dosing group							Total (N = 93)
	APT-1011 3 mg BID (n = 16)	APT-1011 3 mg HS (n = 14)	APT-1011 1.5 mg BID (n = 19)	APT-1011 1.5 mg HS (n = 10)	Placebo (n = 0)	Single-blind APT-1011 3 mg BID (n = 34)	Total APT-1011[a] 3 mg BID (n = 50)	
TEAE[b]	12 (75)	13 (93)	14 (74)	7 (70)	0	22 (65)	34 (68)	68 (73)
Mild	7 (44)	7 (50)	11 (58)	5 (50)	0	17 (50)	24 (48)	47 (51)
Moderate	5 (31)	5 (36)	3 (16)	1 (10)	0	5 (15)	10 (20)	19 (20)
Severe	0	1 (1)	0	1 (10)	0	0	0	2 (2)
TEAE related to study drug	8 (50)	2 (14)	5 (26)	0	0	6 (18)	14 (28)	21 (23)
TEAE leading to study discontinuation	0	0	0	1 (10)	0	0	0	1 (1)
Serious TEAE	0	1 (7)	0	1 (10)	0	0	0	2 (2)
Serious TEAE related to study drug	0	0	0	0	0	0	0	0
TEAE resulting in death	0	0	0	0	0	0	0	0
TEAE of special interest[c]	5 (31)	1 (7)[d]	3 (16)	0	0	2 (6)	7 (14)	11 (12)

	Double-blind dosing group					Total APT-1011 (N = 85)
	APT-1011 3 mg BID (n = 20)	APT-1011 3 mg HS (n = 21)	APT-1011 1.5 mg BID (n = 23)	APT-1011 1.5 mg HS (n = 21)	Placebo (n = 20)	
Esophageal candidiasis	6 (30)	0	2 (9)	0	0	8 (9)
Oral/oropharyngeal candidiasis	2 (10)	1 (5)	2 (9)	0	0	5 (6)



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What to mix Budesonide in?

Vehicle	Number of patients	Number of patients who responded	Peak esophageal eosinophil count before OVB	Peak esophageal eosinophil count after OVB
Splenda™	34	31	50.5 eos/hpf (18 – 100 eos/hpf)	3.9 eos/hpf (0 – 70 eos hpf)
Apple sauce	19	15	56.3 eos/hpf (20 – 100 eos/hpf)	9.8 eos/hpf (0 – 100 eos/hpf)
Honey	7	6	53.7 eos/hpf (15 – 100 eos/hpf)	8.6 eos/hpf^ (0 – 50 eos/hpf)
Banana puree	1	1	8 eos/hpf	0 eos/hpf
Compound	1	1	30 eos/hpf	0 eos/hpf
Hot cocoa mix	1	1	30 eos/hpf	0 eos/hpf
Pear sauce	1	1	30 eos/hpf	0 eos/hpf
Rice cereal	1	0	100 eos/hpf	41 eos/hpf
Tapioca starch	1	1	10 eos/hpf	3 eos/hpf
Xanthan gum	1	1	70 eos/hpf	0 eos/hpf

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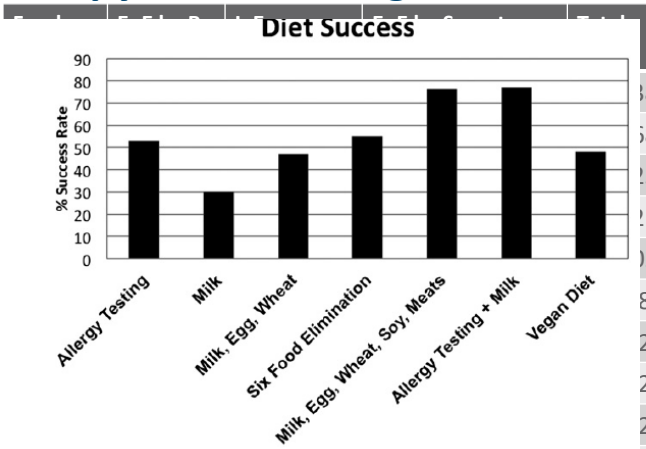
Lee et al, J Allergy Clin Immun Practice 2016,

23

Skin testing and Atopy Patch Testing

- 75% atopic
- Allergy testing identified corrected around 50%
- Skin testing only about 15%



Pork	16	0	30	46

Spergel et al J Allergy Clin Immunol 2012; 130:461-7

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Selective Diet: Guess

- 60 children
  - 35 on SFGED
  - 25 Children on elemental diet
- Repeat Endoscopy 6 weeks later
  - 74% of SFGED had <10 eos/hpf
  - 88% of elemental diet had <10 eos/hpf
- Single Food Reintroduction in 36 children
  - 74% to milk
  - 26% to wheat
  - 17% to egg
  - 10% to soy
  - 6% to peanut
- Single food in 72%, 2 foods in 8% and 3 foods in 8%

Kagalwalla et al. Clin Gastro Hepatol 2006
Kagalwalla et al. JPGN 2011

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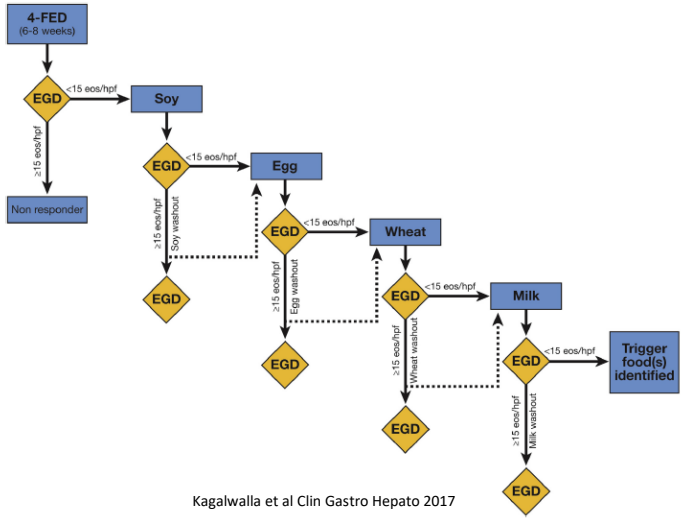
Four Food Elimination: Step-Down



Kagalwalla et al Clin Gastro Hepato 2017

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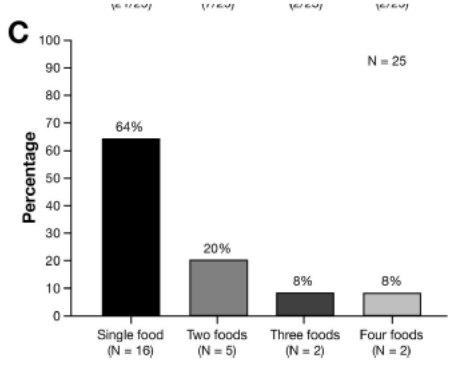
Four Food Elimination-Milk, wheat, egg and soy

- Multi-center Pediatric trial in the US in 78 children
  - 8 weeks elimination of 4 foods and 8 weeks addition of single food
- Response rate of 63% (<15 eos/hpf)
  - 43 eos/hpf to 3 eos/hpf
  - Causative foods
    - cow's milk (85%), egg (35%), wheat (33%), and soy (19%).
  - 2 subjects added back all foods



Kagalwalla et al Clin Gastro Hepato 2017

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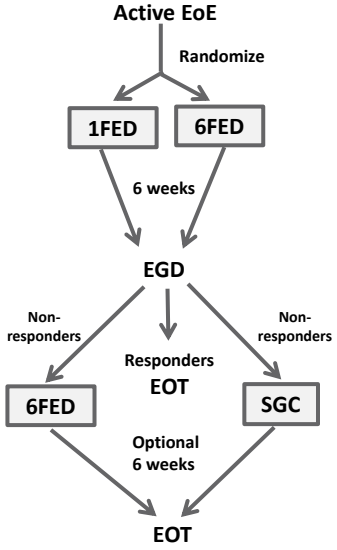
Clinical Project 2-EoE Intervention Trial
Six vs One Food Elimination EoE Diet Trial (SOFEED)



	1FED (n = 67)		6FED (n = 62)		Difference**	p-value
	n	% (95% CI)	n	% (95% CI)	% (95% CI)	
Histologic Response						
<15 eos/hpf*	23	34 (23 to 46)	25	40 (28 to 53)	6 (-11 to 23)	0·58
≤ 10 eos/hpf	20	30 (19 to 41)	23	37 (25 to 49)	7 (-9 to 24)	0·46
≤ 6 eos/hpf	12	18 (9 to 27)	20	32 (21 to 44)	14 (-0 to 29)	0·07
≤ 1 eos/hpf	4	6 (0 to 12)	12	19 (10 to 29)	13 (2 to 25)	0·031

Data are compared between groups using Fisher's exact test.
* Primary endpoint
** 6FED vs 1FED

CEGiR Consortium of Eosinophilic Gastrointestinal Disease Researchers

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Kliewer et al in press

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PCORI Trial: Dietary treatment – 1 vs 4 food

- First reported RCT for dietary therapy
  - Children (6 to 17 yrs) with EoE were randomized to 1FED (n=38) and 4FED (n=25) over 10 sites
  - Primary endpoint: PEESS v2.0
    - Change in total symptom score was greater in 4FED (-25.0 points) compared with 1FED (-14.3 points) (p=0.04).
  - Histologic response (<15 eos/hpf)
    - 4FED 41% vs 1FED 44% (p=1.0)
  - QoL improved in 1FED > 4FED

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Kliewer, Rothenberg et al, DDW, 2019 – talk 817, 5/21

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Conclusion from Dietary Trials

- Milk in the main trigger
- Consider starting with a simple milk elimination
- Should work 30-40% of children or adults

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IgE and EoE Overlap

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Is EoE an IgE mediated Disease?

- In murine models, IgE knockout have no effect on disease
- SPT/Immunocap and Microarray do not work well (<15%)
- Omalizumab does not work
- Oral Immunotherapy induces EoE
- DO NOT SKIN TEST

NO, But

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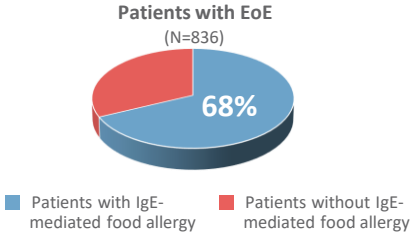
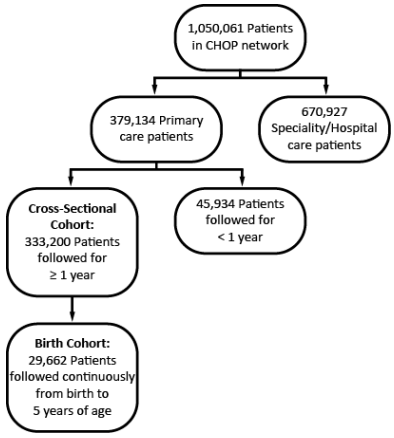
Co-Occurrence of IgE-Mediated Food Allergy and EoE Is High[1]

Rate of IgE-mediated food allergy in patients with EoE





Rate of EoE in patients with IgE-mediated food allergy

- EoE in general population: 0.04%
- EoE in patients with IgE-mediated food allergy: 4.7% (greater than 100x increase)

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1. Hill DA, et al. *J Allergy Clin Immunol Pract*. 2017;5(2):369-375. 2. Dellon ES, et al. *Am J Gastroenterol*. 2013;108(12):1854-1860.

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OIT and EoE

- Reviewed all published abstracts and articles

	Discontinuation (any reason)	SPR-EoE by:			EoE (biopsy)	Discontinuation due to:	
		Organ System	Specific Symptom			SPR-EoE	EoE or SPR-EoE
Rate		GI Symptoms	Abdominal Pain	Vomiting			
Overall	14%	34%	32%	12%	5.3%	4.7%	5.6%
Egg	11%	ND	28%	17%	4.9%	2.7%	3.1%
Milk	12%	18%	30%	21%	5.4%	3.9%	4.6%
Peanut	16%	56%	40%	20%	5.2%	6.7%	8.5%

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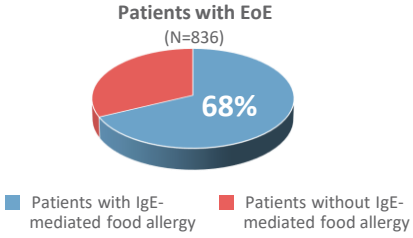
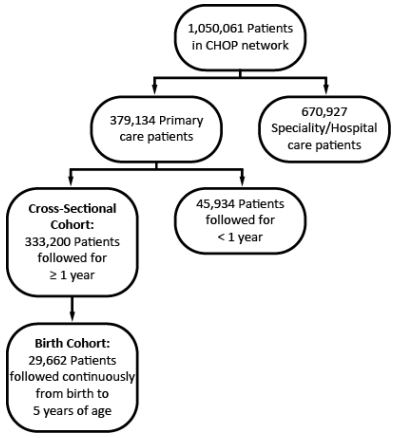
Petroni Spergel Ann Allergy Asthma 2018

34

Co-Occurrence of IgE-Mediated Food Allergy and EoE Is High[1]

Rate of IgE-mediated food allergy in patients with EoE





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OIT and EoE

- Reviewed all published abstracts and articles

	Discontinuation (any reason)	SPR-EoE by:			EoE (biopsy)	Discontinuation due to:	
		Organ System	Specific Symptom			SPR-EoE	EoE or SPR-EoE
Rate		GI Symptoms	Abdominal Pain	Vomiting			
Overall	14%	34%	32%	12%	5.3%	4.7%	5.6%
Egg	11%	ND	28%	17%	4.9%	2.7%	3.1%
Milk	12%	18%	30%	21%	5.4%	3.9%	4.6%
Peanut	16%	56%	40%	20%	5.2%	6.7%	8.5%

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Petroni Spergel Ann Allergy Asthma 2018

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Can you get IgE food allergy after EoE?

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5 case reports

- Milk avoidance x 2 yr, hives on reintroduction in 3 yo
- Wheat avoidance x 13 months, anaphylaxis in 65 yo
- Soy avoidance unclear time on OFC, anaphylaxis in 13 yo after six food elimination diet
- Milk avoidance x 1 yr, anaphylaxis at 7 yo
- Milk avoidance x 16 mo, urticaria at 20 month

Hill et . J Allergy Clin Immunol Pract 2015; Gottlieb et al. Ann Allergy Asthma Immunol 2019-412
Alsalamah et al. Am J Gastro 2016; Ho Chehade J Allery Clinic Immunol Pract 2018

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Biologics?

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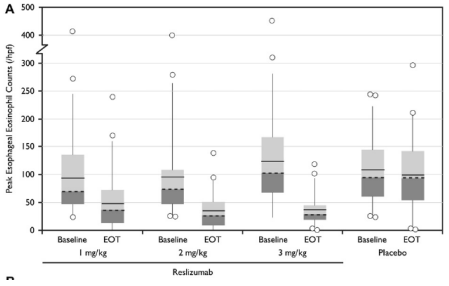
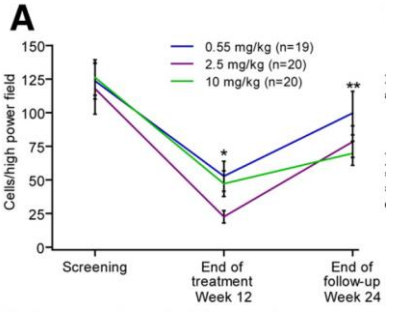
Biologicals in the treatment of EoE: IL5 Inhibitors

Reslizumab



Mepolizumab



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Spergel et al, JACI 2012; Assad et al Gastro 2011

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Lirentelimab and Benralizumab

- DBPC Phase 2/3 trial with Lirentelimab (siglec 8 inhibitor) on 276 patients
- 24 week trial with pre/post endoscopy

Co-Primary Endpoints	Lirentelimab High Dose (n=91)	Lirentelimab Low Dose (n=93)	Placebo (n=92)
Histologic Endpoint: Proportion of responders (eos ≤6 /hpf) as determined by esophageal tissue eosinophil counts [1]	87.9% (p<0.0001)	92.5% (p<0.0001)	10.9%
Symptom Primary Endpoint: Absolute mean change in patient reported Dysphagia Symptom Questionnaire (DSQ)[2]	DSQ Baseline: 34.2	DSQ Baseline: 36.4	DSQ Baseline: 35.2
	-17.4 (p=0.237)	-11.9 (p=0.247)	-14.6

- Phase 2/3 with Benralizumab in 210 patients(>12 yo)
- Dosing every 4 weeks
- 24 week trial with pre/post endoscopy
- "*The results from the MESSINA Phase III trial in eosinophilic esophagitis confirm that Fasenra achieved near complete depletion of tissue eosinophils, consistent with its mechanism of action, however this did not translate into an improvement in dysphagia symptoms.* "

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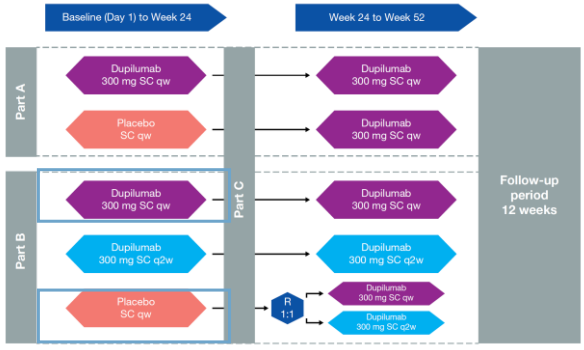
Phase 3 LIBERTY EoE TREET study

- In Part A of the 3-part, double-blind, placebo-controlled, phase 3 LIBERTY EoE TREET study (NCT03633617), dupilumab 300 mg qw SC vs placebo demonstrated significant improvements in symptomatic and histologic aspects of the disease up to 24 weeks in adults and adolescents with EoE and was generally well tolerated. In patients from Part A who continued to Part C, efficacy was sustained to Week 52[1]
- Part B assessed the efficacy and safety of dupilumab 300 mg qw or q2w vs placebo up to 24 weeks in a larger sample size of adults and adolescents with EoE
- Here we present the dupilumab 300mg qw results of Part B



Patients enrolled in Part A cannot participate in Part B. Non-eligible patients who do not enter Part C will enter a 12-week follow-up period. Enrollment for Part B began immediately after the last patient was enrolled in Part A. q2w, every 2 weeks; qw, weekly; R, randomization; SC, subcutaneous.

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1. Dellon ES, et al. Presented at UEGW E-congress 2021; October 3, abstract LB10.

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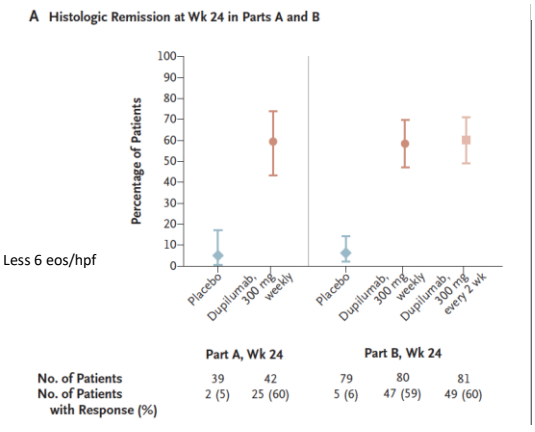
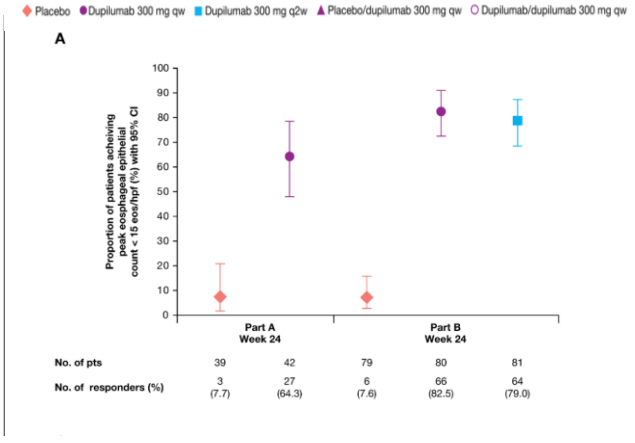
Histologic Response



Less 6 eos/hpf



Dellon et al, NEJM 2022

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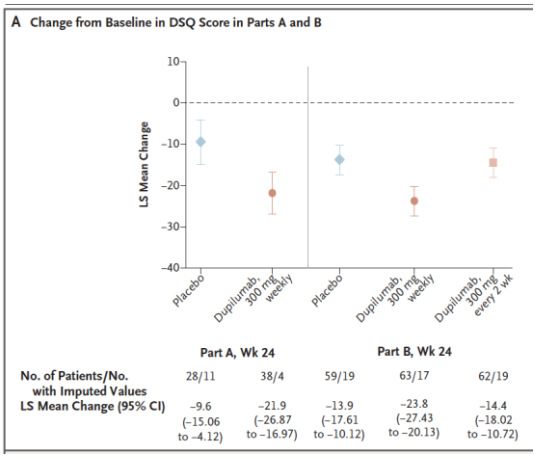
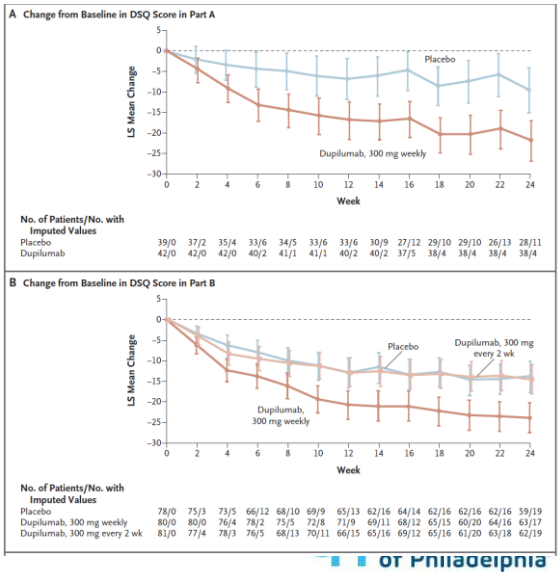
Symptom and Endoscopy Response





Dellon et al, NEJM 2022

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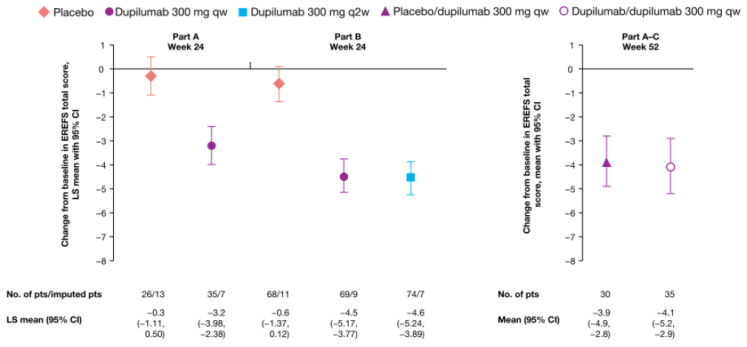
Endoscopy Response

E



Dellon et al, NEJM 2022

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Dupilumab 300mg qw demonstrated an acceptable safety profile at Week 24

Abstract presented at DDW 2022

Patients with event, n (%)	Part A		Part B	
	Placebo (n = 39)	Dupilumab 300 mg qw (n = 42)	Placebo (n = 78)	Dupilumab 300 mg qw (n = 80)
TEAEs	32 (82.1)	36 (85.7)	55 (70.5)	67 (83.8)
Deaths	0	0	0	0
Treatment-emergent SAEs[a]	0	2 (4.8)[b]	1 (1.3)[c]	5 (6.3)[d]
TEAEs leading to discontinuation	0	1 (2.4)	2 (2.6)	2 (2.5)
TEAEs occurring in ≥ 10% of patients in any group				
Injection-site reaction	4 (10.3)	7 (16.7)	16 (20.5)	16 (20.0)
Injection site erythema	5 (12.8)	3 (7.1)	9 (11.5)	8 (10.0)
Nasopharyngitis	4 (10.3)	5 (11.9)	0	0
Injection site pain	3 (7.7)	4 (9.5)	4 (5.1)	7 (8.8)
Injection site swelling	1 (2.6)	3 (7.1)	2 (2.6)	10 (12.5)
Diarrhea	2 (5.1)	2 (4.8)	8 (10.3)	1 (1.3)
Headache	4 (10.3)	2 (4.8)	9 (11.5)	6 (7.5)
Rash	4 (10.3)	0	0	0

[a]All assessed as not related to study drug. [b]Abdominal pain and uterine polyp. [c]Mental status changes. [d]Depression suicidal, Campylobacter colitis, blood creatine phosphokinase abnormal, breast cancer, pneumonia aspiration. SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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Dupilumab for other conditions and its effect on patients with concomitant EoE

54 patients identified with diagnosis of EoE and prescribed dupilumab

- 4 patients excluded as they did not receive any dose of dupilumab
- 5 patients excluded as they had no follow-up

45 patients identified with diagnosis of EoE and received >1 dose of dupilumab

26 patients with follow-up upper endoscopy

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Spergel et al, Annals Allergy Asthma Immunol 2022

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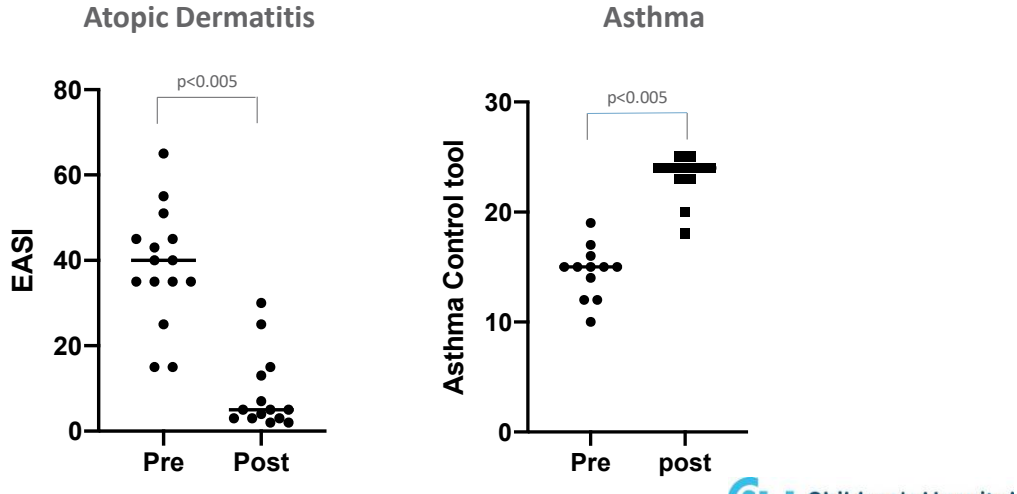
Dupilumab for other conditions and its effect on patients with concomitant EoE



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Spergel et al, Annals Allergy Asthma Immunol 2022

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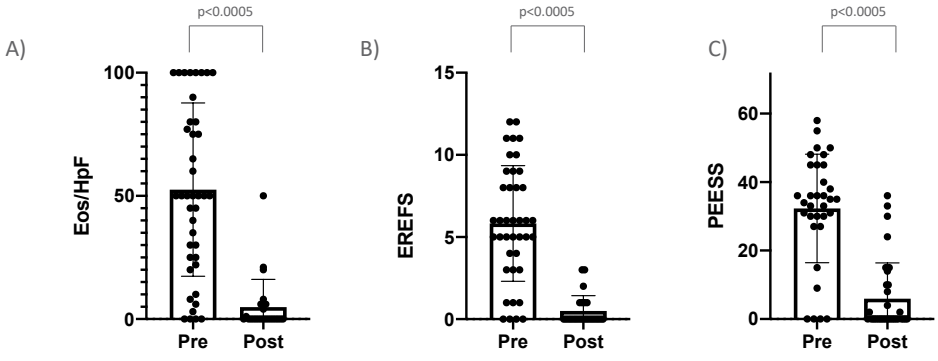
Improvement in Eosinophilic Esophagitis



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Spergel et al, Annals Allergy Asthma Immunol 2022

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FDA Question:

Management of asymptomatic EoE and/or EGID patients who have histologic abnormalities suggesting pathologic, allergic eosinophilic inflammation

- Patients can have poor perception of symptoms
- Is esophageal eosinophils risk factor for later complications
  - Adults have more fibrosis
  - Untreated disease has more fibrosis and strictures
- In medicine, inflammation needs to be controlled
  - Diabetes
  - Hypertension
  - Cholesterol
  - Inflammatory Bowel Disease
  - Asthma

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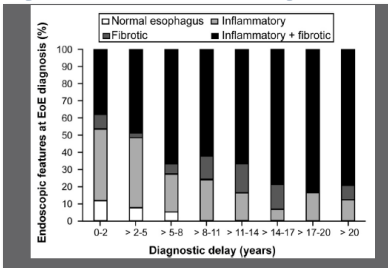
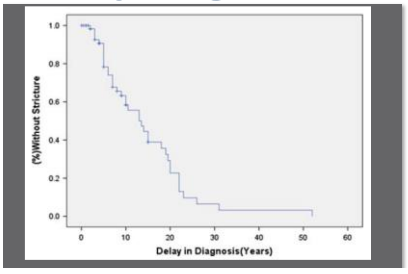
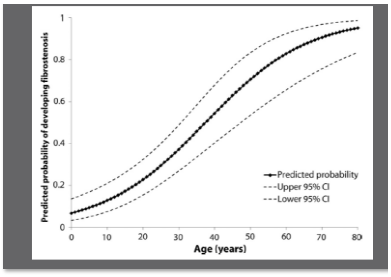
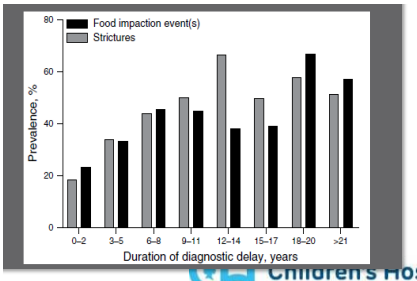
Natural History of Eosinophilic Esophagitis

Increased progression to esophageal stricture with longer duration of untreated disease









Schoepfer AM et al. *Gastroenterol*. 2013;145(6):1230-1236; Dellon ES, et al. *Gastrointest Endosc*. 2014;79(4):577-585; Lipka S, et al. *J Clin Gastroenterol*. 2016;50(2):134-140; Warners MJ, et al. *Am J Gastroenterol*. 2018; 113(6): 836-844.

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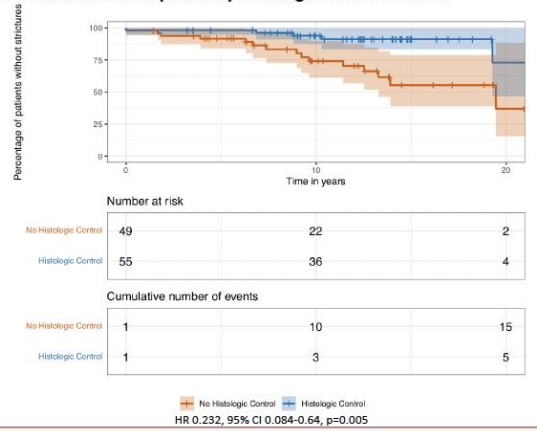
Disease Control has better natural History

- Examined 105 CHOP-Penn Patients
- 12 years of follow-up
- Histologic remission was defined as < 15 eosinophils/hpf. Histologic disease control was defined as having ≥2 consecutive endoscopies with histologic remission.

	HR [95% CI]	P-Value
Histologic Disease Control*	0.232 [0.084-0.64]	0.005
Age > 9	1.14 [1.03-1.27]	0.014
Lowest Eosinophil count < 10 /HPF	1.105[1.027-1.189]	0.007
Histologic Remission	0.108 [0.019-0.6016]	0.01
Dysphagia on Presentation	8.71 [2.83-26.8]	0.0002
Impaction on Presentation	4.87 [1.72-13.8]	0.003

Figure 1. Stricture Development by Histologic Disease Control



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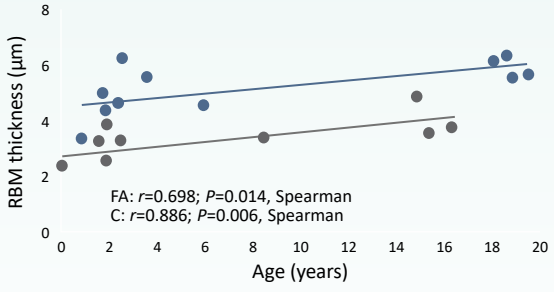
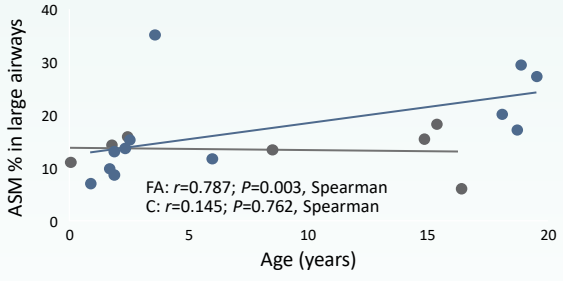
Airway Remodeling Persists and Increases With Age in Pediatric Asthma

Post-mortem lung autopsies from 12 fatal asthma cases and 8 non-asthmatic control subjects (aged 0.1-19.5 years)

Thickness of reticular basement membrane vs age



ASM % in large airways vs age



● Fatal asthma ● Control

Patients with asthma show evidence of thickened reticular basement membrane at an early age, which leads to ASM hypertrophy later in adolescence

- ASM, airway smooth muscle; C, control; FA, fatal asthma; RBM, reticular basement membrane.
- Malmström K, et al. *Respir Res*. 2017;18(1):94.

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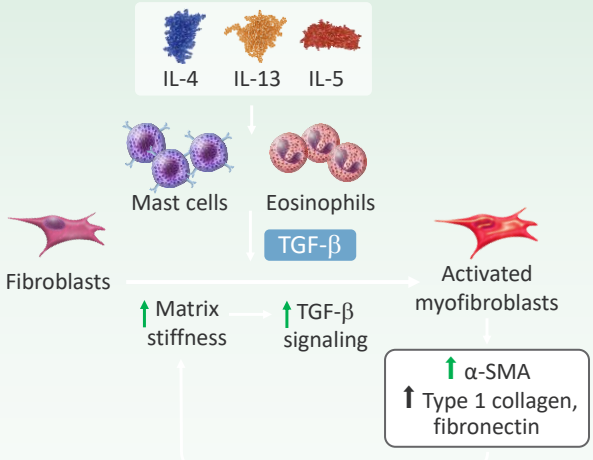
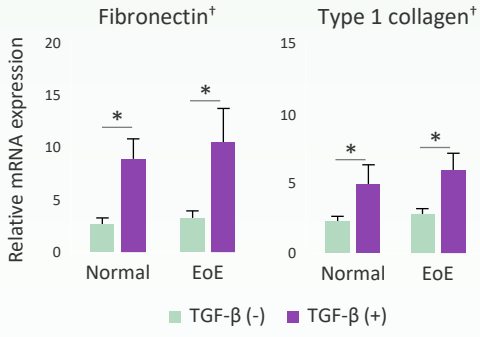
Inflammatory Environment Contributes to Esophageal Fibrosis and Remodeling[1-5]



Esophageal Fibrosis[1]



- *P<0.05.
- †Human esophageal fibroblasts were derived from biopsies from pediatric patients with EoE and without EoE (normal), all of whom were on high-dose proton pump inhibitor therapy for at least 6 weeks prior to biopsy, and stimulated with TGF-β,[1] which is produced by esophageal mast cells and increases esophageal smooth muscle contraction.[2]
- α-SMA, smooth muscle alpha-actin; EoE, eosinophilic esophagitis; IL, interleukin; TGF-β, transforming growth factor beta.
- 1. Muir AB, et al. *J Pediatr Gastroenterol Nutr*. 2016;63(2):200-209. 2. Aceves SS, et al. *J Allergy Clin Immunol*. 2010;126(6):1198-1204.e4. 3. Barni S, et al. *Ital J Pediatr*. 2018;44(1):1[illegible]. 4. Straumann A, et al. *Gut*. 2013;19(8):1005-1013. 5. Ferguson AE, et al. *Clin Rev Allergy Immunol*. 2018;55(1):43-55.

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Novel Ways to Monitor Therapy

- Endoflip
- String Test
- Confocal Video Endoscopy
- Cytosponge
- Transnasal endoscopy

Photo courtesy Children's Coloardo Webpage

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Summary

- EoE
  - Clinical Diagnosis
  - Pathogenesis overlap with asthma and atopic dermatitis
- Treatment Options
  - Diet
  - Swallowed Steroids
  - Biologics
  - Aeroallergens
  - Combinations
- Untreated disease is a risk factor for strictures
- New Name-ToE (T cell Esophagitis)

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Presentations for Saturday, June 24, 2023

8:00 am – 8:45 am	**Genetic Testing for the Clinical Allergist/Immunologist** *Ivan Chinn, MD*
8:45 am – 9:00 am	**2022 PAERF Grant Recipient Presentation** **Impact of Anaphylaxis Plans in Multiple Languages in an Outpatient Pediatric Allergy Clinic Setting** *Kim Nguyen, MD*
9:00 am – 9:45 am	**Biologic Therapy for Allergic Skin Diseases** *Marc Serota, MD*
9:45 am – 10:15 am	**Annual Business Meeting**
10:45 am – 11:30 am	**Approach to the Allergy Patient with Hypereosinophilia** *Amy Klion, MD*
11:30 am – 12:15 pm	**Noninfectious Manifestations of Inborn Errors of Immunity** *Ivan Chinn, MD*
12:15 pm – 1:00 pm	**What's New and Different in Antibiotic Allergy?** **Penicillin Allergy: Then and Now** *Marcus Shaker, MD, MS, FAAP, FAAAAI, FACAAI*
1:15 pm – 2:15 pm	**WORKSHOP: Hypereosinophilic Syndromes-Evaluation and Management** (Slides not Included) *Amy Klion, MD*

PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Genetic Testing for the Clinical Allergist/Immunologist

Presented by:

Ivan Chinn, MD

Saturday, June 24, 2023

8:00 a.m. – 8:45 a.m.

Genetic Testing for the Clinical Allergist/Immunologist

Ivan Chinn, M.D.

June 24, 2023

74th Pennsylvania Allergy & Asthma Association Annual Meeting

1

FAQs

- What test should I order?
  - What are the options?
  - How do I choose?
- What do the results mean?

2

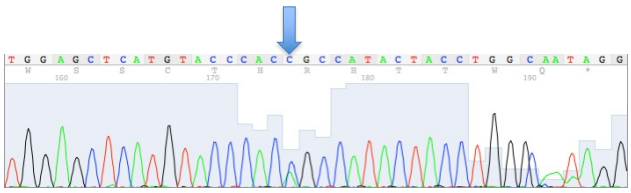
Genetic testing options (average A/I provider):

- Single gene sequencing
- Targeted panel testing
- Exome sequencing
- ~~Whole genome sequencing~~
- Chromosomal microarray analysis

4

Sanger Sequencing of Individual Genes

- Advantages:
  - ≥99% sequencing accuracy
  - Rapid turnaround time



- Disadvantages
  - Over 480 genetic conditions (!)
  - Allelic dropout
  - Unreliable recognition of mosaicism

5

High-Throughput Massively Parallel Sequencing

- Targeted gene panels
- Exome sequencing

6

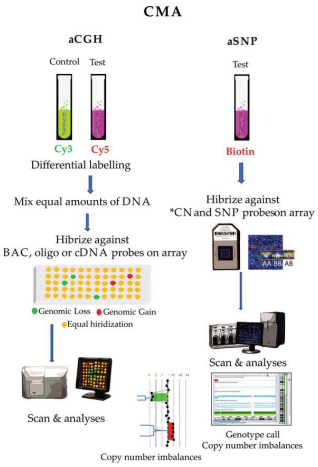
Targeted Panels vs. “Focused” Exomes: What Are You Getting?

- True targeted panels
  - Capture probes are custom designed
  - Very high read depth
  - Cannot be expanded
- “Focused” exomes
  - Exome sequencing platform
  - Variants reported only in genes requested
  - Standard exome read-depth (much lower)
  - Future additional analyses possible (*e.g.*, research pipelines, novel genes)

8

Chromosomal Microarrays

- Array comparative genomic hybridization
  - Sample vs. reference competitive binding to a custom probe set
  - "FISH on an array"
- Single nucleotide polymorphism (SNP) array
  - Binding of sample DNA to probes against hundreds of thousands of SNPs
  - "MLPA on an array"



Pinto PP et al. *Cytogenetics* Ch. 8: Cytogenomic Microarray Testing; https://doi.org/10.5772/intechopen.80514

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Types of Genetic Defects

- Aneuploidy (*e.g.*, trisomy 21)
- Microduplications or deletions (*e.g.*, 22q11.2, Jacobsen syndrome [11q23del], 14q32del, etc.)
- Smaller copy number variants (CNVs)
- Indels (<50 Kb)
- Single nucleotide variants (SNVs)
  - Stop gain (or loss)
  - Frameshift
  - Initiation
  - Splice site
  - Nonsynonymous
  - Noncoding

Most pathogenic variants cause loss of function, but beware of gain-of-function changes!

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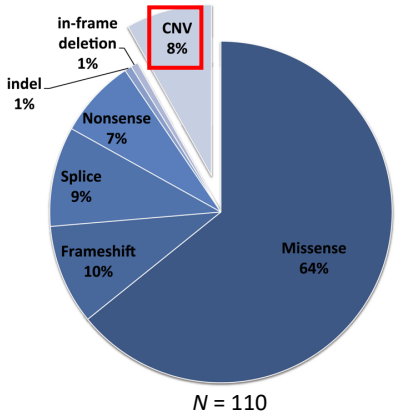
Most IEIs are caused by SNVs



Stray-Pedersen et al. *J Allergy Clin Immunol* 2017;139:232-245

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Variant classification is driven by American College of Medical Genetics and Genomics (ACMG) guidelines

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 OR observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

Richards et al. *Genet Med* 2015;17:405-24

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Benign	(i) 1 Stand-alone (BA1) *OR* (ii) ≥2 Strong (BS1–BS4)
Likely benign	(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) *OR* (ii) ≥2 Supporting (BP1–BP7)
Uncertain significance	(i) Other criteria shown above are not met OR (ii) the criteria for benign and pathogenic are contradictory

"VUS" usually means that the laboratory does not have enough information

(but you might have or be able to obtain that information)

Pathogenic	(i) 1 Very strong (PVS1) *AND* (a) ≥1 Strong (PS1–PS4) *OR* (b) ≥2 Moderate (PM1–PM6) *OR* (c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) *OR* (d) ≥2 Supporting (PP1–PP5) (ii) ≥2 Strong (PS1–PS4) *OR* (iii) 1 Strong (PS1–PS4) *AND* (a)≥3 Moderate (PM1–PM6) *OR* (b)2 Moderate (PM1–PM6) *AND* ≥2 Supporting (PP1–PP5) *OR* (c)1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)
Likely pathogenic	(i) 1 Very strong (PVS1) *AND* 1 moderate (PM1–PM6) *OR* (ii) 1 Strong (PS1–PS4) *AND* 1–2 moderate (PM1–PM6) *OR* (iii) 1 Strong (PS1–PS4) *AND* ≥2 supporting (PP1–PP5) *OR* (iv) ≥3 Moderate (PM1–PM6) *OR* (v) 2 Moderate (PM1–PM6) *AND* ≥2 supporting (PP1–PP5) *OR* (vi) 1 Moderate (PM1–PM6) *AND* ≥4 supporting (PP1–PP5)

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AAAAI Working Group Report

American Academy of Allergy Asthma & Immunology

Diagnostic interpretation of genetic studies in patients with primary immunodeficiency diseases: A working group report of the Primary Immunodeficiency Diseases Committee of the American Academy of Allergy, Asthma & Immunology

Check for updates

J Clin Allergy Immunol 2020;145:46-69

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Table 4. Evidence and criteria for determination of variant pathogenicity

Type of Criteria	Benign Evidence		Pathogenic Evidence			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Collected population data	MAF exceeds disease prevalence MAF in controls inconsistent with disease penetrance	Reputable source suggests variant is benign	Reputable source suggests variant is pathogenic	Absent or appropriately rare in population databases	Statistically higher prevalence in cases compared to controls	
Functional and biological data	Functional studies demonstrate no deleterious effect		Missense in gene with many pathogenic missense variants Likely functional impact in immunologically plausible gene candidate[a]	In mutational hot spot or domain with no known benign variation	Functionally validated to produce a deleterious effect[b]	
Allelic distribution data	Nonsegregation with immunologic phenotype Inappropriate segregation with disease[c]	In *cis* with a pathogenic variant in the same gene	Cosegregation with disease in affected family members	Increased cosegregation with disease in family members *De novo* (parents unconfirmed) In *trans* with a pathogenic variant in the same gene	Even greater cosegregation with disease in family members *De novo* (parents confirmed)	
Variant-based computational data		Computational evidence argues against impact on gene product	Computational evidence supports a deleterious effect on gene product	Novel missense change at same residue known to be affected by pathogenic missense change(s) Predicted to alter protein length	Same amino acid change as confirmed pathogenic variant	Predicted null variant in gene for which loss of function causes disease
Other		Alternate cause detected	Phenotype or family history highly specific for gene[d]			

Classification Scheme[e]

Pathogenic					1	1
				2		1
			1	1		1
			2			1
					2	
				3	1	
			2	2	1	
			4		1	
Likely pathogenic				1		1
				1	1	
			2		1	
				3		
			2	2		
			4	1		
Benign	1 or 2[f]					
Likely benign	1	1				
		2				

J Allergy Clin Immunol 2020;145:46-69

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Overall variant interpretation parameters

- Population data
- Functional and biological data
- Allelic distribution data
- Computational data
- Phenotype data

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Most variant analysis is now automated or semi-automated

Blueprint Genetics Variant Classification Scheme for Dominant Monogenic Disorders

CLASSIFICATION	CATEGORY	
PATHOGENIC	1 Point Needed	1. Well-established mutation and wide consens publications support pathogenicity. – **1 Point** 2. In the setting of a novel disease in the family, mechanism of pathogenicity for patient's disea 3. LOF variant seen in at least 3 patients with t exon or in the last 50 base pairs of the penultir
	OR	
	5 Points Needed	**COMPULSORY A OR B:** A) Positive segregation with the disease (≥2 fa **OR** B) ≥ 5 cases (one of which can be the current p **ADDITIONAL POINTS:** 1. Variant is novel or very rare in control popula 2. Loss of gene function has been established 3. A missense variant predicted deleterious by 4.De novo variant in the setting of a novel dise 5. Variants considered deleterious (a substitute 6. Deficient protein function in appropriate fun 7. Well-characterized other mutation at the sar 8. Other strong data supporting pathogenic cla
LIKELY PATHOGENIC	2 Points Needed	1. Alterations resulting in premature truncation mechanism of pathogenicity for patient's disea 2. Variant is novel or very rare in control popula
	OR	
	4 Points Needed	1. Clear genotype phenotype correlation exist 2. Variant is novel or very rare in control popula 3. Missense variant predicted deleterious by m 4. A variant predicted to have an effect to the s 5. An inframe deletion affecting conserved as 6. Variant has been reported in trans with a 7. Variant is a well-established pathogenic m 8. *De novo* alteration in the setting of a novel d 9. Variants considered deleterious (a substitute causality in the disease type. – **1 Point** 10. Deficient protein function in appropriate fu 11. Well-characterized mutation at the same co 12. Other strong data supporting pathogenic c
Variant of unknown significance (VUS)		Variant has characteristics of being a
LIKELY BENIGN	1 Point Needed	1. Control population minor allele frequency (1
	OR	
	2 Points Needed	1. MAF <0.001 in control populations but varia 2. Homozygous variant in a gene with no asso 3. Co-occurrence with a pathogenic mutation i 4. Majority of the in silico tools predict the sub 5. Intact protein function observed in appropric 6. Other data supporting benign classification.
BENIGN	2 Points Needed	1. Does not segregate with the disease in fami 2. Any additional criteria described below. – **1 I**
	OR	
	4 Points Needed	1. Control population minor allele frequency (1 2. Homozygous variant in a gene with no asso 3. Intact protein function observed in appropri 4. Co-occurrence with a pathogenic mutation i 5. No disease association in small case-contro 6. Majority of the in silico tools predict the sub 7. Other data supporting benign classification. – **1 Point**

Blueprint Genetics Variant Classification Scheme for Recessive Monogenic Disorders

CLASSIFICATION	CATEGORY	CRITERIA
PATHOGENIC	1 Point Needed	1. Well-established variant and wide consensus in the field on pathogenicity of the variant. – **1 Point** **OR** 2 . ≥2 cases (one of which can be the current patient) with the same phenotype and the same truncating variant (nonsense, frameshift, consensus splice site (+/-1, 2), start codon): in one patient observed in homozygous or compound heterozygous state (confirmed in trans) and in one patient observed together with another disease-causing variant in the same gene (phase not determined) **AND** Variant frequency in control populations is consistent with an autosomal recessive disorder **AND** Loss of gene function is a well-established disease mechanism – **1 Point**
	OR	
	4 Points Needed	**COMPULSORY A OR B:** **A)** ≥3 cases (one of which can be the current patient) with the same phenotype and the same non-truncating variant (missense, splice region): • In at least two patients the variant is observed in homozygous or compound heterozygous state with a disease-causing variant (confirmed in trans) • One patient may be included where the variant is observed either in homozygous state or together with another disease-causing variant in the same gene (phase not determined) - 1 Point **OR** **B)** ≥5 cases (one of which can be the current patient) with the same phenotype and the same non-truncating variant: • In at least four patients the variant is observed together with a well-established variant in the same gene (phase not determined) • One patient may be included where the variant is observed either in homozygous state or together with another disease-causing variant in the same gene (phase not determined) - 1 Point **ADDITIONAL POINTS:** 1. Clear gene-phenotype correlation exists (e.g. *USH2A* and USH2) – **1 Point** 2. Variant frequency in control populations is consistent with an autosomal recessive disorder - **1 Point** 3. A missense variant predicted deleterious by majority of *in silico* tools applied - **1 Point** 4. Deficient protein function in appropriate functional assay(s) – **1 Point** 5. Well-characterized other disease-causing variant at the same codon or same consensus splice site (+/-1, 2) - **1 Point** 6. Variant occurs in trans with a pathogenic or likely pathogenic variant in the same gene – **1 Point** 7. *De novo* variant is observed together with pathogenic or likely pathogenic variant in the same gene - **1 Point**
LIKELY PATHOGENIC	2 Points Needed	1. Alterations resulting in premature truncation (e.g. frameshift, nonsense or consensus splice site (+/-1, 2), start codon) in a gene where loss-of gene function has been established as a mechanism of pathogenicity - **1 Point** **AND** 2. Variant frequency in control populations is consistent with an autosomal recessive disorder - **1 Point**
	OR	
	4 Points Needed	1. Clear gene-phenotype correlation exists (e.g. *USH2A* and USH2) – **1 Point** 2. Variant frequency in control populations is consistent with an autosomal recessive disorder - **1 Point** 3. Missense variant predicted deleterious by majority of *in silico* tools applied – **1 Point** 4. ≥2 cases (one of which can be the current patient) with the same phenotype and the same non-truncating variant (missense, splice region): in one patient observed in homozygous or compound heterozygous state (confirmed in trans) and in one patient observed either in homozygous state or together with a pathogenic or likely pathogenic variant in the same gene (phase not determined) **OR** Variant has been reported in *trans* with a pathogenic or likely pathogenic variant in the same gene **OR** ≥3 cases (one of which can be the current patient) with the same phenotype and the same non-truncating variant together with a well-established variant in the same gene (phase not determined) – **1 Point** 5. Variant occurs in trans with a pathogenic or likely pathogenic variant in the same gene (Note: This requires testing of parents to determine phase or close proximity of the variants, when NGS data is used to determine the phase) – **1 Point** 6. Deficient protein function in appropriate functional assay(s) – **1 Point** 7. Well-characterized other disease-causing variant at the same codon or same consensus splice site – **1 Point** 8. Other strong data supporting pathogenicity – **1 Point**
Variant of uncertain significance (VUS)		Variant has characteristics of being a disease-causing variant, however, insufficient or conflicting evidence exists.
LIKELY BENIGN	1 Point Needed	The allele frequency of the variant or the number of individuals homozygous for the variant in gnomAD or other publicly available database is greater than expected for the disorder (the prevalence of the disease in the population and the fraction explained by the specific gene must be taken into consideration) – **1 Point**
BENIGN	1 Point Needed	The allele frequency of the variant in gnomAD or other publicly available database is more than 5% - **1 Point**

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Suggested variant interpretation parameters to review

- Population data
  - Penetrance
  - "Control" data
- Functional and biological data
- Allelic distribution data: family members (test parents, if necessary)
- Phenotype data: variable expressivity

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gnomAD contains potential immune disease cohort data

- Inflammatory Bowel Disease:
  - 1000IBD project
  - Helsinki University Hospital Finland
  - NIDDK IBD Genetics Consortium
  - Quebec IBD Genetics Consortium
- The Cancer Genome Atlas

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Case #1:

- 4 month-old term girl
- Difficulty with thrush at 1 month – no other infections
- Initially presented with encephalopathy: positive influenza test
- Developed seizures followed by cardiac arrest
- Placed on ECMO and weaned off
- In PICU: pseudomonal sepsis and HLH
- Candidal esophagitis
- Ecthyma gangrenosum (*Pseudomonas*-positive) and bilateral necrosis of nasal and basilar skull bones with erosion extending through middle ear to tympanic membranes: *E. coli*, *E. faecalis*, and enteric organisms
- Found to be neutropenic and placed on G-CSF

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Genetic Results

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
C5	c.1680G>A (p.Trp560*)	heterozygous	PATHOGENIC
ELANE	c.639del (p.His213Glnfs*27)	heterozygous	Uncertain Significance ???
G6PD	c.376A>G (p.Asn126Asp)	heterozygous	Uncertain Significance
GUCY2C	c.1024A>C (p.Asn342His)	heterozygous	Uncertain Significance
HYOU1	c.1647C>T (Silent)	heterozygous	Uncertain Significance
RTEL1	c.2600C>T (p.Pro867Leu)	heterozygous	Uncertain Significance
TOP2B	c.113A>T (p.Asn38Ile)	heterozygous	Uncertain Significance

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Variant Summary

ELANE, Exon 5, c.639del (p.His213Glnfs*27), heterozygous, Uncertain Significance

- This sequence change creates a premature translational stop signal (p.His213Glnfs*27) in the ELANE gene. While this is not anticipated to result in nonsense mediated decay, it is expected to disrupt the last 55 amino acid(s) of the ELANE protein.
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with ELANE-related conditions.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

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What do we know about *ELANE* (and congenital/cyclical neutropenia)?

