PAAA

Pennsylvania Allergy & Asthma Association

2021 ANNUAL MEETING

VIRTUAL | JUNE 25-27, 2021

ATTENDEE GUIDE

PURPOSE AND TARGET AUDIENCE

To provide allergists, immunologists, pulmonologists, family practitioners, certified registered nurse practitioners and physician assistants with the most current and up-to-date treatments and scientific information regarding allergy, asthma and immunology.

PROGRAM OUTCOMES

At the conclusion of this learning activity, participants should be able to:

- Apply new knowledge in a variety of settings to help practices
  - choose from various treatment options for patients with food allergy.
  - choose appropriate biologics when treating patients with severe and difficult to treat asthma.
  - choose appropriate management plan for patient with EoE.
  - choose appropriate diagnostic tools and strategies to identify and manage disorders of innate immune system.
  - identify disorders of NK cells and immunodeficiencies which impact NK Cells.
  - educate their patient with variety of allergic conditions about prevention of allergic disorders.
  - use the best and proper approach when managing infants with food allergy or at risk of developing food allergy.
- Apply new knowledge for understanding the pathogenesis and management of atopic dermatitis
- Recognize immunologic drug reactions of diverse types and define the epidemiology of antibiotic allergy, including common drug culprits beyond penicillin (e.g., other beta-lactams, sulfonamide antibiotics, fluoroquinolones, macrolides, and vancomycin).
- Apply risk-stratification rules or algorithms to address inpatient drug allergies
- Apply techniques to determine how to distinguish primary from secondary disorders of mast cells based on clinical presentation, laboratory biomarkers, and pathogenesis.
- Determine which tests to consider ordering under varying clinical circumstances in order to provide optimal patient care in apteints with anaphylaxis.

ACCREDITATION

For Physicians:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education through the joint providership of the Pennsylvania Medical Society and the Pennsylvania Allergy and Asthma Association. The Pennsylvania Medical Society is accredited by the ACCME to provide continuing medical education for physicians.

The Pennsylvania Medical Society designates this live activity for a maximum of ***12.25 AMA PRA Category 1 Credits™***. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Faculty and all others who have the ability to control the content of continuing medical education activities sponsored by Pennsylvania Medical Society are expected to disclose to the audience whether they do or do not have any real or apparent conflict(s) of interest or other relationships related to the content of their presentation(s).

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In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards and the policy of the Pennsylvania Allergy and Asthma Association, the following presenters and developers of this course have indicated that they have a relationship which, in the context of their presentation, could be perceived by some as a real or apparent conflict of interest, (e.g., ownership of stock, or honoraria or consulting fees), but these presenters do not consider that it will influence their presentation.

Name	Company Name	Nature of Relationship
Hey Chong, MD*	Horizon Pharma	Ad Board
Evan Dellon, MD**	Abbott, Adare, Aimmune, Allakos, Amgen, Arena, AstraZeneca, Biorasi, Calypso, Celgene/Receptos, Eli Lilly, EsoCap, GSK, Gossaer Bio, Parexel, Regeneron, Robarts, Salix, Shire/Takeda	Consulting
Gisoo Ghaffari, MD*		Nothing to disclose
Sarah Henrickson, MD, Ph*D		Nothing to disclose
Kirsi Järvinen-Seppo, MD, PhD**	Merck, DBV, and Janssen	Research & Development
Allyson Larkin, MD*		Nothing to disclose
Ian Myles, MD, MPH**	R. Mucosa Treatment-Forte Bioscience	Patent
Jordan Orange, MD**	ADMA, Grifols, CSL, Takeda, Enzyvant	Scientific Advisory Board
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	ThermoFisher-Phadia (Tryptase Test)	Millipore, Santa ruz, BioLegend, Hycult Biotech (mAbs);
	Genentech (Tryptase Inhibitor)	Up-To-Date Card (royalties) Cecil's Textbook of Medicine Anaphylaxis chapter (royalties)
	NIH Study Section	Honoraria

CME DISCLOSURES (CONTINUED)

Name	Company Name	Nature of Relationship
Rebecca Saff, MD, PhD**		Nothing to disclose
Sally Wenzel, MD**	Astra Zeneca, GSK, Saofi-Genzyme, Knopp Pieris	Consultant Investigator Initiated Research
Hugh Windom, **	Aimmune, DBV	Investigator Multi-center Studies
Robert Zemble*		Nothing to disclose

*** Designates a Scientific Meeting program committee member/** Designates a Speaker**

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Evan Dellon, MD, MPH
Professor of Medicine, Adjunct Professor of Epidemiology
Director, Center for Esophageal Diseases and Swallowing
Division of Gastroenterology and Hepatology
University of North Carolina School of Medicine, Chapel Hill, NC