- Autosomal dominantly inherited
- Disease is caused by protease malfunction, *not haploinsufficiency* (*e.g.*, pLI = 0) *or biallelic loss*
  - Entire gene deletions do not produce neutropenia
  - Humans and mice with biallelic loss produce normal neutrophils with normal cell counts
  - Knock out of the mutant allele in human cells restores neutrophil maturation

Zuzanna et al. *Front Immunol* 2021;12:653932

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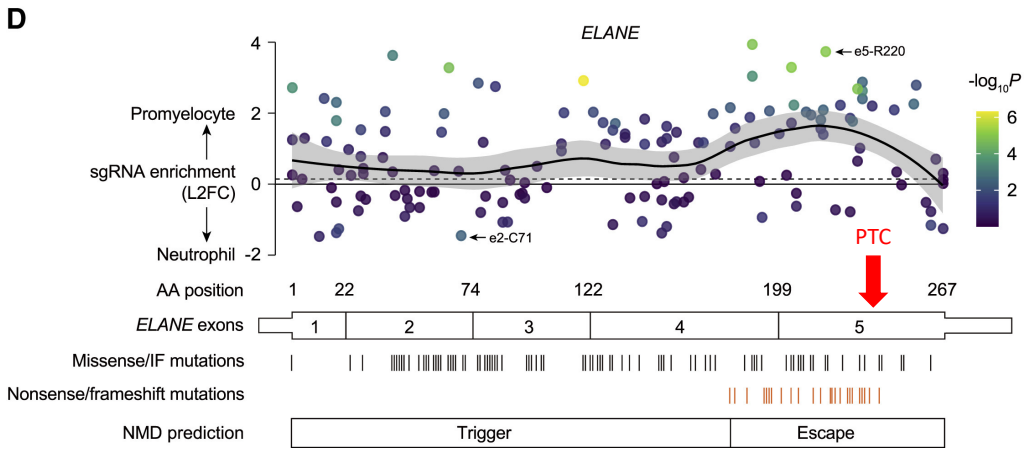
Mutagenesis CRISPR screening in human HSCs



Rao S et al. *Cell Stem Cell* 2021;28:833-845

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Parental Results

- Father

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION	RESULT
TOP2B	c.113A>T (p.Asn38Ile)	heterozygous	Uncertain Significance	Detected
C5	c.1680G>A (p.Trp560*)	N/A	PATHOGENIC	Not detected
ELANE	c.639del (p.His213Glnfs*27)	N/A	Uncertain Significance	Not detected
GUCY2C	c.1024A>C (p.Asn342His)	N/A	Uncertain Significance	Not detected

- Mother

20%

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION	RESULT
C5	c.1680G>A (p.Trp560*)	heterozygous	PATHOGENIC	Detected
ELANE	c.639del (p.His213Glnfs*27)	possibly mosaic	Uncertain Significance	Detected
GUCY2C	c.1024A>C (p.Asn342His)	heterozygous	Uncertain Significance	Detected
TOP2B	c.113A>T (p.Asn38Ile)	N/A	Uncertain Significance	Not detected

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Parental mosaicism is well-known in this disease

Two paternal mosaicism of mutation in *ELANE* causing severe congenital neutropenia exhibit normal neutrophil morphology and ROS production

Qiao Liu[a], Liang Zhang[a], Zhou Shu[b], Yuan Ding[b], Xue-Mei Tang[b], Xiao-Dong Zhao[a,b,c,*]

[a] Chong Qing Key Laboratory of Child Infection and Immunity, Children's Hospital of Chongqing Medical University, Chongqing 400014, China
[b] Division of Immunology, Children's Hospital of Chongqing Medical University, Chongqing 400014, China
[c] Ministry of Education Key Laboratory of Child Development and Disorders, Key Laboratory of Pediatrics in Chongqing, Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, Children's Hospital of Chongqing Medical University, Chongqing 400014, China

Clinical Immunology 203 (2019) 53–58

Mosaicism of an *ELANE* Mutation in an Asymptomatic Mother

Tomonari Shigemura[1] · Norimoto Kobayashi[1] · Kazunaga Agematsu[2] · Osamu Ohara[3] · Yozo Nakazawa[1]

Journal of Clinical Immunology (2019) 39:106–111

Paternal Somatic Mosaicism of a Novel Frameshift Mutation in *ELANE* Causing Severe Congenital Neutropenia

Hee-Jung Kim, MD, PhD,[1]* Min-Jung Song,[1] Ki-O Lee,[2] Sun-Hee Kim,[1] and Hee-Jin Kim[1]

Pediatr Blood Cancer 2015;62:2229–2231

Mosaicism of an *ELANE* Mutation in an Asymptomatic Mother in a Familial Case of Cyclic Neutropenia

Osamu Hirata[1] · Satoshi Okada[1] · Miyuki Tsumura[1] · Shuhei Karakawa[1] · Itaru Matsumura[2] · Yujiro Kimura[3] · Toshiro Maihara[4] · Shin'ichiro Yasunaga[5] · Yoshihiro Takihara[5] · Osamu Ohara[6] · Masao Kobayashi[1]

J Clin Immunol (2015) 35:512–516

Paternal mosaicism proves the pathogenic nature of mutations in neutrophil elastase in severe congenital neutropenia

Phil J. Ancliff, Rosemary E. Gale, Michael J. Watts, Ri Liesner, Ian M. Hann, Stephan Strobel, and David C. Linch

BLOOD, 15 JULY 2002 • VOLUME 100, NUMBER 2

Mechanism:

- De novo event in the parent very early in embryogenesis
- Negative selection pressure during myelopoiesis

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Our classification:

- Population data: 1 moderate
- Functional/biological data: 1 moderate
- Allelic distribution data: 1 strong
- Computational data: 1 strong (downgraded for truncation)
- Other: 1 supporting

Classification: pathogenic

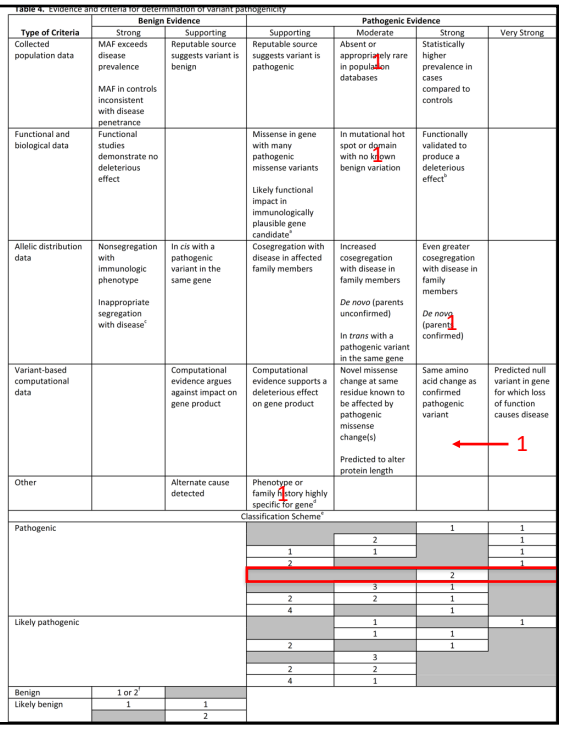

Table 4. Evidence and criteria for determination of variant pathogenicity

Type of Criteria	Benign Evidence		Pathogenic Evidence			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Collected population data	MAF exceeds disease prevalence MAF in controls inconsistent with disease penetrance	Reputable source suggests variant is benign	Reputable source suggests variant is pathogenic	Absent or appropriately rare in population databases	Statistically higher prevalence in cases compared to controls	
Functional and biological data	Functional studies demonstrate no deleterious effect		Missense in gene with many pathogenic missense variants Likely functional impact in immunologically plausible gene candidate[c]	In mutational hot spot or domain with no known benign variation	Functionally validated to produce a deleterious effect[b]	
Allelic distribution data	Nonsegregation with immunologic phenotype Inappropriate segregation with disease[c]	In *cis* with a pathogenic variant in the same gene	Cosegregation with disease in affected family members	Increased cosegregation with disease in family members *De novo* (parents unconfirmed) In *trans* with a pathogenic variant in the same gene	Even greater cosegregation with disease in family members *De novo* (parents confirmed)	
Variant-based computational data		Computational evidence argues against impact on gene product	Computational evidence supports a deleterious effect on gene product	Novel missense change at same residue known to be affected by pathogenic missense change(s) Predicted to alter protein length	Same amino acid change as confirmed pathogenic variant	Predicted null variant in gene for which loss of function causes disease
Other		Alternate cause detected	Phenotype or family history highly specific for gene[d]			

Classification Scheme[a]

Pathogenic					1	1
				2		1
			1	1		1
			2			1
					2	
				3	1	
			2	2	1	
			4		1	
Likely pathogenic				1		1
				1	1	
			2		1	
				3		
			2	2		
			4	1		
Benign	1 or 2[f]					
Likely benign	1	1				
		2				

J Allergy Clin Immunol 2020;145:46-69

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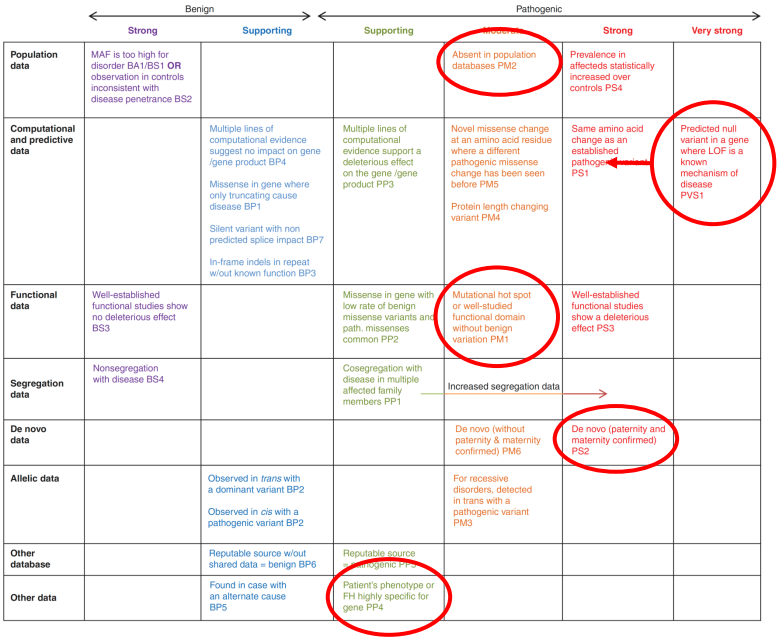
Or using ACMG:

- PM2
- PVS1_Strong
- PM1
- PS2
- PP4

2 Strong + 2 Moderate + 1 Supporting =

Pathogenic



	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR** observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7 In-frame indels in repeat w/out known function BP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data		
De novo data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity and maternity confirmed) PS2	
Allelic data		Observed in *trans* with a dominant variant BP2 Observed in *cis* with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

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Conclusions

- Genetic testing is strongly indicated in patients with suspected inborn errors of immunity
- Choose a test based upon various considerations
  - Sequencing provides the greatest diagnostic yield
  - CNV analyses can add a measurable increase
- Variant analysis by clinical laboratories is imperfect
- Automated and semi-automated methods cannot yet replace the expertise of a trained allergy/immunology provider: review the results carefully
- Pursue your intuitions!

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

2022 PAERF Grant Recipient Presentation

Impact of Anaphylaxis Plans in Multiple Languages in an Outpatient Pediatric Allergy Clinic Setting

Presented by:

Kim Nguyen, MD

Saturday, June 24, 2023

8:45 a.m. – 9:00 a.m.

Impact of multi-language anaphylaxis plans in an outpatient pediatric allergy clinic setting

PAERF Grant Presentation

June 24, 2023

Kim Nguyen, MD
Fellow Physician
Division of Allergy & Immunology
Children's Hospital of Philadelphia

Children's Hospital of Philadelphia

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Food allergy

- In the US, >40% of children with food allergy reported ≥1 lifetime allergy related ED visit
- There are significant gaps in recognition and appropriate treatment of anaphylaxis by patients and caregivers.
- Both national and international guidelines recommend the use of anaphylaxis management plans given to patients and caregivers.

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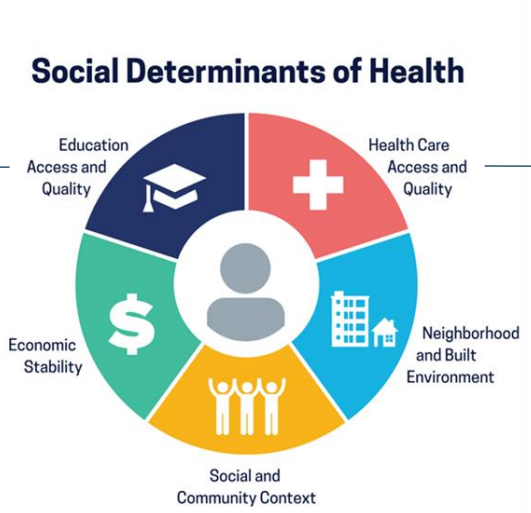
Gupta, R.S, et al. *Pediatrics* (2018)
Kastner M, et al. *Allergy* (2010)
Nurmatov U, Worth A, Sheikh A. *J Allergy Clin Immunol* (2008)

2

Health literacy

Food allergy knowledge



Access to allergist

Food allergy education in primary language

New food allergy treatments

Children's Hospital of Philadelphia

3

Disparities in food allergy

Barriers to proper food allergy management

- Food allergy-related ED visits are more frequent in Black and Hispanic children vs. White children and in those from socioeconomically disadvantaged backgrounds
- Increases in self-reported U.S. food allergy rates are greatest in non-Hispanic Black children
- Food allergy is more likely to occur in children from urban vs. rural areas
- Children from socioeconomically disadvantaged backgrounds are less likely to undergo allergy evaluation
- Children from minority groups are less likely to be given an anaphylaxis plan

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Bozen A,, et al. *Ann Allergy Asthma Immunol* (2020)
Mahdavinia M., et al. *JACI: In Practice* (2017)
Keet C,, et al. *Ann Allergy Asthma Immunol* (2014)
Smith, et al. *WAO Journal* (2015)

4

Background

- There is limited information on language as a barrier to utilization of anaphylaxis plans.
- Impact of limited English proficiency on asthma action plan use:
  - A cross-sectional bilingual survey was distributed at an urban, academic, pediatric emergency department.
  - Surveys were completed by adult caregivers of children with asthma who sought PED care for asthma related chief complaints.
  - Study found a 25% difference ($p = .01$) in action plan use rates between limited English proficiency caregivers (39%) and English proficient caregivers (64%).

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Riera A, Navas-Nazario A. *The Journal of Asthma* (2014)

5

Objective

To evaluate and address language barriers in the setting of food allergy management, specifically the availability and use of anaphylaxis plans in a patient/caregiver's preferred language

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Methods

- Identify most common languages spoken by food-allergic patients and their families seen in allergy clinic at CHOP
- Translate and implement anaphylaxis plans in the most common languages other than English seen in our patient population
- Track distribution of anaphylaxis plans in the primary language of patients' families
- Survey and compare English-speaking and ESL caregivers regarding perception of food allergy education received and level of comfort regarding food allergy management

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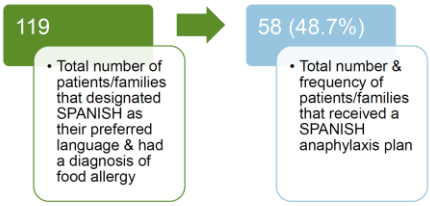
Distribution of preferred languages

- There were 30 different languages (excluding English and unknown) identified among the 15,161 patients seen between July 1, 2018 and July 31, 2021 in all CHOP Allergy sites who had a food allergy listed in their medical record.
- These are the most common preferred languages:

Preferred language	Number of patients
ENGLISH	14,766
SPANISH	119
MANDARIN	35
VIETNAMESE	28
ARABIC	25
PORTUGUESE	22



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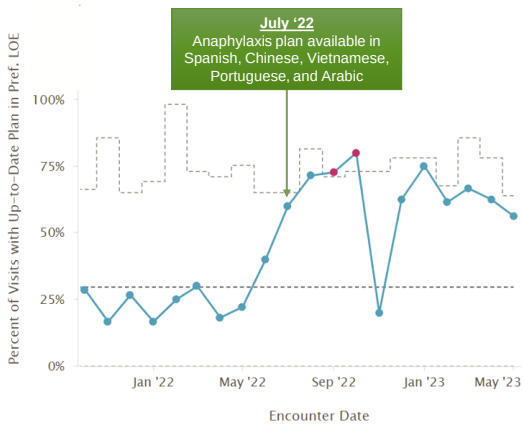
Patients with Up-to-Date Anaphylaxis Plans Provided in Preferred Language Other than English as of Visit

IgE–mediated Food Allergy: LOE – Translated Plan Available



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Allergy Survey

Arabic | Chinese (PRC) | ✓ English | Portuguese | Spanish | Vietnamese

Please complete the survey below.

Thank you!

Background Information

What is your relationship to the patient?
* must provide value

What is your preferred language?
* must provide value

The patient is allergic to (please check ALL that apply):
* must provide value

- ☐ Milk
- ☐ Egg
- ☐ Peanut
- ☐ Soy
- ☐ Wheat
- ☐ Sesame
- ☐ Fish
- ☐ Shellfish
- ☐ Tree Nuts
- ☐ Other foods

Allergy Teaching

Does your child have an epinephrine auto-injector (e.g. EpiPen or Auvi-Q)? ○ Yes ○ No ○ Do not know reset
* must provide value

Were you taught how to use an epinephrine auto-injector? ○ Yes ○ No ○ Do not know reset
* must provide value

What information did you get when the allergy was diagnosed? (please check all that apply)

- ☐ How to recognize an allergic reaction
- ☐ How to avoid food allergens
- ☐ How to treat an allergic reaction
- ☐ I do not remember what information I got
- ☐ I did not receive any information

Did you receive an anaphylaxis plan? ○ Yes ○ No ○ Do not know reset
* must provide value

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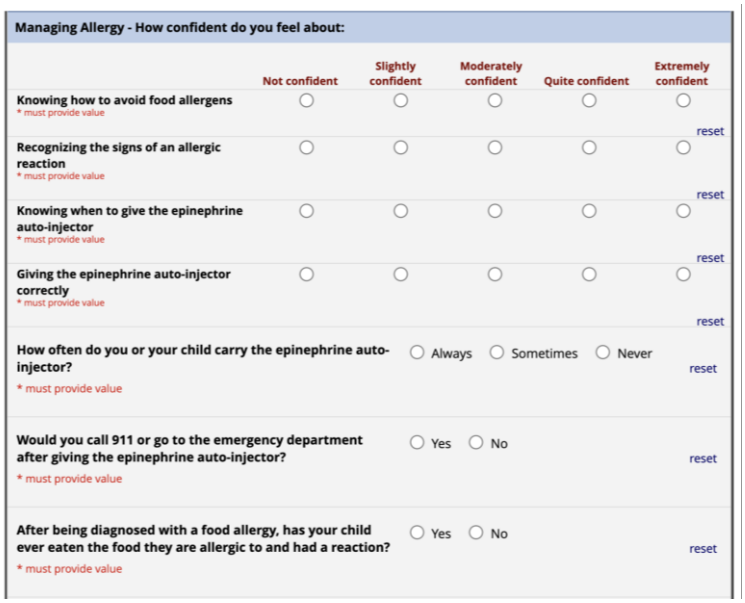

Managing Allergy - How confident do you feel about:

	Not confident	Slightly confident	Moderately confident	Quite confident	Extremely confident	
Knowing how to avoid food allergens * must provide value	○	○	○	○	○	reset
Recognizing the signs of an allergic reaction * must provide value	○	○	○	○	○	reset
Knowing when to give the epinephrine auto-injector * must provide value	○	○	○	○	○	reset
Giving the epinephrine auto-injector correctly * must provide value	○	○	○	○	○	reset

How often do you or your child carry the epinephrine auto-injector? ○ Always ○ Sometimes ○ Never reset
* must provide value

Would you call 911 or go to the emergency department after giving the epinephrine auto-injector? ○ Yes ○ No reset
* must provide value

After being diagnosed with a food allergy, has your child ever eaten the food they are allergic to and had a reaction? ○ Yes ○ No reset
* must provide value

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Recruitment for survey

- Screening
  - Established Allergy patient with known IgE-mediated food allergy
  - Preferred language: English, Spanish, Arabic, Cantonese, Mandarin, Portuguese, or Vietnamese
  - Screen by reviewing upcoming Allergy clinic schedule in Epic, food challenges, and data pulls from prior visits

- Recruit in person during an in-person Allergy visit or via telephone
  - Interpretalk used for ESL families

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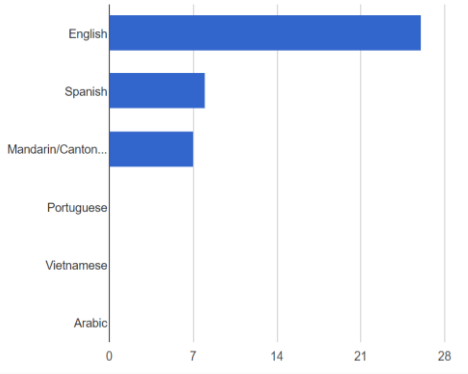
Survey results

- Completed surveys
  - 41 total
    - 26 English
    - 15 non-English
      - 8 Spanish
      - 7 Mandarin



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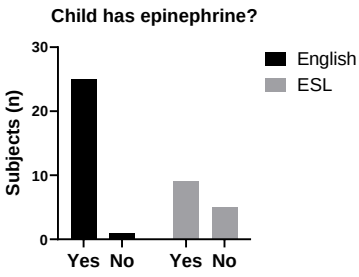
Survey results



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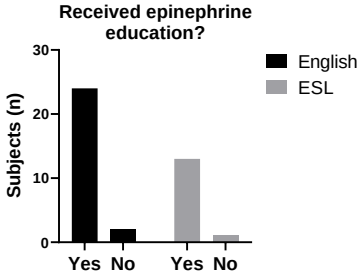
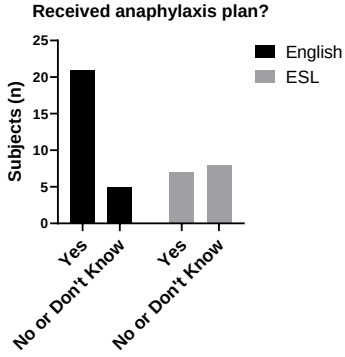


Not significant (NS) by Fisher's exact test



***p*=0.0376** by Fisher's exact test

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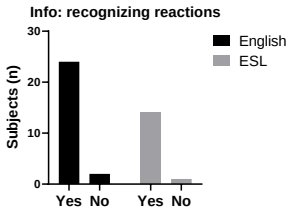
What information did you receive when the allergy was diagnosed?



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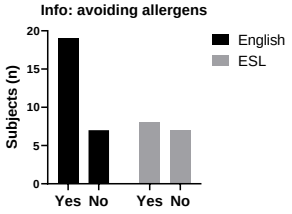

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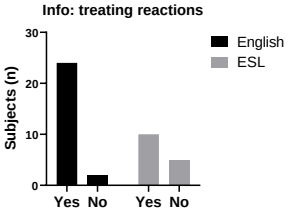

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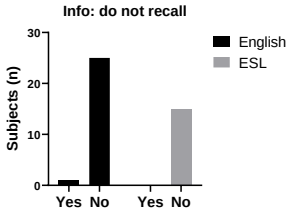

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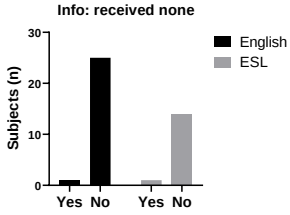

NS by Fisher's exact test

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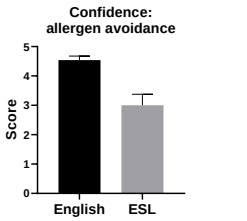
Confidence in food allergy management



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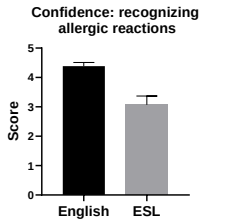
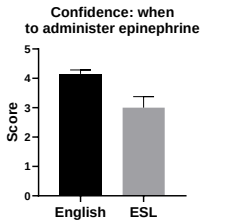


***p*<0.0001** by Mann Whitney test

1 = not confident
2 = slightly confident
3 = moderately confident
4 = quite confident
5 = extremely confident



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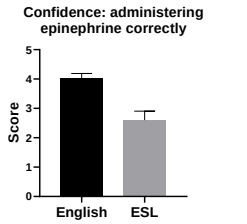

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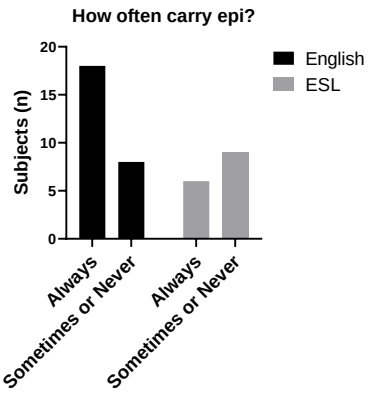
Food allergy management



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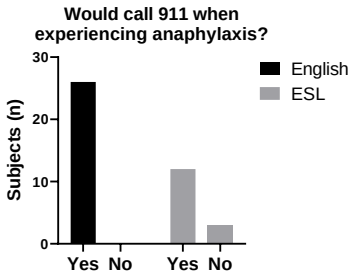

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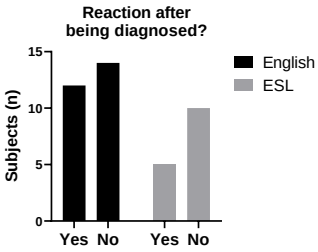
Food allergy management



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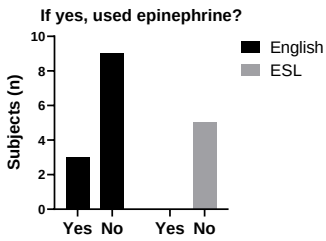

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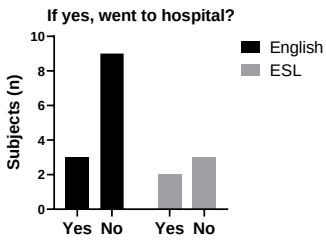

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Barriers and limitations

- Translation of documents takes time and can be costly.
- New staff (providers, nursing) may not be aware of available resources for families. Veteran staff may need reminders/refreshers due to change in normal workflow.
- Recruitment of ESL caregivers for the survey was challenging → small sample size
- Supplementary educational handouts (food allergen avoidance) are available only in English, which may have adverse affect on ESL family knowledge.

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Conclusion

- Having anaphylaxis plans available in multiple languages is a step towards addressing disparities in food allergy education
  - Distribution rate of anaphylaxis plans in a patient/caregiver's preferred language increased after implementation, but can improve with ongoing advocacy
- Results of the survey suggest that when compared to English-speaking families, ESL families…
  - Are less likely to have an epinephrine autoinjector
  - Are less likely to have an anaphylaxis plan or know if they have an anaphylaxis plan
  - Have less confidence and knowledge in food allergy management

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Future directions

- Expand efforts to translate the anaphylaxis plan and supplemental handouts in additional languages.
- Implement an alert within Epic to remind providers of the necessity of providing a language-appropriate anaphylaxis plan
- Examine whether receipt of language-appropriate anaphylaxis plan is associated with fewer adverse outcomes long-term, such as having fewer hospital visits related to anaphylaxis and/or having a higher rate of having an up-to-date epinephrine autoinjector prescription

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Acknowledgements

- Pennsylvania Allergy and Asthma Association PAERF Grant
- CHOP Diversity, Equity, and Inclusion Mentorship Pipeline Award
- CHOP Allergy and Immunology Division
- CHOP Quality and Patient Safety (QPS)
- Juhee Lee, MD - mentor
- Torrin Davis, MPH - QPS improvement advisor
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- Biostatistics and Data Management Core

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Biologic Therapy for Allergic Skin Diseases

Presented by:

Marc Serota, MD

Saturday, June 24, 2023

9:00 a.m. – 9:45 a.m.

~~Biologics~~ Systemics in Allergic Skin Disease

Marc Serota, MD
FAAD, FAAAAI, FACAAI

Peak Dermatology
Rocky Mountain VA Medical Center/University of Colorado

Board Certified:
Dermatology
Allergy/Immunology
Pediatrics

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Disclosures

- Consultant for Regeneron, Sanofi-Genzyme, Genentech, Pfizer, Amgen, Incyte, UCB, Dermavant, Arcutis.

2

Objectives

- 1. Learn the pathophysiology of atopic dermatitis and chronic urticaria.
- 2. Review current treatment options for atopic dermatitis and chronic urticaria.
- 3. Discuss future treatments in development for atopic dermatitis and chronic urticaria.

3

Atopic Dermatitis Principles

- Atopic dermatitis is a multifactorial disease that includes:
  - Genetic factors
  - Environmental factors
  - TH2 mediated inflammation
  - Barrier dysfunction
  - Microbiome abnormalities

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Atopic Dermatitis Overview

- Around 7% incidence in U.S. adults.
- Most cases present initially before age 5 with around 50% persist into adulthood.
- Family history of atopy is the strongest risk factor with around 70% of patients having a family history of atopy.

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Genetic Factors

- Loss of function of *FLG* gene (profilaggrin deficiency).
  - Impaired barrier
  - Impaired tight junction formation.
  - Decreased water retention
  - Altered lipid formation
- 31 loci associated with the epidermal differentiation complex and genes involved in the regulation of innate host defenses and T cell functioning have been identified.

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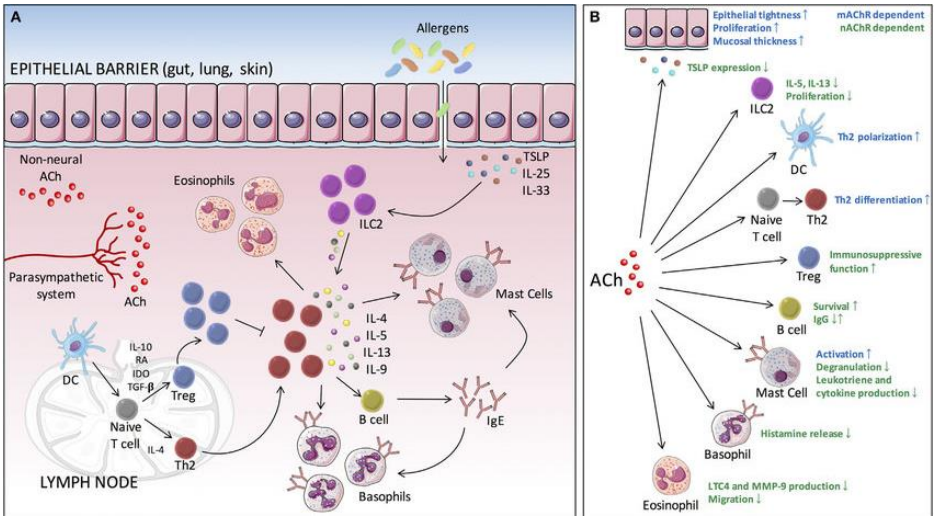
Immune Dysregulation



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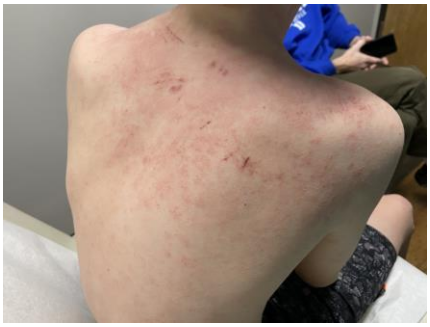
Atopic Dermatitis Pearls

- Antecubital fossae, popliteal fossae.
- Cheeks on a child.
- Doesn't always read the textbook.
- Ask what the movie looks like.
- Pathology rules out mimics.



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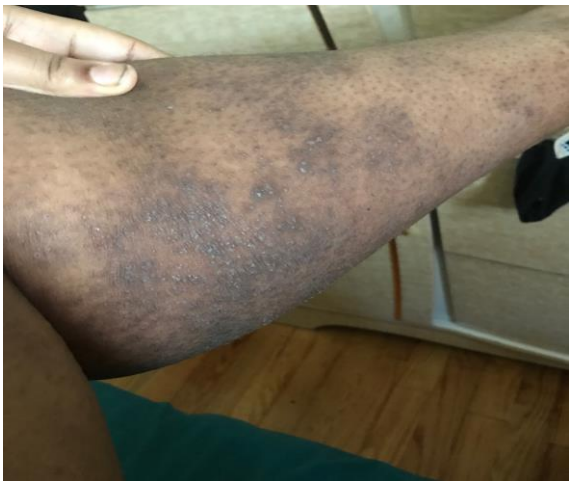
Difficult cases

- Personal or family history of atopy.
- Treatment failures and successes.
- Biopsy for mimics.
- Assess for confounding variables.
- Assess for compliance with treatments.



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Labs

- Elevated IgE
- Multiple elevated positive food allergy tests.
- Eosinophilia.

10

Assessment tools

- IGA (Investigator Global Assessment) score
- EASI (Eczema Area and Severity Index) score
- SCORAD (Scoring Of Atopic Dermatitis) index
- POEM (Patient-Oriented Eczema Measure)
- NRS (Numerical Rating Scale) for pruritus

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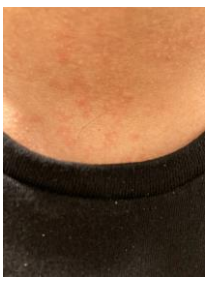
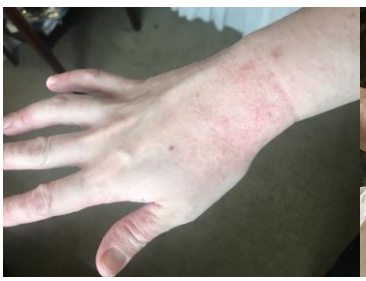
IGA Score

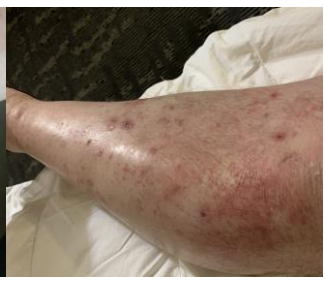
2	3	4
mild	moderate	severe



Mild erythema and mild papulation/ infiltration



Moderate erythema and moderate papulation/ infiltration



Severe erythema And severe papulation/ infiltration

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EASI Score

- Reported as percent improvement from baseline.
- 75% generally considered as a secondary endpoint in trials.

- Area score is recorded for each of the four regions of the body. The area score is the percentage of skin affected by eczema for each body region.

- Severity
  - 0: None
  - 1: Mild (just perceptible)
  - 2: Moderate
  - 3. Severe

- Redness (erythema, inflammation)
- Thickness (induration, papulation, swelling—acute eczema)
- Scratching (excoriation)
- Lichenification (lined skin, furrowing, prurigo nodules—chronic eczema).

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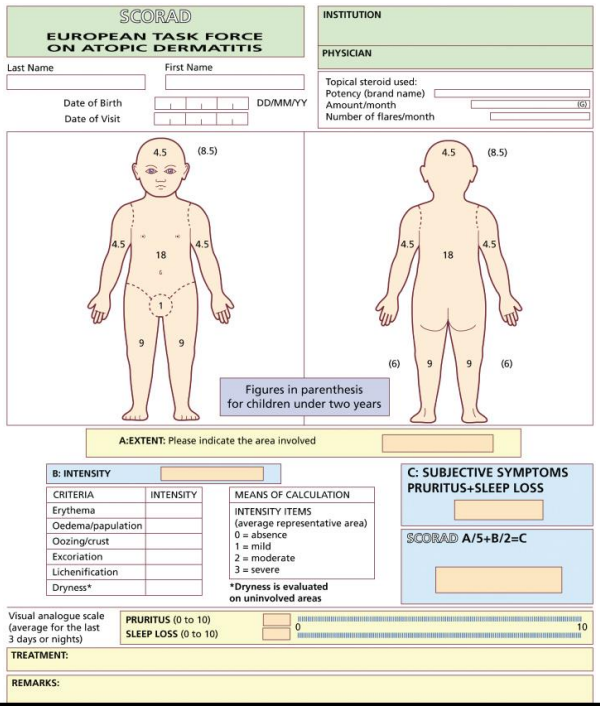

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Patient-Oriented Eczema Measure (POEM)
(Questionnaire for adults or children)

Patient details:	Date:
	Total POEM score: (maximum 28)

Please circle one response for each of the seven questions below. Young children should complete the questionnaire with the help of their parents. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your/your child's skin been itchy because of the eczema?

No days 1–2 days 3–4 days 5–6 days Every day

2. Over the last week, on how many nights has your/your child's sleep been disturbed because of the eczema?

No days 1–2 days 3–4 days 5–6 days Every day

3. Over the last week, on how many days has your/your child's skin been bleeding because of the eczema?

No days 1–2 days 3–4 days 5–6 days Every day

4. Over the last week, on how many days has your/your child's skin been weeping or oozing clear fluid because of the eczema?

No days 1–2 days 3–4 days 5–6 days Every day

5. Over the last week, on how many days has your/your child's skin been cracked because of the eczema?

No days 1–2 days 3–4 days 5–6 days Every day

6. Over the last week, on how many days has your/your child's skin been flaking off because of the eczema?

No days 1–2 days 3–4 days 5–6 days Every day

7. Over the last week, on how many days has your/your child's skin felt dry or rough because of the eczema?

No days 1–2 days 3–4 days 5–6 days Every day

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NRS (Numerical Rating Scale)

- 0-10 how bad is your itch?
- Usually self reported by patient twice per day.
- Success defined as at least a 4 point improvement in score.

No itch

Worst imaginable itch

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Hot Take

- Atopic dermatitis is NOT a skin disease.

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Hot Take

- Atopic dermatitis is NOT a skin disease.

- Atopic dermatitis is a SYSTEMIC disease with CUTANEOUS manifestations.

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Comorbidities – The atopic march

- Patients with atopic dermatitis are more likely to have other atopic diseases.
- Around 50% of atopic dermatitis patients will have another atopic condition.
- Common in childhood, but the atopic march can occur at any age.

Burgess JA, Dharmage SC, Byrnes GB, et al. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. *J Allergy Clin Immunol*. 2008;122(2):280-285. doi: 10.1016/j.jaci.2008.05.018.

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Comorbidities

- Approximately one-third of patients with AD develop asthma, and two-thirds develop allergic rhinitis.

van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol*. 2007;120(3):565-569. doi: 10.1016/j.jaci.2007.05.042.

Spergel JM. Epidemiology of atopic dermatitis and atopic march in children. *Immunol Allergy Clin North Am*. 2010;30(3):269-280. doi: 10.1016/j.iac.2010.06.003.

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The Changing Treatment Paradigm

- OLD:
  - Treat each atopic disease symptomatically and locally.
  - Topical steroids.
  - Topical calcineurin inhibitors.
  - Systemic immunosuppressives as a last resort.
- NEW:
  - Treat atopic disease as a systemic disease.
  - Target Th2 mediated inflammation.
  - Treat multiple atopic diseases at once.
  - Focus on controllers and rescue medications for flares.
  - Try to inhibit the propagation of Th2 differentiation early in the process.

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Non-pharmacological treatment

- Avoid triggers
  - Climate, humidity, irritants, aeroallergens, contact allergens, friction, excoriating.
- Treat skin infections
- Improve barrier dysfunction
  - Emollients, bathing habits.
- Allergens
  - Dust mite covers, remove pets if possible, wash clothing, face and eyes when returning inside during pollen season.

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Non-pharmacologic controversies

- Frequency of bathing:
  - Daily with immediate application of moisturizers while still damp.
- Bath additives (paraffin, oils, colloidal oatmeal, bleach):
  - No.
- Wet wraps:
  - For severe flares with other control measures in mind.

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Non-pharmacologic controversies

- Priobiotics
  - No.
- Dietary supplements (vitamins, fish oil, essential fatty acids).
  - No.
- Melatonin, antihistamines
  - Maybe for sleep disturbance.
- Monteleukast
  - No.

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Non-pharmacologic controversies

- Food avoidance or special diets
  - No, unless a correlation for a specific food is very obvious to you clinically.
  - 50% of kids may have positive skin prick tests but food sensitization is clinically irrelevant in most cases.
- Food allergy IgE panels
  - No. Specific tests based on history. Graded oral challenge with an allergist is the gold standard to rule in/out food allergy.
- IgG testing, muscle strength testing, candida overgrowth, oxidative damage testing, mitochondrial energy production.
  - NO! Be aware of these types of tests.

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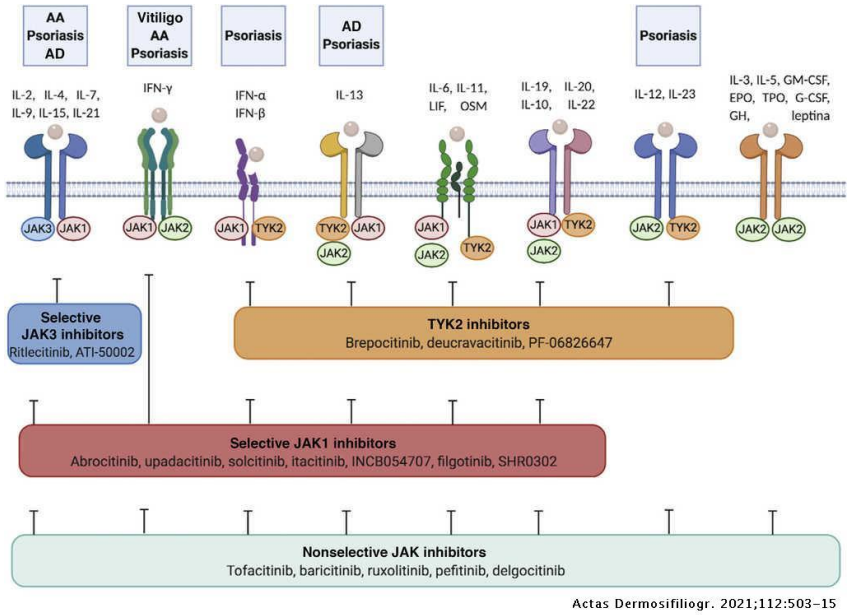

26

Current controller options

- Dupilumab
- Tralokinumab
- Oral abrocitinib
- Oral upadacitinib
- Oral steroids
- Methotrexate
- Cyclosporine
- Cellcept
- Phototherapy

27

Dupilumab (IL-4/IL-13)

- FDA approved for:
  - 6 and older with moderate to severe AD.
  - 6 and older for eosinophilic or corticosteroid dependent asthma.
  - 18 and older for chronic rhinosinusitis with nasal polyps.
  - 12 and older eosinophilic esophagitis.
- Blocks a receptor protein (IL-4Rα that binds and blocks signaling for both IL-4 and IL-13)

28

Dupilumab Efficacy "75/75"

- IGA 0 or 1 at week 16
  - 37% (dupilumab vs. 9% (placebo)
  - 39% (dupilumab + TCS) vs. 12% (placebo + TCS)
- EASI 75 at week 16
  - 48% (dupilumab) vs. 13% (placebo)
  - 69% (dupilumab + TCS) vs. 23% (placebo + TCS)
- Age 6-11: EASI 75 at week 16
  - 75% (dupilumab + TCS) vs. 28% (placebo + TCS)
    - <30 kg (300 mg qmonth)
  - 75% (dupilumab + TCS) vs. 26% (placebo + TCS)
    - >30 kg (200 mg q2wks)

29

Oral Abrocitinib (JAK1)

- FDA Approved: Moderate to severe AD 12 and over.
- Phase III trial 387 patients 12 and older with moderate to severe AD received 100 mg, 200 mg or placebo once daily for 12 weeks.
  - IGA clear or almost clear:
  - 44% (200 mg), 24% (100 mg), 8% (placebo)
  - EASI 75:
  - 63% (200 mg), 40% (100 mg), 12% (placebo)

Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020; 396:255.

30

Oral Abrocitinib (JAK1)

- Phase III trial 838 patients 18 and older with moderate to severe AD received 100 mg, 200 mg, dupilumab 300 mg every 2 weeks or placebo once daily for 12 weeks.
  - IGA clear or almost clear:
  - 48% (200 mg), 37% (100 mg), 37% (dupilumab), 14% (placebo)
  - EASI 75:
  - 73% (200 mg), 59% (100 mg), 58% (dupilumab), 27% (placebo)
  - Nausea occurred in 11.1% of the patients in the 200-mg abrocitinib group and 4.2% of those in the 100-mg abrocitinib group, and acne occurred in 6.6% and 2.9%, respectively.

Bieber T, Simpson EL, Silverberg JI, et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. N Engl J Med 2021; 384:1101.

31

Oral Upadacitinib (JAK1)

- FDA approved: Moderate to severe AD 12 and older.
- Two phase III trials with 847 and 836 patients with moderate to severe AD.
  - EASI 75:
  - 73 and 80% (30 mg daily), 60% and 70% (15 mg daily), 16% and 13% (placebo).
- Acne: 17% (30 mg) vs. 2% (placebo)

Guttman-Yassky E, Teixeira HD, Simpson EL, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021; 397:2151.