Kirsi Järvinen-Seppo, MD, PhD
Associate Professor
Chief and Founders' Distinguished Chair of Pediatric Allergy and Immunology
University of Rochester School of Medicine and Dentistry, Rochester, NY

Ian Myles, MD, MPH
Chief, Epithelial Therapeutics Unit
Medical Research Officer, US Public Health Service Commissioned Corps
National Institutes of Health, Bethesda, MD

Jordan Orange, MD, PhD
Physician-in-Chief, Morgan Stanely Children's Hospital
Ruben S. Carpentier Professor and Chairman of the Department of Pediatrics,
Columbia University, New York, NY

Rebecca Saff, MD
Allergy/Immunology Fellowship Program Director, Massachusetts General Hospital
Instructor, Harvard Medical School, Cambridge, MA

Lawrence Schwartz, MD, PhD
Charles & Evelyn Thomas Professor of Medicine Chair, Division of
Rheumatology Allergy & Immunology
Virginia Commonwealth University, Richmond, VA

Sally Wenzel, MD
Professor of Medicine and Immunology, Rachel Carson Chair in Environmental Health
Chair, Department of Occupational & Environmental Health Acting Director, University of
Pittsburgh Asthma Environmental Lung Health Institute at UPMC
University of Pittsburgh, Pittsburgh, PA

Hugh Windom, MD
Clinical Professor of Medicine, University of South Florida
Windom Allergy Asthma & Sinus, Sarasota, FL

PENNSYLVANIA ALLERGY EDUCATIONAL RESEARCH FOUNDATION (PAERF)

The Pennsylvania Allergy Educational Research Foundation (PAERF) is the charitable arm of the Pennsylvania Allergy and Asthma Association that funds educational and research endeavors related to the field of allergy and immunology. PAERF funds allow the future leaders of our profession the opportunity to share their work through poster presentations and to participate in the meeting.

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POSTERS SUBMITTED FOR DISPLAY

Iwona Dziewa, DO *Penn State College of Medicine*
Response to H1-Antihistamines in Chronic Spontaneous Urticaria Patients with Allergic Rhinitis

Paul Faybusovich, D.O. *Penn State College of Medicine*
Association of Chronic Diseases with Penicillin Allergy Status– A Retrospective Study

Stanislaw Gabryszewski, MD, PhD *Children's Hospital of Philadelphia*
Self-limited COVID-19 in a Patient with Artemis Hypomorphic SCID

Catherine Popadiuk, DO *Penn State Milton S. Hershey Medical Center*
Cost Assessment of Allergy Procedures to Improve High Value Care Implementation

Amandeep Sandhu, MD, MS *Children's Hospital of Philadelphia*
Cyclophosphamide Desensitization in an Infant with Embryonal Rhabdomyosarcoma

Di Sun, MD, MPH *Children's Hospital of Philadelphia*
Current Practice of Immunophenotyping Pre- and Post- Rituximab Administration

Sebastian Sylvestre, MD *Penn State Milton S. Hershey Medical Center*
Identification is Key : Barriers to Regular Usage of Allergy Identifiers

Paulina Tran, DO *Children's Hospital of Philadelphia*
A CGD Patient Initially Presenting with Basilar Meningitis

VIEW POSTERS HERE

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The Pennsylvania Allergy and Asthma Association gratefully acknowledges the following companies for their support of the 2021 Annual Meeting:

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Regeneron - Saturday

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SCAVENGER HUNT

Visit the virtual booths and complete the scavenger hunt to be eligible for one of our prizes!

Prizes: **• (1) Comp Night @ Hotel Hershey for 2022 Annual Meeting**
• Complimentary 2022 Meeting Registration*

Scavenger hunt will be open until 11:59pm on Sunday, June 27th.
Winners will be announced on Monday via email to all attendees.

**Complimentary meeting registration only; guest fees still apply*

SAVE THE DATE:

PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION

73RD PAAA ANNUAL MEETING

JUNE 24-26, 2022 | THE HOTEL HERSHEY, HERSHEY, PA

June 24-26, 2022
The Hotel Hershey
Hershey, PA

Reservations for 2022 can be made by phone no more than one year in advance. The PAAA room block rate will be $385.00+tax/night.

To reserve your room, please call the hotel directly at 717-533-2171 or 1-800-HERSHEY (1-800-437-7439) and ask for the Pennsylvania Allergy and Asthma Association room block.

Pennsylvania Allergy & Asthma Association

PRESENTATIONS FOR FRIDAY, JUNE 25, 2021

Prevention of Allergic Disease
Kirsi Järvinen-Seppo, MD, PhD

Outpatient Approach to Antibiotic Allergy
Rebecca Saff, MD, PhD

Microbiome's Impact on Immune
Ian Myles, MD, MPH

Drug Allergy Pearls in the In-Patient Setting
Rebecca Saff, MD, PhD

Advances in Atopic Dermatology
Ian Myles, MD, MPH

Diagnosis and Management of Food Allergy in a Breast-Fed Infant
Kirsi Järvinen-Seppo, MD, PhD

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Pennsylvania Allergy & Asthma Association

Prevention of Allergic Diseases

Kirsi Järvinen-Seppo, MD, PhD

Friday, June 25, 2021
8:00 a.m. - 8:45 a.m.

PAAA does not have permission to share slides

PAAA

Pennsylvania Allergy & Asthma Association

Outpatient Approach to Antibiotic Allergy

Rebecca Saff, MD, PhD

Friday, June 25, 2021
8:45 a.m. - 9:30 a.m.

Outpatient Approach to Antibiotic Allergy

Rebecca Saff, MD, PhD
Division of Rheumatology, Allergy & Immunology
Massachusetts General Hospital
Boston, MA

Disclosures

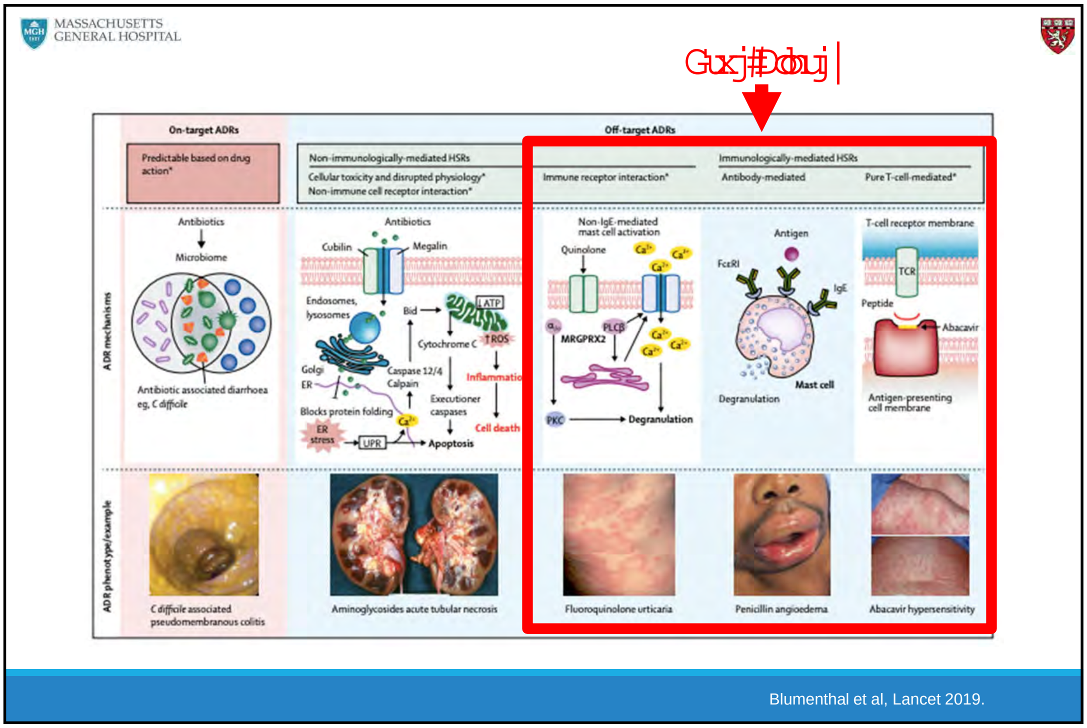
None

Objectives

- Discuss how to the evaluate and manage patients with antibiotic allergies
- Discuss diagnostic strategies including skin testing and drug challenge and understand when each is appropriate
- Review specific drug allergy scenarios