32

Tralokinumab (Anti-IL-13)

- FDA Approved: Moderate to severe AD 18 and over.
- Dosing: 300 mg SC divided in 2 sites q2weeks.
  - "May decrease to q4weeks after 16 weeks if clinical response achieved".
- Load: 600 mg SC divided in 4 sites x 1.

- Phase 3 moderate or severe AD in adults Monotherapy:

- IGA 0 or 1
  - 15 % vs. 7% placebo.
  - 22% vs. 11% placebo.

- EASI-75
  - 25% vs. 12% placebo.
  - 33% vs. 11% placebo.

33

Tralokinumab (Anti-IL-13)

- Tralokinumab + TCS
  - IGA 0 or 1: 39%,
  - EASI 75: 56%

- Placebo +TCS
  - IGA 0 or 1: 26%
  - EASI 75: 36%

- 78% and 91% (IGA 0/1 and EASI-75, respectively) of patients who responded at week 16 (with tralokinumab plus TCS administered 300 mg every two weeks for those 16 weeks) maintained response at week 32 when switched from 2 week to 4 week dosing.

AAD VMX 2020

34

Nemolizumab anti-IL-31

- Against the receptor for IL-31
- Associated with chronic skin inflammation and pruritus.

- Phase II, 12-week 264 adults with moderate to severe AD.
  - Improvement from baseline in the score on the pruritus visual analogue scale:
  - Decreased by: 44% (0.1 mg monthly), 60% (0.5 mg), 63% (2 mg), 21% (placebo).

  - BSA of AD decreased by:
  - 8% (0.1 mg), 20% (0.5 mg), 19% (2 mg), 16% (placebo).

35

Nemolizumab anti-IL-31

- Phase 3 clinical trial, evaluating the efficacy, safety, pharmacokinetics and immunogenicity of nemolizumab compared with placebo in adult patients with prurigo nodularis after a 16-week treatment period.

- 16 weeks: 38 % clear or almost clear skin lesions vs. 11% placebo.

- 56 % achieved 4 point itch reduction vs. 21% placebo.

36

Lebrikizumab (Anti-IL-13)

- Binds soluble IL-13.
- Phase 2 trial: 280 adult patients with moderate to severe AD. Change in baseline EASI scores:
  - 125 mg every 4 weeks: -62%,
  - 250 mg every 4 weeks -69%
  - 250 mg every 2 weeks -72.1%
  - Placebo-treated patients: 4.5%
- Common adverse effects in the lebrikizumab groups included upper respiratory tract infection, nasopharyngitis, headache, injection site pain, and fatigue.
- Phase 3: Monotherapy: "Lebrikizumab led to significant improvements with at least 75 percent skin clearance in more than half of people with moderate-to-severe atopic dermatitis (AD), as measured by EASI, in ADvocate 1 and ADvocate 2 Phase 3 clinical trials. Primary and all key secondary endpoints, including skin clearance and itch improvement, were met at Week 16." –August 2021.

Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial. JAMA Dermatol 2020; 156:411.

37

Drug	Company	Delivery	Approved	Age	Asthma	EASI-75	Safety	Head to Head	Other indications
Dupilimab (Dupixent)	Regeneron Sanofi	SQ Q2wk Q4wk (peds)	2017	>6 months	Yes	69%	Conjunct-ivitis Facial redness	No	1. Asthma >6) 2. CRS w/ nasal polyps (>18) 3.EE (>12) 4. Prurigo Nodularis (>18)
Tralokinumab (Adbry)	Leo	SQ Q2wk	2022	>18	No	33%	Conjunct ivitis	No	None
Abrocitinib (Cibinqo)	Pfizer	Oral	2022	>12	No	73%	Black Box warning	73% v. 58% dupi	None
Upadacitinib (Rinvoq)	Abbvie	Oral	2022	>12	No	80%	Black Box warning	71% v. 61% dupi	1. RA 2. PsA 3. AS 4. UC
Baracitinib (Olumiant)	Lilly Incyte	Oral	?	>18	No	?	Black Box Warning	No	1. RA 2. AA
Lebrikizumab (?)	Almirall	SQ	?	>18	No	51%	?	No	None

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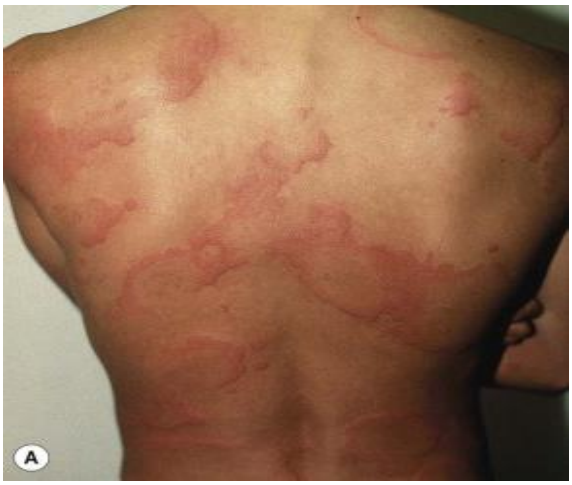
Chronic Urticaria

- Pruritic, erythematous, blanching, circumscribed macular or raised lesions involving the superficial layers of the skin.
- May be present with wheals, angioedema or both.
- Individual wheals last < 24 hrs ("here today, gone tomorrow")



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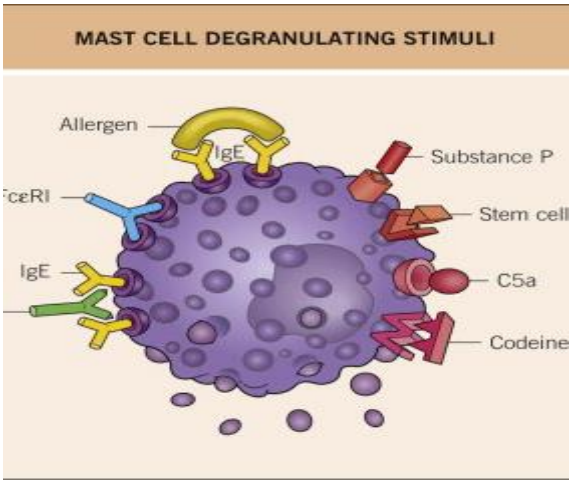
When To Consider Alternate Diagnoses

- Lack of pruritus.
- Individual lesions that last for days to weeks.
- Angioedema without urticaria.
- Lesions that are localized to only one area of the body or are very well defined.
- A review of systems suggestive of systemic disease.
- Failure to respond to therapy.

40

Pathophysiology

- Mast cell is primary effector cell.
- Two types of mast cells:
  - MC_T - skin
  - MC_{TC} – respiratory tract
- Degranulation: Cross-linking of two or more adjacent FcεRI.



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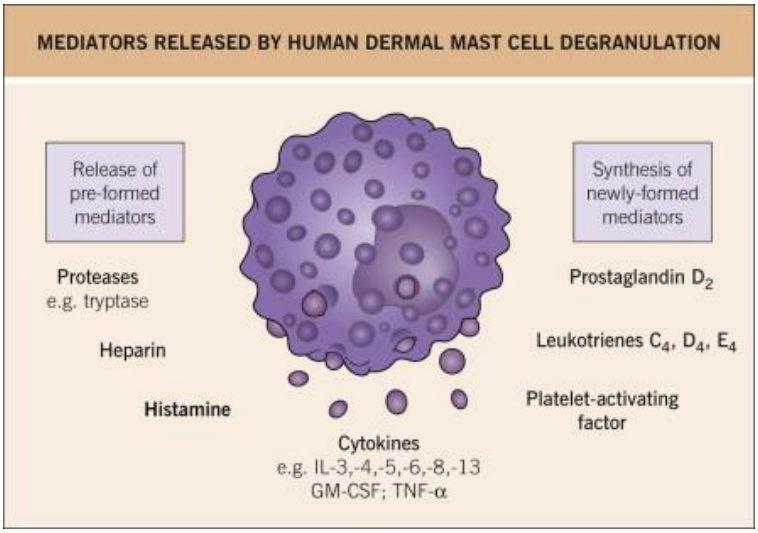
Pathophysiology



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Urticaria

Acute		Chronic	
IgE	Non-IgE	Lab Normal	Abnormal
Idiopathic	Narcotics	CIU	Thyroid
Infection	Vancomycin	Idiopathic	Infection (parasite)
Food	Radiocontrast	Physical	Urticarial vasculitis
Drug	Muscle relaxants		
Insect sting			
Contact			

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Causes of Acute Urticaria

- 50% - Idiopathic
- 40% - URI/Infections
- 9% - Drugs
- 1% - Food
- < 1% - Other

44

Alternate Diagnoses

- Urticarial vasculitis: Hives are painful rather than pruritic, > 48 hrs, cause ecchymosis or PIH.
- SLE: Hives + systemic symptoms.
- Cryoglobulinemia: Cold induced urticarial or vasculitic lesions. Associated with Hep B or C.
- Schnitzler's syndrome: Monoclonal gammopathy with fever, weight loss, bone pain, adenopathy, and urticaria.

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Alternate Diagnoses

- PUPP: Polymorphic eruption of pregnancy, pruritic dermatitis, erythematous papules within abdominal striae with periumbilical sparing.
- Hypereosinophilic syndrome: group of disorders with persistent overproduction of eosinophils that infiltrate and damage tissues, blood eosinophilia of ≥1500/microliter.
- Cryopyrin Associated Periodic Syndromes (CAPS): periodic fever, urticaria, leukocytosis, conjunctivitis, and muscle and skin tenderness after exposure to cold.
  - Muckle-Wells: not cold sensitive, experience sensorineural hearing loss and arthritis, and can progress to amyloidosis.

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Chronic Urticaria

- Alternate Diagnoses
- Urticarial Vasculitis
- Physical Urticarias
- Chronic Autoimmune Urticaria

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AAAAI/ACAAI Guidelines

- 1. Avoidance of triggers/physical factors if present
- 2. Standard dose 2nd generation antihistamines
- 3.
  - Add another 2nd generation antihistmaine
  - Add H2 antagonist.
  - Add leukotriene receptor antagonist
  - Add 1st generation antihistamine at bedtime

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AAAAI/ACAAI Guidelines

- 4. Dose advancement of 2nd generation anthistamine (2-4 times) standard dose.
- 5. Add alternative agent
  - Omalizumab
  - Cyclosporine
  - Other anti-inflammatory or immune suppressants.

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EAACI/WAO Guidelines

- 1. Monotherapy with 2nd generation antihistamine.
- 2. Increase 2nd generation antihistamine up to 4 times normal.
- 3. Omalizumab plus 2nd generation antihistamine.
- 4. If not controlled after 6 weeks 2nd generation antihistamine plus cyclosporine.

Zuberbier, T. et al (2018). The EAACI/GA(2)LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy, 73*(7), 1393-1414. doi:10.1111/all.13397

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Serota

1. High dose 2nd generation anthistamine, H2 antagonist
   - Cetirizine 10-20 mg twice per day
   - Famotidine 40 mg daily (used to use ranitidine 150 mg twice per day)
   - Omalizumab handout to patient

2. Assess after 1 month. Add omalizumab 300 mg qmonthly.

3. Assess after 2 months. Consider Omalizumab q2 week dosing.

4. Assess after 2 months. If no improvement, make sure you have the diagnosis right. Then, consider least immune suppressing options (Dapsone or Sulfasalazine).

5. Assess after 2 months. If no improvement consider cyclosporine.

Once stable maintain therapy for at least 1 year and for at least 3 months of being symptom free before considering weaning.

51

Omalizumab

- A meta-analysis of seven randomized trials (1312 patients)
- 300 mg dose: 36% achieved a complete response (urticaria activity score of 0).
  - UAS is a measure of itch (scored 0-3 and hive count scored 0-3).
- Significant reduction in weekly itch and weekly wheal scores.
  - Decrease of 67% for omalizumab 300 mg vs. 25% with antihistamines alone.
- Adverse event rates and specific events were similar with omalizumab and placebo.

Zhao, Z. T. et al. (2016). Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol, 137*(6), 1742-1750 e1744. doi:10.1016/j.jaci.2015.12.1342

Saini, S. et al. (2015). Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria who Remain Symptomatic on H1 Antihistamines: A Randomized, Placebo-Controlled Study. *J Invest Dermatol, 135*(3), 925. doi:10.1038/jid.2014.512

52

Omalizumab Black Box Warning

WARNING: Anaphylaxis

Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported to occur after administration of XOLAIR. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after XOLAIR administration. Health care providers administering XOLAIR should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur.

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Omalizumab Black Box Warning

Anaphylaxis
Anaphylaxis has been reported to occur after administration of XOLAIR in asthma premarketing clinical trials and in postmarketing spontaneous reports. The frequency of anaphylaxis attributed to XOLAIR use was estimated to be 0.1% and at least 0.2% (based on an estimated exposure of about 57,300 patients from June 2003 through December 2006), respectively.

A case-control study showed that among XOLAIR users, patients with a history of anaphylaxis to foods, medications, or other causes were at increased risk of anaphylaxis associated with XOLAIR, compared to those with no prior history of anaphylaxis.

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Omalizumab Black Box Warning

- Omalizumab Joint Task Force (AAAAI and ACAAI)
  - Concluded that 35 patients had 41 episodes of anaphylaxis associated with Xolair (omalizumab) administration between June 1, 2003, and December 31, 2005.
  - 39,510 patients receiving Xolair (omalizumab)
  - Anaphylaxis-reporting rate of 0.09% of patients.
  - 36 events for which the time of reaction was known
    - 22 (61%) reactions occurred in the first 2 hours after one of the first 3 doses.
    - 5 (14%) of the events after the fourth or later doses occurred within 30 minutes.
  - Considering the timing of these 36 events, an observation period of 2 hours for the first 3 injections and 30 minutes for subsequent injections would have captured 75% of the anaphylactic reactions.

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Serota Recommendations

- There have been no deaths from anaphylaxis due to omalizumab.
- Anaphylaxis rates for CIU are lower than for asthma patients.
- Prefilled syringe.

- Observe for 2 hours for first 3 injections and for 30 min thereafter.
- If patient is administering at home (after 3rd injection) make sure patient has epinephrine autoinjector and has nearby access to an ER in their community.

56

Dupilumab for CSU

- Two Phase 3 randomized, double-blind, placebo-controlled trials evaluating the efficacy and safety of Dupixent in two different patient populations with uncontrolled CSU.
- Study A evaluated Dupixent as an add-on therapy to standard-of-care H1 antihistamines compared to antihistamines alone in 138 patients with CSU aged 6 years and older who remained symptomatic despite antihistamine use and were not previously treated with omalizumab.
- Study B evaluated Dupixent in 108 patients with CSU aged 12 to 80 years who remained symptomatic despite standard-of-care treatment and were intolerant or incomplete responders to omalizumab.

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Dupilumab for CSU

- 64% reduction from baseline ISS7 at Week 24 vs 38% with placebo.
- 65% reduction from baseline HSS7 at Week 24 vs 39% with placebo.
- 31% of patients achieved UAS7 of 0 and 46% achieved a UAS7 ≤ 6 (defined as well controlled).

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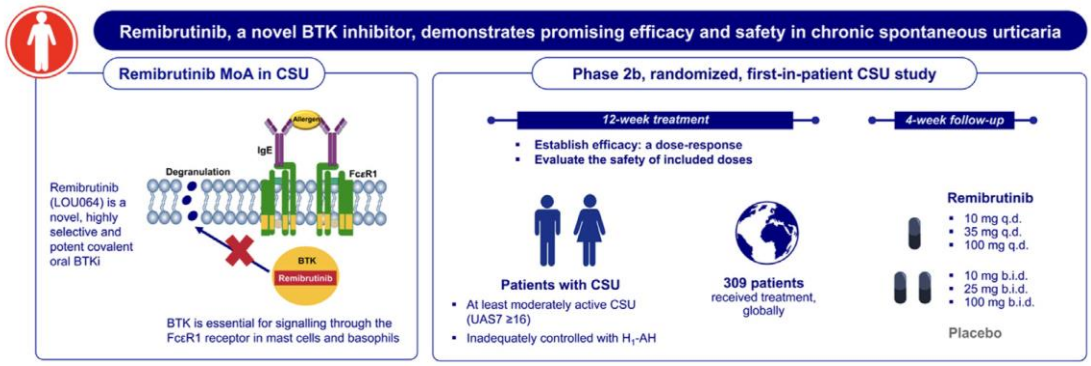
Remibrutinib For CSU



Maurer, M., et al. (2022). "Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria." J Allergy Clin Immunol **150**(6): 1498-1506 e1492.

59

Remibrutinib For CSU

- Bruton's tyrosine kinase (BTK), which is located downstream of the IgE receptor, is a cytoplasmic kinase expressed in selected immune cells such as mast cells, basophils, B cells, macrophages, and platelets.
- Cross-linking of FcεRI promptly activates BTK in mast cells and basophils; studies have shown that the release of histamine and inflammatory cytokines by mast cells and basophils is reduced in BTK-null mice and patients with BTK deficiency.
- The high selectivity and tolerability of remibrutinib are likely attributable to its ability to bind to an inactive conformation of BTK. In a recent study involving healthy volunteers, remibrutinib was effective in inhibiting basophil activation.

Maurer, M., et al. (2022). "Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria." J Allergy Clin Immunol **150**(6): 1498-1506 e1492.

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Remibrutinib For CSU

- 311 patients were randomized.
- Reduced symptom score was observed for all remibrutinib doses from week 1 until week 12, with weekly Urticaria Activity Score change from baseline at week 4: −19.1 (10 mg once daily), −19.1 (35 mg once daily), −14.7 (100 mg once daily), −16.0 (10 mg twice daily), −20.0 (25 mg twice daily), −18.1 (100 mg twice daily), and −5.4 for placebo (nominal $P < .0001$ for all doses vs placebo).
- UAS7 of 0 in around 30% of patients.
- Most adverse events were mild or moderate, with no dose-dependent pattern.

Maurer, M., et al. (2022). "Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria." J Allergy Clin Immunol **150**(6): 1498-1506 e1492.

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Remibrutinib For CSU

AEs by PT (≥5% in any treatment group)								
Headache	1 (2.3)	7 (15.9)	4 (8.5)	3 (6.8)	6 (14.0)	5 (11.1)	26 (9.7)	6 (14.3)
Nasopharyngitis	7 (15.9)	2 (4.5)	2 (4.3)	4 (9.1)	4 (9.3)	4 (8.9)	23 (8.6)	3 (7.1)
CSU	3 (6.8)	2 (4.5)	3 (6.4)	4 (9.1)	2 (4.7)	2 (4.4)	16 (6.0)	1 (2.4)
Nausea	2 (4.5)	3 (6.8)	1 (2.1)	1 (2.3)	1 (2.3)	2 (4.4)	10 (3.7)	0
Upper respiratory tract infection	1 (2.3)	2 (4.5)	2 (4.3)	0	3 (7.0)	0	8 (3.0)	1 (2.4)
Diarrhea	2 (4.5)	0	0	4 (9.1)	0	1 (2.2)	7 (2.6)	2 (4.8)
Pyrexia	3 (6.8)	0	0	2 (4.5)	1 (2.3)	0	6 (2.2)	0
Discontinued study treatment due to AE(s)	0	0	0	3 (6.8)	1 (2.3)	3 (6.7)	7 (2.6)	0

Maurer, M., et al. (2022). "Remibrutinib, a novel BTK inhibitor, demonstrates promising efficacy and safety in chronic spontaneous urticaria." J Allergy Clin Immunol **150**(6): 1498-1506 e1492.

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Top 5 Clinical Pearls

- 1. Address the barrier dysfunction and the immune dysregulation.
- 2. Excessive Th2 mediated inflammation is a systemic condition.
- 3. Ask what the movie looks like.
- 4. Assess comorbidities.
- 5. Treat with the least immune suppressing medication that considers efficacy, safety and comorbidities.

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Annual Business Meeting

Saturday, June 24, 2023

9:45 a.m. – 10:15 a.m.

Welcome to the
2023 Pennsylvania Allergy & Asthma Association
Annual Business Meeting

Saturday, June 24, 2023
9:45 – 10:15 am

Pennsylvania Allergy & Asthma Association

1

Bylaws Amendment Ballot

Those eligible to vote received a ballot at registration.

Complete Ballot and return to ballot box at entrance by **10:00am**

2

AGENDA

I. Call to Order (*Robert Zemble, MD*)
II. Approval of Minutes of June 25, 2022, Annual Business Meeting (*Robert Zemble, MD*)
III. President's Report (*Robert Zemble, MD*)
IV. Treasurer's Report (*Hey Chong, MD*)
V. Membership Report (*Janet Beausoleil, MD*)
VI. Nominating Committee Report & Elections (*Sigrid DaVeiga, MD*)
VII. PAERF (*Sarah Henrickson, MD*)
VIII. New/Old Business - Bylaws Amendment – Expansion of Training Membership (*Robert Zemble, MD)*
IX. In Memoriam (Janet Beausoleil, MD)
X. Recognition of Outgoing President and Remarks (*Janet Beausoleil, MD and Robert Zemble, MD*
XI. Incoming President's Remarks *(Janet Beausoleil, MD and Gisoo Ghaffari, MD)*
XII. Adjournment

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APPROVAL OF THE MINUTES
June 25, 2022

I. Call to Order – Dr. Sigrid DaVeiga, PAAA President, called the meeting to order at 9:45 a.m. A quorum was present. She reviewed the eligibility requirements for those permitted to vote and explained the voting procedure to be followed for the proposed bylaws amendments and other matters.

II. Approval of Minutes of June 26, 2021, Annual Business Meeting – On a motion made and seconded, those present voted unanimously by acclamation to approve the minutes of the 2021 Annual Business Meeting.

III. President's Report – Dr. DaVeiga thanked everyone for coming to the annual meeting and annual business meeting, the first in-person meeting since the onset of the pandemic. Dr. DaVeiga expressed her appreciation and thanks to Planning Committee, and its chair Hey Chong, MD who could not be present for the meeting. Dr. DaVeiga congratulated the Planning Committee for the excellent educational program and speakers assembled for this year's meeting. She urged PAAA members to get actively involved in the work of the organization.

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IV. **Treasurer's Report/Finance Committee** – Dr. Gisoo Ghaffari reported on the financial statement as of December 2021. She commented on PAAA's total assets and total liabilities. On a motion made and seconded, those present unanimously accepted the financial statement.

V. **Report of the Membership Committee** – Dr. Janet Beausoleil reported on the membership statistics. She reported that PAAA gained twenty new members since June 2021. The current membership stands at 168 dues-paying members and 64 emeritus or in-training members for a total membership of 232.

VI. **Report of the Nominating Committee** – Dr. Allyson Larkin presented the Nominating Committee slate and called for any nominations from the floor. Hearing none, on a motion made and seconded, those present voted unanimously by acclamation to accept the slate as presented.

VII. **PAERF – Dr. Sarah Henrickson** reviewed the PAERF financial report as of May 31, 2022, thanked those who donated to PAERF in the last year, recognized the 2022 $10K PAERF Research Grant recipient Dr. Kim Nguyen, and 2021 PAERF $10K grant recipient Dr. Stanislaw Gabryszewski and 2021 $2500 mini-grant recipients grants Dr. Patrick Gleeson and Dr. Amandeep Sandhu . The 2022 PAERF poster presenters were also recognized.

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VIII. **New/Old Business –** Amendment of the PAAA Bylaws. President Sigrid DaVeiga reviewed the proposed Bylaws amendment that sought to add a new standing committee devoted to Diversity, Equity, and Inclusion. Ballots were provided to those eligible to vote. The amendment passed with the support of more than two-thirds of those present and eligible to vote.

IX. **Recognition of Long-Standing Attendees and In Memoriam –** PAAA Historian, Dr. Janet Beausoleil recognized fellow 2022 long standing attendee Robert Rabinowitz, DO, and remembered two PAAA stalwarts who passed in 2022, Drs. Fireman and Israel.

X. **Recognition of Out Going President –** PAAA Historian Dr. Janet Beausoleil presented Dr. Sigrid DaVeiga with the PAAA President's Award in recognition of her outstanding leadership and tenure as PAAA president. Dr. DaVeiga thanked the Board of Regents for their support and hard work and passed the mantle of leadership to Dr. Robert Zemble.

XI. **Remarks of Incoming President –** Dr. Zemble thanked Dr. DaVeiga for her leadership and remarked that he looks forward to working with the Board of Regents in the coming year to continue to strengthen PAAA and the great job it does supporting its members and their patients with education, advocacy, and shared experience.

There being no further business, the meeting adjourned at 10:20 a.m.

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PRESIDENT'S REPORT

Robert Zemble, MD

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TREASURER'S REPORT

Hey Chong, MD, PhD

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TREASURER'S REPORT

Pennsylvania Allergy and Asthma Association
Statement of Financial Position
December 31, 2022

	YEAR TO DATE	PRIOR YEAR TO DATE
ASSETS		
Cash - Checking	$300.00	$0.00
Cash Management - Fulton	39,128.17	70,046.56
Long Term Investment	427,225.75	497,440.92
Total Cash	466,653.92	567,487.48
Accounts Receivable	0.00	150.00
Prepaid Expenses	5,890.50	0.00
TOTAL ASSETS	472,544.42	567,637.48
LIABILITIES AND NET ASSETS		
Accounts Payable - General	$1,768.05	2,291.90
Accounts Payable - PAMED	6,890.07	6,561.38
Unearned Revenue	6,750.00	48,950.00
Total Liabilities	15,408.12	57,803.28
Net Assets, January 1	509,834.20	469,949.14
Change in Net Assets	(52,697.90)	39,885.06
Net Assets, Year to Date	457,136.30	509,834.20
TOTAL LIAB AND NET ASSETS	472,544.42	567,637.48

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MEMBERSHIP REPORT

Janet Beausoleil, MD

10

MEMBERSHIP COMMITTEE REPORT

Current Membership	
Active	155
Associate	1
Corresponding	7
Emeritus	50
In-training	18
Total Members	231

New Members Since June 2022

Active
Antonella Cianferoni, MD
Warden Hwan, MD
Anar Dossumbekova, MD, PhD
Scott Feldman, MD, PhD
Rehan Mujahid, DO

Corresponding
Ramin Beheshti, MD

In Training
Jennifer Anne Brennan, DO
Timothy Buckey, MD, MBE
Sheryl Mathew, MD
Catherine Murray, MD
Isma Shah, MD
Colleen Shannon, MD, MPH
Nicole Wolfset
Justyna Zybaczynska

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NOMINATING COMMITTEE REPORT

Sigrid DaVeiga, MD

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NOMINATING COMMITTEE REPORT

2023-2024 Board of Regents Nominees
Officers

Name	Position
Hey Chong, MD Pittsburgh, PA	President-Elect
Magee DeFelice, MD Philadelphia	Secretary/Treasurer

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NOMINATING COMMITTEE REPORT

2023-2024 Board of Regents Nominees
Members At- Large

Name	Position
Christine Malloy, MD, Blue Bell, PA	Member-At-Large (4-year term)
Mosopefoluwa Lanlokun, MD Pittsburgh, PA	Member-At-Large (4-year term)
Timothy Buckey, MD, Philadelphia, PA	FIT (1-year term)

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NOMINATING COMMITTEE REPORT

2023-2024 Board of Regents Appointments

Name	Position
Sarah Henrickson, MD	Program Chair
Megan Ford	Assistant Program Chair

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PAERF REPORT

Sarah Henrickson, MD, PhD

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PAERF Financial Report as of May 31, 2022

Pennsylvania Allergy Education and Research Fund
Statement of Financial Position May 31, 2023

ASSETS:		
Cash Management - General	12,398.13	
Long-term Investments, at Market	127,084.68	
Total, Cash and Investments		139,482.81
Accounts Receivable		0.00
Prepaid Expenses		0.00
TOTAL, ASSETS 139,482.81		
LIABILITIES AND NET ASSETS:		
Accounts Payable - General	0.00	
Unearned Revenue	0.00	
Total, Liabilities		0.00
Net Assets, January 1, 2023	129,369.12	
Change in Net Assets	10,113.69	
Net Assets, May 31, 2023		139,482.81
TOTAL, LIABILITIES AND NET ASSETS 139,482.81		

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PAERF DONORS

Platinum

Corinna S. Bowser, MD
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Thank you PAERF Donors!

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PAERF DONORS

Silver

Janet L Beausoleil, MD
Hey J. Chong, MD
Megan Ford, MD
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Sarah E. Henrickson, MD
Sharon Hwang MD
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Pooja B. Jhaveri, MD
Katie L. Kennedy, MD
Christine Malloy, MD
Gregory V. Marcotte, MD
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Thekkemadom P. Ramakrishnan, MD
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Robert M. Zemble, MD

Bronze

Sigrid P. DaVeiga, MD
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Michael J. Palumbo, MD
Matthew Straesser, MD

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2023 & 2022 PAERF RESEARCH GRANT RECIPIENTS

2023 Grant Recipient

- $7,500 grant to Dr. Timothy Buckey - Food Allergy Health Equity: An Assessment of Prevalence and Outcomes in a Pediatric Food Challenge Center Based on Patients' Demographics

2022 Grant Recipient

- $10,000 grant to Dr. Kim Nguyen - Impact of anaphylaxis plans in multiple languages in an outpatient pediatric allergy clinic setting

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2023 PAERF POSTERS

Jennifer Brennan, DO
Timothy Buckey, MD, MBE
Stanislaw Gabryszewski, MD, PhD
Hannah Harrison, MD
Lauren Kaminsky, MD, PhD
Sheryl Mathew, MD
Sunjay Modi, MD
Catherine Murray, MD,
Kim Nguyen, MD
Matthew Norris, MD
Marvi Rizwan, MD
Isma Shah, MD
Nicole Wolfset, MD

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2023 PAERF TRAVEL STIPEND RECIPIENTS

Nemours Children's Hospital Sidney Kimmel Medical College at Thomas Jefferson University

Hannah Harrison, MD
Isma Shah, MD

University of Pennsylvania

Timothy Buckey, MD
Sheryl Mathew, MD
Marvi Rizwan, MD

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NEW/OLD BUSINESS – BYLAWS AMENDMENT

Robert Zemble, MD

23

NEW/OLD BUSINESS

Pursuant to the 30-day notice requirement of the Pennsylvania Allergy and Asthma Association Bylaws Article VIII – Amendment of Bylaws, below please find a proposed amendment to Article II – Members, Section 1. d. Training

The amendment seeks to expand the existing Training Membership category by amending Article II – Members, Section 1. d. Training to include residents and medical students, to afford residents and medical students the same rights, benefits, and privileges available to fellows, and to provide for an abbreviated membership application process to facilitate "automatic" membership in PAAA.

ARTICLE II - MEMBERS

Section 1. The membership of this Association shall consist of the following classes:

…

d. Training - a physician (MD or DO) or medical student enrolled in a recognized regional fellowship program in allergy and immunology, medical residency program or medical school is eligible for a training membership. This class of membership shall continue until the end of the calendar year in which the fellowship, residency, or medical school training ends. A training member may serve on a committee (but not as chair), but may not vote, or hold elective office. Training members are not responsible for dues or assessments. Elevation from training to active membership requires notification of successful completion of the two-year fellowship. Training members will complete an abbreviated membership application process established by the Membership Committee.

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Pennsylvania Allergy & Asthma Association

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IN MEMORIAM

Dr. Richard J. Greene

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Pennsylvania Allergy & Asthma Association

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RECOGNITION OF OUTGOING PRESIDENT AND REMARKS

Janet Beausoleil, MD
Robert Zemble, MD

26

REMARKS OF INCOMING PRESIDENT

Gisoo Ghaffari, MD

27

Save the Date!

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ADJOURNMENT

PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Approach to the Allergy Patient with Hypereosinophilia

Presented by:

Amy Klion, MD

Saturday, June 24, 2023

10:45 a.m. – 11:30 a.m.

National Institute of Allergy and Infectious Diseases

Laboratory of Parasitic Diseases

Approach to the Allergy Patient with Hypereosinophilia

Amy Klion, MD
Laboratory of Parasitic Diseases
June 24. 2023

1

Disclosures

- No conflicts of interest
- None of the drugs that I will discuss are approved for HES except for imatinib and mepolizumab

2

Learning Objectives

Review controversies in the definition and classification of HES

Describe the heterogeneity of clinical presentations of hypereosinophilia

Discuss the approach to targeted therapy of hypereosinophilic syndromes

3

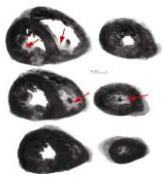
Evolution of the definition of HES

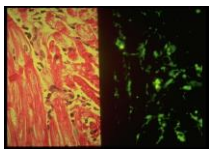
Case Reports

FIBROPLASTIC ENDOCARDITIS WITH EOSINOPHILIA (LÖFFLER'S ENDOCARDITIS PARIETALIS FIBROPLASTICA): CASE REPORT AND REVIEW OF LITERATURE *

By F. G. Hoffman, Lt. Colonel, USAF (M.C.), *Waterloo, N. Y.*, David Rosenbaum, M.D., and P. D. Genovese, M.D., *Indianapolis, Indiana*

In 1936 Löffler published a report of two patients with a hitherto unclassified type of endocarditis.[1-3] This entity, subsequently referred to as fibroplastic endocarditis or Löffler's endocarditis parietalis fibroplastica, is characterized by an afebrile course, progressive, refractory congestive failure and a striking eosinophilia. The cases reported by Löffler, in addition, exhibited signs of mitral valvulitis, though these were inadequate to account for the clinical picture.





H & E Anti-MBP

(Hoffman, Rosenbaum and Genovese 1955 Ann Intern Med)

Case Series

- Blood eosinophilia ≥1.5 x 10^9/L for longer than 6 months (or death before 6 months associated with signs and symptoms of HES)
- Lack of evidence for parasitic or other known causes of eosinophilia
- Presumptive signs of organ involvement , such as heart failure, gastrointestinal dysfunction, central nervous system abnormalities, fever or weight loss

(Chusid, Dale, West and Wolff 1975 Medicine (Baltimore)

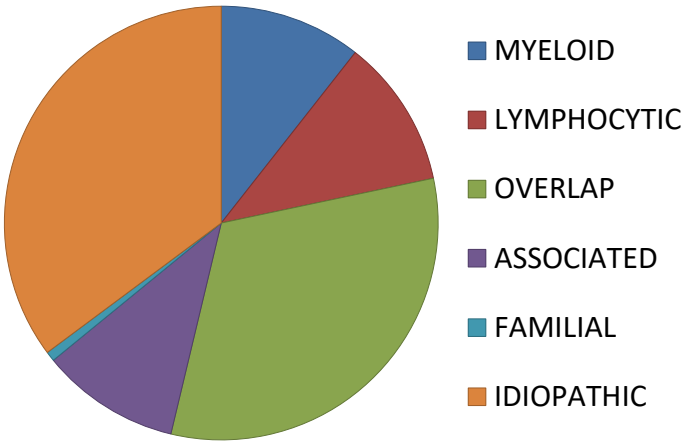
Consensus Definition

- Blood eosinophilia ≥1.5 x 10^9/L on at least two occasions or evidence of prominent tissue eosinophilia associated with marked blood eosinophilia
- Evidence of end organ damage attributable to eosinophilia

(Klion et al. JACI 2006; Simon et al. JACI 2010; Valent JACI 2012; Valent Allergy 2022)

4

HES clinical subtypes



NIH cohort (n=650)

(Valent et al. Allergy 2022)
(Arbor et al. Blood 2022)

5

Myeloid HES

- *PDGFRA*-positive MN (>80%)
- Other mutation-positive MN*
- CEL-NOS
- Idiopathic HES with myeloid features

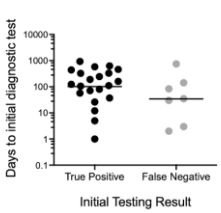
***PDGFRA*-positive MN**
- Male gender
- Anemia and/or thrombocytopenia
- Dysplastic eosinophils and myeloid precursors in periphery
- Splenomegaly
- Hypercellular marrow
- Increased serum B12 and/or tryptase levels
- **30% mortality at 3 years**

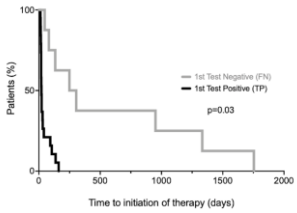
*Marked eosinophilia occurs in a variety of myeloid neoplasms and myeloproliferative disorders, including those associated with *PDGFRB*, *FGFR1*, *KIT*, and *JAK2*

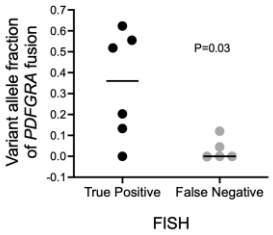
6

"Idiopathic" myeloid HES update

- FISH is relatively insensitive for the detection of *FIP1L1::PDGFRA* compared to PCR







(Pongdee Acta Haem 2022)

- The number of new recurrent mutations associated with HES identified by NGS continues to increase (i.e., *STAT5b* N642H – Cross Leukemia 2019*, JAK2 exon 13* – Patel Blood 2019)
- These are often not part of standard NGS panels.

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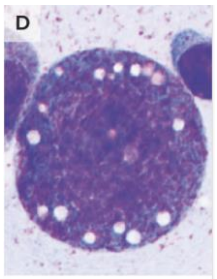
Germline mutations and myeloid HES

- 74 year old man with history of macrocytic anemia since childhood, episcleritis, and relapsing polychondritis presents with hypereosinophilia (AEC 1659/μL), pruritic rash, transfusion-dependent anemia and elevated serum tryptase (29 pg/mL)
- Bone marrow: normocellular with trilineage hematopoiesis, eosinophilia, no obvious increase in mast cells or fibrosis; cytogenetic and initial molecular studies unrevealing
- Diagnosis?

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome



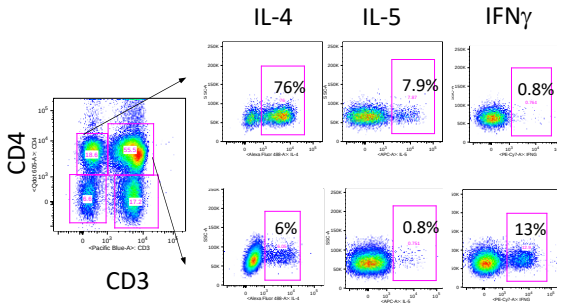
UBA1 Met41Thr; VAF 58%

(Beck et al. NEJM 2020)

8

Lymphocytic variant HES

- Associated with populations of phenotypically aberrant or clonal T cells secreting eosinophilopoetic cytokines
- Equally common in men and women
- Predominance of skin manifestations
- Associated with elevated serum IgE, TARC levels
- May progress to lymphoma in up to 30%

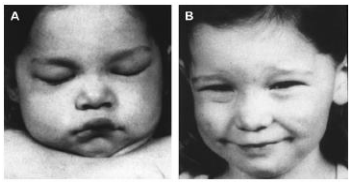


9

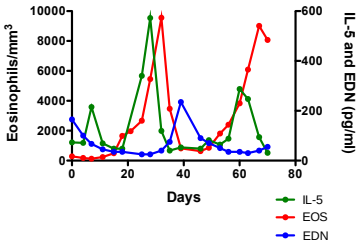
Rare LHES variants

36 year old man with recurrent episodes of bilateral hand and foot swelling x 3 months

Gleich's syndrome



(Katzen Am J Dis Child 1986)



Vascular aneurysm

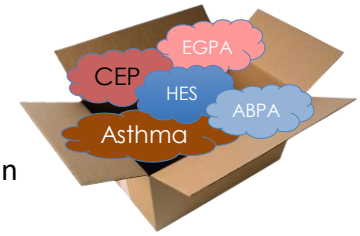
Additional features

- CD3-CD4+ clonal T cell population
- Elevated IgM
- Multilineage involvement

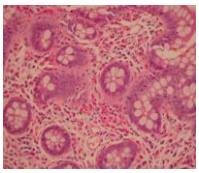
(Khoury et al. Haematologica 2015)

10

Overlap HES



- Single organ eosinophilic disorders that overlap in presentation with idiopathic HES and may be associated with marked peripheral eosinophilia
- Examples include EGID, eGPA, chronic eosinophilic pneumonia, atopic dermatitis
- Important to recognize since the therapeutic approach may be different



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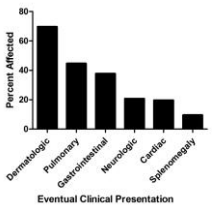
Clinical manifestations of HES are extremely heterogeneous and do not reliably distinguish between clinical subtypes

Table 1. Frequency of Organ Involvement in HES From American,[13] French,[26] and English[31] Series

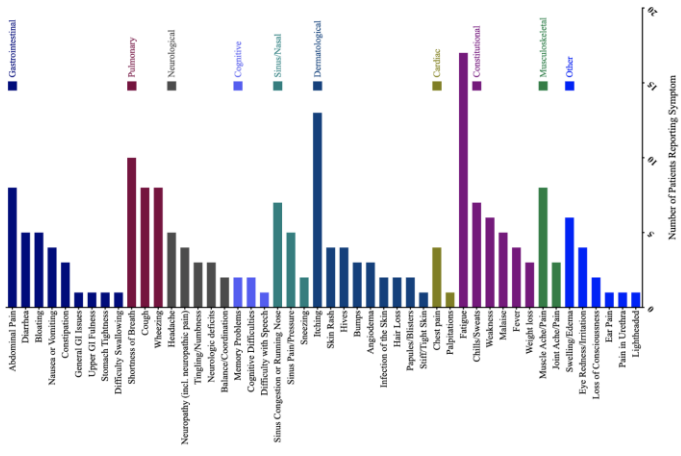
Organ System	Series (no. of patients) American (50)	French (40)	English (15)	Overall (105)
Hematologic	100	100	100	100
Cardiovascular	54	58	73	58
Cutaneous	56	50	73	56
Neurologic	64	35	73	54
Pulmonary	40	63	40	49
Splenic	46	33	60	43
Hepatic	32	28	—	30
Ocular	18	15	60	23
Gastrointestinal	14	23	53	23

Values are percentages.

(Weller and Bubley 1994 Blood)



(Ogbogu et al. 2009 JACI)



(Kovacs et al. 2020 JACI Pract)

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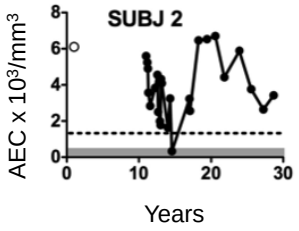
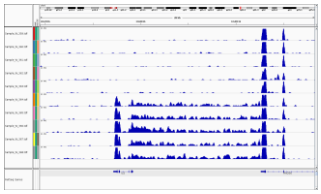
Hypereosinophilia in the absence of clinical manifestations

- Sporadic HEus
  - Defined by AEC ≥1.5 x 10^9/L without clinical manifestations off therapy for 2-5 years
  - May be associated with clonal/aberrant lymphocyte population and rarely, mutations consistent with myeloid neoplasm
  - Rarely progresses to overt HES (Chen et al. 2013; Helbig et al. 2014)
- Familial eosinophilia
  - Autosomal dominant eosinophilia associated with dysregulation of IL-5 transcription and lack of clinical manifestations (Klion et al 2004; Babu et al. 2017)
  - Recent identification of a single nucleotide variant that creates an aberrant transcription start site (2022 ASH oral presentation 583)

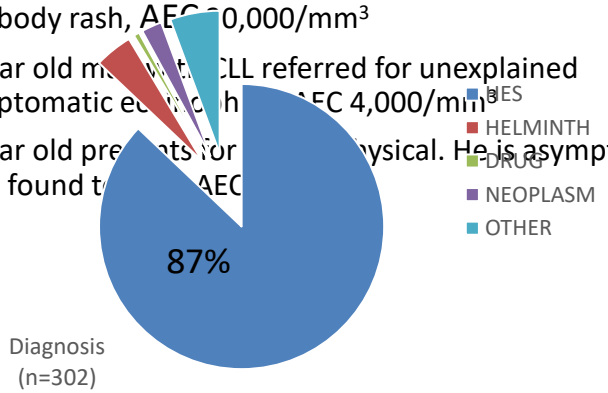




13

Secondary causes of eosinophilia can mimic idiopathic HES

- 50 year old Iraqi rug salesman with pruritus and erythematous total body rash, AEC 0,000/mm³
- 76 year old m[illegible] CLL referred for unexplained asymptomatic e[illegible] AEC 4,000/mm³
- 22 year old pre[illegible] for [illegible] ysical. He is asymptomatic, but is found t[illegible] AEC



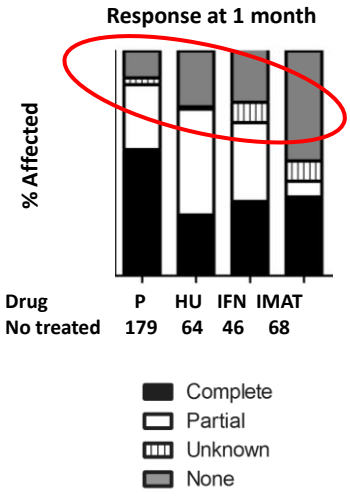
14

Approach to Treatment

- Potentially life-threatening?
- Secondary treatable cause?
- Most likely clinical subtype?

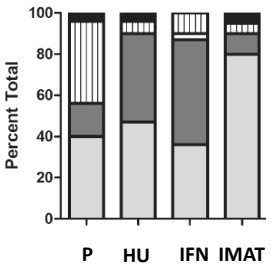
15

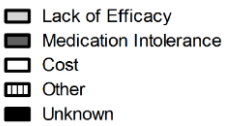
Conventional therapy for HES is unsatisfactory



Discontinuation of Therapy

PRED 42%
HU 76%
IFN 84%
IMAT 60%



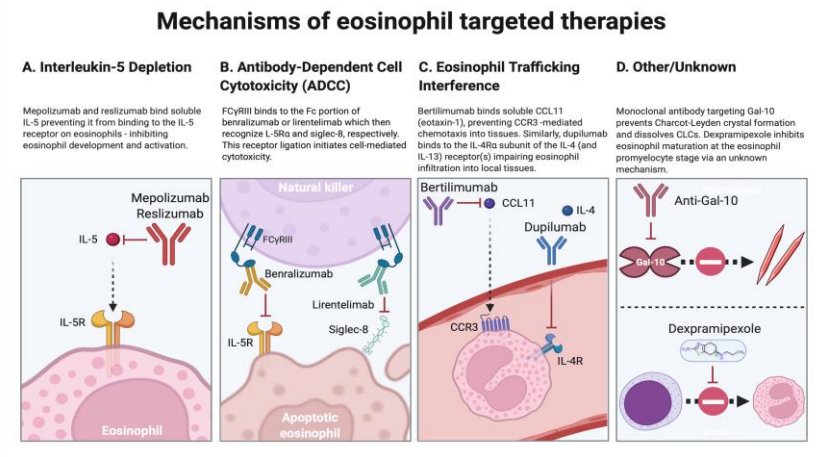


(Ogbogu et al. JACI 2009)

16

Eosinophil-targeted therapies

- The number of therapies that target eosinophil directly and/or indirectly is increasing exponentially
- Mepolizumab is the only eosinophil-targeted therapy FDA-approved for the treatment of all HES
- Efficacy and safety concerns may be different across the different clinical subtypes and overlap conditions

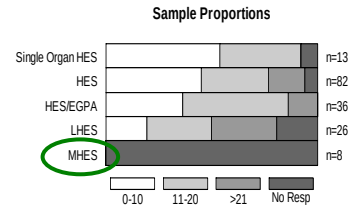


(Constantine and Klion, Faculty Rev 2022)

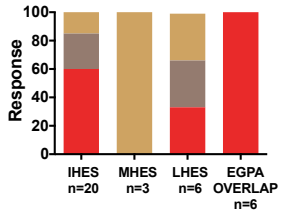
17

Clinical subtype predicts treatment responses In HES

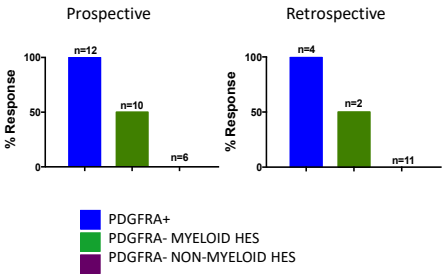
Glucocorticoids



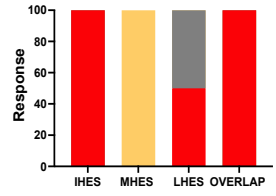
Mepolizumab



Imatinib



Benralizumab



(Khoury JACI Pract 2017 and Allergy 2016; Kuang JACI:P 2018 and NEJM 2019)

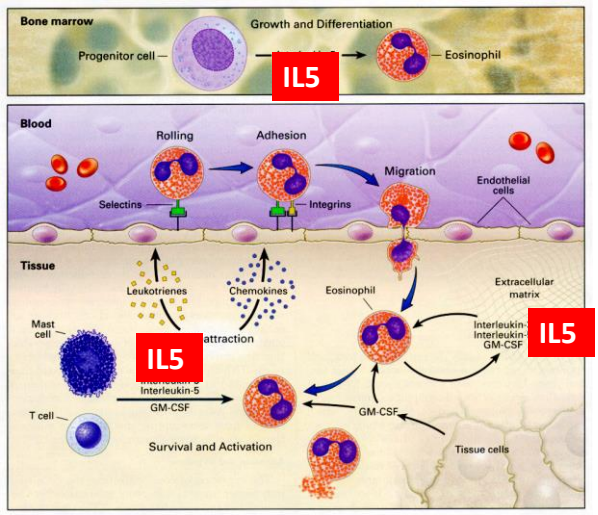
18

Case 1

- 54 year old woman presented with an 8 year history of marked eosinophilia , sinusitis, nasal polyps, urticaria, dermatitis and dyspnea and an AEC of 23400/µL
- Evaluation revealed no evidence of myeloid or lymphocytic variant HES and endomyocardial fibrosis with severe mitral regurgitation
- She underwent valve replacement and tricuspid repair and was treated with prednisone without response
- Eosinophil count remained elevated (33700/µL) and she developed severe prosthetic valve stenosis requiring a second valve surgery
- She was treated with conventional therapy (high dose steroids, hydroxyurea, cyclophosphamide, interferon), and FDA-approved targeted therapy (mepolizumab) without response.