Determining type of reaction

	Type I	**Type II**	**Type III**	**Type IV**
Location of Antigen	Soluble	Bound to Cell or Matrix	Soluble	Soluble or Cell Bound
Immune Mediator	IgE	IgG	IgG	T Cells
Mechanism	Antigen binds and crosslinks IgE on mast cells and basophils, leading to their degranulation.	Antigen specific IgG binds to antigen that is already bound to cell surface or matrix components. Bound IgG leads to activation of phagocytes or killer cells leading to destruction of whatever the antigen originally associated with.	Antigen specific IgG binds to soluble antigen forming "immune complexes" of antibody–antigen. These activate the complement system or phagocytic cells leading to either diffuse disease or disease at sites of deposition.	Antigen specific T cell receptors bind to presented antigens. This activates the T cells, which then activate effector cells such as macrophages, eosinophils or cytotoxic T cells.
Clinical result	Anaphylaxis Angioedema Urticaria	Hemolytic Anemia Thrombocytopenia Organ specific reactions	Serum Sickness Drug Fever Arthus Reaction SJS/TEN	Contact dermatitis Chronic rhinitis, asthma SJS/TEN
Timeframe	Immediate (minutes to hours)	Days to weeks	Days to weeks	Days to weeks
Examples	Anaphylaxis due to β lactams.	Hemolytic anemias after penicillin and sulfonamide exposure.	Minocycline induced serum sickness.	Maculopapular rashes in response to many antibiotics.
Clinical Testing	Tryptase (within 2 hours of reaction) Skin testing	Reaction specific Coomb's testing (hemolytic anemia)	Complement levels	Test Dose Patch testing


MASSACHUSETTS GENERAL HOSPITAL

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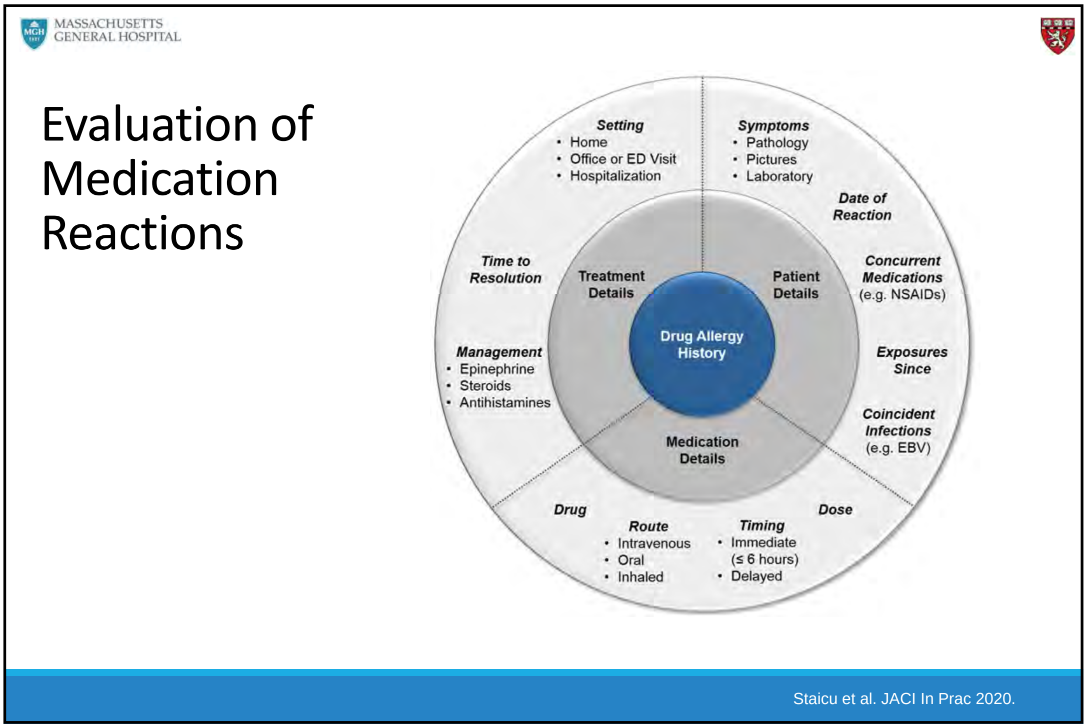
Blumenthal et al, Lancet 2019.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Evaluation of Medication Reactions

Drug Allergy History

Treatment Details

Patient Details

Medication Details

Setting
- Home
- Office or ED Visit
- Hospitalization

Symptoms
- Pathology
- Pictures
- Laboratory

Date of Reaction

Concurrent Medications (e.g. NSAIDs)

Exposures Since

Coincident Infections (e.g. EBV)

Dose

Timing
- Immediate (≤ 6 hours)
- Delayed

Route
- Intravenous
- Oral
- Inhaled

Drug

Management
- Epinephrine
- Steroids
- Antihistamines

Time to Resolution

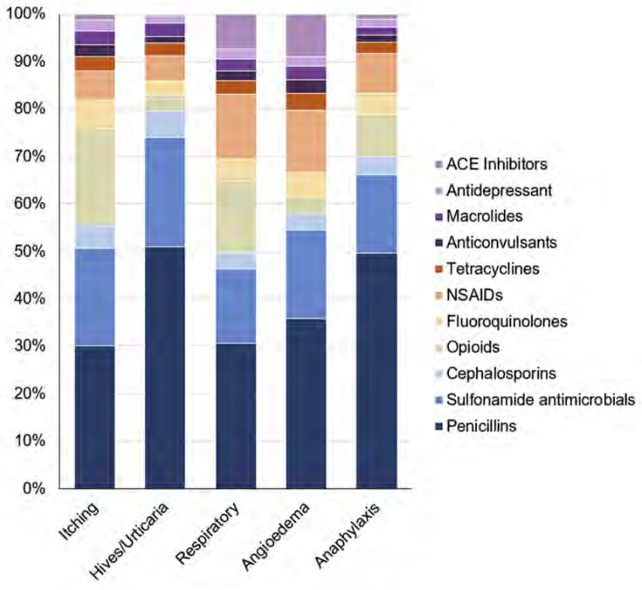
Staicu et al. JACI In Prac 2020.

Immediate Hypersensitivity Reactions

IgE Mediated

- Timing: Occurs in minutes to hours (<6 hours)
  - \- Recurs/worsens with repeat exposure
- Associated with symptoms such as itch, hives, swelling, throat tightness, difficulty breathing, hypotension
  - \- Can lead to anaphylaxis
- Diagnostic testing: Skin testing, Drug challenges

Immediate Hypersensitivity Reactions



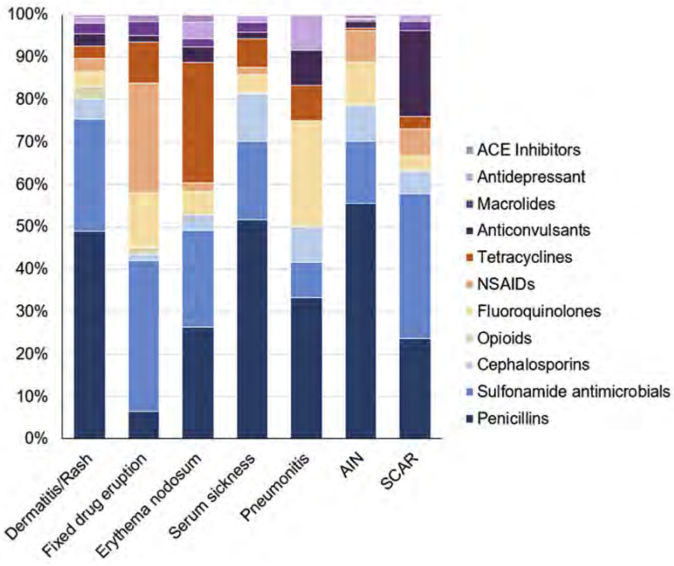
Wong et al. JACI In Prac 2019.

Delayed Hypersensitivity Reactions

T cell Mediated

- Timing: Occurs in days
- Often associated with maculopapular rash
  - Usually benign/self-limited but can evolve into SCAR
  - May have associated fever, eosinophilia, LFT abnormalities
- May not recur on subsequent exposures
- Diagnostic testing: Not well-validated
  - Delayed intradermal skin testing
  - Patch Testing

Delayed Hypersensitivity Reactions



Wong et al. JACI In Prac 2019.

Severe Cutaneous Adverse Reactions (SCAR)

- Drug Rash Eosinophilia and Systemic Symptoms (DRESS)
- Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis (SJS/TEN)
- Acute generalized exanthematous pustulosis (AGEP)
- Erythema Multiforme

Associated with systemic symptoms

Some evidence patch testing can be helpful

Rechallenge can be life-threatening

Barbaud et al, Br J Dermatol 2013; Peter et al, J Allergy Clin Immunol Pract 2017.

Role of Skin Testing in Drug Allergy

Skin testing is the most rapid, sensitive, and cost-effective testing modality for the detection of IgE-mediated disease

Results within 15-20 minutes

Patients can see the reaction and this helps them understand that they are or are not allergic to a given substance

Validated and standardized only for the evaluation of penicillin allergy

Shenoy et al. JAMA 2019.

Skin Testing

Percutaneous

Intradermal

Shenoy et al. JAMA 2019.