19

IL-5 plays a crucial role in all stages of the eosinophil life cycle



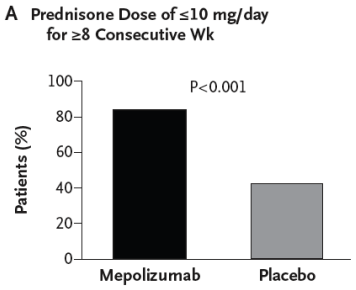
(from Rothenberg 1998 NEJM)

1-2% of peripheral blood leukocytes; $t_{1/2}$ in blood = 18 hours

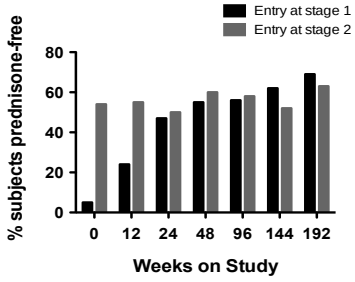
IL5 receptor α is found only on eosinophils, basophils and mast cells

20

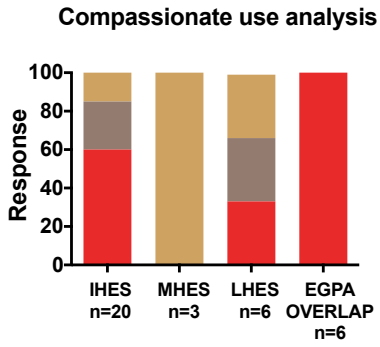
Mepolizumab (750 mg iv) is safe and effective therapy for PDGFRA-negative HES

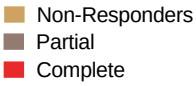


(Rothenberg NEJM 2009)



(Roufosse JACI 2012)

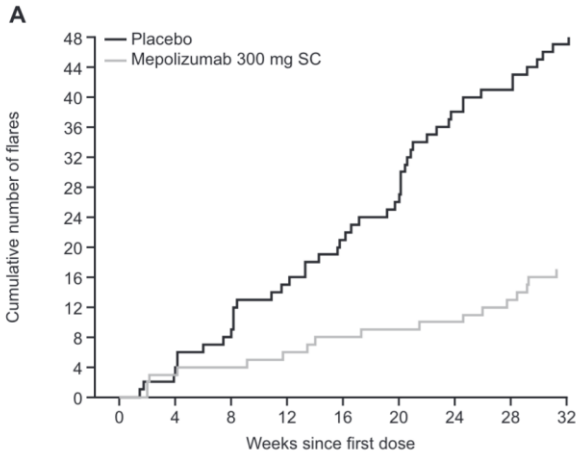




(Kuang JACI:P 2018)

21

Mepolizumab (300 mg sc) prevents flares in steroid-responsive HES



This study led to FDA approval for mepolizumab for HES

(Roufosse et al. JACI 2020)

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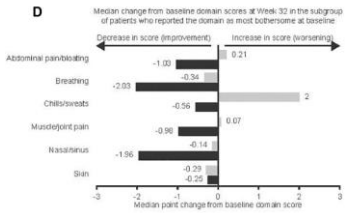
Mepolizumab – additional information

- Mepolizumab been in use for more than 20 years with excellent safety profile
- Also approved for asthma, eGPA and chronic sinus disease with polyps
- Clinical trials did not show efficacy in reducing symptoms in eosinophilic esophagitis
- In the phase 3 trial, skin symptoms were relatively resistant based on the most bothersome symptom analysis at 32 weeks (Roufosse Frontiers Med 2023)



- May be less effective in steroid-resistant HES, especially lymphocytic variant
- Depemokimab (long-acting anti-IL5; GSK3511294) is currently in clinical trials

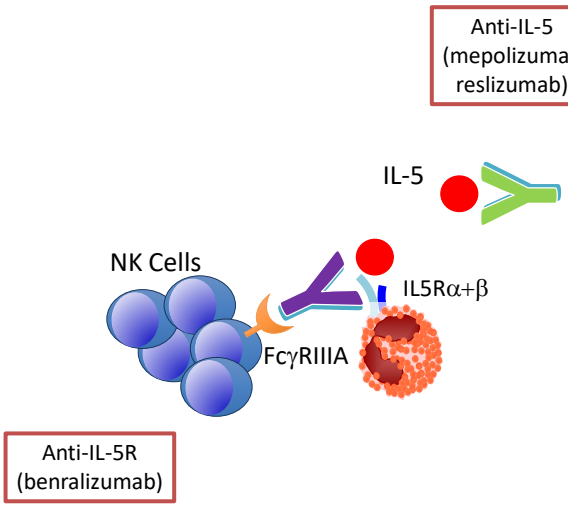
23

Case 1

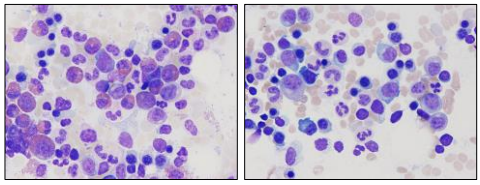
- She was referred to the NIH on interferon, mepolizumab and pulsed iv cyclophosphamide with AEC 4920/μL, ground glass pulmonary infiltrates and severe restrictive pulmonary disease
- Mepolizumab and interferon were discontinued and she was subsequently enrolled on a phase 2 placebo-controlled trial of benralizumab for treatment-refractory HES.
- At week 13, her AEC was 0/μL and cyclophosphamide was discontinued.
- She has remained clinically well without progression of cardiac disease with AEC 0/μL for >7 years.

24

Key differences between anti-IL-5 and anti-IL-5R antibodies



Mechanism of action
Effect on eosinophil precursors
Degree of tissue depletion

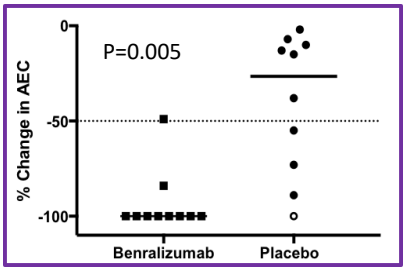


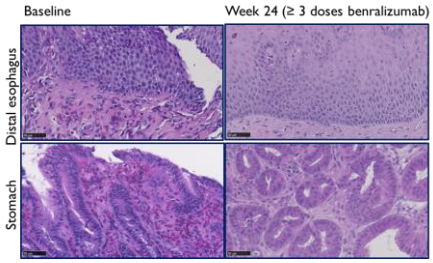
Pre-treatment Post-treatment

(Kuang et al. NEJM 2019)

25

Benralizumab was well-tolerated and effective in depleting eosinophils in HES





- The primary study endpoint was met (proportion of subjects with >50% decrease in AEC at 12 weeks)
- At week 13, AEC was <50/mm3 in 17/19 evaluable subjects
- At week 52, AEC remained suppressed in 14 subjects despite reduction or discontinuation of background therapy
- At 5-8 years, 10 of the initial 19 participants remain on benralizumab

(Kuang et al. NEJM 2019; unpublished data)

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Targeting IL-5/IL-5R in HES: next steps

- How does dosing affect response in HES?
  - Mepolizumab: 100 sc vs 300 sc vs 700 iv
  - Mepolizumab fixed dose vs. reslizumab weight-based
  - Benralizumab q4 week vs. q 8 week
- Which biologic for which patient?
- Safety and efficacy of multiple biologics
- Novel formulations
  - depemokimab (long-acting anti-IL5; GSK3511294)

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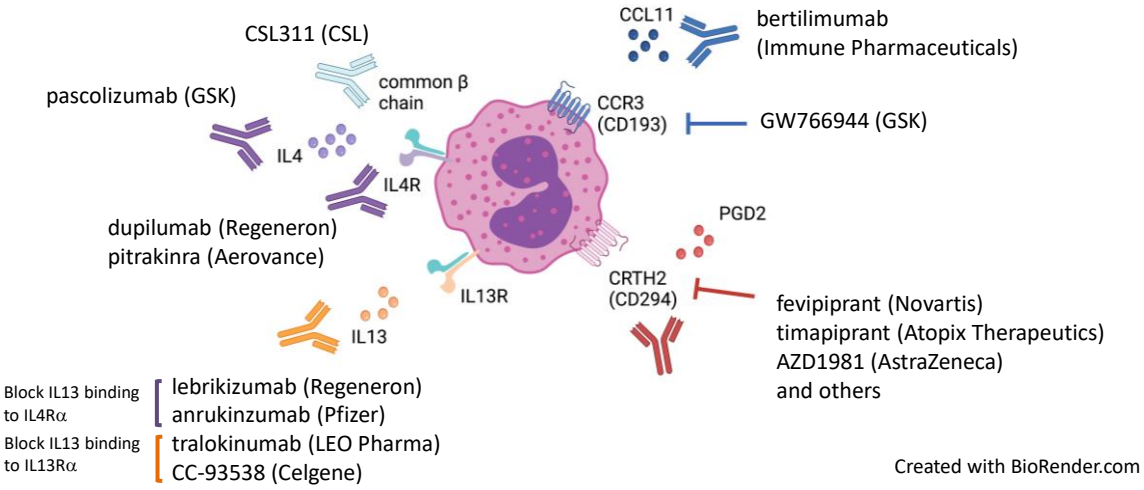
Targeting chemotaxis



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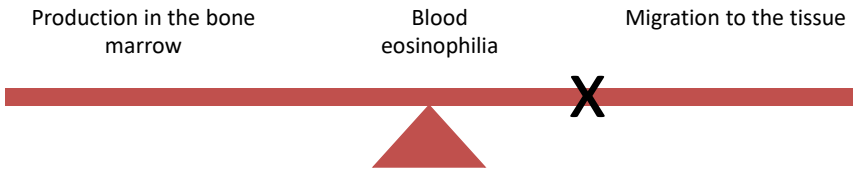
Pros and cons of targeting chemotaxis in HES



- Clinical trials have demonstrated significant reduction in tissue eosinophilia and symptoms in a variety of eosinophil-associated disorders (excluding HES)
- Most, but not all, of the clinical manifestations of HES are related to eosinophilic inflammation in the tissues
- Although peripheral eosinophilia has been described with most of the therapeutics targeting the IL4/13 axis, this has been transient and asymptomatic in most, but not all, cases

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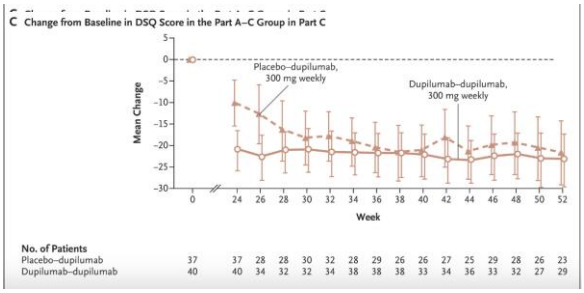
Dupilumab

- Monoclonal antibody to the IL4 receptor that blocks IL-4 and IL13 signaling
  - IL-4 and IL-13 are important in driving eotaxin-mediated trafficking of eosinophils to inflamed tissue
  - IL-13 is an important mediator of fibrosis
- Approved for asthma but not eGPA, atopic dermatitis, chronic rhinosinusitis with nasal polyps and eosinophilic esophagitis
- Most effective of the biologics for the treatment of CRSwNP (Cai et al. JACI Pract 2022) and only biologic approved for EoE (Dellon et al. NEJM 2022)
- Associated with transient increased blood eosinophil count with cases of eosinophilic complications, including eGPA, reported

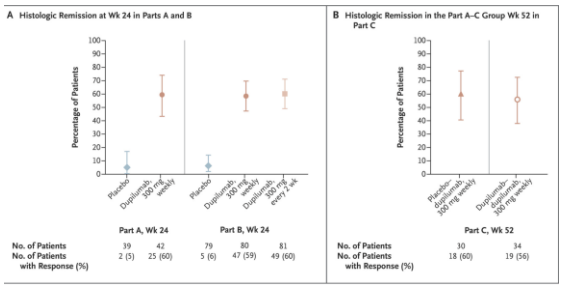
30

Dupilumab is effective in reducing symptoms and improving histology in EoE

Symptomatic improvement



Histologic remission



(Dellon et al. NEJM 2022)

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Case 2

- 58 year old man with a lifelong history of allergic rhinitis, mild asthma and severe eczema complicated by recurrent cellulitis and Staphylococcal bacteremia in 2015. AEC was 500/µL in May 2017 off all therapy.
- He was started on dupilumab 300 mg every 2 weeks in 2018 due to worsening pruritus despite prednisone, methotrexate and topical therapies. AEC was 2,320/µL in February 2020 on dupilumab monotherapy.
- The dupilumab dose was increased to 600 mg every 2 weeks in April 2020 due to persistent symptoms.
- In early 2021, he was admitted to the hospital for severe pruritus, diarrhea and weight loss. AEC was 12,930/µL. Dupilumab was discontinued and his eosinophil count gradually decreased to 3,190/µL by the end of the month.

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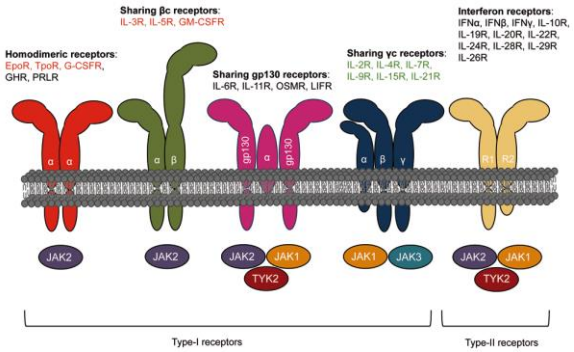
Other agents targeting eosinophils

Ruxolitinib (InCyte)

- Reversible inhibitor of JAK1/2
- FDA-approved for the treatment of polycythemia vera and myelofibrosis
- Adverse events occur in 25-35% of patients and include cytopenias, reactivation of viral infection and TB, and secondary malignancy
- Two small studies in lymphocytic variant HES showed promising results; anecdotal data in *JAK/STAT* mutation-positive HES



(Vainchenker F1000 Res 2018)

33

Case 2

- Prior to being seen at NIH, the patient restarted dupilumab with return of eosinophilia and development of an eosinophilic pleural effusion (34% eos).
- Prednisone 20 mg daily was started with resolution of the pleural effusion and improvement in his asthma but persistent pruritus.
- He was enrolled on an open label phase 2 clinical trial of ruxolitinib 15 mg po bid for steroid-refractory HES.
- Within 1 day his pruritus had improved. He recently returned for 12 week followup feeling “better than I have felt in years”. His skin is markedly improved, his AEC has normalized, and a steroid taper has been initiated.
- To date, 17 of 20 patients have been enrolled on study and results are encouraging.

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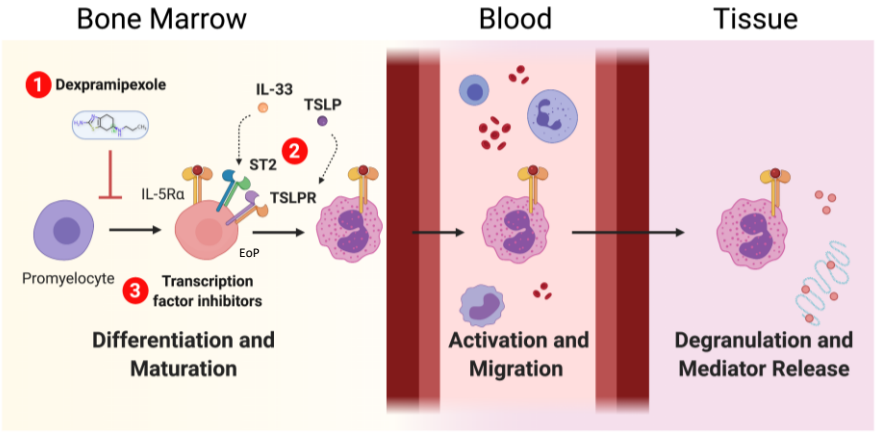
Other agents - targeting eosinophil development

Dexpramipexole, anti-IL33/ST2/TSLPR antibodies, transcription factor inhibitors



Note: EoPs can also be found in the blood and tissue in low numbers

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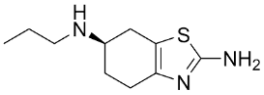
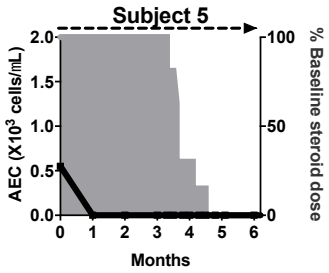
35

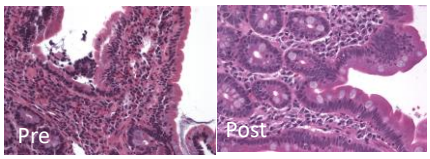


Dexpramipexole

- A small molecule enantiomer of an <u>oral</u> drug used to treat Parkinson's disease that was found to be neuroprotective in *in vitro* assays (Knopp Biosciences LLC)
- Target: unknown
- Failed to meet primary endpoint in phase 3 trial in ALS but was incidentally noted to dramatically reduce peripheral eosinophil counts
- Met dual steroid-sparing primary endpoints in pilot open-label phase 2 trial in HES (Panch et al. Blood 2018)
- Recently shown to deplete eosinophils and improve FEV1 in a phase 2 randomized placebo-controlled trial in moderate to severe asthma (Prussin et al. ATS 2021)
- Currently in phase 3 trials in severe asthma

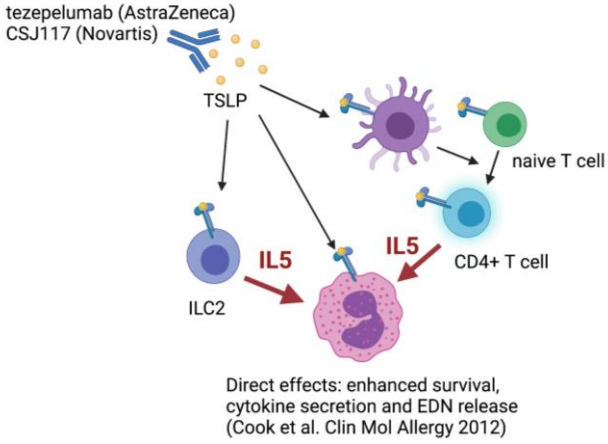


35 year old woman with HES/EGPA overlap on 15 mg prednisone equivalent with lung, GI, skin and sinus involvement.



36

TSLP as a therapeutic target



Tezepelumab has been shown to significantly decrease peripheral blood eosinophils (Corren 2017 NEJM, Menzies-Gow NEJM 2021) and, in the one study where this was assessed, decrease tissue eosinophilia and blunt the eosinophilic response to allergen challenge in the lungs (Diver et al. Lancet Respir Med 2021)

Tezepelumab was approved for the treatment of severe asthma in December 2021

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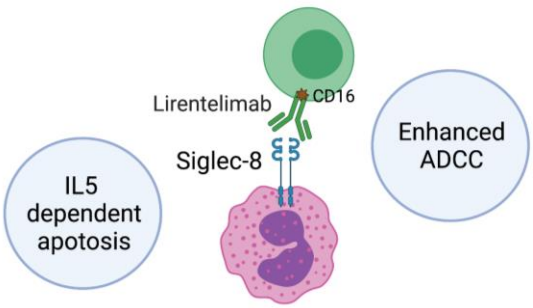
Other agents - targeting eosinophil receptors

Lirentelimab (Allakos)



- A placebo-controlled phase 2 study of lirentelimab for the treatment of eosinophilic gastritis and duodenitis depleted tissue eosinophils by 86% and reduced symptom scores by 53% (compared to 24% in the placebo group; p<0.001) (Dellon et al. NEJM 2020)
- Adverse events were comparable between the two groups with the exception of mild-moderate infusion reactions, which were more common in patients who received lirentelimab
- A phase 3 trial in eosinophilic gastritis and duodenitis did not meet the primary endpoint.

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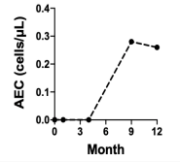
What about safety?

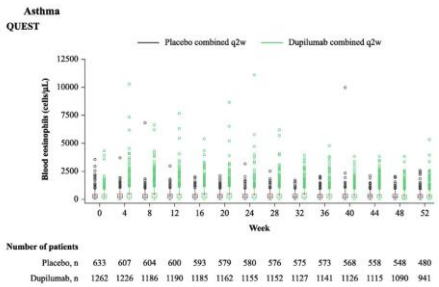
- Eosinophil depletion has not been associated with any major safety signals to date
- Interference with eosinophil trafficking is associated with transient peripheral eosinophilia and rarely, with eosinophilic complications
- Targeting multiple pathways and/or lineages with dual biologics may lead to unanticipated consequences

Healthy baby born to a mother on benralizumab



Normal growth, development, and vaccine responses at 1 year despite eosinopenia that resolved at 9 months

(Manetz et al. JACI:Pract 2020)



(Wechsler et al. JACI Pract 2022)

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Factors to consider when choosing a therapy for HES

- Clinical HES subtype and pattern of clinical involvement
- Concomitant conditions (chronic sinus disease, asthma,…..)
- Drug route (iv vs. sc), administration (doctor vs. patient) and frequency
- Potential side effects
- Insurance 
- Role of serum IL-5 levels is controversial

40

How to choose?

Mepolizumab

- Approved for severe asthma, HES and eGPA
- The 100 mg dose approved for asthma is insufficient for many patients with eGPA and HES (Chen et al. JACI 2022)
- Recently approved for CRSwNP (9% still required surgery and 25% OCS within 52 weeks)

Dupilumab

- Approved for asthma, atopic dermatitis, EoE, polyps but not HES or eGPA
- Associated with transient increased blood eosinophil count with cases of eosinophilic complications, including eGPA, reported
- Most effective of biologics for the treatment of CRSwNP (Cai et al. JACI Pract 2022)

Role for dual biologics?

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Conclusions

- Because HES is a heterogeneous disorder with a wide range of etiologies that overlap in clinical presentation but differ in response to therapy and prognosis, an inclusive approach to diagnosis is warranted.
- Although eosinophil-targeted therapies offer the promise of less toxic, more effective treatment for HES, there are many unresolved questions regarding efficacy and long-term safety.

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Thank you for your attention!

Too numerous to list collaborators
Irina Maric
Cindy Dunbar
Sandhya Panch
AstraZeneca
GlaxoSmithKline
Knopp/Areteia

Clinical Parasitology Group
Thomas Brown
Nicole Holland
Lauren Thumm
Perla Adames Castillo
Lauren Wetzler
JeanAnne Ware
Celeste Nelson

Our patients

Past Members of the Human Eosinophil Section
Fei Li Kuang
Princess Ogbogu
Nick Kovacs
Senbagavalli Babu

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Noninfectious Manifestations of Inborn Errors of Immunity

Presented by:

Ivan Chinn, MD

Saturday, June 24, 2023

11:30 a.m. – 12:15 p.m.

Noninfectious Manifestations of Inborn Errors of Immunity

Ivan Chinn, M.D.

June 25, 2023

74th Pennsylvania Allergy & Asthma Association Annual Meeting

1

Which patient has an underlying inborn error of immunity? Answer: ALL THREE

Patient 1

- 2 year-old boy
- Recurrent sinopumonary tract infections
- Chronic requirement for antibiotics

BTK

Patient 2

- 14 year-old girl
- Cerebral palsy
- Diarrhea "since birth"
- Some sinopulmonary tract infections
- Strong reactions to vaccines
- Idiopathic thrombocytopenic purpura since 13 years of age

CTLA4

Patient 3

- 15 year-old girl
- Recurrent pulmonary hemorrhages since 4 years of age
- Positive C-ANCA
- No recurrent infections

COPA

3

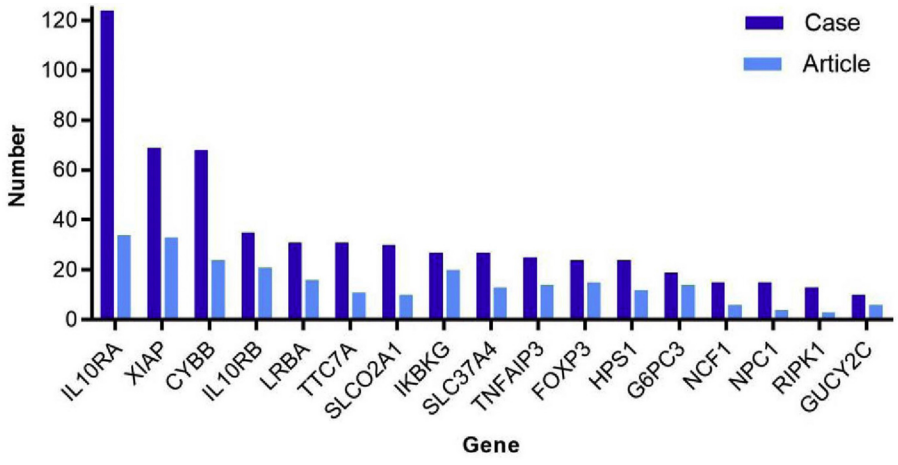
Genetic Errors of Immunity are NOT RARE

Estimated prevalence of 1 in 1,200 – 2,000 individuals

And not all patients have infections

4

Common Monogenic Causes of IBD (Systematic Review)



Nambu et al. *Clin Gastroenterol Hepatol* 2022;20(4):e653-63

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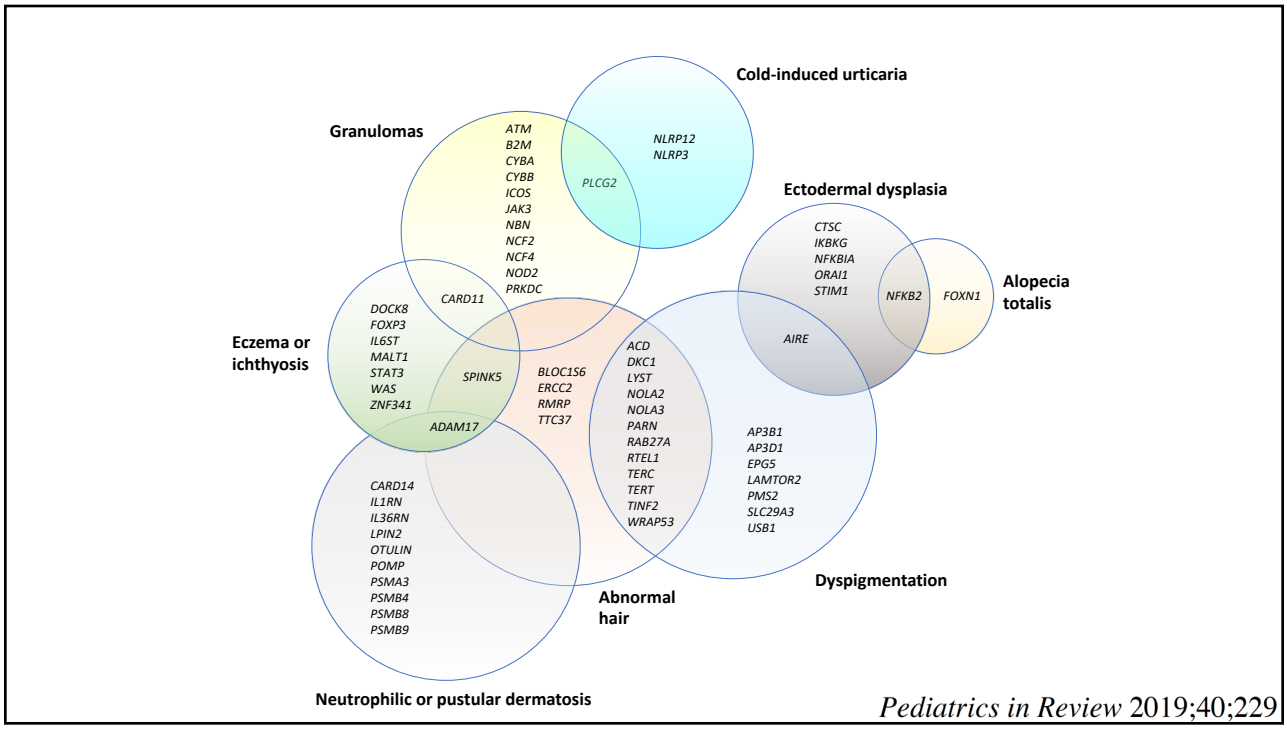

Pediatrics in Review 2019;40;229

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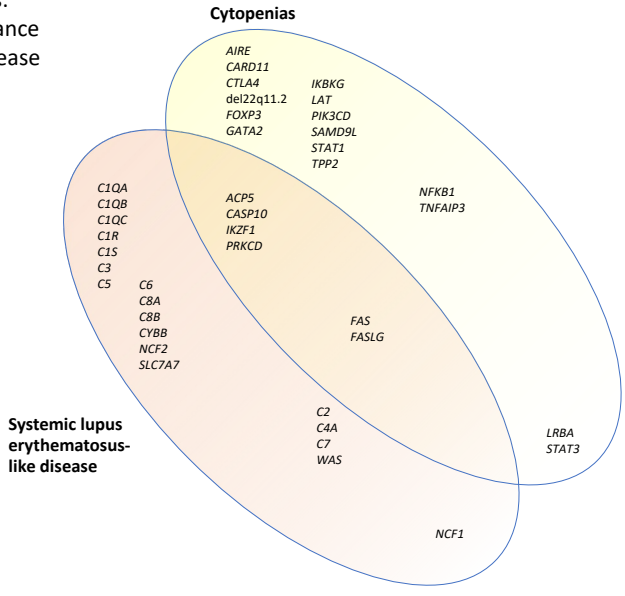
Key mechanisms:

- Loss of tolerance
- ALPS-like disease



"Autoimmune" Manifestations of IEIs

Pediatrics in Review 2019;40;229

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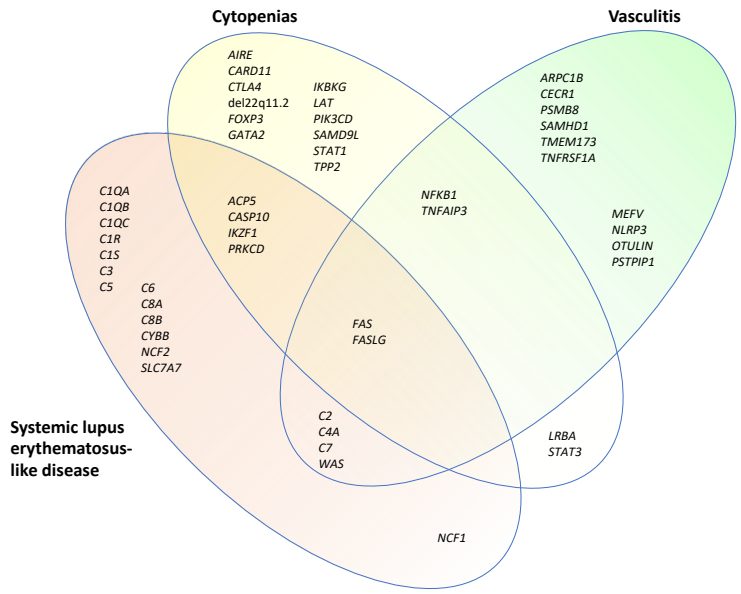

Key mechanism: inflammasome hyperactivity

"Autoimmune" Manifestations of IEIs

Pediatrics in Review 2019;40;229

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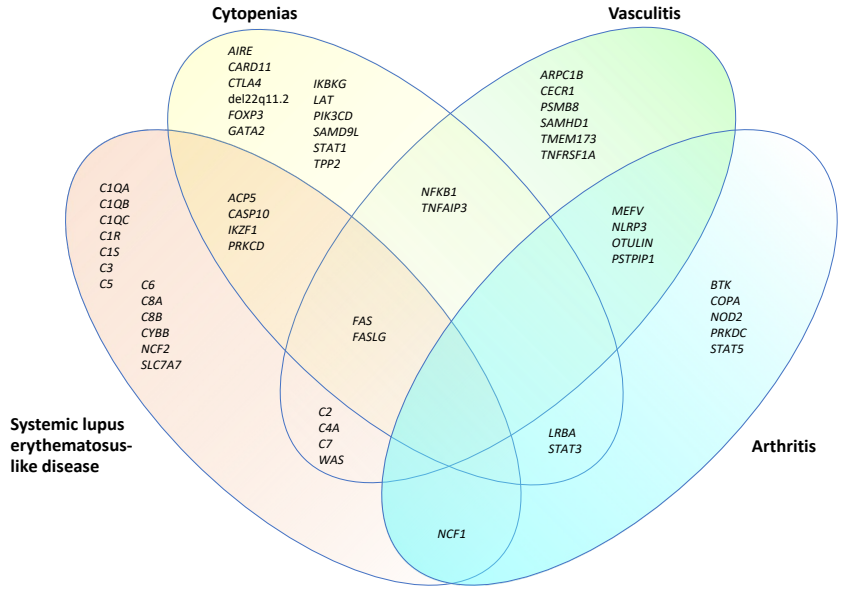

"Autoimmune" Manifestations of IEIs

Pediatrics in Review 2019;40;229

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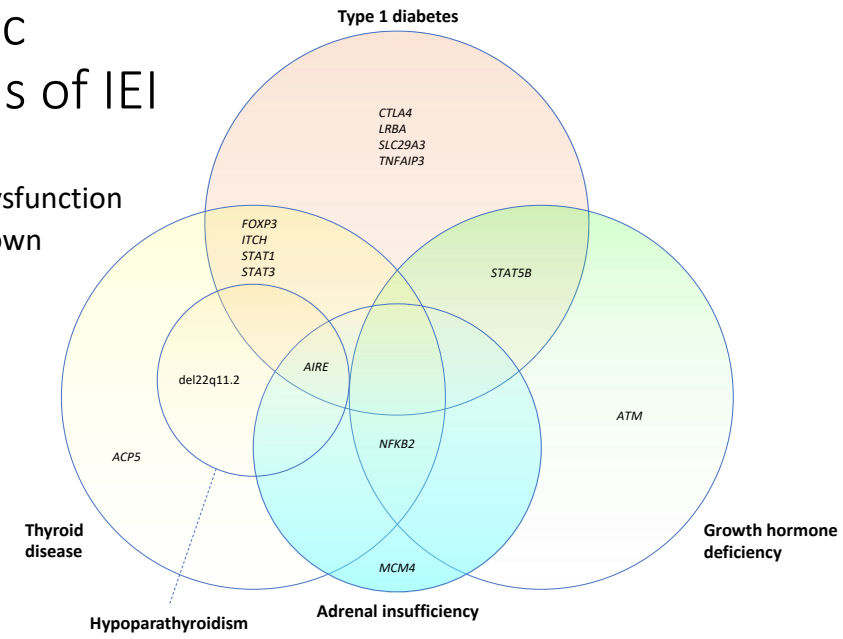
Endocrinologic Manifestations of IEI

Mechanisms:

- Regulatory T cell dysfunction
- Many others unknown



Pediatrics in Review 2019;40;229

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Hematologic/Oncologic Manifestations of IEIs

- Lymphoid hyperplasia or lymphoproliferative disease
- Hemophagocytic lymphohistiocytosis

CONDITION	ASSOCIATED PID GENES
Lymphoid hyperplasia or lymphoproliferative disease	*AICDA, CASP8, CASP10, CD27, CD70, CECR1, CTLA4, FAAP24, FAS, FASLG, ITK, LAT, LRBA, MAGT1, MVK, PIK3CD, PIK3R1, PRKCD, RASGRP1, RBCK1, SH2D1A, SLC29A3, STAT3, STAT5B, STK4, TPP2, UNG, XIAP*
Hemophagocytic lymphohistiocytosis	*AP3B1, ATM, BTK, CARMIL2, CD27, CD3E, CYBA, CYBB,* del22q11.2*, DKC1, FAS, IKBKG, IL2RG, IL7R, ITK, LYST, MAGT1, MEFV, NCF1, NLRC4, ORAI1, PIK3CD, PRF1, RAB27A, RAG1, RAG2, SH2D1A, STAT1, STAT2, STAT3, STX11, STXBP2, TNFRSF1A, UNC13D, WAS, XIAP*

Pediatrics in Review 2019;40;229

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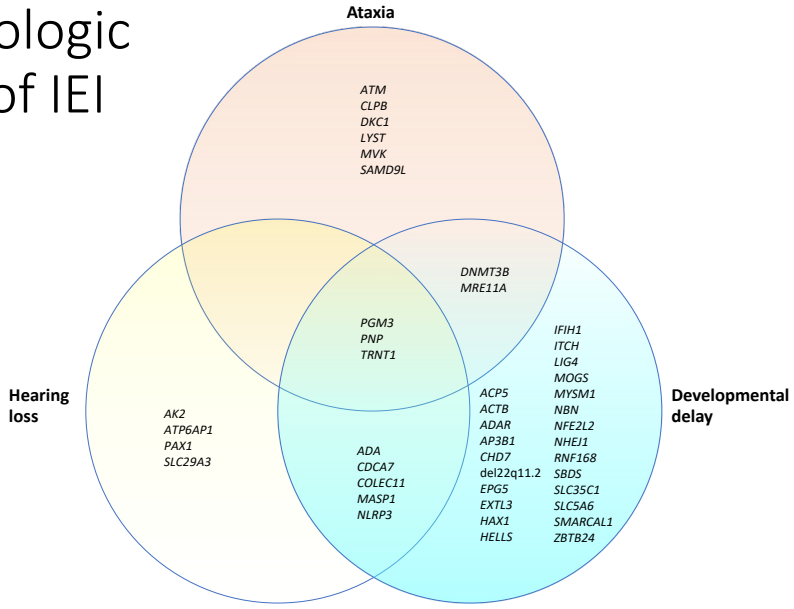
Important Neurologic Manifestations of IEI

Mechanisms:

- Shared gene function between neurologic and immune pathways
- Defective DNA/RNA processing
- Disorders of glycosylation
- Inflammation



Pediatrics in Review 2019;40;229

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Important Pulmonologic Manifestations of IEI

CONDITION	ASSOCIATED PID GENES
Interstitial lung disease	*COPA, ITCH, STAT3, TMEM173, TNFAIP3, XIAP*
Pulmonary alveolar proteinosis	*CD40LG, CSF2RA, GATA2, SLC7A7*
Capillaritis and hemorrhage	*COPA*
Eosinophilic pneumonia	*NSMCE3*

Pediatrics in Review 2019;40;229

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Additional Manifestations of IEIs

CONDITION	ASSOCIATED PID GENES
Allergies	*CARD11, CARMIL2, CTLA4, DOCK8, FOXP3, PGM3, SPINK5, WAS, WIPF1*
Skeletal dysplasia	*ACP5, ADA, ALG12, EXTL3, NBAS, PGM3, RNU4ATAC, RMRP, SMARCAL1*

Pediatrics in Review 2019;40;229

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Conclusions

- High index of suspicion is necessary: IEIs can present in a number of different ways to various subspecialties and do not require infections as the initial manifestation
  - Educate primary care providers
  - Inform the other subspecialties (not just Infectious Diseases)
- Broad genetic testing is indicated
  - Phenotypic overlap: numerous clinical tests
  - Too many genes to consider simultaneously

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

What's New and Different in Antibiotic Allergy? Penicillin Allergy: Then and Now

Presented by:

Marcus Shaker, MD, MS, FAAP, FAAAAI, FACAAI

Saturday, June 24, 2023

12:15 p.m. – 1:00 p.m.

What's New and Different in Antibiotic Allergy?

Penicillin Allergy: Then and Now

Marcus Shaker, MD, MS
Professor of Pediatric and Medicine
Dartmouth Geisel School of Medicine

1

Learning Objectives

Upon completion of this activity, participants should be able to:

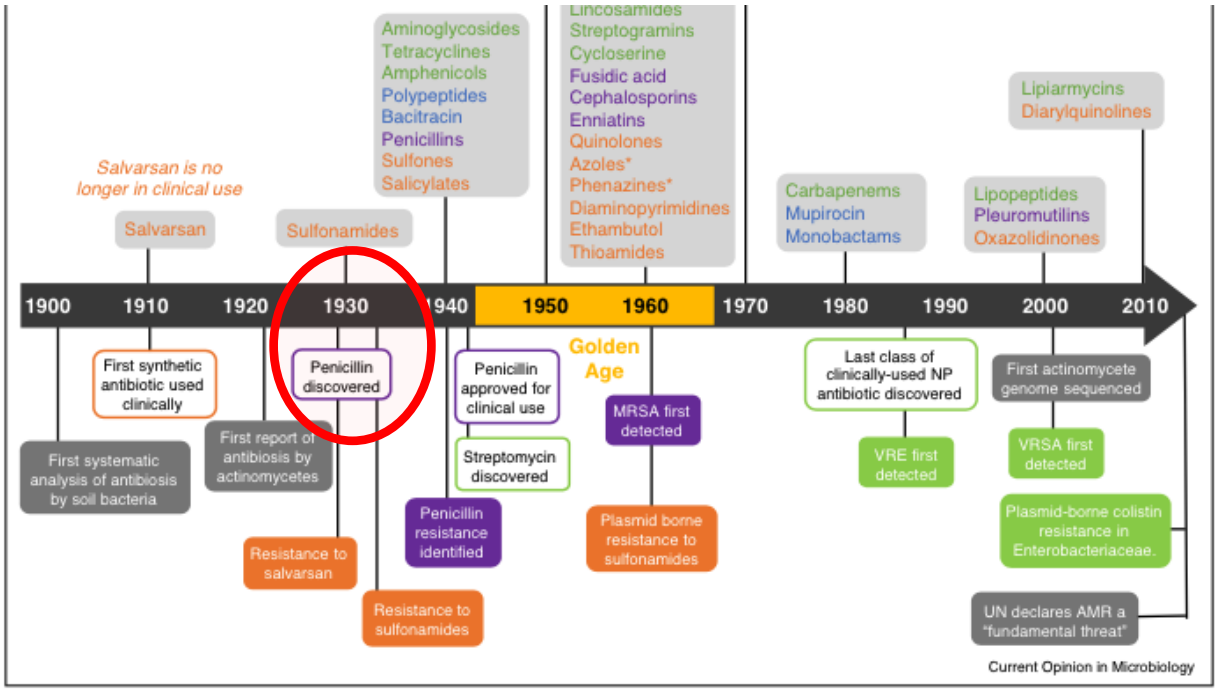
- **Identify patients suitable for direct oral challenge**
- **Apply the 2022 Drug Allergy Practice Parameter recommendations to clinical practice**
- **Describe the relationship of GRADE, evidence certainty, strength of recommendations, and shared decision making**

2

Lest we forget…

medium.com

3



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Clinical Notes, Suggestions and New Instruments

ANAPHYLACTIC DEATH FROM PENICILLIN

GEORGE L. WALDBOTT, M.D.
Detroit

Most allergic reactions from penicillin occur a few days after its administration, namely, as serum sickness or dermatitis. Such manifestations as asthma, vasomotor rhinitis or urticaria arising within a few hours are much less common. A search of the literature reveals no case reports of anaphylactic [1] shock from injections of penicillin. In one instance so designated [1a] there were symptoms of serum sickness.

The following fatality from penicillin is reported here because it represents typical anaphylactic shock. The circumstances leading to death conformed in every respect with my knowledge of this syndrome gained from experience with injections of horse serum, pollen and other antigenic substances.[2]

REPORT OF A CASE

Miss L. K., 39 years old, had had severe bronchial asthma since March 1945, which followed grass hay fever of eighteen years' duration and had been persistent since July 1946. Thorough diagnostic studies had been made, including roentgenograms of the chest, bronchograms, diagnostic bronchoscopic studies and intradermal tests. These revealed allergic asthma associated with decided emphysema and considerable emaciation. The patient had received the usual symptomatic treatment and a thorough hyposensitization regimen, both at a large allergy

COMMENT

Although no autopsy could be done, the diagnosis of anaphylactic shock appears definite because of the characteristic symptoms (tightness in nose and throat, severe dyspnea associated with urticaria) and because of the onset within a few seconds after the hypodermic administration of penicillin. That the injection must have been given intravenously through accidental puncture of a vein is indicated by the appearance of blood at the site of injection and by the "strange taste" in the mouth which is so characteristic in intravenous therapy [3]—an ominous sign to anyone who deals constantly with allergic persons. The patient had had no drug or medication other than the routine antigenic injections given four hours previously; this could not have accounted for this accident.[2]

It must be assumed that sensitization to penicillin resulted from previous injections; otherwise the patient could not have tolerated the preceding penicillin treatment as well as she did. She would have had some manifestation of allergy, probably an aggravation of the asthma. I have seen severe asthma occur in 1 case shortly after the initiation of a second course of penicillin and in another after the first injection of a third course. In the former the attack was so severe that it required several days of intensive treatment before its effect was overcome. It is likely that in this case death would have resulted had the injection of penicillin been made intravenously. In the other patient, the asthmatic seizure was less severe and protracted.

In a review of my record, it was noted that this patient had had severe urticaria, some aggravation of asthma, joint pains and slight fever during the first part of July, about one week after the administration of penicillin. This had not been identified at the time as serum sickness from penicillin, but in all probability presented the outward signs of the development of sensitization to penicillin.

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was again given 2 vials of penicillin containing 200,000 units each, which was to be administered by her sister, a registered nurse, in doses of 50,000 units. She received her routine hyposensitization treatment (consisting of 2,800 units of short and long ragweed, 600 units of English plantain combined with 0.1 cc. of an extract of alternaria, monilia, torula, smut and yeast) and, in addition, ⅓ of a 3¾ grain ampule (0.08 Gm.) of aminophylline intravenously. When she left the office, after thirty minutes, the site of the antigenic injection showed no unusual degree of local edema and the wheezing had improved from the administration of aminophylline. After arrival at her home, she had only one slight coughing spell during luncheon (12:30 p. m.), but otherwise felt comfortable. At about 1:45 p. m., the first dose of penicillin (50,000 units) was administered into the gluteal region. Within five seconds the patient complained of a strange taste in her mouth and tongue and swelling and tightness in the throat and nose; her face became flushed, bloated and extremely cyanotic; she felt itchy "all over." Leaning over the kitchen table and asking for a glass of water, she collapsed and died immediately..

Waldbott G. JAMA 1949

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The Journal of Allergy

VOL. 24 JANUARY, 1953 No. 1

Original Articles

FATAL AND NEAR-FATAL PENICILLIN ANAPHYLAXIS

THREE NEW CASES WITH A NOTE ON PREVENTION

SHEPPARD SIEGAL, M.D., ROGER W. STEINHARDT, M.D.,
AND ROBERT GERBER, M.D., NEW YORK, N. Y.

THAT penicillin may occasionally be a dangerous and even fatal drug should be known to the profession. In terms of direct toxicity the extraordinary antibiotic efficacy of this drug appears to have been matched by its innocuousness and as a result it is being used very freely. Allergic reactions have constituted the sole toxic manifestation attendant upon its administration.

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Fatal Penicillin Allergy

- Fortunately, fatal penicillin anaphylaxis is rare, estimated to occur at a rate of 0.002%.
  - For oral: one case in 35 years and 100 million courses
- Most common cause of fatal drug anaphylaxis in the US and UK
- In a review of 151 deaths due to penicillin between 1951-1965
  - No sex predominance
  - Most between 25-65 years old
  - 44% had respiratory infections
  - 28% had pre-existing allergies
  - 69% had reported prior exposure to penicillin
  - 36% had prior reactions to the drug
  - Symptom onset was typically rapid (< 15 minutes) and death occurred within an hour

Castells, Khan, Phillips. NEJM 2019

9

Penicillin Allergy

- Most common drug allergy identified in medical records
  - 6-25% reported prevalence
- Most common symptoms are benign cutaneous eruptions
- Rates of positive skin testing seem to have decreased over the decades, with one center reporting positive penicillin skin test rates of:
  - 1995: 15%
  - 2007: 3%
  - 2013: 0.3%
- Many, many, many non-IgE mediated rashes associated with oral aminopenicillins
  - Benign delayed exanthems
  - Acute generalized exanthematous pustulosis (AGEP)

Castells, Khan, Phillips. NEJM 2019

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Table 1. Drug Allergic Reactions and Syndromes

	Clinical manifestations	Examples of causative agents
IgE mediated	Urticaria, angioedema, bronchospasm, anaphylaxis	β-Lactam antibiotics, platinum-based chemotherapeutics, perioperative agents
Cytotoxic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Immune complex	Serum sickness	Penicillin, infliximab, thymoglobulin
Delayed type hypersensitivity	Contact dermatitis, exanthems	Neomycin, glucocorticoids, penicillin, sulfonamide antibiotics
Hypersensitivity vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil
DRESS	Cutaneous, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Pulmonary drug hypersensitivity	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Systemic drug-induced lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Cutaneous drug-induced lupus erythematosus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium channel blockers, ACE inhibitors
Drug-induced granulomatous disease	Churg-Strauss syndrome, Wegener's granulomatosis	Propylthiouracil, leukotriene modifiers
Immunologic hepatitis	Hepatitis, cholestatic jaundice	Para-aminosalicylic acid, sulfonamides, phenothiazines
Blistering disorders	Erythema multiforme, SJS, TEN	Sulfonamides, cephalosporins, imidazole anticonvulsants, NSAIDs
Serum sickness–like reactions	Erythema multiforme, arthralgias	Cefaclor, cefprozil
Immunologic nephropathy	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol

Abbreviations: ACE, angiotensin-converting enzyme; DRESS, drug rash with eosinophilia and systemic symptoms; NSAIDs, nonsteroidal anti-inflammatory drugs; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Solensky R, Khan D, et al. Drug Allergy: An Updated Practice Parameter. Annals of Allergy, Asthma, and Immunology. 2010

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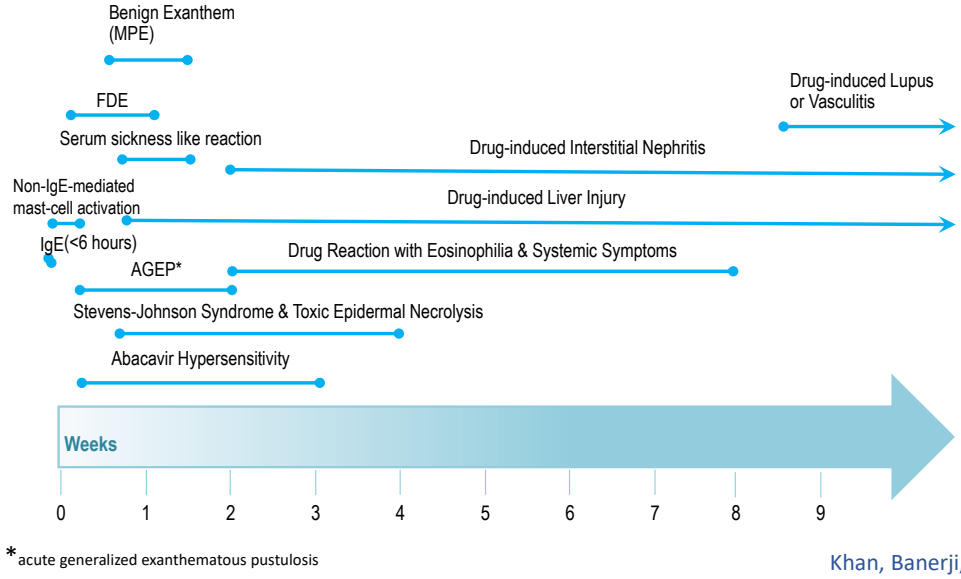
Timeline of Drug Hypersensitivity Reactions



*acute generalized exanthematous pustulosis

Khan, Banerji, et al 2022

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"He is allergic to amoxicillin"

- Carlos, an 18-month old child, was treated for a bilateral ear infection 12 months ago.
- Carlos developed a rash on his face, torso, and extremities after 4 days.
- The amoxicillin was stopped and the rash improved within a week
- Carlos' parents were told Carlos is allergic to amoxicillin and to avoid penicillin
- Carlos subsequently received a course of azithromycin for a subsequent ear infection

Children's Mercy Kansas City. What's the Diagnosis? June 2020

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Carlos is diagnosed with a drug allergy

Children's Mercy Kansas City. What's the Diagnosis? June 2020

How would you manage this patient?