Non-Irritating Concentrations for ST

Use highest concentration of each drug that does not elicit irritant skin test

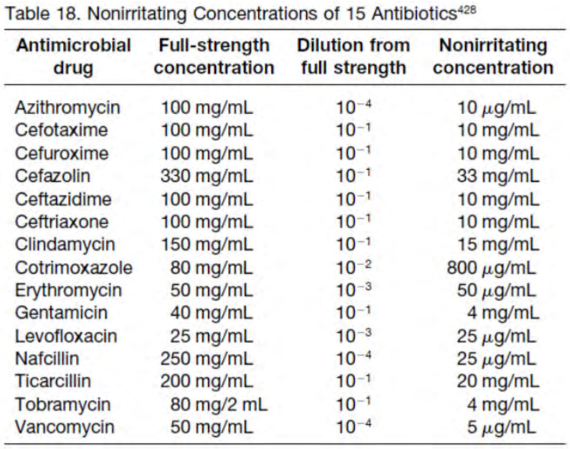


Table 18. Nonirritating Concentrations of 15 Antibiotics[428]

Antimicrobial drug	Full-strength concentration	Dilution from full strength	Nonirritating concentration
Azithromycin	100 mg/mL	10^{-4}	10 μg/mL
Cefotaxime	100 mg/mL	10^{-1}	10 mg/mL
Cefuroxime	100 mg/mL	10^{-1}	10 mg/mL
Cefazolin	330 mg/mL	10^{-1}	33 mg/mL
Ceftazidime	100 mg/mL	10^{-1}	10 mg/mL
Ceftriaxone	100 mg/mL	10^{-1}	10 mg/mL
Clindamycin	150 mg/mL	10^{-1}	15 mg/mL
Cotrimoxazole	80 mg/mL	10^{-2}	800 μg/mL
Erythromycin	50 mg/mL	10^{-3}	50 μg/mL
Gentamicin	40 mg/mL	10^{-1}	4 mg/mL
Levofloxacin	25 mg/mL	10^{-3}	25 μg/mL
Nafcillin	250 mg/mL	10^{-4}	25 μg/mL
Ticarcillin	200 mg/mL	10^{-1}	20 mg/mL
Tobramycin	80 mg/2 mL	10^{-1}	4 mg/mL
Vancomycin	50 mg/mL	10^{-4}	5 μg/mL

Positive irritant skin test was considered to be an increase in wheal diameter over baseline of 2 x 2 mm

Empedrad et al, JACI 2003.
Drug Allergy Practice Parameters 2010.

Drug Challenge/Test Dose

Confirm no allergy in patient with negative skin testing

Exclude drug hypersensitivity in patient with non-suggestive or distant history

Exclude cross-reactivity in related but structurally unrelated drugs (Cephalosporins in PCN allergy)

Provide reassurance in patients with high level of anxiety

Drug Challenge: How many steps?

Comparison of 1 or 2 step vs multistep challenge

- Similar rate of reactions
- No concern for induction of tolerance

2 step challenge with 30-60 minutes steps

- 10% dose then 90% dose
- 25% dose then 75% dose

Iammatteo et al. J Allergy Clin Immunol Pract 2014.

Value of Placebo Challenge

229 patients with at least 1 single-blind placebo-controlled graded challenge

- 170 beta-lactams (70.8%)
- 42 nonsteroidal anti-inflammatory drugs (17.5%)
- Reaction rate to drug and placebo similar
  - During beta-lactam challenges (9.4% vs 8.2%)
  - During NSAID challenges (14% vs 7%)
- Only 10 patients (4.4%) had objective findings during drug challenges

Iammatteo et al. J Allergy Clin Immunol Pract 2017.

Value of Placebo Challenge

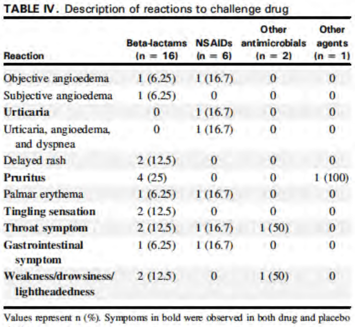


TABLE IV. Description of reactions to challenge drug

Reaction	Beta-lactams (n = 16)	NSAIDs (n = 6)	Other antimicrobials (n = 2)	Other agents (n = 1)
Objective angioedema	1 (6.25)	1 (16.7)	0	0
Subjective angioedema	1 (6.25)	0	0	0
Urticaria	0	1 (16.7)	0	0
Urticaria, angioedema, and dyspnea	0	1 (16.7)	0	0
Delayed rash	2 (12.5)	0	0	0
Pruritus	4 (25)	0	0	1 (100)
Palmar erythema	1 (6.25)	1 (16.7)	0	0
Tingling sensation	2 (12.5)	0	0	0
Throat symptom	2 (12.5)	1 (16.7)	1 (50)	0
Gastrointestinal symptom	1 (6.25)	1 (16.7)	0	0
Weakness/drowsiness/ lightheadedness	2 (12.5)	0	1 (50)	0

Values represent n (%). Symptoms in bold were observed in both drug and placebo challenges.