- A. No additional management needed, simply avoid penicillins
- B. Schedule a skin testing visit for testing to major and minor determinants and ampicillin, by prick and intradermal testing
- C. Schedule skin testing to Penicillin G and PrePen
- D. Schedule a visit for direct oral challenge to amoxicillin (single dose) without skin testing
- E. Schedule a visit for direct oral challenge to amoxicillin (5-7 day course) without skin testing
- F. Avoid penicillins for now but consider further evaluation after another 6-12 months

Solensky R, Khan D, et al. Drug Allergy: An Updated Practice Parameter. Annals of Allergy, Asthma, and Immunology. 2010

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To Test or Not to Test…

That is the Question!

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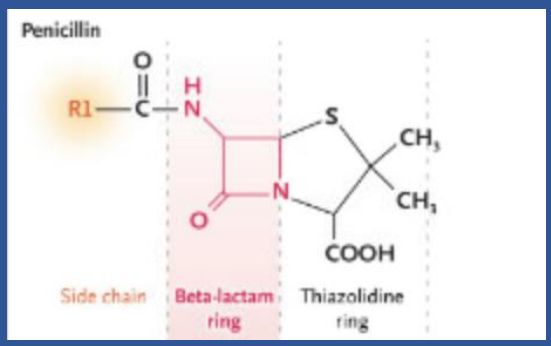
Penicillin Allergy Evaluation

- Use of major and minor determinant for skin testing began in the early 1960's
- Early studies suggested 50-75% PPV and 93% NPV
- More recent data suggests a sensitivity around 31% and specificity around 97%



Castells, Khan, Phillips. NEJM 2019; Suosa-Pinto et al JACI 2021

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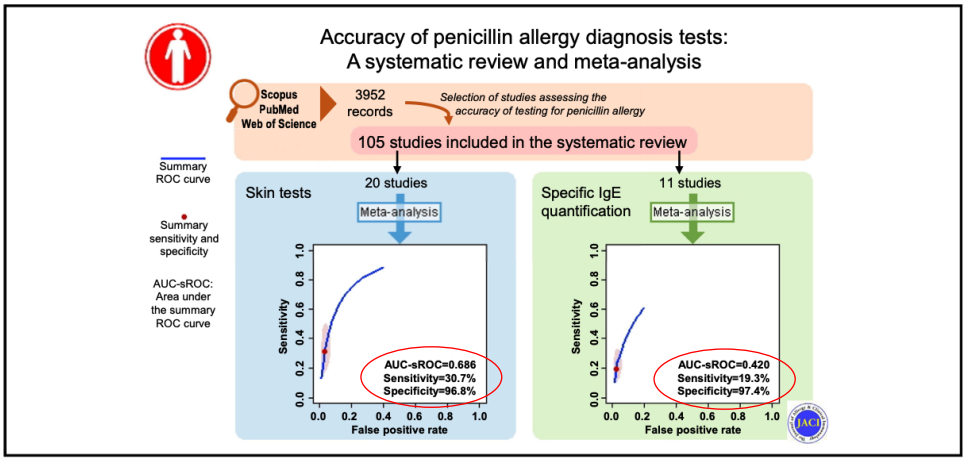
Accuracy of penicillin allergy diagnostic tests: A systematic review and meta-analysis

Check for updates

Bernardo Sousa-Pinto, PhD,[a,b,c]* Isabel Tarrio, MD,[a]* Kimberly G. Blumenthal, MD,[d,e] Luís Araújo, MD,[b,c] Luís Filipe Azevedo, PhD,[a,b] Luís Delgado, PhD,[b,c] and João Almeida Fonseca, PhD[a,b] *Porto, Portugal, and Boston, Mass*

GRAPHICAL ABSTRACT



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Original Investigation

Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children

Christopher Mill, MPH; Marie-Noël Primeau, MD; Elaine Medoff, MD; Christine Lejtenyi, MD; Andrew O'Keefe, MD; Elena Netchiporouk, MD; Alizee Dery, BSc; Moshe Ben-Shoshan, MD, MSc

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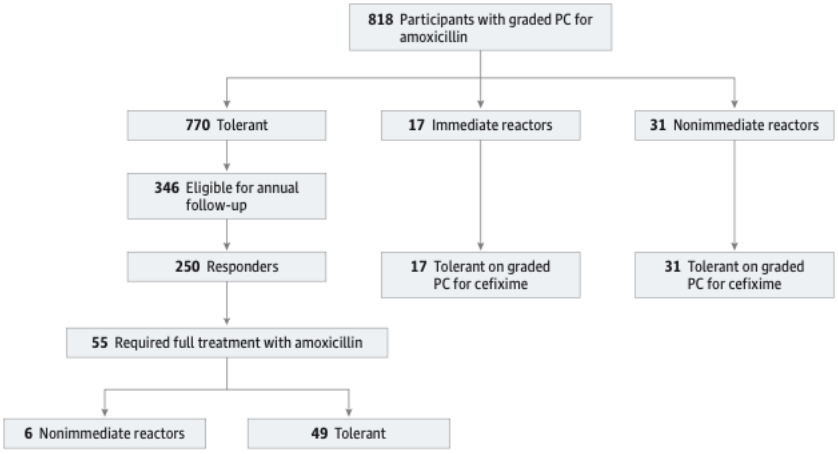
Amoxicillin direct oral challenge



- 94% of children were tolerant of amoxicillin
- 2.1% reacted within an hour
- 3.8% had non-immediate reactions
- Of those tolerating the initial oral challenge, 89.1% tolerated a subsequent course

Mill et al. Assessing the diagnostic properties of graded oral provocation challenge for the diagnosis of immediate and nonimmediate reactions to amoxicillin in children. JAMA Pediatrics. 2016

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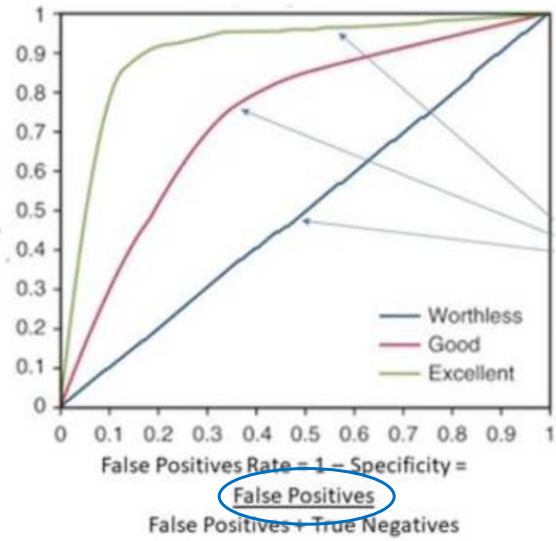
True Positive Vs. False Positives

True Positive Rate
Sensitivity

$$\frac{\text{True Positives}}{\text{True Positives + False Negatives}}$$

A good test should produce more true positives than false positives…



Various Thresholds

Ideal Threshold gives only true positives and no false positives

Abrams E, Chan E, Portnoy J, et al. Evolving interpretation of screening and diagnostic tests in allergy. JACI In Practice. 2021

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In additional to considering true positives and false positives, we also need to be aware of the impact of disease prevalence…

	Disease present	Disease absent	
Positive Test	True Positive (TP)	False Positive (FP) *Type I Error*	PPV = TP / (TP+FP)
Negative Test	False Negative (FN) *Type II Error*	True Negative (TN)	NPV = TN / (FN+TN)
	Sensitivity = TP / (TP+FN)	Specificity = TN / (TN+FP)	

- Sensitivity/Specificity are TEST characteristics
- PPV/NPV are properties of both the TEST and the likelihood of disease

Abrams E, Chan E, Portnoy J, et al. Evolving interpretation of screening and diagnostic tests in allergy. JACI In Practice. 2021

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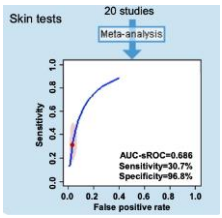
History + Evidence

History

- Carlos is 18-months old and developed a maculopapular rash 4 days into treatment of a bilateral otitis media

Testing (if performed)

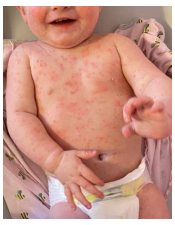
- Sn = 30.7%
- Sp = 96.8%



Evidence

- 94% of children tolerant of direct oral challenge

	Disease +	Disease -	
Skin Test +	(60*0.307) = 18.4	(940-910) = 30	Skin Test PPV = 38.0%
Skin Test -	(60-18.4) = 41.6	(940*0.968) = 910	Skin Test NPV = 95.6%
	Pretest prob 6% = 60	(1000-60) = 940	Total patients = 1000



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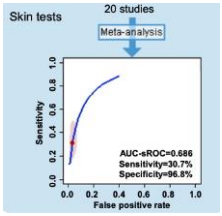
(Alt example…)

History

- 54-year-old woman who develops urticaria, angioedema, wheezing, and hypotension 10 minutes into an ampicillin infusion

Testing (if performed)

- Sn = 30.7%
- Sp = 96.8%



Evidence

- High pretest probability of at least 50% based on history (probably higher)

	Disease +	Disease -	
Skin Test +	**(500*0.307) = 154**	**(500-484) = 16**	**Skin Test PPV = 91.0%**
Skin Test -	**(500-154) = 346**	**(500*0.968) = 484**	**Skin Test NPV = 58.3%**
	Pretest prob 50% = 500	**(1000-500) = 500**	**Total patients = 1000**

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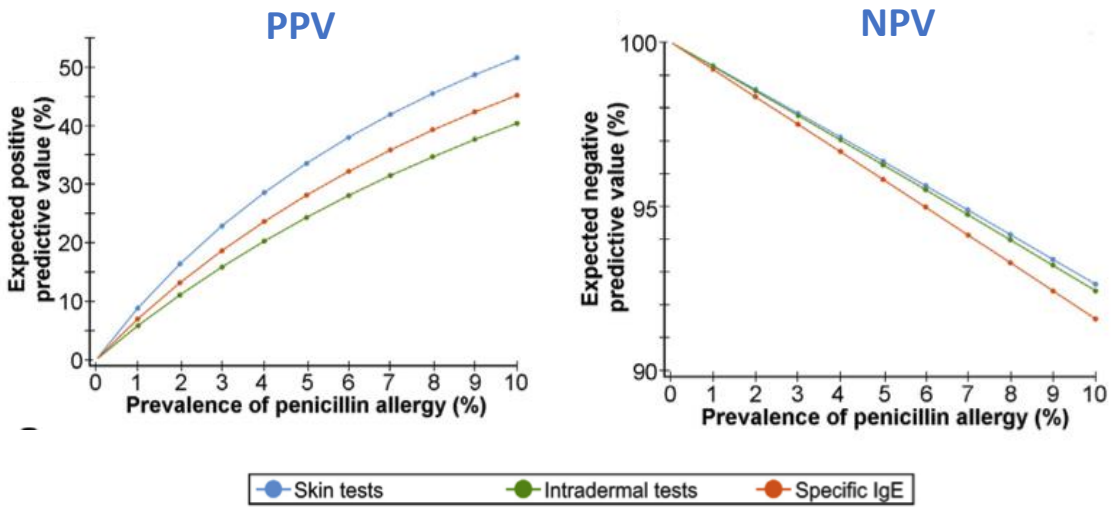
Predictive value and disease prevalence



Sousa-Pinto et al JACI 2021

24

Is NPV the MPV?

- Negative predictive value is important
- Without good negative predictive value, drug re-administration could cause a repeat reaction

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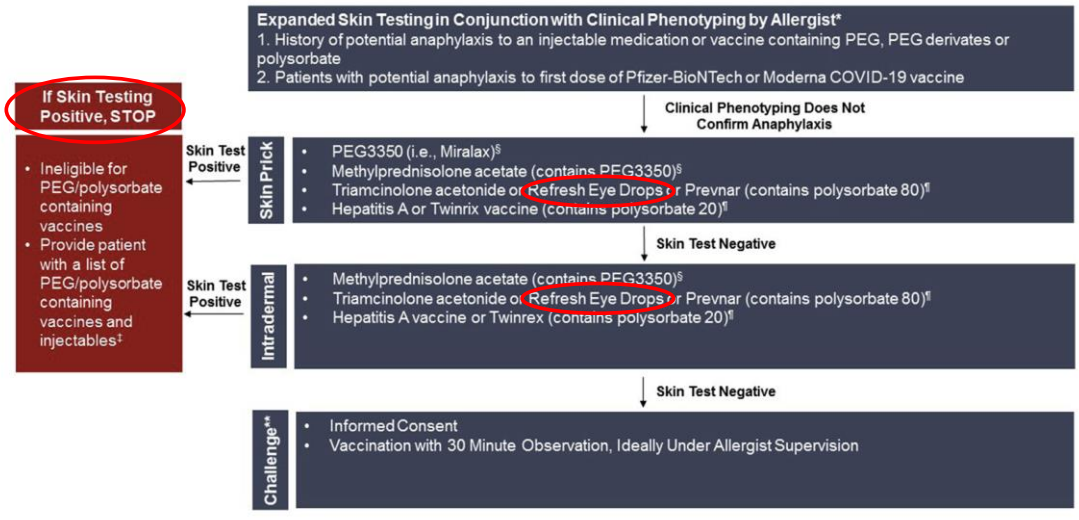
Why PPV matters, an example…



Banerji et al. mRNA vaccines to prevent COVID-19 disease and reported allergic reactions: current evidence and a suggested approach. JACI In Practice 2021

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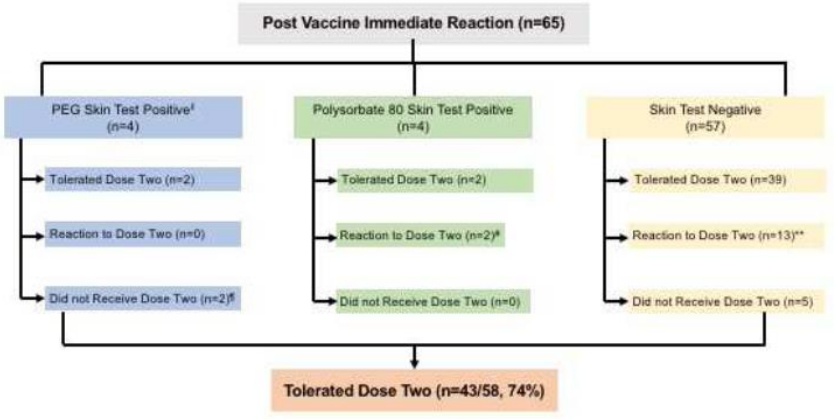
Limited Role of Excipient Skin Testing for COVID-19 Vaccination



Refresh Tears: False positive by intradermal testing in 52% of controls tested

Wolfson A, Robinson L, Li L, et al. First dose mRNA COVID-19 vaccine allergic reactions: Limited role of excipient skin testing. JACI In Practice. 2021

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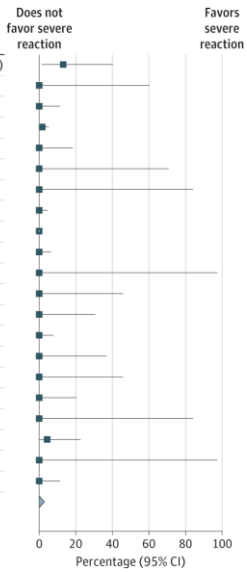
Recurrent COVID-19 Anaphylaxis

Source	Second doses administered	Second dose anaphylaxis	Percentage (95% CI)
Tuong et al,[14] 2021	15	2	13.33 (1.66-40.46)
Krantz et al,[15] 2021	4	0	0.00 (0.00-60.24)
Rasmussen et al,[16] 2021	30	0	0.00 (0.00-11.57)
Krantz et al,[17] 2021	162	3	1.85 (0.38-5.32)
Kessel et al,[19] 2021	18	0	0.00 (0.00-18.53)
Kelso,[20] 2021	3	0	0.00 (0.00-70.76)
Mustafa et al,[21] 2021	2	0	0.00 (0.00-84.19)
Vanijcharoenkarn et al,[22] 2021	73	0	0.00 (0.00-4.93)
Robinson et al,[23] 2021	860	0	0.00 (0.00-0.43)
Eastman et al,[24] 2021	53	0	0.00 (0.00-6.72)
Park et al,[25] 2021	1	0	0.00 (0.00-97.50)
Arroliga et al,[26] 2021	6	0	0.00 (0.00-45.93)
Loli-Ausejo et al,[27] 2021	10	0	0.00 (0.00-30.85)
Pitlick et al,[28] 2021	44	0	0.00 (0.00-8.04)
Yacoub et al,[29] 2021	8	0	0.00 (0.00-36.94)
Shavit et al,[30] 2021	6	0	0.00 (0.00-45.93)
Kohli-Pamnani et al,[31] 2021	16	0	0.00 (0.00-20.59)
Inoue et al,[32] 2021	2	0	0.00 (0.00-84.19)
Warren et al,[33] 2021	22	1	4.55 (0.12-22.84)
Carpenter et al,[34] 2021	1	0	0.00 (0.00-97.50)
Kaplan et al,[35] 2021	30	0	0.00 (0.00-11.57)
Overall: I^2 = 0.3%	1366	6 (1360 successes)	0.16 (0.01-2.94)



- The global prevalence of immediate severe allergic reactions to the mRNA COVID-19 vaccines is 7.91/million doses
- A systematic review and meta-analysis of 22 studies and 1366 patients with 1st dose immediate allergic reactions to mRNA COVID-19 vaccine who were then re-vaccinated with a 2nd dose found that 99% safely tolerated re-vaccination.

Greenhawt M, Abrams EM, Shaker MS, et al. JACI In Practice 2021; Chu D, Abrams E, Golden D, et al. JAMA Internal Medicine 2022

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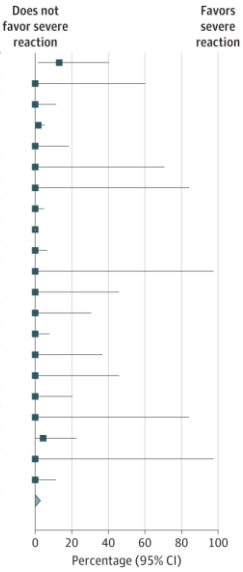
Recurrent COVID-19 Anaphylaxis…

Source	Second doses administered	Second dose anaphylaxis	Percentage (95% CI)
Tuong et al,[14] 2021	15	2	13.33 (1.66-40.46)
Krantz et al,[15] 2021	4	0	0.00 (0.00-60.24)
Rasmussen et al,[16] 2021	30	0	0.00 (0.00-11.57)
Krantz et al,[17] 2021	162	3	1.85 (0.38-5.32)
Kessel et al,[19] 2021	18	0	0.00 (0.00-18.53)
Kelso,[20] 2021	3	0	0.00 (0.00-70.76)
Mustafa et al,[21] 2021	2	0	0.00 (0.00-84.19)
Vanijcharoenkarn et al,[22] 2021	73	0	0.00 (0.00-4.93)
Robinson et al,[23] 2021	860	0	0.00 (0.00-0.43)
Eastman et al,[24] 2021	53	0	0.00 (0.00-6.72)
Park et al,[25] 2021	1	0	0.00 (0.00-97.50)
Arroliga et al,[26] 2021	6	0	0.00 (0.00-45.93)
Loli-Ausejo et al,[27] 2021	10	0	0.00 (0.00-30.85)
Pitlick et al,[28] 2021	44	0	0.00 (0.00-8.04)
Yacoub et al,[29] 2021	8	0	0.00 (0.00-36.94)
Shavit et al,[30] 2021	6	0	0.00 (0.00-45.93)
Kohli-Pamnani et al,[31] 2021	16	0	0.00 (0.00-20.59)
Inoue et al,[32] 2021	2	0	0.00 (0.00-84.19)
Warren et al,[33] 2021	22	1	4.55 (0.12-22.84)
Carpenter et al,[34] 2021	1	0	0.00 (0.00-97.50)
Kaplan et al,[35] 2021	30	0	0.00 (0.00-11.57)
Overall: $I^2 = 0.3\%$	1366	6 (1360 successes)	0.16 (0.01-2.94)

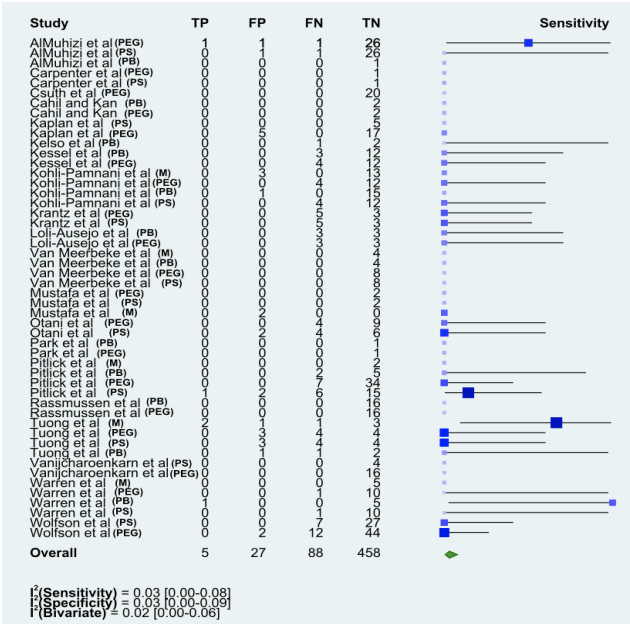


- Among patients with 1st dose immediate allergic reactions the risk of a severe immediate reaction with the second dose was 0.16% (95% CI, 0.01-2.94%)
  - For 1st dose severe reactions, the risk was 4.94% (95% CI, 0.93-22.28%)
- The risk of non-severe immediate reactions was 13.65% (95% CI, 7.76-22.9%)

Chu D, Abrams E, Golden D, et al. JAMA Internal Medicine 2022

29

Recurrent COVID-19 Anaphylaxis – Role of Testing

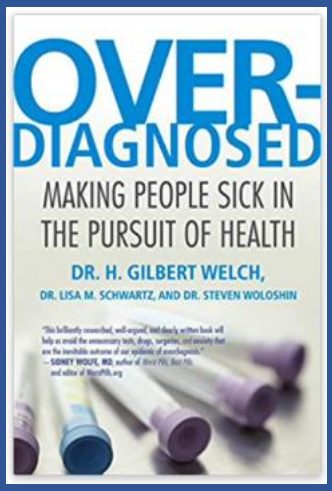


- Among patients with 1st dose immediate allergic reactions to mRNA COVID vaccines
  - PEG Sn: 0.02 (95% CrI 0.00-0.007)
  - PEG Sp: 0.99 (95% CrI 0.96-1)
  - PS Sn: 0.03 (95% CrI 0-0.011)
  - PS Sp: 0.97 (95% CrI 0.91-1)
  - Vaccine Sn: 0.2 (95% CrI 0.01-0.52)
  - Vaccine Sp: 0.97 (95% CrI 0.9-1)
  - Combined Sn: 0.03 (95% CrI 0-0.08)
  - Combined Sp: 0.98 (95% CrI 0.95-1)

PEG: polyethylene glycol; PS: polysorbate 80

Greenhawt M, Shaker M, Golden D, Abrams E, Blumenthal K, et al. Allergy 2023

30



If we ignore PPV, we risk overdiagnosis…

31

Image courtesy of Erin Reigh, MD, MS @AlphaGalMD

32

Some additional studies re: safety of direct oral challenge in kids

Mori F, Cianferoni A, Barni S, Pucci N, Rossi ME, Novembre E. Amoxicillin allergy in children: five-day drug provocation test in the diagnosis of nonimmediate reactions. J Allergy Clin Immunol Pract. 2015; 3: 375-80 e1.

Caubet JC, Kaiser L, Lemaitre B, Fellay B, Gervaix A, Eigenmann PA. The role of penicillin in benign skin rashes in childhood: a prospective study based on drug rechallenge. J Allergy Clin Immunol. 2011; 127: 218-22

Confino-Cohen R, Rosman Y, Meir-Shafrir K, et al. Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity. J Allergy Clin Immunol Pract. 2017; 5: 669-75

Labrossse R, Paradis L, Lacombe-Barrios J, et al. Efficacy and Safety of 5-Day Challenge for the Evaluation of Nonsevere Amoxicillin Allergy in Children. J Allergy Clin Immunol Pract. 2018; 6: 1673-80.

Mustafa et al. Comparing direct challenge to penicillin skin testing for the outpatient evaluation of penicillin allergy: a randomized controlled trial. JACI In Practice 2019

33

Okay Okay, buy what about grown-ups?

34

Are adults just "big kids"?

- Data for direct oral challenge to amoxicillin is stronger in pediatrics
- Adults are less likely to experience benign viral exanthems and are more likely to have severe or fatal penicillin anaphylaxis
  - Still, estimated rates of penicillin anaphylaxis are between 0.015-0.004% with fatality rates from anaphylaxis between 0.0015-0.002% of treated patients
- Still, in adults with reactions more than 1-10 years ago, limited to the skin without angioedema, blistering, or exfoliative features, without systemic symptoms or anaphylaxis, direct oral challenge is also an option

Idsoe O, Guthe T, Willcox RR, de Weck AL. Nature and extent of penicillin side-reactions, with particular reference to fatalities from anaphylactic shock. Bull World Health Organ. 1968; 38: 159-88; Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. J Allergy Clin Immunol. 2014; 134: 1318-28 e7.

35

Are adults just "big kids"?

- In a prospective RCT comparing skin testing to direct oral challenge:
  - Adults and children, mean age 35.3 years (SD 25.3)
  - 70/80 (87.5%) of patients were skin test negative and all tolerated amoxicillin challenge
  - In 76/79 (96.2%) of patients with direct oral challenge (without skin testing) was negative, and of those patients with positive challenges reactions were mild.

Mustafa et al. Comparing direct challenge to penicillin skin testing for the outpatient evaluation of penicillin allergy: a randomized controlled trial. JACI In Practice 2019

36

Some additional studies re: safety of direct oral challenge in adults

- Banks TA, Tucker M, Macy E. Evaluating Penicillin Allergies Without Skin Testing. Curr Allergy Asthma Rep. 2019; 19: 27.
- Blumenthal KG, Huebner EM, Fu X, et al. Risk-based pathway for outpatient penicillin allergy evaluations. J Allergy Clin Immunol Pract. 2019; 7: 2411-4 e1.
- Confino-Cohen R, Rosman Y, Meir-Shafrir K, et al. Oral Challenge without Skin Testing Safely Excludes Clinically Significant Delayed-Onset Penicillin Hypersensitivity. J Allergy Clin Immunol Pract. 2017; 5: 669-75
- Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and Outcomes of Oral Graded Challenges to Amoxicillin without Prior Skin Testing. J Allergy Clin Immunol Pract. 2019; 7: 236-43.
- Trubiano JA, Vogrin S, Chua KYL, et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. JAMA Intern Med. 2020; 180: 745-52.
- Tucker MH, Lomas CM, Ramchandar N, Waldram JD. Amoxicillin challenge without penicillin skin testing in evaluation of penicillin allergy in a cohort of Marine recruits. J Allergy Clin Immunol Pract. 2017; 5: 813-5.

37

Red flags for direct oral challenge

Contraindications to Drug Challenges
Severe Cutaneous Adverse Drug Reactions
Drug-Induced Neutrophilic Dermatosis
Drug-Induced Autoimmune Diseases
Bullous or Exfoliative Drug Reactions
Non-Cutaneous Organ Specific Drug Reactions
Drug Induced Vasculitis
Severe Culprit Drug Anaphylaxis

Drug Allergy Practice Parameter Update Joint Task Force on Allergy Practice Parameters. In Preparation

38

Additional Considerations for Direct Oral Challenge

Agent	Considerations (no red flags)
Cephalosporin	No history of anaphylaxis Additional option to skin test first
Macrolides	No history of anaphylaxis
Fluoroquinolones	No history of anaphylaxis
Sulfonamides	No history of anaphylaxis

Drug Allergy Practice Parameters Update, Joint Task Force on Allergy Practice Parameters, In Preparation

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American Academy of Allergy Asthma & Immunology

American College of Allergy, Asthma & Immunology

Key Resource

2022 Drug Allergy Parameter

JOINT TASK FORCE ON PRACTICE PARAMETERS JTF PP

40

Beta-lactam Antibiotics

Consensus Based Statement	Strength of Recommendation	Certainty of Evidence
We suggest penicillin skin testing for patients with a **history of anaphylaxis or a recent reaction suspected to be IgE-mediated**.	**Conditional**	**Low**
We recommend against the routine use of multiple day challenges in the evaluation of penicillin allergy.	**Strong**	**Low**

2022 Drug Allergy Practice Parameter

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Beta-lactam Antibiotics

Consensus Based Statement	Strength of Recommendation	Certainty of Evidence
We recommend against penicillin skin testing prior to direct amoxicillin challenge in pediatric patients with a history of benign cutaneous reaction (such as MPE and urticaria).	**Strong**	**Moderate**
We suggest that direct amoxicillin challenge be considered in adults with a history of distant and benign cutaneous reactions (such as MPE and urticaria).	**Conditional**	**Low**

2022 Drug Allergy Practice Parameter

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Beta-lactam Cross-Reactivity

- Risk for cross-reactivity amongst beta-lactams is lower than previously reported
- Carbapenem may be administered without testing or precautions to anyone with penicillin or cephalosporin allergy, regardless of reaction type

Stratification of Reaction Type	Verified Penicillin Allergy	Unverified Penicillin Allergy	Verified Cephalosporin Allergy	Unverified Cephalosporin Allergy
Anaphylaxis	**Administer** non-cross-reactive cephalosporin without testing or precautions	**Administer** non-cross-reactive cephalosporin without testing or precautions	Penicillin skin testing and drug challenge prior to administration of penicillin therapy	Penicillin skin testing and drug challenge prior to administration of penicillin therapy
Nonanaphylaxis	**Administer** any cephalosporin without testing or precautions	**Administer** any cephalosporin without testing or precautions	**Administer** penicillin without testing or precautions	**Administer** penicillin without testing or precautions

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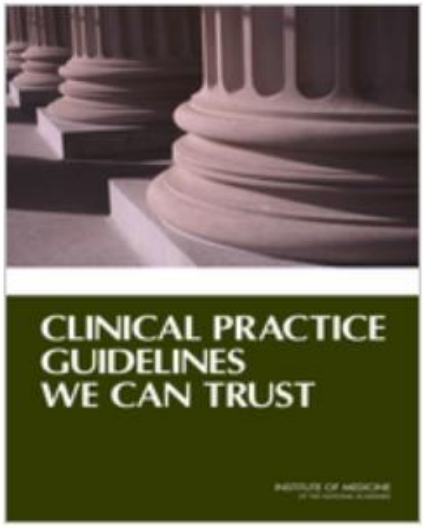
Guidelines and Best Evidence

- **Clear description of evidence rating**
- **Transparency**
- **Up to date**
- **Balanced**
- **Contextual**
- **Unbiased**
- **Fair**
- **Actionable**
- **Cost-effective**



Institute of Medicine 2011

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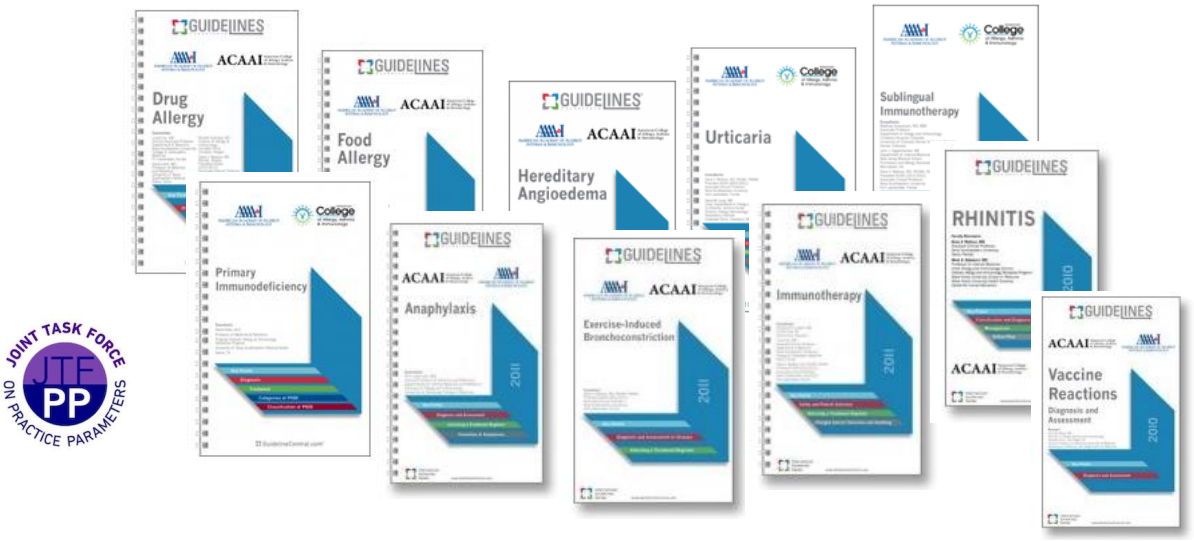
Allergy Guidelines and Practice Parameters



www.allergyparameters.org

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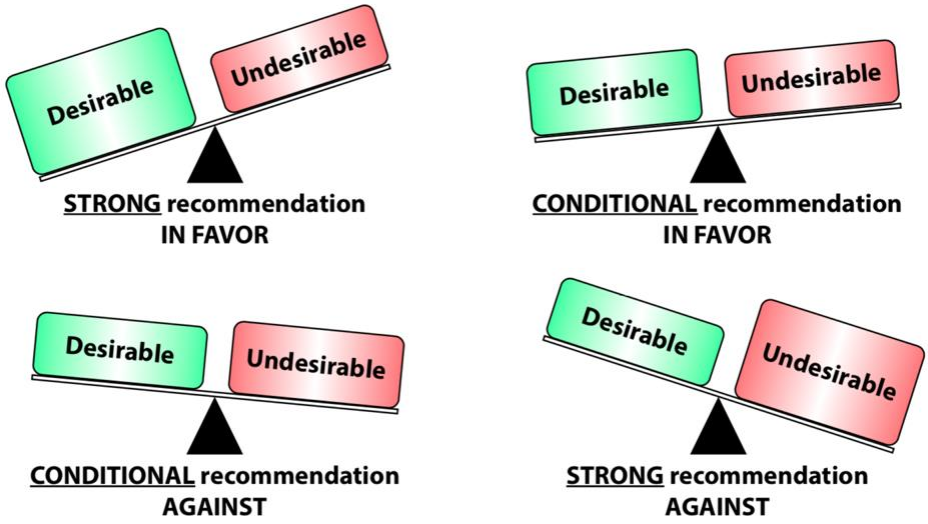
Grading of Recommendations Assessment, Development and Evaluation

- Began in 2000 to develop a common, sensible, clear, and transparent approach to:
- **Grade certainty of evidence**
- **Describe strength of recommendations**

GRADE

46

Strength (and directional) of Recommendation



Shaker M et al. Making the Grade. Annals of Allergy, Asthma, Immunology. 2020

47

Recommendations must incorporate and consider

- Evidence Certainty

Value

- Balance between benefits/harms
- Patient values/preferences
- Equity
- Feasibility

- Acceptance
- Is the problem a priority?
- Policy Implications
- Resource allocation and cost-effectiveness

Shaker M et al. Making the Grade. Annals of Allergy, Asthma, Immunology. 2020

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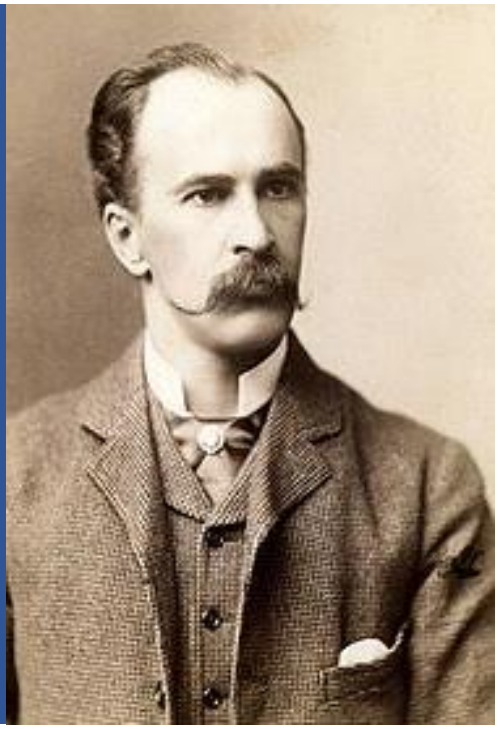
Medicine is a science of uncertainty and an art of probability – William Osler (1849-1919)



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Key Messages

- As Dr. Osler advised, we must appreciate uncertainty of medicine and understand how to incorporate probability of likely and unlikely events when managing patients
- NPV is important in interpreting allergy testing, but PPV cannot be ignored
- Direct oral challenge to antibiotics can be considered contextually. Pediatric patients with benign cutaneous reactions are good candidates
- **The most valuable tool for risk stratification is the clinical history.**

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Thank You

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

WORKSHOP: Hypereosinophilic Syndromes- Evaluation and Management

Presented by:

Amy Klion, MD

Saturday, June 24, 2023

1:15 p.m. – 2:15 p.m.

Slides will be provided to attendees who registered for the workshop.

PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Presentations for Sunday, June 25, 2023

7:45 am – 8:30 am	**Evidence-based Treatment of Chronic Rhinosinusitis** *Anju Peters, MD, MSCI*
8:30 am – 9:15 am	**United Airways: The Clinical Impact of Upper and Lower Airway Connection** *Anju Peters, MD, MSCI*
9:45 am – 10:30 am	**The Psychosocial Impact of Food Allergies: What Every Allergist Should Know** *Hemant Sharma, MD, MHS*
10:30 am – 11:15 am	**From Surviving to Thriving: Rediscovering Fulfillment in Allergy Immunology Practice** *Hemant Sharma, MD, MHS*

PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

Evidence-based Treatment of Chronic Rhinosinusitis

Presented by:

Anju Peters, MD, MSCI

Sunday, June 25, 2023

7:45 a.m. – 8:30 a.m.

1

Objectives

- Be familiar with the pathogenesis of chronic rhinosinusitis
  - Inflammatory endotypes and phenotypes
  - Importance of mixed endotypes
- Be familiar with treatments based on inflammatory endotypes
  - Biologics
  - Steroids
  - Surgery
  - Antibiotics

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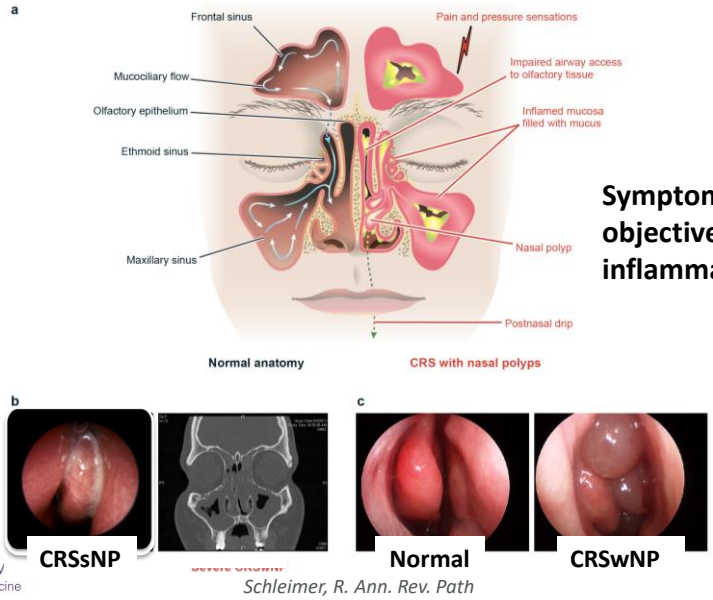
2

Chronic Rhinosinusitis



Symptoms for 12 weeks and objective evidence of inflammation

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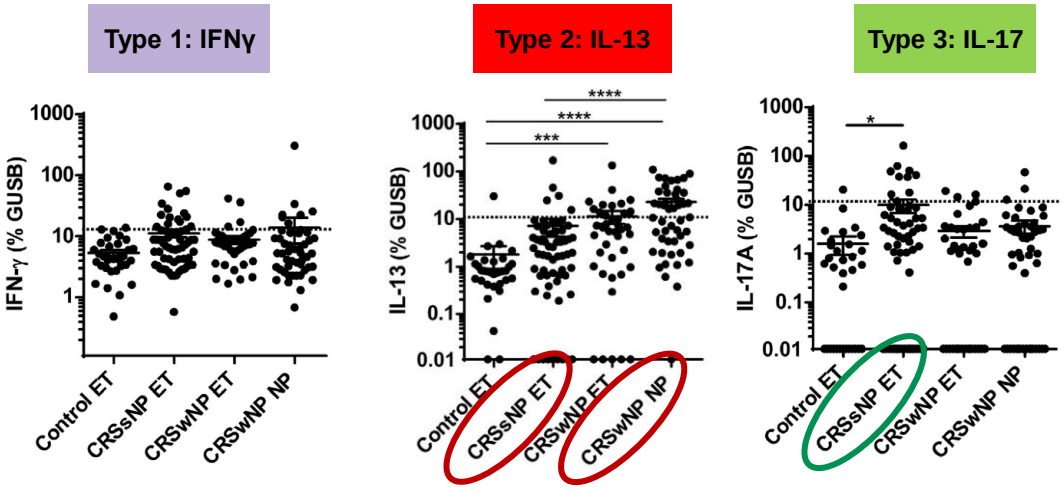
Schleimer, R. Ann. Rev. Path

3

Inflammatory Endotypes in Chronic Rhinosinusitis



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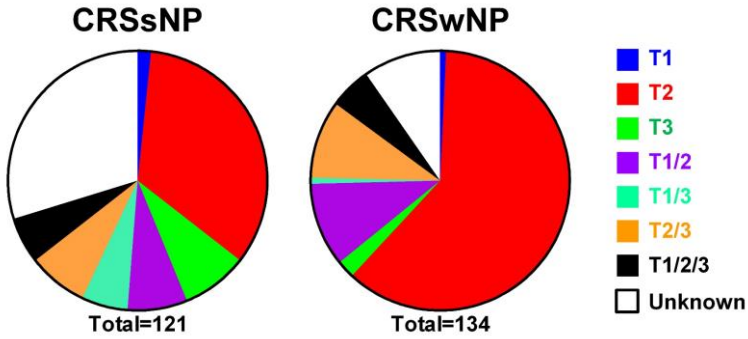
95th percentile expression in healthy ethmoid tissue (ET)

Tan et al. J Allergy Clin Immunol. 2017 Feb;139(2):699-703.

4

Heterogeneity of Inflammatory Endotypes in CRS



T1sNP: total 21%

T2sNP: total 55%

T3sNP: total 27%

T1wNP: total 17%

T2wNP: total 87%

T3wNP: total 18%

Stevens, Peters and Kato 2019
JACI in Practice

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5

Why are endotypes and phenotypes important?

- Comorbidities
- **Disease severity**
- Treatment

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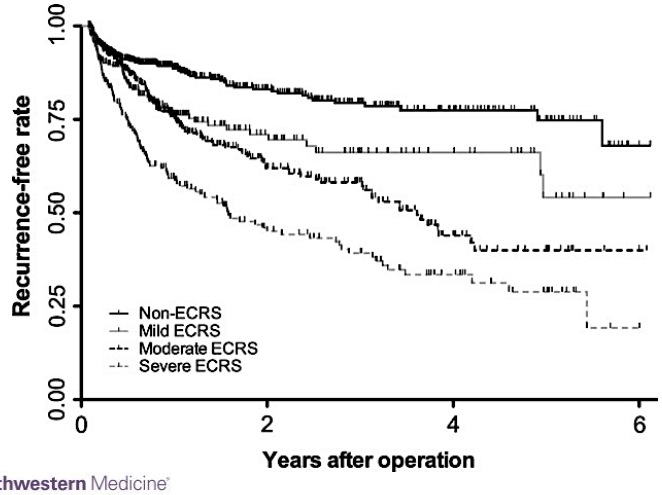
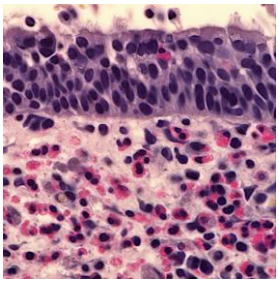
Type 2 Inflammation (Eosinophils) and Worse CRS Disease Severity





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Tokunaga et al. Allergy. 2015 Aug;70(8):995-1003

7

Why is it important to target type 3 (neutrophilic) or mixed inflammation?