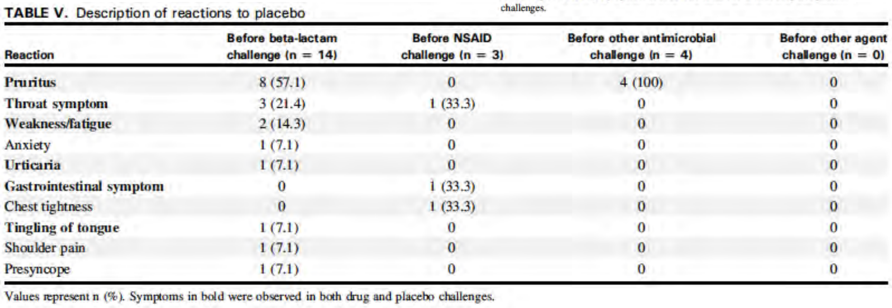


TABLE V. Description of reactions to placebo

Reaction	Before beta-lactam challenge (n = 14)	Before NSAID challenge (n = 3)	Before other antimicrobial challenge (n = 4)	Before other agent challenge (n = 0)
Pruritus	8 (57.1)	0	4 (100)	0
Throat symptom	3 (21.4)	1 (33.3)	0	0
Weakness/fatigue	2 (14.3)	0	0	0
Anxiety	1 (7.1)	0	0	0
Urticaria	1 (7.1)	0	0	0
Gastrointestinal symptom	0	1 (33.3)	0	0
Chest tightness	0	1 (33.3)	0	0
Tingling of tongue	1 (7.1)	0	0	0
Shoulder pain	1 (7.1)	0	0	0
Presyncope	1 (7.1)	0	0	0

Values represent n (%). Symptoms in bold were observed in both drug and placebo challenges.

Iammatteo et al. J Allergy Clin Immunol Pract 2017.

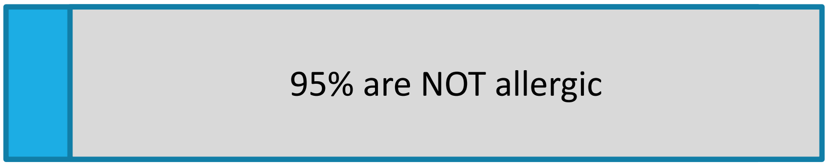
Case 1: Penicillin Allergy

58 year old man is schedule for valve replacement for aortic stenosis in 2 weeks. He has a history of penicillin allergy in childhood.

He does not know the details of his reaction but he remembers going to the ER and being told not to take it again.

Should he be tested for penicillin allergy?

10% of patients report a penicillin allergy



Sacco et al, Allergy 2017.

Risk associated with use of alternative pre-op antibiotics

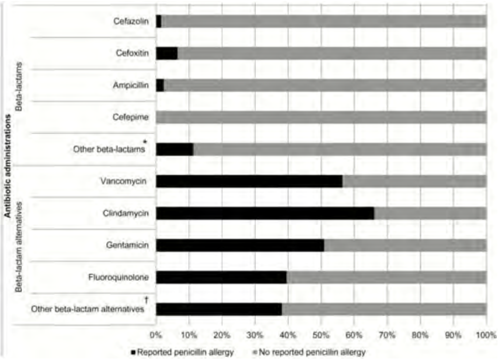
Retrospective study of patients undergoing surgery

11% reported a penicillin allergy, 2.7% had an SSI

- Patients with penicillin allergy had increased odds of SSI (1.5)
- Patients with penicillin allergy given less cefazolin (12% vs 92%)) and more clindamycin, vancomycin, and gentamicin
- Increased SSI risk was entirely mediated by the patient receiving alternative perioperative antibiotic

Blumenthal et al, BMJ 2018.

Risk associated with use of alternative pre-op antibiotics



Patients with a reported penicillin allergy had 50% increased odds of SSI

Between 112-124 patients with reported penicillin allergy would need allergy evaluation to prevent 1 SSI

Blumenthal et al, BMJ 2018.

If he were to develop an infection, are there risk associated with use of alternative antibiotics?

Risk associated with use of alternative antibiotics

64 141 adults with penicillin allergy and 237 258 matched controls evaluated for development of MRSA or *C difficile*

Penicillin allergy label was associated with:

- 69% increased risk of MRSA
- 26% increased risk of *C difficile*

Documented penicillin allergy was associated with an increased risk of MRSA and *C difficile*

Blumenthal et al, BMJ 2018.