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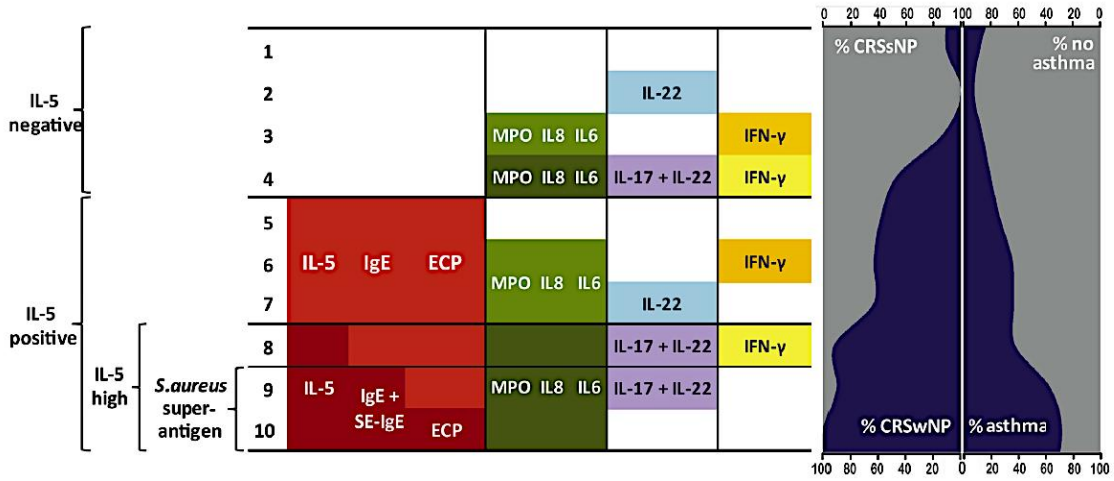
8

CRS Cluster Analysis Based on Cytokines



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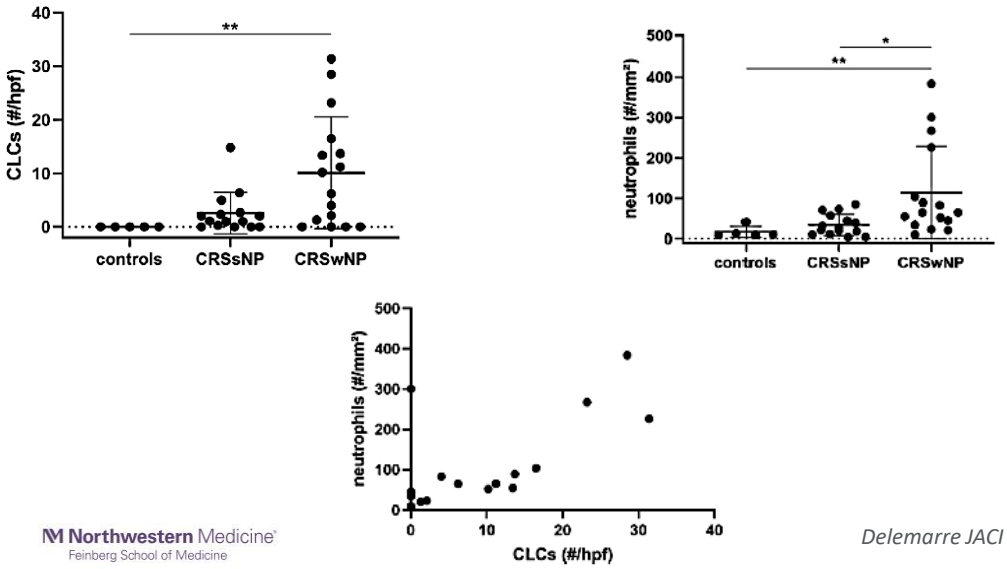
Tommassen JACI 2016

9

Neutrophilic Inflammation in Type 2 CRSwNP



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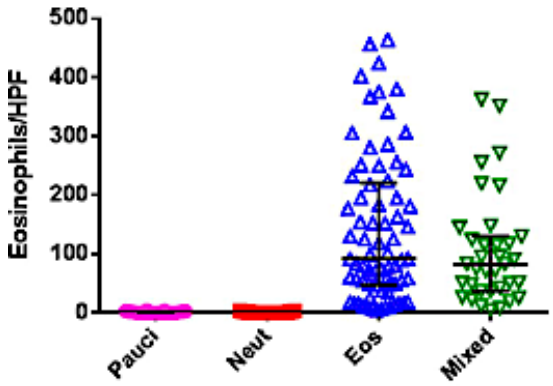
Delemarre JACI 2020

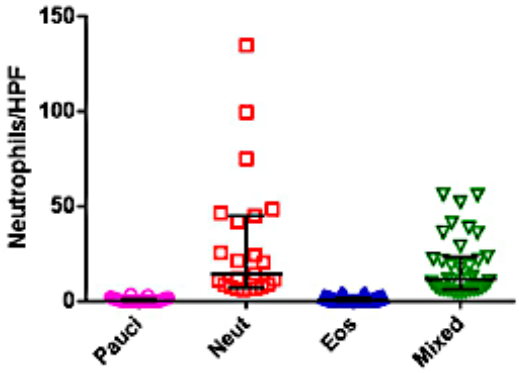
10

Mixed inflammation in chronic rhinosinusitis

Eosinophilic phenotype



Neutrophilic phenotype



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Feinberg School of Medicine

Succar et al. Allergy. 2020 Mar;75(3):713-716

11

	Paucigranulocytic	Neutrophilic	Eosinophilic	Mixed granulocytic	*P*-value
No.	33	23	73	35	
Age (years)	50.3 ± 14.0	54.1 ± 16.6	48.1 ± 13.5	47.5 ± 13.6	.26
Sex, no. (% female)	17 (52)	7 (30)	33 (45)	15 (43)	.47
Race, no. (% white)	29 (88)	20 (87)	60 (82)	30 (86)	.87
Current smoker, no. (%)	2 (6)	2 (9)	5 (7)	1 (3)	.80
BMI (kg/m^2)	30.5 ± 11.2	30.4 ± 6.7	30.5 ± 6.0	28.6 ± 6.4	.68
Nasal polyps, no. (%)	6 (15)	11 (48)	55 (75)	26 (74)	<.0001
Asthma, no. (%)	9 (27)	9 (39)	26 (36)	18 (51)	.21
Allergic rhinitis, no. (%)	19 (58)	12 (52)	45 (62)	26 (74)	.20
AERD, no. (%)	0 (0)	1 (4)	10 (14)	5 (14)	.09
AFRS, no. (%)	1 (3)	1 (4)	12 (16)	7 (20)	.08
NCS, no. (%)	25 (86)	19 (83)	59 (81)	28 (80)	.92
LTR, no. (%)	4 (12)	5 (22)	21 (29)	11 (31)	.22
SNOT-22 score	43.0 ± 19.5	47.0 ± 20.3	41.2 ± 18.5	56.2 ± 21.7	.03
Rhinologic	11.8 ± 5.0	12.4 ± 5.8	11.8 ± 5.2	14.7 ± 4.7	.18
Extranasal	7.9 ± 3.6	8.7 ± 2.9	7.0 ± 3.6	8.0 ± 3.3	.36
Ear/Facial	8.2 ± 4.8	8.0 ± 5.1	7.4 ± 5.2	11.0 ± 5.3	.06

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	Paucigranulocytic	Neutrophilic	Eosinophilic	Mixed granulocytic	P-value
No.	33	23	73	35	
CT score	11.0 (8.0 to 14.0)	15.0 (7.5 to 19.0)	16.5 (13.0 to 20.5)	17.0 (14.0 to 21.0)	<.0001
SIT score	-3.0 (-7.0 to -1.0)	-9.0 (-19.5 to -1.5)	-13.0 (-26.0 to -3.0)	-14.0 (-25.5 to -4.0)	.04
Mucopurulence, no. (%)	11 (33)	14 (61)	12 (16)	9 (26)	.0005
Prior surgery, no. (%)	8 (24)	8 (35)	29 (40)	17 (49)	.21

Patients with mixed inflammation have more severe disease

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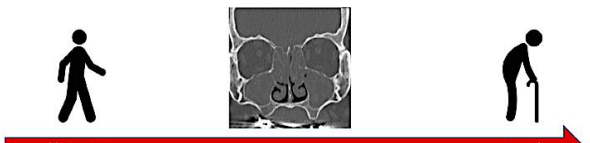
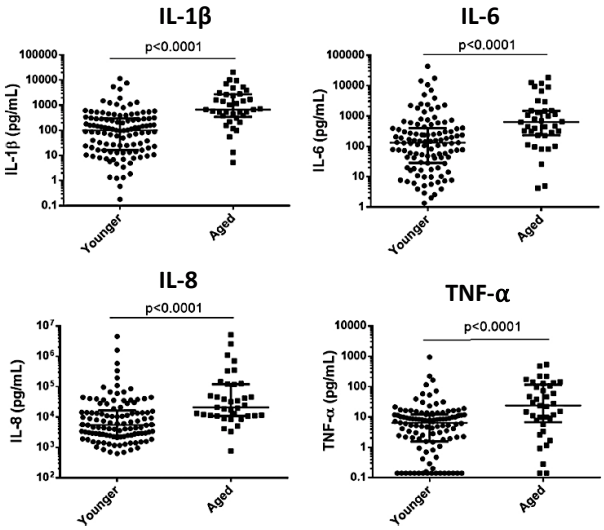
Succar et al. Allergy. 2020 Mar;75(3):713-716

13

Endotypes Vary Based on Age



- ↑Pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α)
- ↑Neutrophilic Tissue inflammation
- Dysfunctional immune response to microbial pathogens



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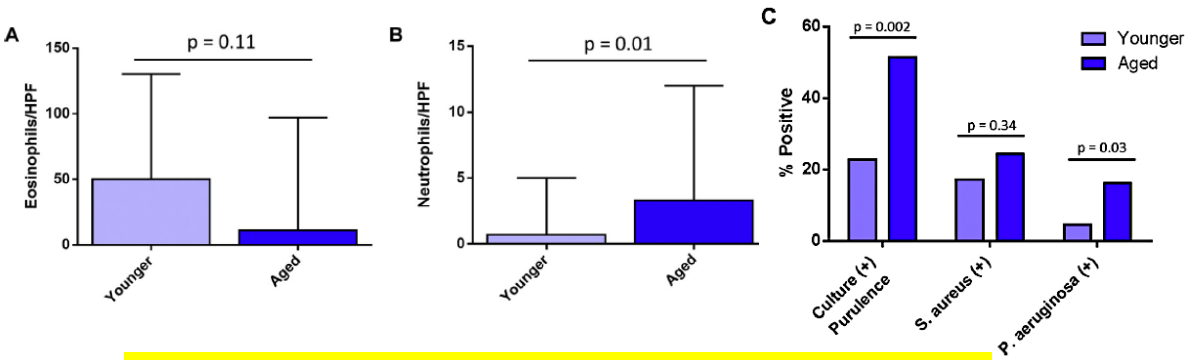
Morse JACI 2019;143:990

14

Type 3 Inflammation in Older Patients with CRS



Clinical Implications: Older patients with CRS may have more neutrophilic inflammation and may not respond as well to steroids or biologics

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Morse JACI 2019;143:990

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How to measure endotype clinically?

Type 2

- Elevated eosinophils in blood (>250/uL) or tissue (>10/hpf)
- Elevated IgE
- Presence of asthma, **allergic rhinitis, or nasal polyps**

Type 1 or 3

- Elevated neutrophils in blood or tissue
- Low eosinophils
- Low IgE
- Low IgG (<500)
- **Presence of CRSsNP**

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THERAPY FOR CRS

- ❑ Steroids
- ❑ Antibiotics
- ❑ Surgery
- ❑ Biologics
- ❑ IgG therapy

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STEROID THERAPY FOR CRS

- ❑ Steroids
- ❑ Antibiotics
- ❑ Surgery
- ❑ Biologics
- ❑ IgG therapy

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Short-course oral steroids as an adjunct therapy for chronic rhinosinusitis (Review)

Cochrane Library

2016

- At end of the treatment course (two to there weeks) there is an improvement in health-related quality of life and symptom severity in patients with CRSwNP taking oral corticosteroids.
  - No improvement after 3-6 months
- More research is needed in patients with CRSsNP

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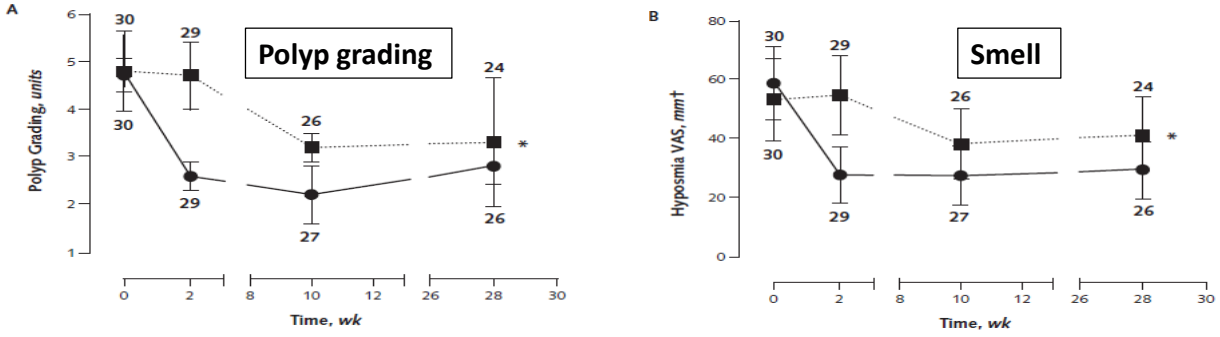
Oral Steroids in CRSwNP

Vaidyanathan et al. Ann Intern Med 2011;154



Oral steroid therapy followed by topical steroid therapy seems to be more effective over 6 months than just topical steroid therapy in decreasing polyp size and improving olfaction

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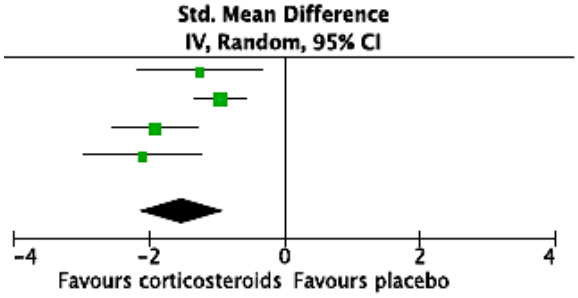
Oral Corticosteroid Use in CRSwNP



EPOS
Fokkens Rhinology 2020;58:Supp 19

Short course for 2-3 weeks

Yardstick: prednisone 40-60 mg with a 2 week taper

Ann Allergy Asthma Immunol 2022:128:118

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Should intranasal (topical) corticosteroid (INCS), rather than no intranasal corticosteroid, be used in chronic rhinosinusitis with nasal polyposis (CRSwNP)?

Statement	Strength of recommendation	Certainty of evidence
In people with chronic rhinosinusitis with nasal polyposis, the guideline panel **suggests** intranasal corticosteroid rather than no intranasal corticosteroid	**Conditional**	**Low**

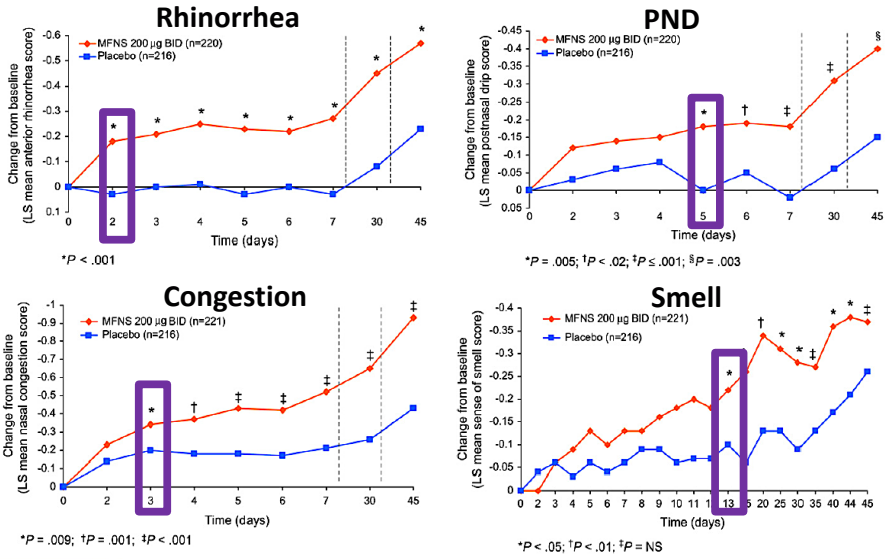
Why conditional recommendation?

- Small to moderate treatment effect
- Ex: QOL improved by 6.83 with steroid rinses and 7.86 with EDS- FLU but less than MID of 8.9 of SNOT-22

22

Small JACI 2008;121:928

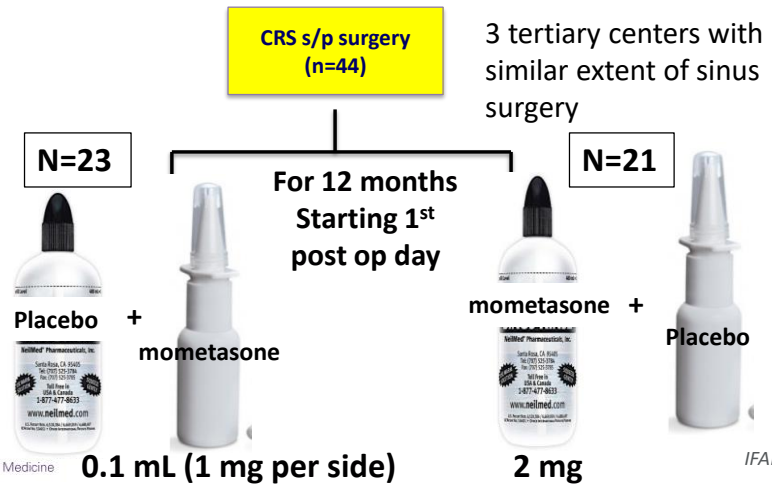
Nasal Mometasone in CRSwNP



24

Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery

Richard J. Harvey, MD, PhD[1,2], Kornkiat Snidvongs, MD, PhD[2,3], Larry H. Kalish, MBBS, MS, MMed (Clin Epi)[4,5], Gretchen M. Oakley, MD[1,6] and Raymond Sacks, MD[2,4,5]



IFAR 2018;8:461

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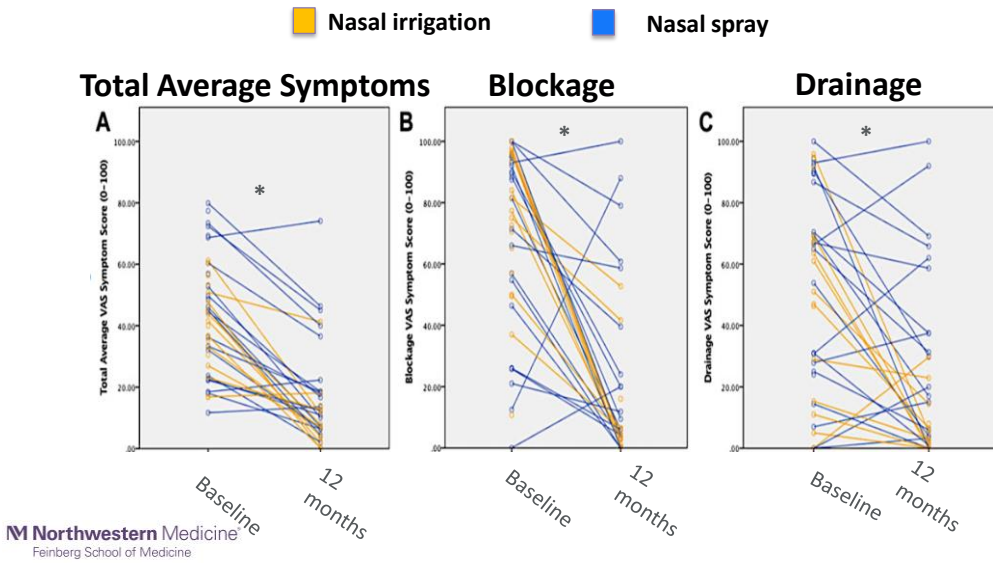
Change in Visual Analog Score



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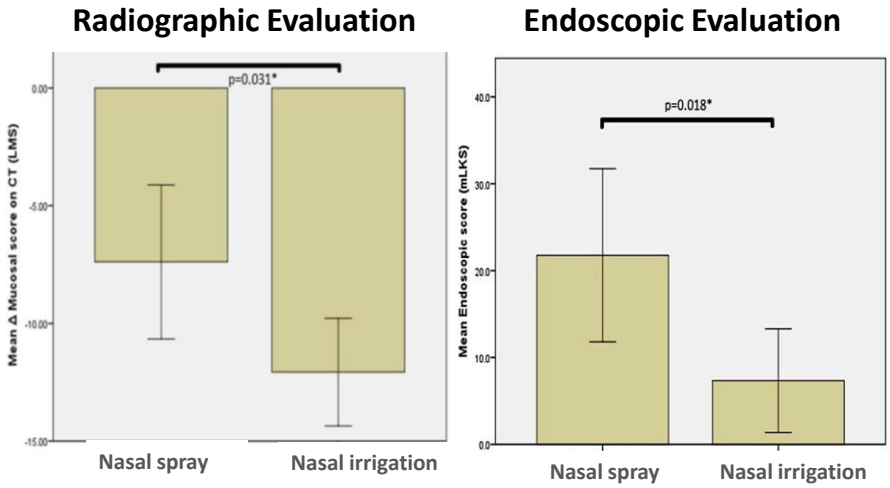
Radiographic and Endoscopic Improvement with Steroid Rinse vs Steroid Nasal Spray



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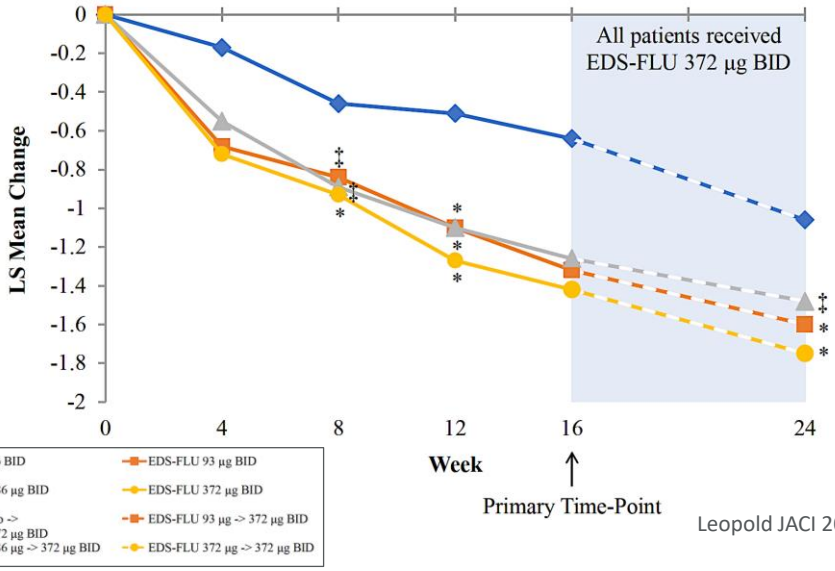
NAVIGATE II: EDS-FLU: Mean Change in Polyp Scores

- Polyps eliminated in 25% on at least 1 side vs 8.7% on placebo
- SNOT 22 improved up to 21.4



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Leopold JACI 2018

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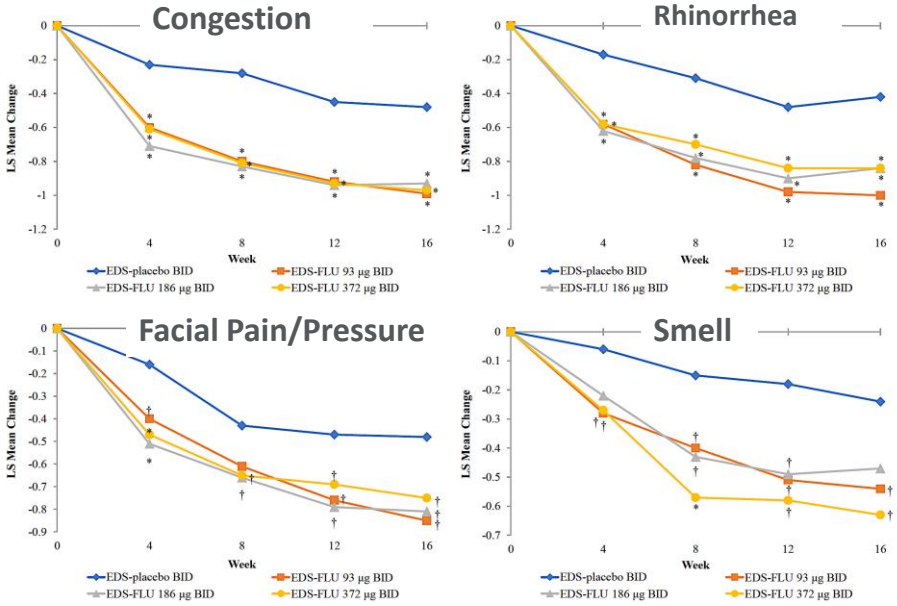
Change in AM Instantaneous Symptoms



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CRS without Nasal Polyps

Optinose Announces Positive Top-line Results of ReOpen2, its second Phase 3 Clinical Trial of XHANCE for Treatment of Chronic Sinusitis. June 13, 2022 (GLOBE NEWSWIRE)

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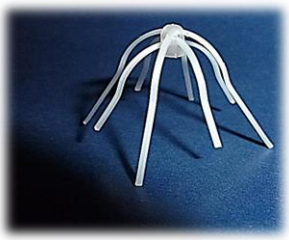
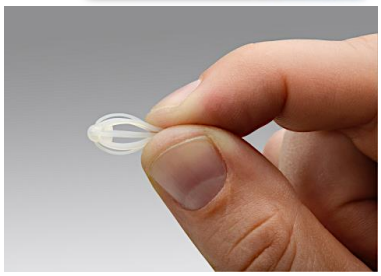
Corticosteroid Stents for CRSwNP

- Dilate the obstructed cavity
- FDA approved
- Delivers steroid directly to ethmoid cavity for 3 months
- **1350 µg of MF**
- Bioabsorbable polymer degrades over 90 days





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	Patient-Important outcomes						
	Critical Outcomes		Important Outcomes				
	HR-QoL SNOT-22 (0-120)	Symptoms (Nasal Obstruction) VAS (0-3)	Smell UPSIT (0-40)	Rescue Surgery	Polyp Size (0-3)	Severe Adverse Events	Any Adverse Events
Placebo (reference)	-19.41	-0.56	3.54	13.58%	-0.60	2.76%	28.66%
Stent	**2.35** (-5.92, 10.62)	**-0.31** (-0.54, -0.08)	**3.81** (1.22, 6.39)	**-10.3%** (-12.9%, -0.2%)	**-0.53** (-1.11, 0.04)	**-1.3%** (-5.6%, 2.9%)	**-4.2%** (-15.5%, 7.0%)
Spray	**-3.62** (-9.27, 2.04)	**-0.51** (-0.61, -0.41)	**3.24** (2.05, 4.42)	**-10.7%** (-13%, -2.1%)	**-0.64** (-0.85, -0.43)	**-0.1%** (-0.8%, 0.5%)	**2.7%** (-0.7%, 6.1%)
Rinse	**-6.83** (-11.94, -1.71)	**-0.21** (-0.76, 0.33)	**2.77** (-0.84, 6.39)		**-0.46** (-1.31, 0.39)	**0.00%** (-4.3%, 4.2%)	**-0.6%** (-8.5%, 7.3%)
EDS	**-7.86** (-14.64, -1.08)	**-0.35** (-0.51, -0.18)	**4.10** (1.69, 6.52)	**-4.3%** (-6.9%, -0.9%)	**-0.56** (-0.97, -0.14)	**-1.0%** (-3.3%, 1.3%)	**2.9%** (-14.8%, 20.7%)
		-0.15	5.03	-11.0%	-1.17	0.8%	3.1%

Among most beneficial / Among most harmful | Among least beneficial / no clear effect compared to placebo | No data (blank) | High/Moderate CoE (Solid) / low/Very Low CoE (shaded)

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Quality of life: EDS or rinse (the rest had either no benefit or least beneficial)

Symptoms: Spray, EDS or stent (Rinse or drop either no benefit or least beneficial)

Smell: Stent > EDS, spray or drops

Rescue surgery: EDS > Spray or stent

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Bognani JACI 2022 in press

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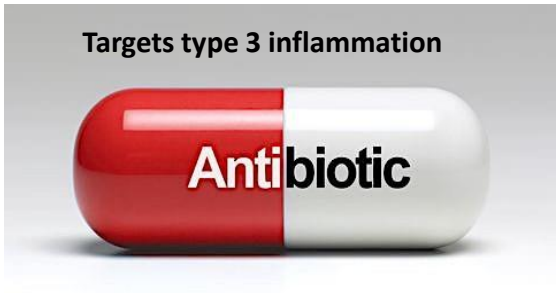
ANTIBIOTICS FOR CRS

- ❑ Steroids
- ❑ **Antibiotics**
- ❑ Surgery
- ❑ Biologics
- ❑ IgG therapy



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Systemic and topical antibiotics for chronic rhinosinusitis (Review)

2016

Cochrane Library

5 RCT (293 participants)

"We found very little evidence that systemic antibiotics are effective in patients with CRS"

"We did find moderate quality evidence of a modest improvement in disease-specific quality of life in adults with CRSsNP receiving three months of a macrolide antibiotic; by 3 months later no difference was found"

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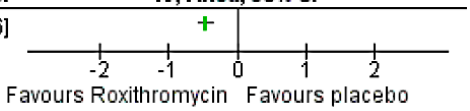
Long-term Antibiotics (Roxithromycin) in CRS

Wallwork Laryngoscope 2006;116:189

SNOT 20: Change from baseline at end of treatment

Roxythromycin			Placebo			Mean Difference	Mean Difference
Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
-0.41	0.23	29	0.05	0.17	35	-0.46 [-0.56, -0.36]	



Results: improved or cured 67% vs 22%
93% improved or cured in those with normal IgE

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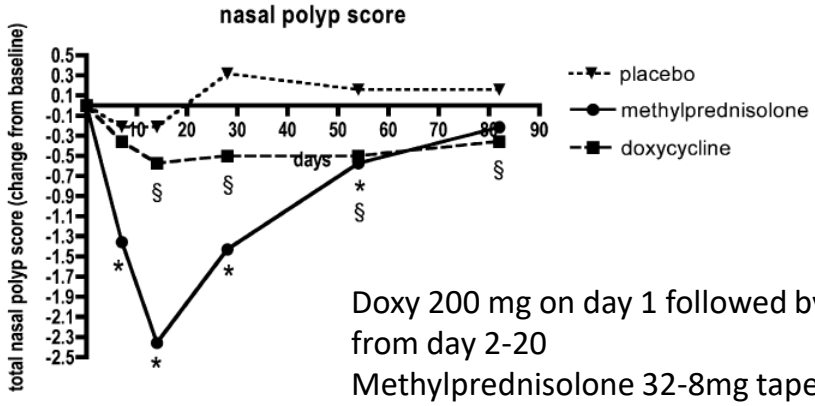
Nasal Polyp Score Improved with Methylprednisolone or Doxycycline

Van Zele JACI 2010;125:1016



Doxy 200 mg on day 1 followed by 100 mg daily from day 2-20
Methylprednisolone 32-8mg taper over 20 days

Results: methylprednisolone and doxycycline each significantly reduced polyp size

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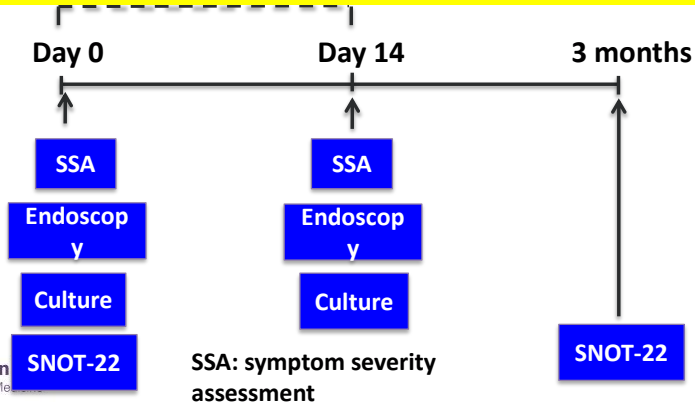
Amoxicillin-clavulanate for patients with acute exacerbation of CRS

(Sabino et al. Int Forum Allergy Rhinol 2017;7:135)

Acute exacerbation of CRS: Adult patients with CRS with worsening sinonasal symptoms for 4 weeks

Amox-Clav or Placebo + mometasone nasal spray + saline rinses



SSA: symptom severity assessment

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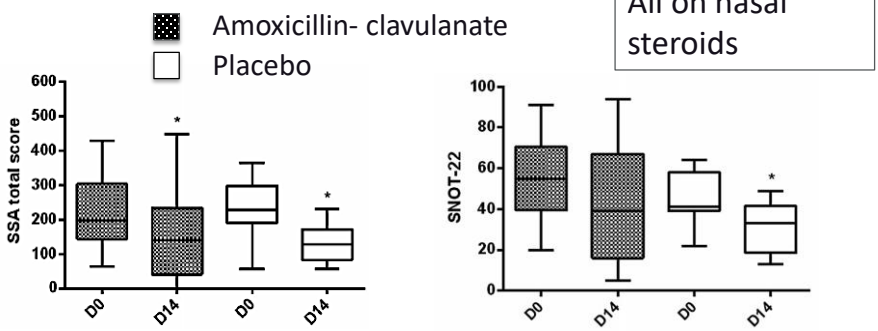
Clinical Outcomes Pre and Post-treatment

All on nasal steroids



Symptom Severity Assessment

SNOT-22

The addition of oral antibiotic to ongoing topical intranasal steroid spray did not provide additional benefit during management of acute exacerbation of CRS

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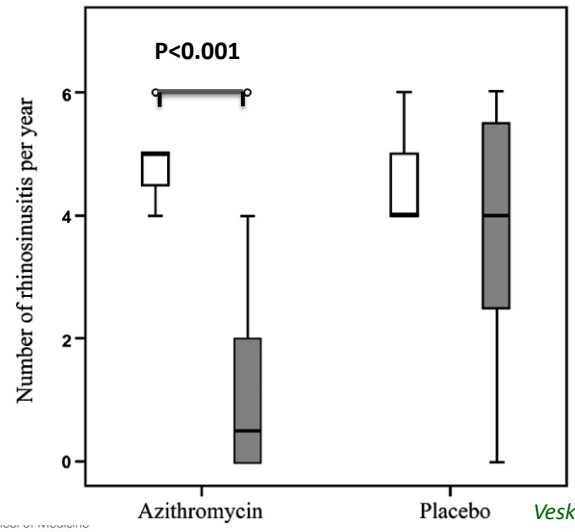
Decrease in recurrent acute sinusitis with azithromycin prophylaxis



Recurrent Acute Sinusitis
- **Received azithromycin MWF or placebo for a year**
- **All on nasal steroids**

Baseline
After received intervention

NNT= 2 to prevent 1 RARS

Veskitkul et al. J Allergy Clin Immunol In Practice 2017

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SURGERY FOR CRS

- ❑ Steroids
- ❑ Antibiotics
- ❑ **Surgery**
- ❑ Biologics
- ❑ IgG therapy

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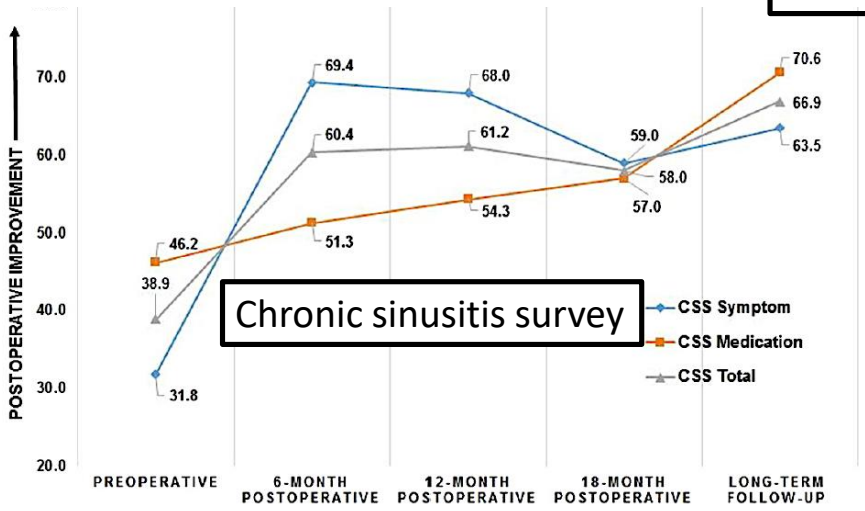
Long-term outcomes of endoscopic sinus surgery in the management of adult chronic rhinosinusitis

Mean f/up 10.9 years



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Smith IFAR 2019;00:1

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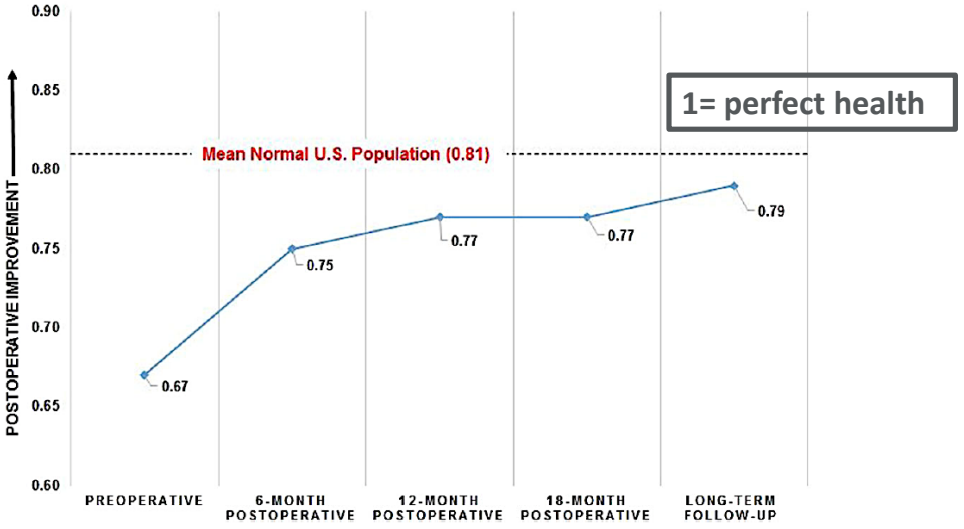
SF-6D Health Utility



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Can Surgery Target Type 2 Inflammation?

Sinus Surgery Is Associated with a Decrease in Aspirin-Induced Reaction Severity in Patients with Aspirin Exacerbated Respiratory Disease

Elina Jerschow, MD, MSc[a], Matthew L. Edin, PhD[b], Yuling Chi, PhD[c], Beth Hurst, PhD[d], Waleed M. Abuzeid, MD[a], Nadeem A. Akbar, MD[a], Marc Gibber, MD[a], Marvin P. Fried, MD[a], Weiguo Han, PhD[c], Teresa Pelletier, MD[c], Zhen Ren, MD, PhD[e], Taha Keskin, MD[a], Gigia Roizen, MD[a], Fred B. Lih, BA[b], Artiom Gruzdev, PhD[b], J. Alyce Bradbury, MS[b], Victor Schuster, MD[a], Simon Spivack, MD[a], David Rosenstreich, MD[a], and Darryl C. Zeldin, MD[b]

Bronx, NY; Research Triangle, NC; Ann Arbor, Mich; and St. Louis, Mo

The Journal of Allergy and Clinical Immunology: In Practice

2019;7:1580

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Results

After FESS: 12/28 (43%) with a hx of positive challenge did not not have any clinical symptoms during aspirin challenge and had a negative challenge

Pre and post FESS

- Decrease in eos from 0.7, (IQR 0.4-0.8 K/uL) to 0.3 (IQR 0.1-0.5 K/uL)

- Reaction to aspirin was less severe
  - FEV1 decrease: -10.0% (IQR -19.0 to -3.8) pre vs -8.6% (IQR -14.0 to -2.4 post, 0.02)

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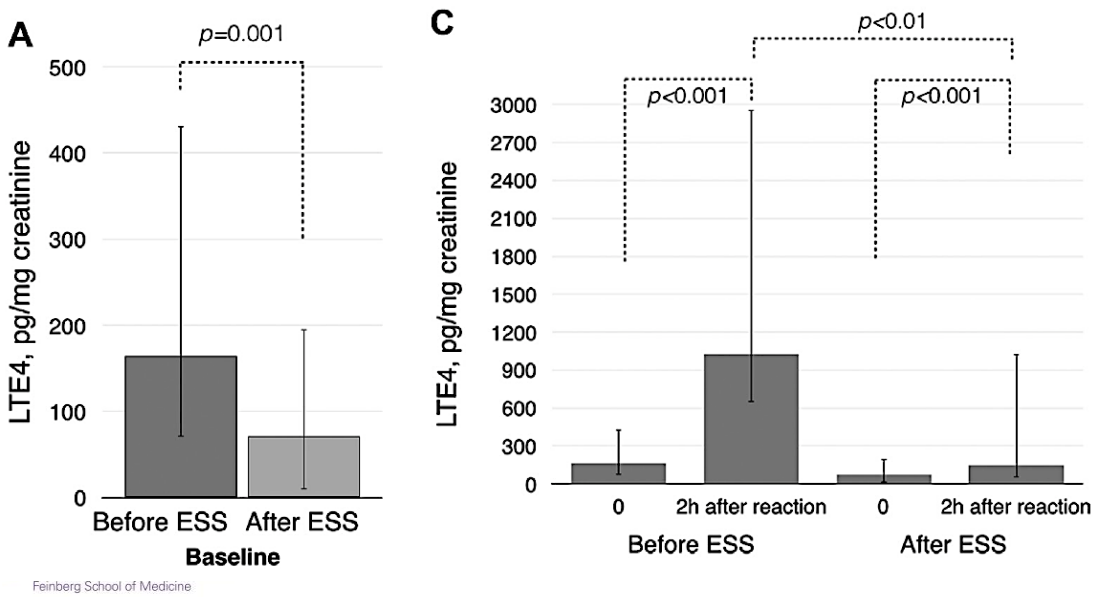
Urinary Leukotriene E4 Reduced After Surgery



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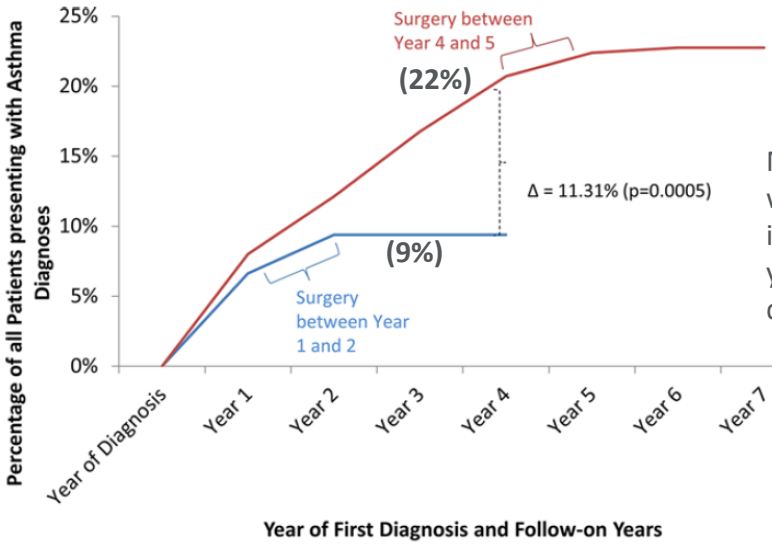
Does Surgery have a Disease-Modifying Effect?

New diagnosis of asthma based on time to surgery



Medically recalcitrant CRS without asthma diagnosis incurs more than 5% risk per year of developing a new diagnosis of asthma

Benninger et al. IFAR 2016;6:124

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Endoscopic sinus surgery with medical therapy versus medical therapy for chronic rhinosinusitis with nasal polyps: a multicentre, randomised, controlled trial

CRSwNP
371 assessed
238 randomized

12 months

ESS + medical therapy
N=121

Medical therapy
N=117

23 crossed over

Lourijsen and Fokkens Lancet Respir Med 2022; 10:337

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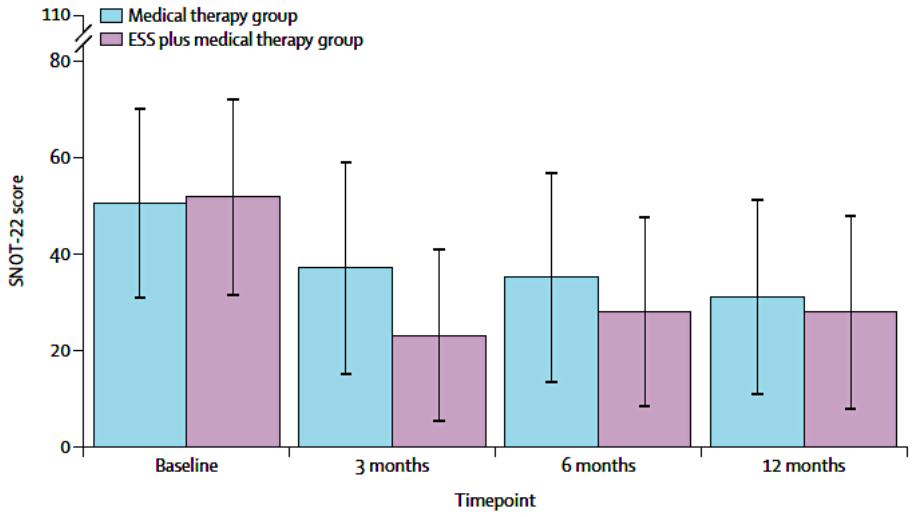
SNOT-22 scores



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Outcomes

	ESS + medical therapy		Medical therapy		Adj outcomes
	Pre	Post	Pre	Post	
Nasal Symptoms (VAS)	79.0 (14.0)	31.5 (29.7)	74.0 (20.0)	45.5 (30.3)	-15.9 (-24.0 to -7.8)
NPS	5.9 (1.0)	2.2 (2.04)	5.7 (1.4)	3.83 (2.52)	-1.7 (-2.4 to –1.1)

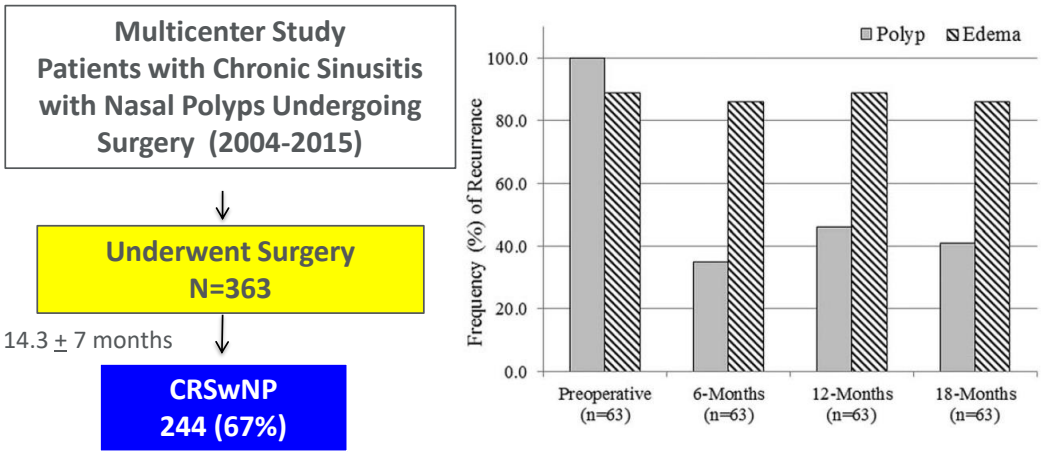
Outcomes

	ESS + medical therapy		Medical therapy		Adj outcomes
	Pre	Post	Pre	Post	
EPOS control Uncontrolled	113 (96%)	46/100 (46%)	112 (97%)	63/99 (64%)	
Anosmia	87 (74%)	54/100 (54%)	79 (68%)	49/95 (52%)	

Post hoc analysis

- **ESS+ medical therapy** used 266mg (SD 505) prednisolone
- **Med therapy:** 587 mg (740); diff of 316 mg (95% CI -468 to -166)
- No difference in antibiotic use
- Many patients in both groups continued to have symptoms
- Limitations: not blinded, pre biologics

Polyp Recurrence After Sinus Surgery

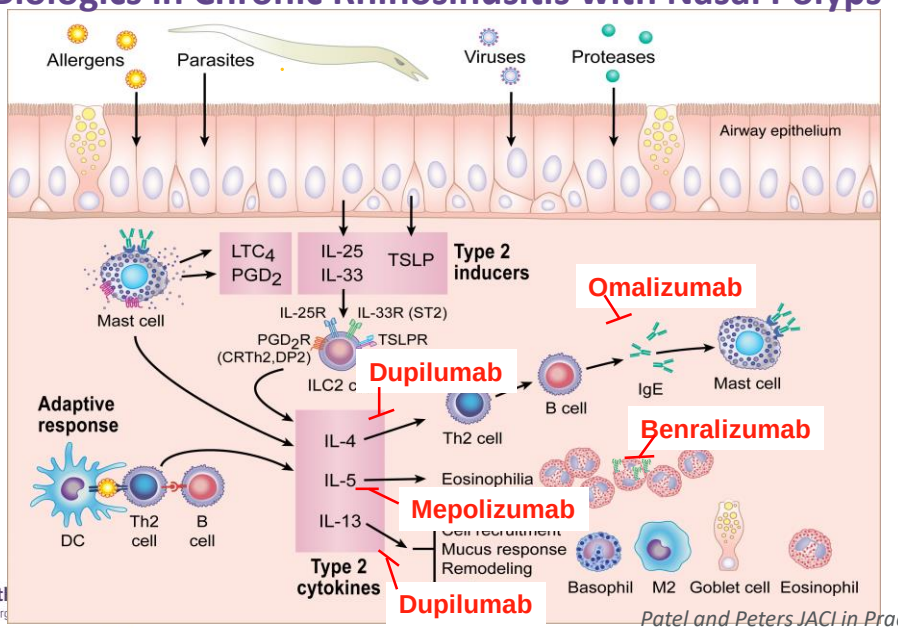


DeConde Laryngoscope 2017;127:550

BIOLOGICS FOR CRS

- ❑ Steroids
- ❑ Antibiotics
- ❑ Surgery
- ❑ **Biologics**
- ❑ IgG therapy

Biologics in Chronic Rhinosinusitis with Nasal Polyps



Patel and Peters JACI in Practice 2019

Should biologics, rather than no biologics, be used in chronic rhinosinusitis with nasal polyps (CRSwNP)?

Statement	Strength of recommendation	Certainty of evidence
In people with CRSwNP, the guideline panel **suggests** biologics rather than no biologics	**Conditional**	**Moderate**

Why conditional: other options including INCS, surgery, or ATAD

The preference and values among different individuals are different

- For those who do ok with other therapies will not prefer biologics
- For patients with high disease burden, biologics may be preferred

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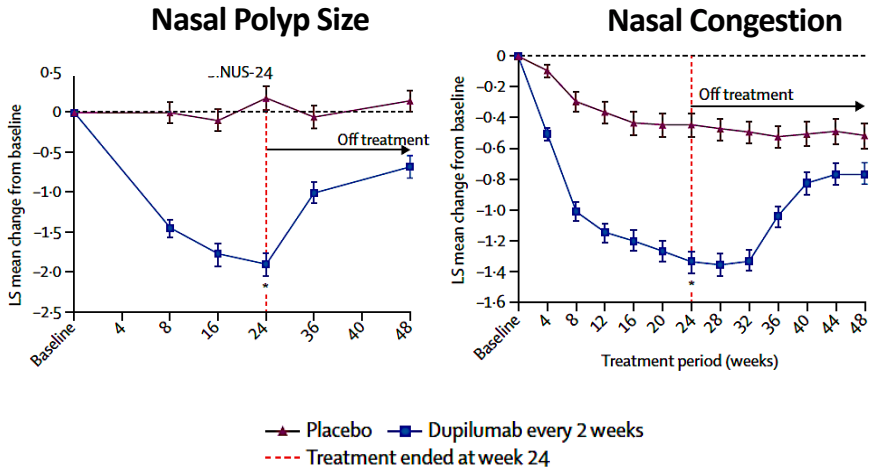
Dupilumab decreases polyp size and improves congestion



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Bachert et al. Lancet. 2019 Nov 2;394(10209):1638-1650.

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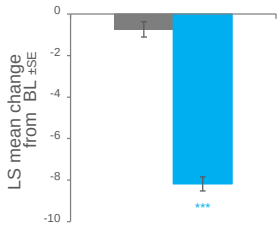
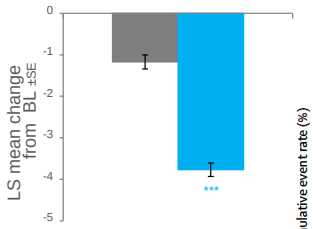
Placebo
Dupilumab 300 mg q2w

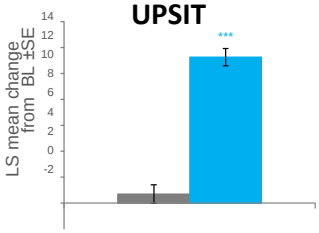
Lund Mackay CT Score



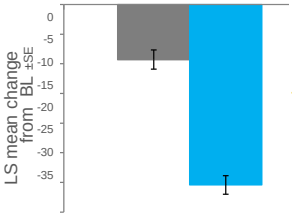
Total Symptoms Score



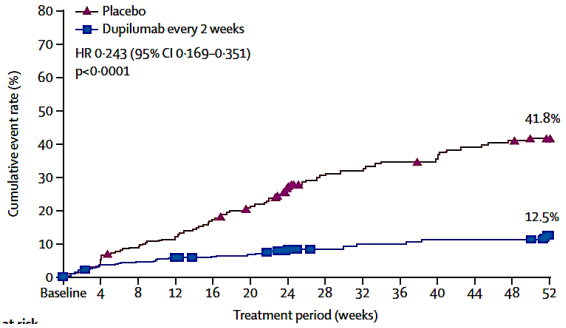
UPSIT



SNOT-22



Need for steroids or surgery



Systemic steroids: 74% reduction;
Surgery: 83% reduction

Bachert Lancet 2019;394:1638

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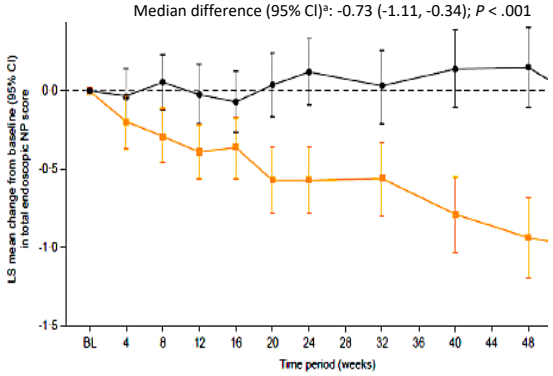
Mepolizumab: SYNAPSE Results

Mepolizumab Placebo

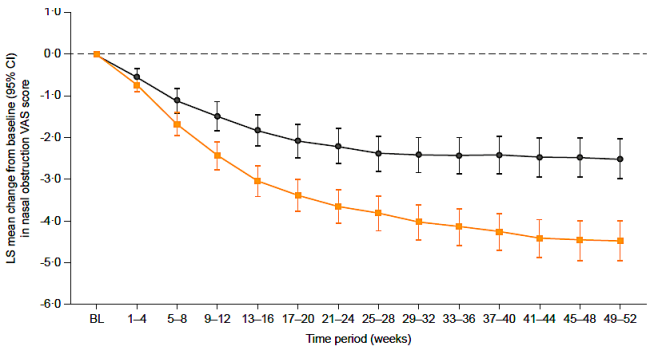
Total Endoscopic NPS (Week 52)

Median difference (95% CI)[a]: -0.73 (-1.11, -0.34); *P* < .001



Nasal Obstruction VAS Score (Weeks 49-52)

Median difference (95% CI)[a]: -3.14 (-4.09, -2.18); *P* < .001



StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab

Han Lancet Respir Med 2021;9:1141

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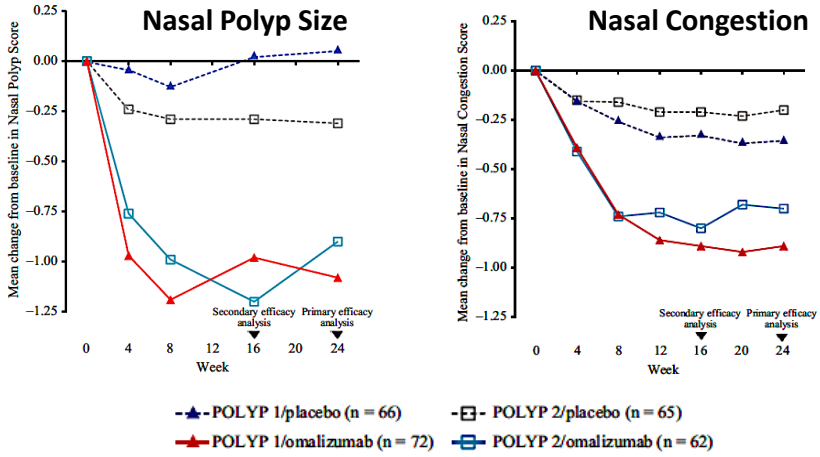
Omalizumab decreases nasal polyp size and nasal congestion



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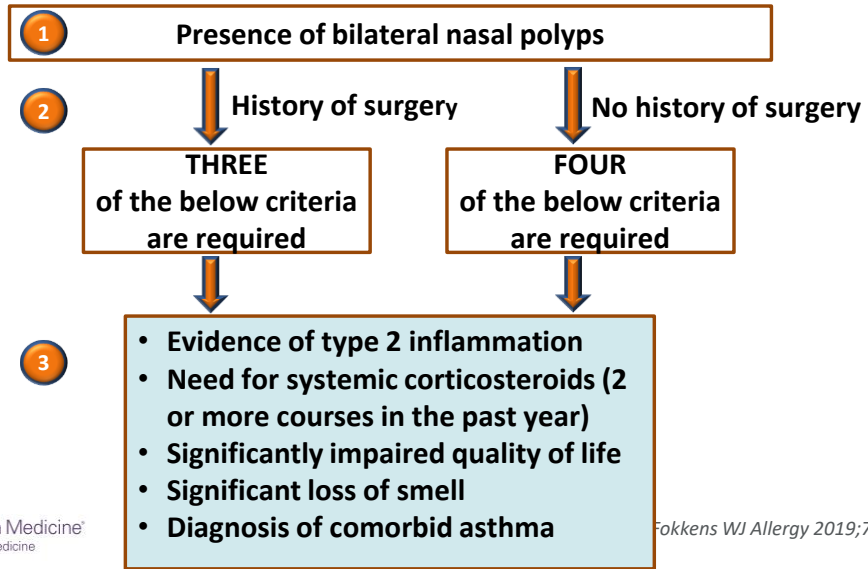
Gaevert et al. J Allergy Clin Immunol. 2020 Jun 7;S0091-6749(20)30752-1.

60

EUFOREA Criteria for Considering Biological Treatment



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Fokkens WJ Allergy 2019;74:2312

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	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	**-19.91** (-22.50, -17.32)	**-3.25** (-4.31, -2.18)	**10.96** (9.75, 12.17)	**-21.73** (-24.61, -18.22) RR 0.32 (0.23, 0.43)	**-16.35** (-18.13, -13.48) RR 0.22 (0.14, 0.36)	**0.13** (-8.12, 9.88) RR 1.00 (0.88, 1.13)	**-2.04** (-2.73, -1.35)	**-7.51** (-10.13, -4.89)
Omalizumab	**-16.09** (-19.88, -12.30)	**-2.09** (-3.15, -1.03)	**3.75** (2.14, 5.35)	**-12.46** (-23.65, 12.78) RR 0.61 (0.26, 1.40)	**-7.40** (-11.04, -2.43) RR 0.65 (0.48, 0.88)	**-2.60** (-15.58, 13.28) RR 0.96 (0.79, 1.18)	**-1.09** (-1.70, -0.49)	**-2.66** (-5.70, 0.37)
Mepolizumab	**-12.89** (-16.58, -9.19)	**-1.82** (-3.13, -0.50)	**6.13** (4.07, 8.19)	**-10.23** (-15.98, -2.88) RR 0.68 (0.50, 0.91)	**-12.33** (-15.56, -7.22) RR 0.41 (0.26, 0.66)	**-3.07** (-13.44, 9.07) RR 0.96 (0.82, 1.12)	**-1.06** (-1.79, -0.34)	
Benralizumab	**-7.68** (-12.09, -3.27)	**-1.15** (-2.47, 0.17)	**2.95** (1.02, 4.88)	**-9.91** (-16.30, -0.96) RR 0.69 (0.49, 0.97)	**-2.53** (-9.05, 7.16) RR 0.88 (0.57, 1.34)	**-1.48** (-13.28, 12.54) RR 0.98 (0.82, 1.17)	**-0.64** (-1.39, 0.12)	**-1.00** (-3.83, 1.83)
Reslizumab					**-18.82** (-20.93, 20.56) RR 0.11 (0.01, 1.98)	**-2.55** (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						**2.54** (-27.11, 31.03) RR 1.03 (0.63, 1.69)	**-0.20** (-1.61, 1.21)	
Etokimab	**-1.30** (-8.99 to 6.40)					**188.14** (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	**-0.33** (-1.58, 0.92)	

Classification of intervention (colour)[24]				Certainty (shading)[24, 29]
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

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Questions for use of biologics in CRS with Polyps

Consider before or with surgery

- Severe asthma
- AERD
- Surgical failures
- Poor surgical candidates
- Other comorbidities

Not clear when to use

- Polyp without asthma
- Use after surgical failures?
- When and for how long?
- Immediately post-op to prevent recurrences in high risk patients?
- **Costs are a huge issue**
- **Duration of use not known**

No Biomarkers

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ENDOTYPE-BASED THERAPY FOR CRS

Type 2
- Steroids
- Biologics
- Surgery

Type 3
- Antibiotics
- **IgG therapy**

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THERAPY FOR CRS

- ❑ Steroids
- ❑ Antibiotics
- ❑ Surgery
- ❑ Biologics
- ❑ **IgG therapy**

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Prevalence of Immunodeficiency in CRS Jan 2010-Feb 2013

Immune Status	Patients
CVID	35 (5.9%)
Specific antibody deficiency	144 (24.2%)
IgA deficiency	16 (2.7%)
No abnormalities	402 (67.6%)
Total	595

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Keswani et al. JACI in practice 2017

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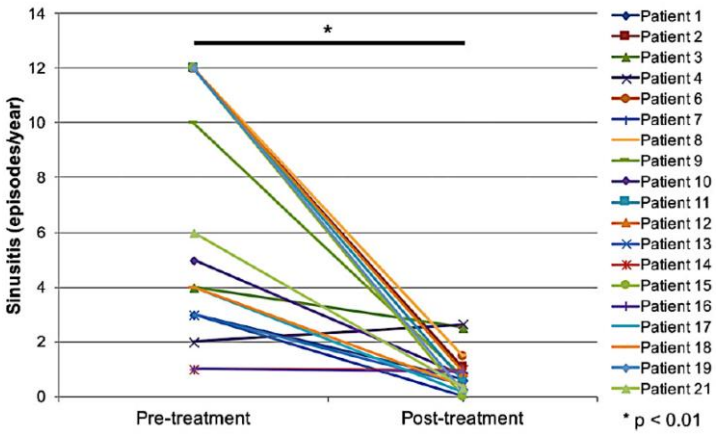
Immunoglobulin Replacement Reduces CRS Exacerbations and Antibiotic Courses



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Walsh et al. IFAR 2016

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How to measure endotype clinically?

Type 2
- Elevated eosinophils in blood (>250/uL) or tissue (>10/hpf)
- Elevated IgE
- Presence of asthma, **allergic rhinitis, or nasal polyps**

Type 1 or 3
- Elevated neutrophils in blood or tissue
- Low eosinophils
- Low IgE
- Low IgG (<500)
- **Presence of CRSsNP**

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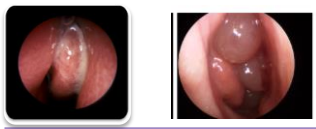
How we think about severe CRS



- **Comorbidities**
- **Workup: Sinus CT scan, CBC with diff, IgE, allergy evaluation, spirometry, immune workup**
- **Shared decision making**

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Acknowledgements

Northwestern Sinus and Allergy Center

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Lydia Suh, BS
Bruce Tan, MD
Robert Schleimer, PhD
Stephanie Shintani-Smith, MD
Kevin Welch, MD

Chronic Rhinosinusitis Integrative Studies Program

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Thank You!!

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

United Airways: The Clinical Impact of Upper and Lower Airway Connection

Presented by:

Anju Peters, MD, MSCI

Sunday, June 25, 2023

8:30 a.m. – 9:15 a.m.

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Unified Airways: The Clinical Impact of Upper and Lower Airway Disease

Anju T Peters, MD MSCI
Professor of Medicine
Director of Clinical Research, Division of Allergy-Immunology
Medical Director, Northwestern Medicine Clinical Research Unit
Northwestern University Feinberg School of Medicine

1

Disclosures

- Research Support
  - Sanofi Regeneron
  - AstraZeneca
  - CRISP (PO145818/AI/NIAID)
- Consulting
  - AstraZeneca
  - Sanofi Regeneron
  - Optinose
  - GSK

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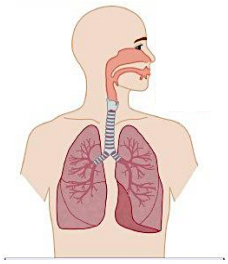
2

Objectives

- Be familiar with the epidemiologic connection of allergic rhinitis, chronic rhinosinusitis, and asthma
- Be familiar with treatments for patients with asthma and CRS
  - Nasal steroids
  - Biologics
  - Surgery



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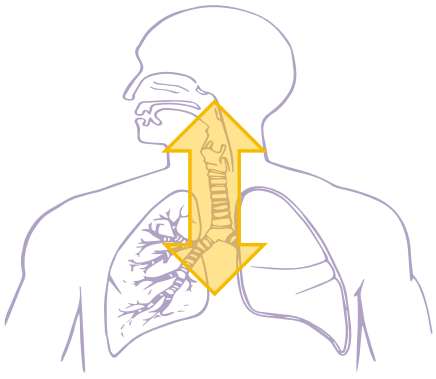
3

Definition of Unified Airway Diseases (UAD)

"The UAD hypothesis proposes that any disease process that affects the upper airway is likely to affect the lower airway, and vice versa, by both direct and indirect means."



Rimmer J, et al. *Med J Aust.* 2006;185:565–71.

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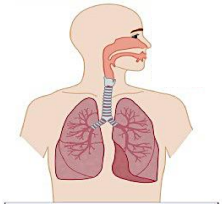
4

Post nasal drainage syndromes and and asthma

Allergic Rhinitis **Rhinosinusitis**

Post nasal drainage
Phlegm
mucus



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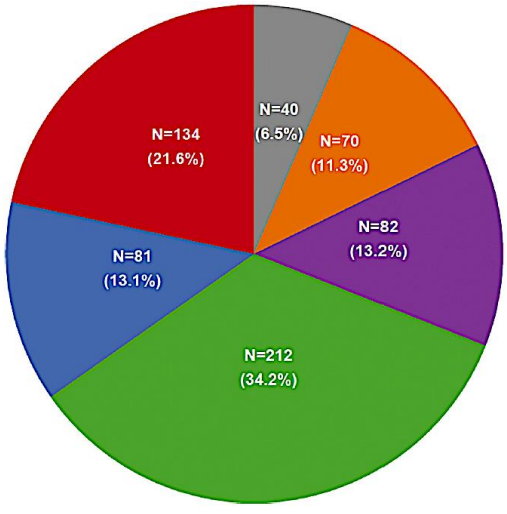
Rhinitis and Asthma in Inner City Children



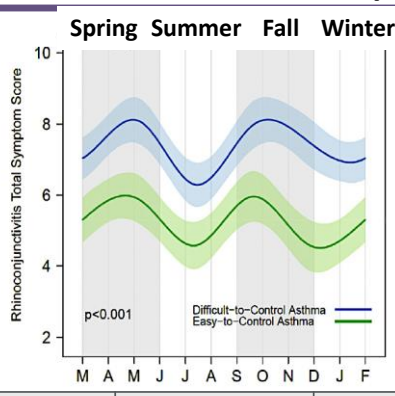
- 93.5% had some rhinitis
- Perennial allergic rhinitis with seasonal exacerbation (PARSE) most common

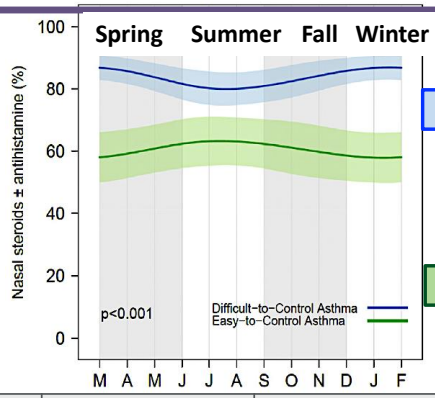
Togias, JACI 2019

SAR PAR PARSE IAR NAR No Rhinitis

6

Relationship Between Rhinitis and Asthma





Difficult -to control-asthma

Easy-to-control asthma

Asthma	Patients with SAR	Patients with PAR	Patients with PARSE	Patients with IAR	Patients with NAR
Difficult to control	53 (21.9%)	28 (11.6%)	**107 (44.2%)**	30 (12.4%)	24 (9.9%) P=0.003
Easy to control	56 (26.5%)	35 (16.6%)	**56 (26.5%)**	33 (15.6%)	31 (14.7%)

7

Chronic Rhinitis Is A High-Risk Comorbidity For 30-Day Re-Admission Of Patients With Asthma And Chronic Obstructive Pulmonary Disease

Asthma: 4,754 patients, 10,111 encounters

Median follow-up time: Asthma: 980 (±760) days, **18% readmitted**

Comorbidity		Comparison groups	Hazard ratio (HR)	95% HR CI		P-value
Chronic Rhinitis	**Allergic**	**Yes vs. No**	**4.4**	3.9	5.0	<.0001
	Non-Allergic		**3.7**	2.9	4.9	

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Singh J Allergy Clin Immunol In Practice; 2018

8

Thunderstorm asthma: Ninth death in Victoria after freak weather event in 2016

ABC News

Updated 24 Jan 2017, 10:36pm

RELATED STORY: Victorian coroner to investigate thunderstorm asthma deaths

8,500 people sought hospital treatment when the weather changed abruptly on November 21, as a cool change and thunderstorms swept across Melbourne.

95% of those that were affected by thunderstorm asthma had a history of hay fever
-96% positive to grass pollen (rye grass)

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- 336 (672%) increase in ED visits
- 476 (992%) excess asthma related admissions to hospital

Thien Lancet 2019

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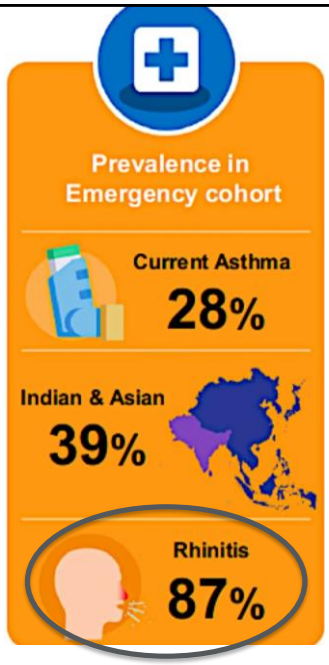

Hew Allergy 2018;74:122

10

Asthma and treatment of rhinitis with nasal steroids

Frequency (rate per 100 person-years) of asthma related ED visits

Nasal steroid (+)	Nasal steroid (-)
N=2276	N=11,568
98 (4.3)	933 (8.1)**

**P<0.0001

Adjusted RR for asthma related ED visit INS prescription

Dispensing rate of INS	N	RR
0	11,568	1.0
1	1511	0.74(0.57-0.99) p<0.05*
>3	242	0.50 (0.23-1.05), p=0.07

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Adams JACI 2002,109:636

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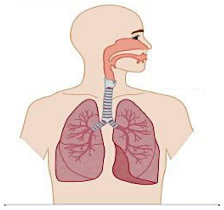
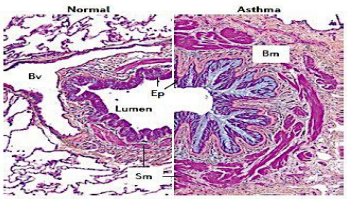


CRS and Asthma



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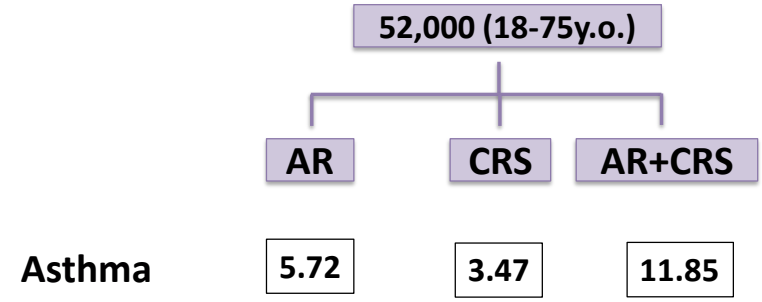
CRS, AR, and Asthma in Europe

Odds ratio for asthma

GA^{2}LEN postal questionnaire
(2008-2009)



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Jarvis Allergy 2013;67:91

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Clinical Characteristics of Chronic Rhinosinusitis

Benjamin JACI in Practice 2019;7:1010

	CRSsNP (n = 507)	CRSwNP (n = 874)	p value
Mean Age (yrs ± SD)	50.77 ± 14.21	50.35 ± 14.42	0.59
Female Sex - no. (%)	319 (63)	393 (45)	<0.0001
Asthma – no. (%)	**183 (36)**	**490 (56)**	**<0.0001**
Allergic Rhinitis – no. (%) *	216 (52)	521 (76)	<0.0001
FEV1 Percent Predicted, Pre-bronchodilation (mean ± SD) †	83.17 ± 20.51	83.60 ± 17.92	0.76
Number of Sinus Surgeries – (mean ± SD)	0.94 ± 0.97	1.42 ± 1.56	<0.0001

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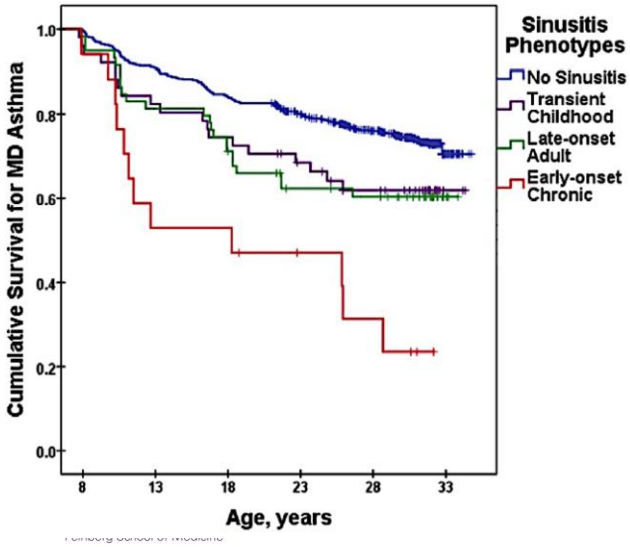
Likelihood of Developing Asthma in the Different Sinusitis Phenotypes



- **Early onset sinusitis vs no sinusitis: HR=4.2; 95% CI 2.3-7.7 (p<0.0001)**
- Early onset sinusitis *vs* transient childhood sinusitis: HR=2.6;95% CI 1.3-5.4 (p=0.009)
- Early onset sinusitis vs late-onset adult sinusitis: HR=2.5; 95% CI 1.2-5.0 (p=0.01)

Chang JACI 2018;141:1291

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Is asthma a risk factor for CRS severity?

YES

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6/19/2023

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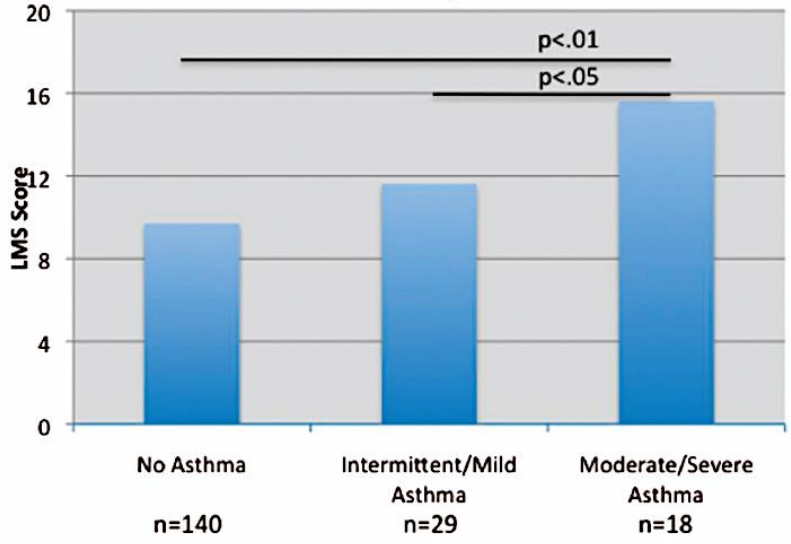
Sinus CT Severity Increases with Asthma Severity



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Lin AJRA 2011;25:205

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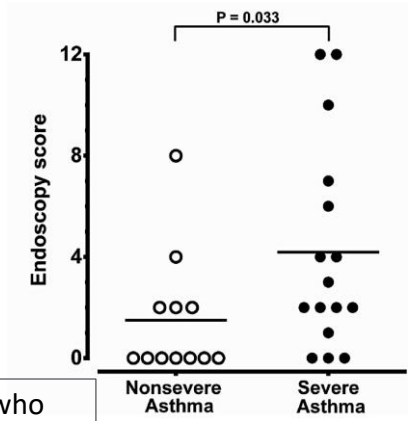
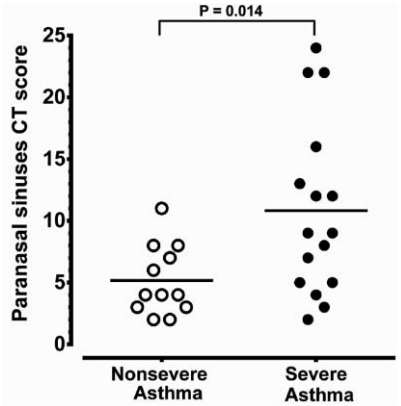
Chronic Rhinosinusitis and Severe Asthma





Asthmatics who underwent surgery

N=12 N=16

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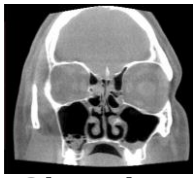
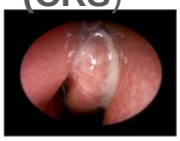
Lee et al. PLOS One 2017

18

Clinical factors associated with acute exacerbations of chronic rhinosinusitis



Chronic Rhinosinusitis (CRS)



N=3109

Jan 2014 – May 2016

19.3% of patients with CRS experience frequent exacerbations (≥ 4 antibiotics in 1 year)

N=600

Kwah JACI 2020;145:1598

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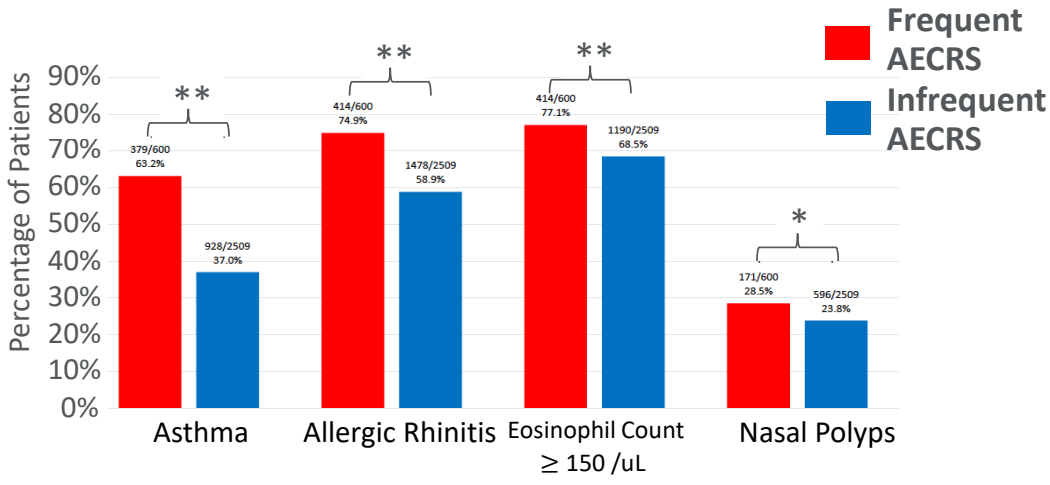
Factors are associated with frequent AECRS episodes



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Clinical associations with frequent AECRS

Variable	Adjusted odds ratio	95% CI
Asthma	2.61	2.14-3.18
Allergic rhinitis	1.96	1.58-2.42
Eosinophil count ≥150/μL	1.54	1.21-1.97
Autoimmune disease	1.68	1.36-2.07

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Who is at risk for recurrence after surgery?

Revision surgery rates in chronic rhinosinusitis with nasal polyps: meta-analysis of risk factors

Catherine A. Loftus, MS, Zachary M. Soler, MD, MSc, Sina Koochakzadeh, BS, Vincent M. Desiato, DO, Frederick Yoo, MD, Shaun A. Nguyen, MD and Rodney J. Schlosser, MD

IFAR 2019

- **AFRS (28.7%)**
- **AERD (27.2%)**
- **Asthma (22.6%)**
- **Prior polypectomy (26%)**

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Do patients with severe asthma have higher prevalence and severity of of CRS?

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Severe asthma and CRS

- Severe Asthma Research Program (SARP)

SARP

Severe Asthma Research Program
A National Institute of Health/National Heart, Lung & Blood Institute Sponsored Network

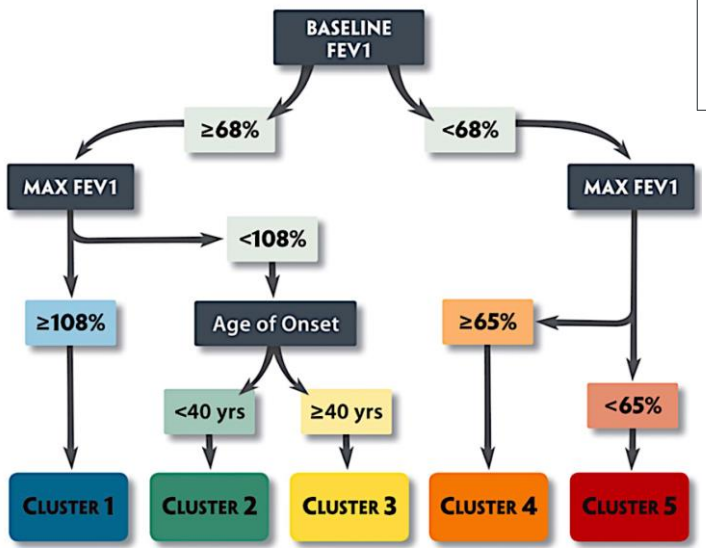
- U-Biopred- 509 adult asthmatics (mild, moderate, and severe) from Europe

U-BIOPRED

24

Severe

N=726 (304 with severe asthma)



Sinusitis 40 41 63 45 53

Moore et al. AJRCC 2010;181(4):315

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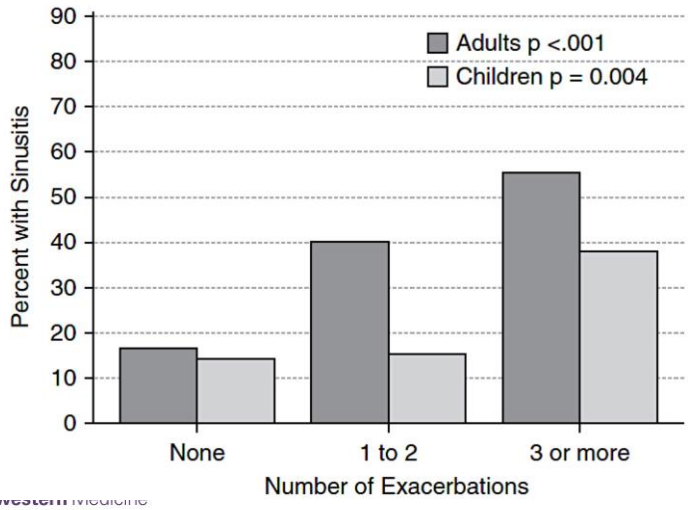
Prevalence of rhinosinusitis in severe Asthma



Denlinger AJRCCM 2017;195

26

Clinical characteristics of U-BIOPRED adult severe asthma cohort

Shaw et al. Eur Resp J 2015;46:1227

	Severe nonsmoking	Mild/moderate nonsmokers	Healthy nonsmoking controls
FEV1 % pred	67.5	89.5	101.7
Allergic rhinitis dx (%)	**59.2**	**60**	**16.7**
SNOT 20	**31.8**	**15.4**	
Nasal polyp dx (%)	**35.4**	**9.2**	**8.8**

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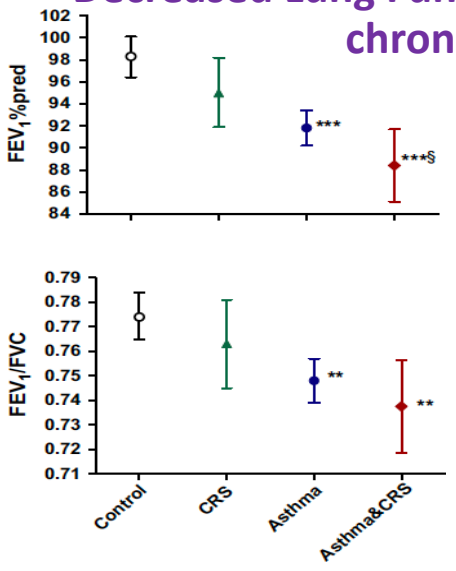
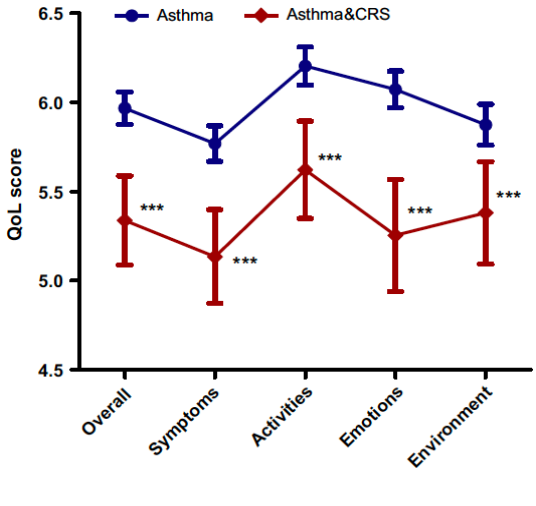
Decreased Lung Function and QOL in asthma with chronic rhinosinusitis





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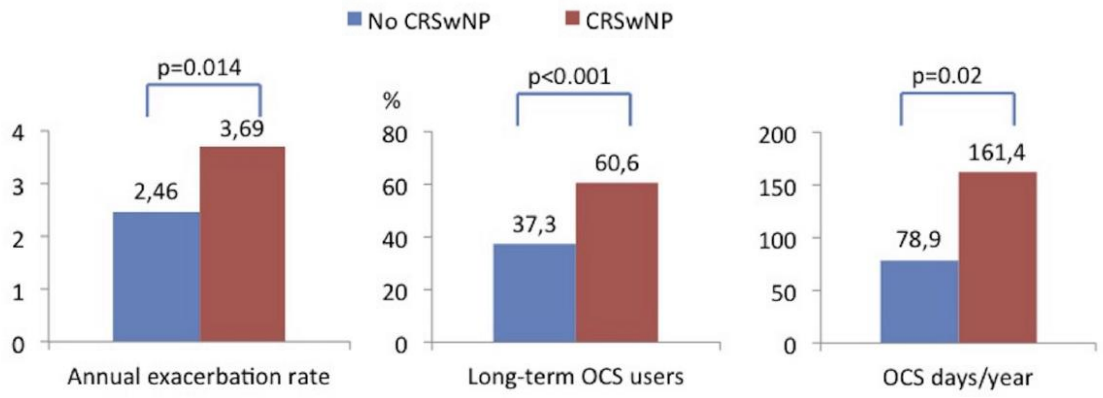
Impact of CRSwNP in Severe Asthma Patients: Evidence from the Severe Asthma Network Italy (SANI) Registry



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Canonica GW et al. *Respir Med*. 2020;166:105947.

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42 y.o. woman with asthma and CRS has had 3 asthma exacerbations in the past year needing oral steroids. She reports frequent URIs that settle into her chest?

1. should you suggest sinus surgery?
2. should you suggest a biologic?

Both are options to improve her asthma

- **potentially her asthma will improve more with biologics than in those without sinus disease**

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A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis

Rishi Vashishta, MD[1], Zachary M. Soler, MD, MSc[1], Shaun A. Nguyen, MD, MA[1] and Rodney J. Schlosser, MD[1,2]

Efficacy	% (95% CI)
Overall improvement	76.1 (71.9-80.3)
Decrease in asthma exacerbations	84.8 (76.6-93.0)
Decreased use of oral steroids	72.8 (67.5-78.1)

No change in lung function

Int Forum Allergy Rhinol 2013;3:788 31

Better asthma improvement with mepo in patients with CRSwNP

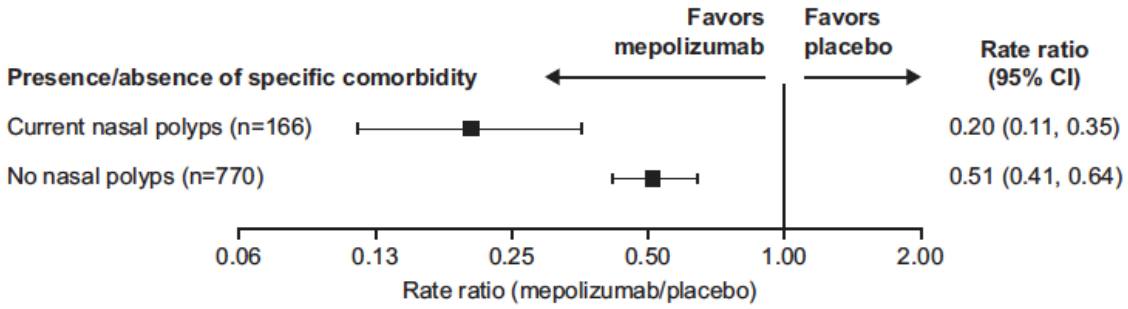
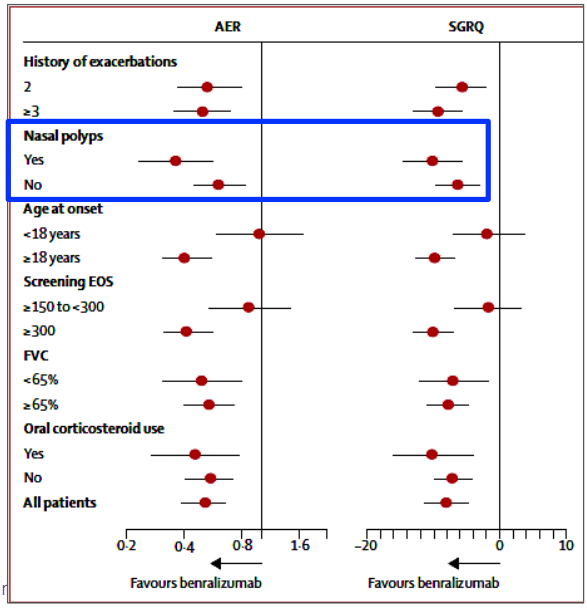


FIG 2. Rate ratio of on-treatment annual clinically significant exacerbations* by presence of NP in patients with SEA who took part in the MENSA and MUSCA studies. *Analyzed using a negative binomial regression model adjusted for treatment group, baseline maintenance oral corticosteroid therapy, region, number of exacerbations in the year before the study, and baseline % predicted prebronchodilator FEV_1. Annualized rates were calculated from the full treatment period of each study (32 weeks for MENSA, 24 weeks for MUSCA).

Howarth JACI 2020;145:1713

Severe Eosinophilic Asthma on Benralizumab: ANDHI study



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Harrison Lancet Respir Med 2021;9:260

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42 y.o. woman with asthma and CRS has had 3 asthma exacerbations in the past year needing oral steroids. She reports frequent URIs that settle into her chest. You recommend starting a biologic for asthma. She wants to know if a biologic would decrease the frequency of her CRS exacerbations?

Yes, in asthmatics, biologics can decrease CRS exacerbations

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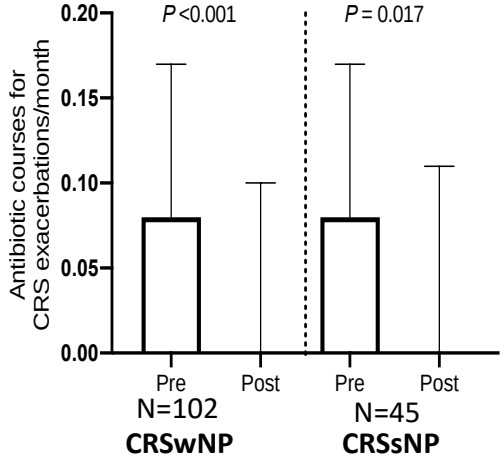
Type 2 biologics decrease the number of acute exacerbations of CRS in patients with asthma and CRS



- Biologics utilized:
  mepolizumab (n=42)
  benralizumab (n=45)
  dupilumab (n=58)
  reslizumab (n=7)

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Patel Allergy Proceedings 2021

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Is CRS a risk factor for developing asthma?

36

Received: 22 February 2023 | Revised: 12 April 2023 | Accepted: 26 April 2023
DOI: 10.1111/all.15771

Allergy WILEY

ORIGINAL ARTICLE

Sinus inflammation and chronic rhinosinusitis are associated with a diagnosis of new onset asthma in the following year

Brian S. Schwartz[1,2] | Jonathan S. Pollak[1] | Karen Bandeen-Roche[3] | Annemarie G. Hirsch[2] | Ashton E. Lehmann[4] | Robert C. Kern[5] | Bruce K. Tan[5] | Atsushi Kato[6] | Robert P. Schleimer[5,6] | Anju T. Peters[6]

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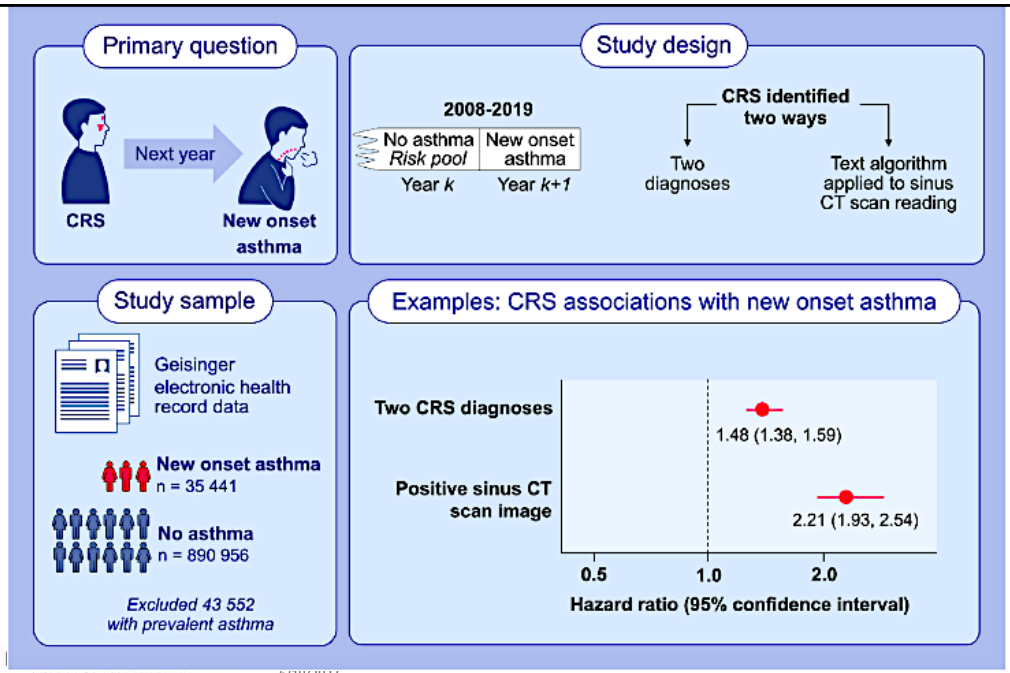

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Case

- 12/2023: Patient with asthma and CRS presents for the 3rd asthma exacerbation to an Urgent Care in the last 2 months. She has been treated with her CRS with abx/steroids and is on steroid rinses. Her FEV1 was normal a week prior in your clinic. She reports sudden onset shortness of breath and has had 3 courses of oral steroids in the past 3 months
- UC sends her back to you

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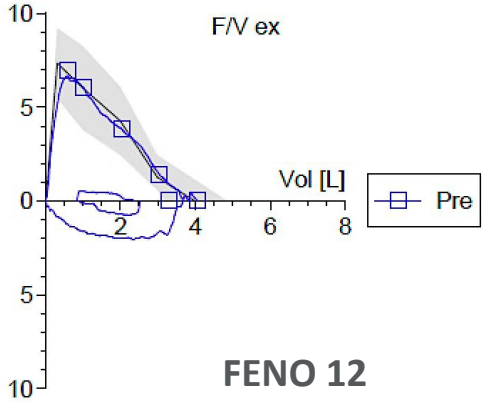
1/3/23

-sudden onset shortness of breath

- Oxygen sats OK
- Symptoms on inhalation
- Talks a lot for work
- Hoarse voice
- Increased pitch to voice
- Sudden onset and sudden relief

		Ref	Pre	Pre Z-Score	Pre%Ref	LLN	ULN
FVC	L	3.98	4.05	0.14	102	3.17	4.83
FEV1	L	3.23	3.31	0.21	103	2.57	3.87
FEV1/FVC	%	82	82	0.01	100	71	91
FEF25-75%	L/s	3.29	3.43	0.16	104	1.98	4.88
PEF	L/s	7.35	6.96	-0.35	95	5.50	9.20
FIVC	L	3.98	3.67	-0.62	92	3.17	4.83
FEF25%	L/s	6.01	6.05	0.03	101	3.79	8.23
FEF75%	L/s	1.27	1.49	0.40	118	0.60	2.43
FIF50%	L/s		1.98				
FEF50%	L/s	4.27	3.89	-0.35	91	2.46	6.08
FEV/FIV_0.5			2.36				
PIF	L/s	6.18	2.10	-0.39	34	3.78	8.58
FET100%	sec		4.13				



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All that wheezes is not asthma!!

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Question

- Pt has had multiple visits and she is not improving? What are you now thinking?

1. You, your nurse, and the patient should do mindful breathing
2. You are upset as you are not a concierge allergy healthcare worker
3. Why did the speaker put a light bulb in the previous slide?
4. Could this patient have vocal cord dysfunction?

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Answer #4: Vocal Cord Dysfunction

- Females > males (2, to 3x greater)
- Typically diagnosed in ages 30-40s
- Consider in patients with sudden dyspnea, poor response to optimal medical treatment
- Dx: history, physical, PFTs and laryngoscopy

Malaty AAFP 2021;104:471

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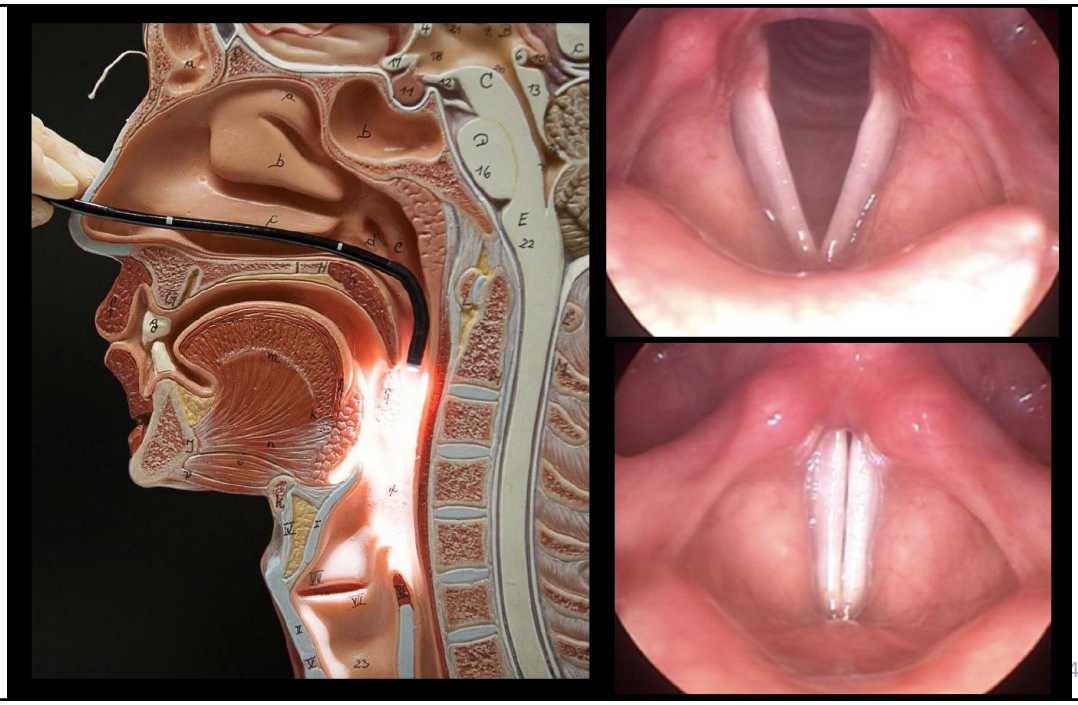

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Laryngeal pathologies that may mimic asthma

- Foreign body obstruction
- Airway malacia
- Infection
  - history
- Masses
- Vocal cord dysfunction
- Habit cough
- Idiopathic suglottic stenosis
- Tracheal stenosis

History

- Dysphagia
- Stridor
- Abnormal voice or cry
- Shortness of breath (not responding to therapy)
- Diagnostic workup
  - Bronchoscopy
  - CT scans

45

Prevalence and impact of comorbid laryngeal dysfunction in asthma: A systematic review and meta-analysis

21 studies with 1637 patients
Queried for VCD, laryngospasm, paradoxic vocal fold movement, and inducible laryngeal obstruction (ILO)

-25% had laryngeal dysfunction
-more common in severe asthma

Lee JACI 2020;145:1165

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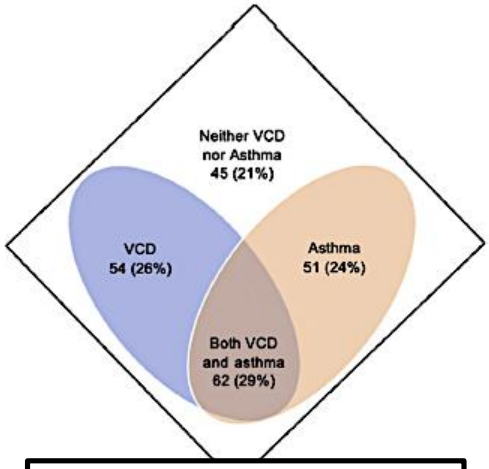
Diagnostic and Therapeutic Outcomes Following Systematic Assessment of Patients with Concurrent Suspected Vocal Cord Dysfunction and Asthm



66/90 (73%) improved with speech therapy

Stojanovic JACI in Practice 2022;10:602

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Treatment: Speech therapy

- Retrain vocal cords
- Focus on exhale when taking a rescue breath
- Sniff thru nose (short)
- Breather out through pursed lips (focus on exhale)
- Breath out for a count of 4 and breath in for a count of 2

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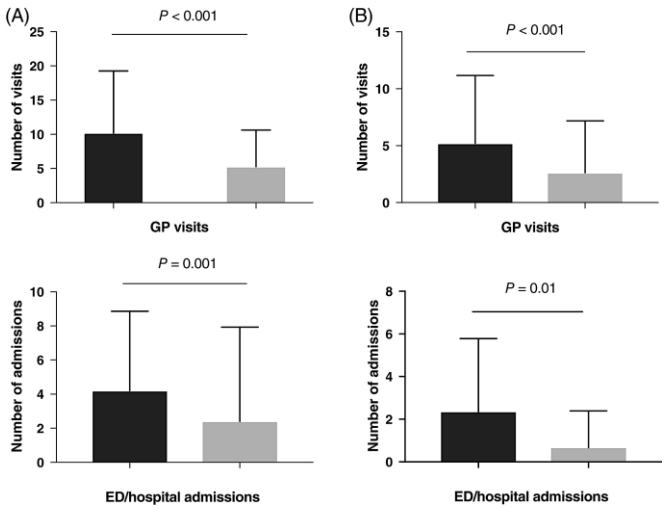
Multidisciplinary team clinic for vocal cord dysfunction directs therapy and significantly reduces healthcare utilization



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Respirology, 2019; 24 (8): 758-764

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Conclusion

- AR and CRS (CRSwNP > CRSsNP) are common in asthma
- CRS and asthma is associated with worse disease than CRS or asthma alone
- Nasal steroid use may improve asthma outcomes
- Sinus surgery is associated with asthma improvement and decrease in oral steroids, but lung function doesn't change much
- Biologics that target type 2 inflammation improve CRSwNP and also asthma
- Consider VCD in patients with difficult to control asthma
- Speech therapy may improve health care utilization.

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Acknowledgements

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Kevin Welch, MD

Chronic Rhinosinusitis Integrative Studies Program
P01 AI145818/AI/NIAID

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

The Psychosocial Impact of Food Allergies: What Every Allergist Should Know

Presented by:

Hemant Sharma, MD, MHS

Sunday, June 25, 2023

9:45 a.m. - 10:30 a.m.

The Psychosocial Impact of Food Allergies: What Every Allergist Should Know

Hemant Sharma, MD, MHS
Division of Allergy and Immunology
Children's National Hospital

Children's National

1

Disclosures

Research Support:

- NIAID
- DBV Technologies
- Aimmune Therapeutics

2

Objectives

1. Review **common psychosocial challenges** experienced by patients with food allergies and their caregivers.
2. Discuss how allergists-immunologists may **assess for psychosocial concerns**.
3. Consider indications for **referring to a mental health professional** and models for **co-management**.
   - Understand need for increased access to mental health services for patients with food allergy.

3

Food Allergy-Related Psychosocial Concerns

- Key psychosocial concerns among patients with food allergies and their caregivers/families:
  - **Stress** related to food allergy management
  - Reduced health-related **quality of life**
  - **Anxiety, fear, worry** re:
    - Unpredictable nature of allergic reactions
    - Diagnostic procedures
    - Treatments
    - After allergic reactions
  - **Bullying**

4

Psychosocial Impact of FA: A Growing Research Focus

Review article

Psychosocial functioning in pediatric food allergies: A scoping review

Check for updates

Grace K. Cushman, PhD,[a] Kristine Durkin, PhD,[a] Rebecca Noga, ScM,[b] Frances Cooke, BA,[c] Linda Herbert, PhD,[c,d] Cynthia Esteban, MSN, MPH,[e] and Elizabeth L. McQuaid, PhD[a] *Providence, RI, and Washington, DC*

- > 250 research articles since 2000 (50% after 2015)
- Psychosocial constructs:
  - Children: QOL, anxiety, bullying, depression,
  - Caregivers: anxiety, QOL, stress, confidence and/or self-efficacy, depression
- Geographic regions: Mostly North America & Europe
- Race and ethnicity:
  - Only 26% of studies reported race and ethnicity
  - In 55% of those studies, at least 85% of participants were White

Cushman GK et al. J Allergy Clin Immunol. 2023 Jan;151(1):29-36.

5

Food Allergy Psychosocial Concerns may be Different than Other Chronic Illnesses

- Food allergy management is mostly **preventative**, not active medical care
- Primary drivers of psychosocial concerns:
  - Daily anxiety
  - Fear about unpredictability of reactions
  - Threat of life-threatening consequence
- Potential impact:

↑ Caregiver Anxiety

↓ Caregiver Self-efficacy

⇨

Caregiver may limit:
- Child's role in self-management
- Developmentally typical activities (social, family, school)

⇨

↓ Child Quality of Life

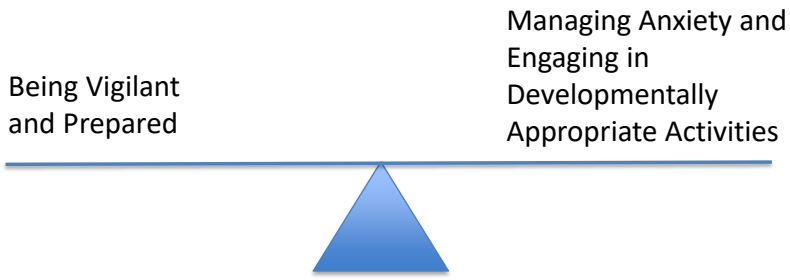
↑ Child Anxiety

↓ Child's Sense of Empowerment

6

Striking the Right Food Allergy Balance

Our goal: Help patients and families achieve **balance**



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Key Periods of Food Allergy Adjustment

- The first allergic reaction
- Diagnosis
- Initial food allergy management
- Stable disease management periods
- Cycles of uncertainty
  - Allergic reactions
  - New allergies/information
  - Oral food challenges
  - Food reintroduction
  - **Developmental changes**
  - Transitions
- Treatments (immunotherapy)

8

Psychosocial Concerns by Developmental Stage: Early Childhood

- Caregivers are necessarily responsible for food allergy management at this age
- Caregivers commonly experience **anxiety** about their ability to keep child safe

- Specific **caregiver concerns**:
  - Introduction of new foods
  - Monitoring for reactions in preverbal child who cannot describe symptoms
  - Concerns for exposures related to frequent mouthing behaviors at this stage

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13
LeBovidge JS, Herbert LJ, Ramos A, at al. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2552-2558.

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Psychosocial Concerns by Developmental Stage: Early Childhood

- Caregiver Stress and Social Limitations
  - Most food allergic reactions in this age occur when eating away from home
  - In study of parents of children diagnosed for <1 year:
    - Most avoided restaurants
    - Half restricted social activities with other children and/or travel
    - Some reduced work hours due to food allergy
- Highly involved parenting practices
  - Caregiver may attend social activities with child beyond the age other parents do
  - Children with food allergy may exhibit more separation anxiety

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13
LeBovidge JS, Herbert LJ, Ramos A, at al. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2552-2558.

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Psychosocial Concerns by Developmental Stage: School-Aged Children

- Children assume more responsibility at this age
- **Caregiver anxiety** related to transitions (school entry) that require reliance on third parties and greater child self-management
- **Perceptions of risk** and safety shift around **age 8-9 years**
  - Previously tolerated situations may now be sources of anxiety and stress. Why?
    - Child has greater cognitive awareness of risks
    - Misperceptions about level of risk with casual allergen contact
    - Child has more independence in food allergy management

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13

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Psychosocial Concerns by Developmental Stage: School-Aged Children

- **Child Anxiety**
  - Children who perceive greater illness severity have greater psychosocial concerns
  - Fear of death with allergen exposure outweighs objective risk
  - Perceived history of anaphylaxis and vivid memories related to more anxiety and greater impact on daily life
- Children have greater awareness of **differences from peers** due to food allergy
  - Management should emphasize both safety and social inclusion to foster confidence
- **Food allergy-related Bullying**

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13
LeBovidge JS, Herbert LJ, Ramos A, at al. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2552-2558.

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Food Allergy-Related Bullying

- Based on a 2013 study, 35-45% of children with FA have experienced food allergy-related bullying or teasing, mostly during school by classmates
  - 3/4 reported continued bullying one year later
- Children with FA twice as likely to be bullied compared to those without
- 49% of parents unaware of bullying experienced by their child
- Children who are bullied and their parents report decreased quality of life, even after accounting for illness severity

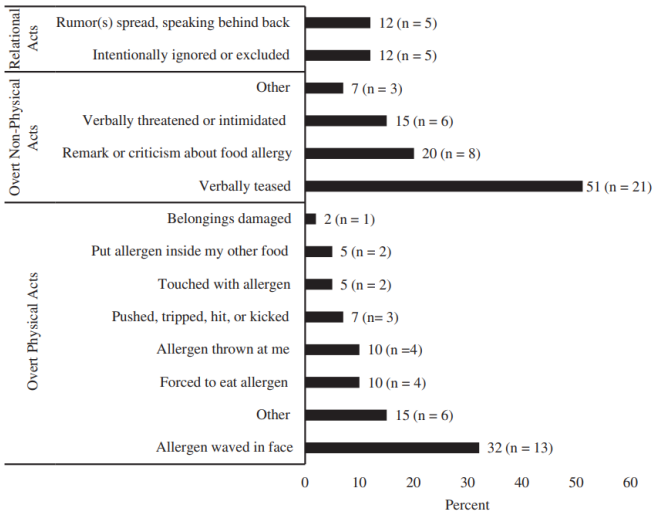
Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13
Bingemann T et al. J Allergy Clin Immunol Practice 2019

13

Food Allergy-Related Bullying Among Children and Adolescents

Frances Cooke, [1] BA, Ashley Ramos, [1,2] PhD, and Linda Herbert, [1,2] PhD

- A 2022 study found prevalence of bullying differed by assessment method:
  - Single-item (yes/no): 17%
  - 6-item: 31%
- Disagreement between parent and child report: 12% of parents reported child had been bullied due to FA
  - 14% of parents reported they were teased due to child's FA
- School setting
  - Classmates, as well as teachers and school staff



Cooke F, Ramos A, Herbert L. J Pediatr Psychol. 2022 Mar 5;47(3):318-326.

14

Food Allergy-Related Bullying Among Children and Adolescents

Frances Cooke,[1] BA, Ashley Ramos,[1,2] PhD, and Linda Herbert,[1,2] PhD

- Potential impact of FA bullying:
  - Poor psychosocial outcomes (sadness, anxiety, low self-esteem)
  - May be directly dangerous
  - Indirectly dangerous as child may be less likely to:
    - Disclose FA to others and therefore not get help when needed
    - Engage in important FA management behaviors
- What can Allergy clinicians do?
  - Ask both child and parent
  - Ask about FA bullying in multiple ways
  - Ask open-ended questions about peer experiences

Cooke F, Ramos A, Herbert L. J Pediatr Psychol. 2022 Mar 5;47(3):318-326.

15

Food Allergy-Related Bullying: Assessment by Allergists

TABLE I. Asking about teasing/bullying in pediatrics patients with food allergy during clinic visits

Question	All of the time, % (N)	Some of the time, % (N)	Rarely, % (N)	Never, % (N)
Do you ask patients about teasing/bullying during your clinic visits?	8.3% (8 of 96)	49.0% (47 of 96)	26.0% (25 of 96)	16.7% (16 of 96)
Do you ask parents/guardians whether their children experience teasing/bullying during your clinic visits?	7.4% (7 of 94)	45.7% (43 of 94)	29.8% (28 of 94)	17.0% (16 of 94)
Do you ask patients whether they experience teasing/bullying during your clinic visits?	7.3% (7 of 96)	40.6% (39 of 96)	30.2% (29 of 96)	21.9% (21 of 96)

Question	Very comfortable, % (N)	Somewhat comfortable, % (N)	Neutral, % (N)	Somewhat uncomfortable, % (N)	Very uncomfortable, % (N)
How comfortable do you feel asking parents/guardians and patients about teasing/bullying?	42.7% (41 of 96)	31.3% (30 of 96)	19.8% (19 of 96)	5.2% (5 of 96)	1.0% (1 of 96)
How comfortable do you feel in helping patients and families appropriately address teasing/bullying concerns?	21.9% (21 of 96)	42.7% (41 of 96)	14.6% (14 of 96)	19.8% (19 of 96)	1.0% (1 of 96)

Barriers: Lack of time, knowledge and resources

Bingemann T, Herbert LJ, Young MC et al. J Allergy Clin Immunol Pract. 2020 Jan;8(1):343-345.

16

Food Allergy-Related Bullying: How Allergists can Assess and Address It

TABLE E1. Suggestions to assess and address teasing/bullying

- Assess both the child and the parent about teasing/bullying using open-ended questions and statements
  - Tell me what it's like to manage food allergy at school.
  - How comfortable do you feel at school?
  - Tell me what it's like during lunch and special school activities that involve food.
  - Do you feel you are treated differently or poorly because of your food allergy?
  - Are there circumstances that make you uncomfortable at school?
  - What are your biggest challenges at school?
  - In what ways do your classmates help/hurt your food allergy management?
- Actions to recommend to parents
  - Check in with children routinely about school experiences.
  - Speak with school teachers/administrators for more information and to inform them what is happening.
  - Find out the school's teasing/bullying policy.
  - Encourage the child to establish a buddy system and identify trusted adults that the child can go to if needed.
  - Discourage the child from confronting the bully.
  - Teach the child coping strategies.
  - Promote social interactions outside of school so children can develop self-esteem in other areas.
  - List of resources (6)
    - www.stopbullying.gov
    - www.upstand.org
    - www.foodallergy.org/its-not-a-joke
    - https://healthychildren.org/English/safety-prevention/at-play/Pages/Bullying-
    - https://store.samhsa.gov/apps/knowbullying/index.html

Bingemann T, Herbert LJ, Young MC et al. J Allergy Clin Immunol Pract. 2020 Jan;8(1):343-345.

17

Psychosocial Concerns by Developmental Stage: Adolescence

- Food allergy management transitions from parent to child
  - Families must negotiate who is responsible for each management task based on child's readiness
  - Continued caregiver support needed (planning, problem-solving)
- **Poor Adherence & Risk-taking Behaviors**
  - Many adolescents cannot identify anaphylaxis or when to use epinephrine, purposefully ingest allergens, and do not always carry epinephrine autoinjectors (EAIs)
  - Why?
    - Concerns about fitting in, feeling embarrassed, or being teased
    - EAI device size/convenience
    - Perception of low risk based on behavior (ie not planning to eat)
    - Uncertainty about anaphylaxis symptoms and how/when to use EAI

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13
LeBovidge JS, Herbert LJ, Ramos A, at al. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2552-2558.

18

Psychosocial Concerns by Developmental Stage: Adolescence

- New situations pose safety issues (romantic relationships, exposure to drugs and alcohol)
- Greater Risk
  - Many anaphylactic reactions and most fatal reactions occur during adolescence and young adulthood
  - More than 2/3 of adolescents with FA experienced an allergic reaction in past 5 years
- **Peer Influence**
  - Epinephrine carriage varies by social activity, location and perceived peer norms
  - Teens want their peers to know about their FA, but are reluctant to be the ones to educate

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13
LeBovidge JS, Herbert LJ, Ramos A, at al. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2552-2558.

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Psychosocial Concerns by Developmental Stage: Early Adulthood

- Patient has primary responsibility for day-to-day food allergy management
- Patient should understand how to manage food allergies in shared living situations, college, workplace and romantic relationships
- Patient must understand how to manage own health care (scheduling medical appointments, filling prescriptions, understanding insurance, coverage and copayments)

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13
LeBovidge JS, Herbert LJ, Ramos A, at al. J Allergy Clin Immunol Pract. 2022 Oct;10(10):2552-2558.

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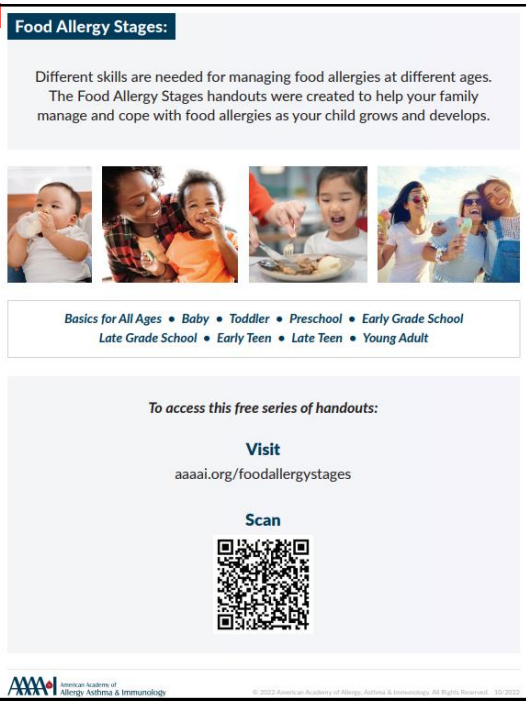

Food Allergy Stages:

Food Allergy Basics for All Ages

Food Allergy Stages:

- Released in 8/2022
- Free Patient Handouts from AAAAI developed by psychologists and allergists tailored to each developmental stage

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AAAAI Work Group Report

American Academy of Allergy Asthma & Immunology

The Development of Age-Based Food Allergy Educational Handouts for Caregivers and Patients: A Work Group Report of the AAAAI Adverse Reactions to Foods Committee

Jennifer S. LeBovidge, PhD[a,b], Linda J. Herbert, PhD[c,d], Ashley Ramos, PhD[c,d], Nancy Rotter, PhD[b,e], Scott H. Sicherer, MD[f,g], Michael C. Young, MD[a,h], Michael Pistiner, MD, MMSc[a,h], Wanda Phipatanakul, MD, MS[a,h], Lisa M. Bartnikas, MD[a,h,*], and Theresa A. Bingemann, MD[i,j,*] *Boston, Mass; Washington, DC; New York, NY; and Rochester, NY*

Among patients who reviewed the handouts:

- 79% rated the amount of information as "just right"
- 63% very likely and 35% somewhat likely to use the handouts
- >88% agreed handouts used plain language and clear communication

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Assessing and Addressing Psychosocial Concerns

TABLE I. Common psychosocial food allergy–related questions that parents may ask

Early childhood
How do I…
…teach my child about food allergy in a developmentally appropriate way?
…teach other caregivers about food allergy and encourage them to take it seriously?
…help my child safely participate in activities outside the home?
School-aged children
How do I…
…teach my child about food allergy without scaring him?
…help my child cope with food allergy–related anxiety?
…help my child navigate peer situations that include food?
…help my child who is being bullied for her food allergies?
…support my child's overall self-worth?
Adolescence
How do I…
…successfully transition food allergy management responsibility from me to my child?
…impress the seriousness of allergen avoidance/epinephrine carriage on my child?
…encourage my child to disclose his food allergy to peers?
…help my child navigate peer situations in which she may experience peer pressure?
…help my child cope with food allergy–related anxiety?
…prepare my child for college/living on her own?

- **Tips for Allergy Providers:**

- Many families will benefit simply from provider listening, and discussing that feelings are normal and they will adjust over time

- Referral to local support groups: Meeting other families and social support can facilitate healthy adjustment

- Educational materials: To supplement verbal communication

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13

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The Food Allergy Parent Mentoring Program: A Pilot Intervention

Ashley Ramos,[1,2] PhD, Frances Cooke,[1] BA, Emily Miller,[1] BS, and Linda Herbert,[1,2] PhD

- Parents of young children with newly diagnosed food allergy (FA) paired with an experienced parent of an older child for 6 months
- Mentors communicated with mentees at least 2 times per month (via in-person meetings, phone, text, email)

- Mentees reported high acceptability for the intervention
- Improvements observed in social support, FA-related stress, confidence in FA management, and positive changes in FA parenting behaviors

Ramos A, Cooke F, Miller E, Herbert L. J Pediatr Psychol. 2021 Aug 11;46(7):856-865.

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Questions Medical Providers Can Ask

- **Tips for Allergy Providers:**

- Open-ended questions
- Ask both parent and child
- Developmentally appropriate
- Specific to treatment plan (e.g. oral food challenges)

Food allergy management
Who is responsible for allergen avoidance when you are at home/not at home?
Who is responsible for epinephrine carriage when you are not at home?
Do you and other caregivers agree on how to manage your child's food allergies?
Do you have concerns about your family's ability to manage your child's food allergies?
Do you have any concerns about your child's food allergy management at day care/school?
Does your child feel safe during lunch/snacks?
Peer experiences
Does your child ever say that he is left out or teased because of food allergies?
Does your child ever not want to participate in social activities because of food allergies?
Emotional aspects of food allergies
Has your family ever not participated in social activities because of food allergies?
Do you or your child ever feel sad or down about food allergies?
Do you or your child ever feel worried or anxious about food allergies?
Does your child ever refuse to eat a food that you know is safe because of worry/anxiety?
Does your child ever refuse to eat in specific locations even if it is safe?
Oral food challenges
How do you feel about completing an oral food challenge?
Do you or your child feel hesitant to complete an oral food challenge due to worry/anxiety?

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13

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TABLE II. When to refer to a mental health professional

Family would benefit from additional psychoeducation about food allergy
Parent has difficulty asserting food allergy needs with other caregivers
Family needs assistance with food allergy–related management concerns at home, school…
Child recently experienced an allergic reaction and expresses worry about future reactions
Child has difficulty asserting food allergy needs outside of the home
Parent or child has difficulty coping with food allergy–related anxiety
Family would benefit from assistance preparing for an oral food challenge or clinical trial
Family needs assistance transitioning food allergy management to child/adolescent
Food allergy–related concerns are only one component of a broader mental health disorder
Parent or child has a diagnosable mental health disorder

Indications to Refer:

Food Allergy-Related Psychosocial Concerns Allergists Should Look For

Herbert L, Shemesh E, Bender B. J Allergy Clin Immunol Pract 2016;4:205-13

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Availability of Mental Health Services for Patients with Food Allergy

- 2019 survey of 28 FARE Clinical Network Centers of Excellence
  - Only 21% had a mental health professional in their Division
  - Many had a psychologist (86%) or psychiatrist (68%) in their institution to refer to
  - Fewer had a psychologist (54%) or psychiatrist (18%) in the community to refer to
  - 61% did not have mental health support for clinical trial participants, yet 81% wanted it.

TABLE I. Mental health concerns among food allergy patients observed by CE site coordinators

Mental health concern	n (%)
Parent anxiety about living with a food allergy	26 (92.90)
Child anxiety about living with a food allergy	27 (96.40)
Needle phobia or other medical procedure anxiety	23 (82.10)
Avoidance of safe foods or unnecessarily restricted diets	25 (89.30)
Food allergy–related bullying	20 (71.40)
Parent/child anxiety about oral food challenges	27 (96.40)
Panic attacks	19 (67.90)
Minimization of food allergy severity	17 (60.70)
Adherence concerns	20 (71.40)

TABLE II. CE Coordinators' perceptions of when patients would benefit from mental health services

Time point	n (%)
At time of diagnosis	25 (89.30)
After an allergic reaction	19 (67.90)
Before an oral food challenge	20 (71.40)
During an oral food challenge	10 (35.70)
Once a year	6 (21.40)
Before notable developmental transitions	22 (78.60)
Only if clinically indicated	4 (14.30)

Herbert L at al. J Allergy Clin Immunol Pract 2019 May 14. pii: S2213-2198(19)30453-2.

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Co-Management Models: Case 1 Parental Anxiety after Food Allergy Diagnosis

- 9-month-old girl recently diagnosed with food allergies to peanut, milk and egg after anaphylaxis
- At a follow-up visit, parents report to allergist that the diagnosis has caused increased stress, worry and anxiety:
  - Mother reports near constant fear of reactions
  - Parents repeatedly changing clothes and washing hands to avoid allergen exposure
  - Allergist recommended additional "safe" food introductions, but parents report feeling too anxious to try those foods
- Parental food allergy-related anxiety and stress → referral to mental health professional
  - Allergist provides psychologist with specific examples of anxiety-related behaviors and adverse effects

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Case 1: Parental Anxiety and Stress after New Diagnosis

- Parents begin seeing the psychologist who provides:
  - Psychoeducation
  - Cognitive behavioral therapy
  - Food exposure therapy and supervised food introduction
- Joint visits with allergist and psychologist
  - Allergist reviews test results and addresses parental concerns re: introduction of safe foods
- After 3-4 months, child has tolerated supervised introduction of foods and parents report decreased stress and additional food introduction at home

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Co-Management Models: Case 2 Increased Anxiety after a Recent Reaction

- 13-year-old boy with multiple food allergies (milk, egg, wheat, peanut, tree nuts, seeds) who recently experienced anaphylaxis after an accidental exposure to milk
- He has always been very vigilant in avoiding his allergens, but when asked how he has been doing since the reaction, his parents share that he has shown concerning signs of increased anxiety:
  - Checking ingredient lists repeatedly, even for safe foods
  - Seeing food and thinking that he is having a reaction to it
  - Refusing to participate in social activities due to fear of allergen exposure
- Food allergy-related anxiety → referral to mental health professional
  - Allergist provides psychologist with specific examples of anxiety-related behaviors and adverse effects

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Case 2: Increased Anxiety after a Recent Reaction

- He begins seeing the psychologist and components of cognitive behavioral therapy used include:
  - Self-monitoring
  - Coping skills training
  - Exposure therapy
- Joint visits with allergist and psychologist
  - Allergist reviews medical risks associated with various exposures to provide "evidence" to challenge anxious thoughts
- After three months, he and parents report decreased anxiety and increased confidence using food allergy management strategies

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Acknowledgments

Children's National Food Allergy Parent Task Force
David and Leighan Rinker Foundation
NIAID

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PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

74th PAAA Annual Meeting

JUNE 23-25, 2023

The Hotel Hershey, Hershey, PA

PAAA
Pennsylvania Allergy & Asthma Association

From Surviving to Thriving: Rediscovering Fulfillment in Allergy Immunology Practice

Presented by:

Hemant Sharma, MD, MHS

Sunday, June 25, 2023

10:30 a.m. – 11:15 a.m.

Children's National

From Surviving to Thriving: Rediscovering Fulfillment in Allergy Immunology Practice

Hemant Sharma, MD MHS
Division of Allergy and Immunology
Clinician Well-being Program
Children's National Hospital

1

Disclosures

Research Support:

- NIAID
- DBV Technologies
- Aimmune Therapeutics

2

Learning Objectives

- Explore the drivers of your professional well-being, and the prolonged impact of the COVID-19 pandemic on those drivers.
- Reflect on your current individual well-being and opportunities for professional and personal growth.
- Identify strategies you can adopt in your practice environment to allow you to thrive professionally.

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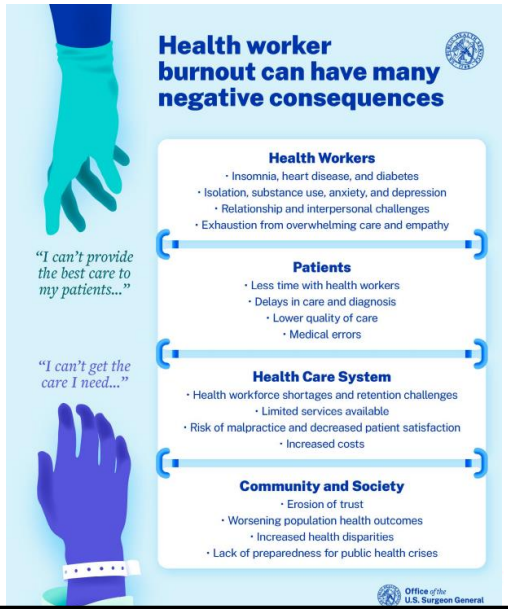
3

You are not alone

The COVID-19 pandemic has exacerbated already high rates of burnout:

- **Impact of Pandemic:**
  - **Burnout** among US physicians increased from **38% in 2020** to **63% in 2021**[1]
  - **Emotional exhaustion** in healthcare workers rose from **32% in 2019** to **40% in 2021** (41% to 49% among nurses)[2]
- **Consequences:**
  - **Annual cost** of burnout: $9 billion for nurses, $6.3 billion for physicians[3]
  - **1 in 15 US physicians has thoughts of suicide**[3]



[1] Shanafelt TD et al. *Mayo Clin Proc*. 2022.
[2] Sexton JD et al. JAMA Open Network. 2022.
[3] Addressing Health Worker Burnout: The U.S. Surgeon General's Advisory, 2022.

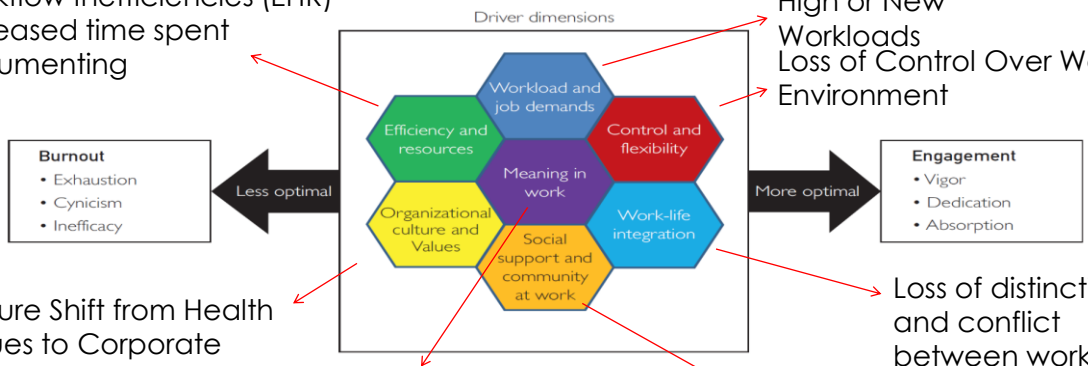
4

What drives Engagement vs. Burnout?

Workflow Inefficiencies (EHR)
Increased time spent documenting

High or New Workloads

Loss of Control Over Work Environment



Culture Shift from Health Values to Corporate Values

Loss of distinction and conflict between work and life

Loss of Meaning at Work

Social Isolation at Work

Shanafelt TD, Noseworthy JH. *Mayo Clin Proc*. 2017;92(1):129-146.

5

Well-being: 20% Individuals + 80% Systems

Leadership
Values Alignment
Voice/input
Meaning in work
Community/collegiality
Peer Support
Appreciation
Flexibility
Culture compassion

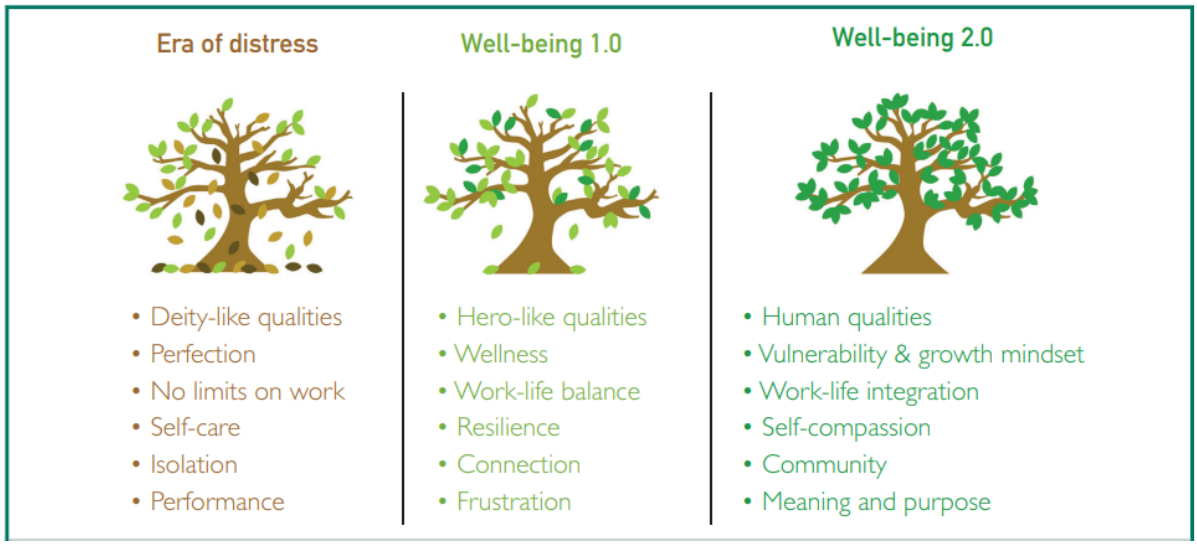
EHR usability
Triage
Scheduling
Patient portal
Documentation method
Team-based care
OR turnaround times
Staffing

Self-care (sleep, exercise, nutrition)
Self-compassion
Meaning in work
Work-life integration
Social support
Cognitive/emotional flexibility

Bohman et al, NEJM Catalyst 2016

6

Culture of Health Care Professions: Present and Future



Shanafelt T. Mayo Clin Proceedings. Oct 2021

7

What is Wellness-Centered Leadership?

- Integrative model of leadership proposed by Shanafelt et al 2021*
- Designed to cultivate *leadership behaviors* that promote engagement and professional fulfillment
- 3 elements
  - Care about people always
  - Cultivate individual and team relationships
  - Inspire change

*Shanafelt T et al. Acad Med 2021;96:641-651

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Complaints

Partner #1 : Complain about <u>all</u> the things that are bothering you now. (2 min)

Partner #2 : Listens attentively without responding.

Switch…

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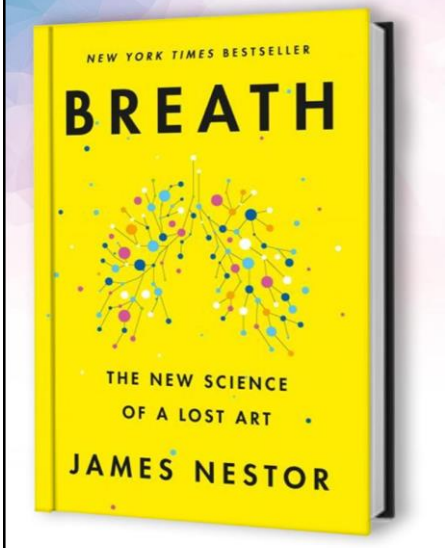
Element	Mindset	Behaviors	Outcomes
Care about people always	• Recognition of the role leaders play in the well-being, professional fulfillment, and vitality of team members and the team as a whole • Curious and respectful • Empathetic and understanding	• Recognize and appreciate individual contributions and talents • Give credit • Discover individual needs and gifts through dialogue • Demonstrate gratitude • Discuss and model self-care and self-valuation • Lead conversations about work–life integration • Adapt communication based on need (including people in distress) • Provide resources, support, and education on well-being • Recognize signs of distress • Role model concern for sleep, rest, vacations, and personal relationships through vulnerable and authentic self-disclosure • Listen for what is important to others and ask open-ended questions • Demonstrate humble inquiry • Practice "agenda-less" listening	• Team members feel valued and appreciated as individuals • Psychological safety for individuals • Improved health for individuals and the community • Team members believe self-care is valued and is demonstrated through support of reasonable working hours, scheduling, vacation, and time off • People proactively discuss their well-being needs without being prompted • Team members help cross cover each other and support one another's wellness

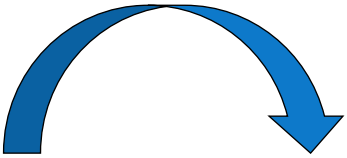
"Caring about people always begins with caring for self"

"Empathy for others promotes leadership effectiveness more than cognitive task proficiency"

11

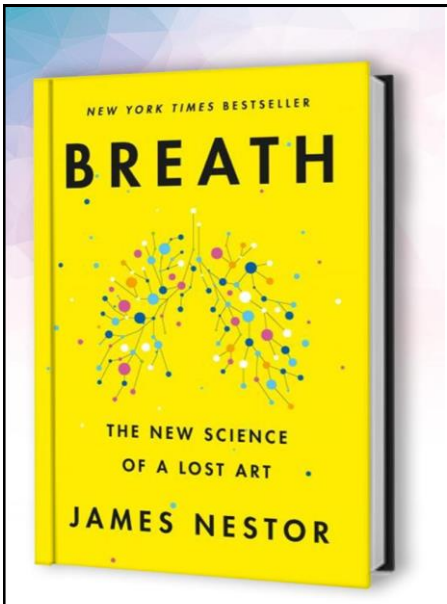


"There is nothing more essential to our health and wellbeing than breathing.. Yet, as a species, humans have lost the ability to breathe correctly, with grave consequences."



Emotions **Breathing**

12



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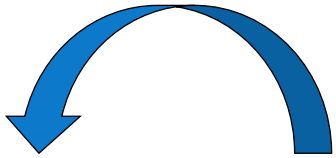

Emotions **Breathing**

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Breathwork Practice!!

Pranayam = Housing of the Life Force Energy

Yogic Breathing

14

SKY Breath Workshop: Virtual Implementation as part of Pandemic Response

In Spring and Summer 2020, as a rapid response to the pandemic, Children's National approached the Art of Living Foundation's *Healing Breaths* Program to offer virtual workshops to its healthcare professionals.

- Overwhelming Response: >300 CNH HCPs participated in a total of 9 workshops offered over 3 time periods
- Workshop Logistics:
  - 2.5-hour session/day over 3 consecutive days
  - 100% virtual conducted online via Zoom
  - Taught by trained instructors from Art of Living Foundation

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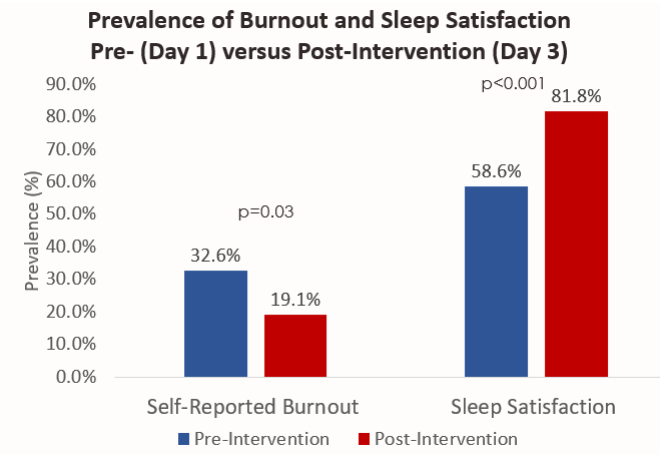
15

Virtual SKY Workshops: Key Outcomes

Study population: 99 HCPs from across the US who participated in virtual SKY Breath Meditation workshops as part of the Healing Breaths program in Spring-Summer 2020



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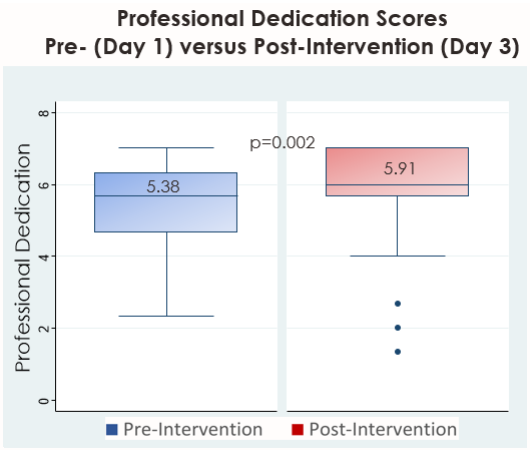
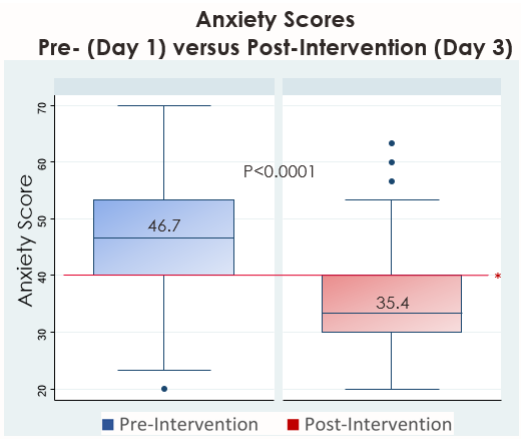
Virtual SKY Workshops: Key Outcomes



Professional Dedication = Being involved in one's work, finding meaning in one's work, being challenged, and experiencing sense of enthusiasm, inspiration and pride.



* A cut-off score of 40 is commonly used to define probably clinical levels of anxiety.

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Self-Appraisal

Partner #1 : List 10 positive qualities and 10 negative qualities about yourself. (2 min)

Partner #2 : Listens attentively without responding.

Switch…

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18

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Element	Mindset	Behaviors	Outcomes
Cultivate individual and team relationships	• Deep respect for the individual, recognizing people are both (1) good and capable now (rather than broken and in need of being fixed) and (2) immensely able to grow and improve • Each person has a unique career, personal and professional goals, and a path of development that may be different from their leader's or their peers' • Humble • Health care is emotionally demanding work, and health care professionals are dependent on the support of their colleagues • People work more effectively in respectful and supportive relationships with coworkers • Being part of a supportive team provides meaning and purpose • A leader plays an important role in the cultivation, success, and failures of a team • A leader plays an important role in keeping the community informed of organizational goals and needs	• Demonstrate respect for the choices others have made • Focus colleagues on what they are passionate about (the 20% principle[17,66]) • Help people manage their reputation through respectfully giving feedback and advice • Help others develop in the way they want (by asking): enrichment (in current role), moving into leadership, making lateral moves, or (when appropriate) transitioning to another profession • Help others derive meaning from their work (reconnecting them to purpose) • Listen for a sense of calling and aspects of work that bring the greatest meaning • Give options rather than directions • Guide others to coach rather than direct • Allow others to contribute to the leader's own development • Identify people's values (and other sources of intrinsic motivation) by asking open-ended questions • Help team members recognize their interdependence and the importance of providing support to colleagues • Develop a collective vision and shared sense of purpose using alignment methodology • Lead by consensus and empowerment • Tell stories to create shared meaning • Ensure everyone has a voice and is respected • Build alignment between people who disagree • Align values and norms • Advocate for the needs of the community • Connect individuals to each other on the basis of shared core values and interests • Keep community informed of organizational goals at appropriate intervals and shape communications to align with professional values • Promote formal and informal events that allow the community to connect, recognize shared experiences, and support one another	• Greater retention and engagement • Recruitment is more effective • Each team member's goals are understood, and the leader is invested in supporting them and supports professional development opportunities • Leader has formal and informal conversations with team members regularly to listen and provide support and guidance • Values are aligned between team members • There is a culture of teamwork • Psychological safety within the team • Sense of community at work • Higher levels of engagement from team members • People feel empowered to engage in collective problem solving without being prompted • Improved collaboration across the care continuum • Strong working relationships and collegiality throughout the community

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Praise

Partner #1 : Praise yourself. (2 min)

Partner #2 : Listens attentively without responding.

Switch…

Children's National

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Praise

Partner #1 : Praise your partner. (2 min)

Partner #2 : Listens attentively without responding.

Switch…

Children's National

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you are enough

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Inspire change
Cultivate relationships
Individuals
Teams
Care about people always
The foundation of Wellness-Centered Leadership

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Element	Mindset	Behaviors	Outcomes
Inspire change	• A critical job of leadership is to motivate teams to achieve meaningful results • Team members have the best insights on how to improve the work environment • The leader's role is to build consensus regarding priorities for improvement • Providing team members with the ability to shape and help lead change builds a sense of community, meaning, and purpose • Recognize the complexity and interdependence of health care • Diversity (in all respects) and healthy debate lead to better decisions and outcomes • Recognition that leaders are change agents, embracing and leading teams through change • Recognition of others' capacity for inspiring growth and performance • "Show me" (i.e., modeling the desired change) is more convincing than "tell me"	• Consistently model desired change • Guide team to identify priorities for change • Empower team to lead change in prioritized domains • Establish mutual respect • Influence others and build consensus • Delegate tasks that others are capable of performing and interested in doing • Follow up in a way that is empowering • Believe and respond to feedback from others • Evaluate performance from a growth mindset • Align goals with intrinsic motivation and extrinsic rewards • Build alignment on priorities • Communicate the value leaders place on personal relationships and work–life integration • Deliver quick wins that demonstrate commitment to values and vision and recognize/celebrate the wins of individuals, the community, and the organization • Seek advice and input	• Sense of co-ownership of the work unit among team members (we/us not they/them) • Belief that change is possible • Increased satisfaction with work–life integration • People know leaders see in them the capacity for growth and performance • Improved results (e.g., quality, safety, productivity) and patient confidence in physicians • Acceptance of (or ideally buy-in on) decisions • Inspiring performance that goes beyond expectations

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Team-Based Care

Table 2
Components of the Team-Based Model of Care

Strategy	Tactics
Previsit planning	• Team member obtains outside medical records and laboratory results • The patient completes the previsit questionnaire
Previsit laboratory testing	• Physician or designee orders next visit's laboratories at the end of the visit
Team huddle	• Preclinic huddle with all team members to plan clinic day's activities
Expanded rooming	• Nurse or MA enters certain elements of medical history into EHR and performs medication reconciliation • Nurse or MA hands off to the provider • Provider validates entered data
Team documentation	• Nurse, MA, or scribe documents visit while the provider obtains additional history and develops a treatment plan • Nurse or MA prepares an after-visit summary
Expanded discharge	• Nurse or MA provides patient education, reviews plan of care, and conducts follow-up care coordination
Documentation sign-off	• The provider reviews, modifies, and signs note in EHR

Abbreviations: EHR, electronic health record; MA, medical assistant.

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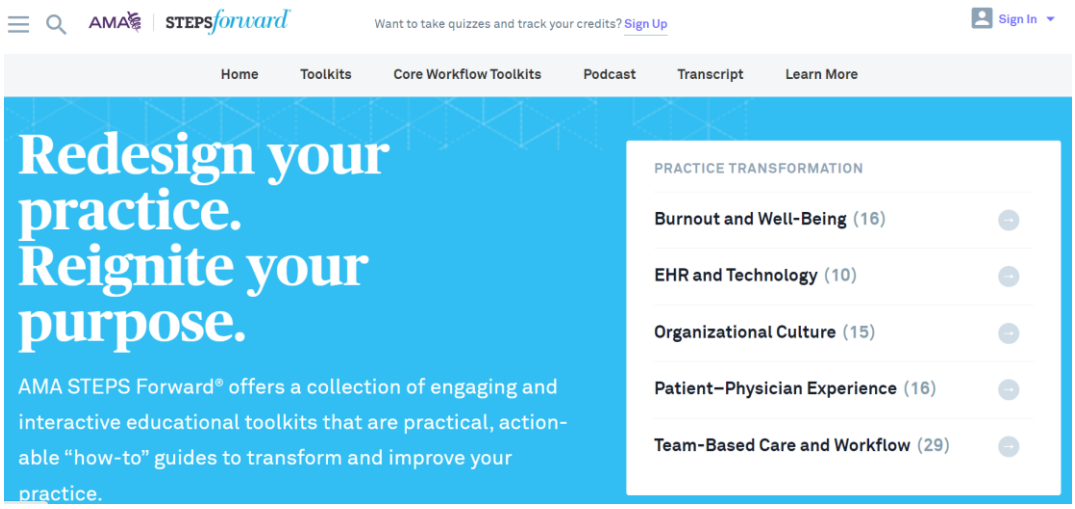
Other Resources:
AMA Steps Forward – Success Stories of What Works

AMA Steps Forward: Transform your Practice | AMA STEPS Forward | AMA Ed Hub (ama-assn.org)



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Well-being: 20% Individuals + 80% Systems

Leadership
Values Alignment
Voice/input
Meaning in work
Community/collegiality
Peer Support
Appreciation
Flexibility
Culture compassion

EHR usability
Triage
Scheduling
Patient portal
Documentation method
Team-based care
OR turnaround times
Staffing

Self-care (sleep, exercise, nutrition)
Self-compassion
Meaning in work
Work-life integration
Social support
Cognitive/emotional flexibility

Bohman et al, NEJM Catalyst 2016

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