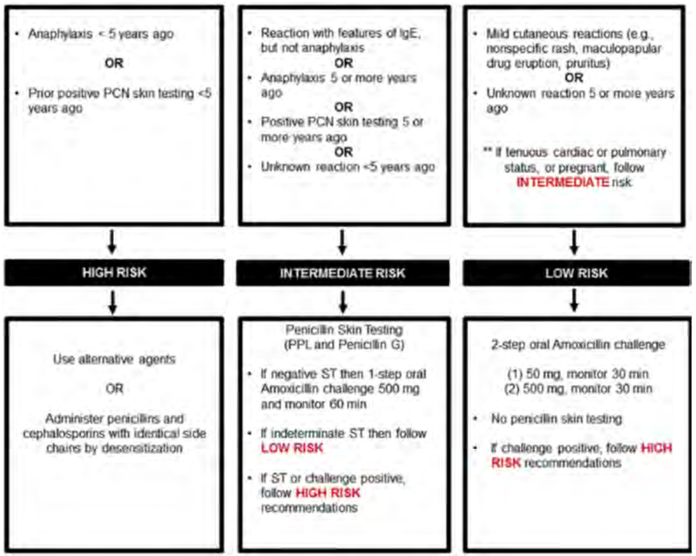
Risk associated with penicillin allergy

Increased

- Surgical Site Infection
- MRSA
- C. Diff
- Treatment Failures
- Adverse Events
- Mortality

Blumenthal et al, BMJ 2018.

Penicillin Pathway



- Anaphylaxis < 5 years ago

  OR

- Prior positive PCN skin testing <5 years ago

HIGH RISK

Use alternative agents

OR

Administer penicillins and cephalosporins with identical side chains by desensitization

- Reaction with features of IgE, but not anaphylaxis

  OR

- Anaphylaxis 5 or more years ago

  OR

- Positive PCN skin testing 5 or more years ago

  OR

- Unknown reaction <5 years ago

INTERMEDIATE RISK

Penicillin Skin Testing
(PPL and Penicillin G)

- If negative ST then 1-step oral Amoxicillin challenge 500 mg and monitor 60 min
- If indeterminate ST then follow **LOW RISK**
- If ST or challenge positive, follow **HIGH RISK** recommendations

- Mild cutaneous reactions (e.g., nonspecific rash, maculopapular drug eruption, pruritus)

  OR

- Unknown reaction 5 or more years ago

** If tenuous cardiac or pulmonary status, or pregnant, follow **INTERMEDIATE** risk

LOW RISK

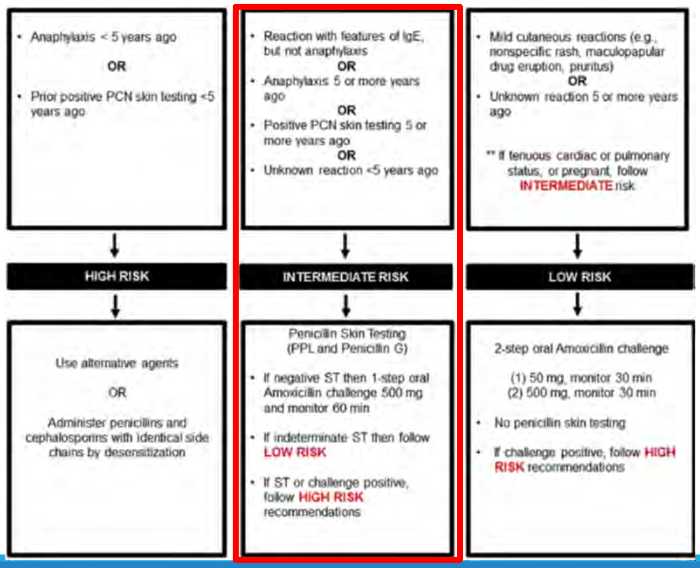
2-step oral Amoxicillin challenge

(1) 50 mg, monitor 30 min
(2) 500 mg, monitor 30 min

- No penicillin skin testing
- If challenge positive, follow **HIGH RISK** recommendations

Blumenthal et al, J Allergy Clin Immunol Pract 2019.

Penicillin Pathway



- Anaphylaxis < 5 years ago

OR

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HIGH RISK

Use alternative agents

OR

Administer penicillins and cephalosporins with identical side chains by desensitization

- Reaction with features of IgE, but not anaphylaxis

OR

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OR

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(PPL and Penicillin G)

- If negative ST then 1-step oral Amoxicillin challenge 500 mg and monitor 60 min
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- Mild cutaneous reactions (e.g., nonspecific rash, maculopapular drug eruption, pruritus)

OR

- Unknown reaction 5 or more years ago

** If tenuous cardiac or pulmonary status, or pregnant, follow **INTERMEDIATE** risk

LOW RISK

2-step oral Amoxicillin challenge

(1) 50 mg, monitor 30 min
(2) 500 mg, monitor 30 min

- No penicillin skin testing
- If challenge positive, follow **HIGH RISK** recommendations

Blumenthal et al, J Allergy Clin Immunol Pract 2019.

Penicillin Pathway

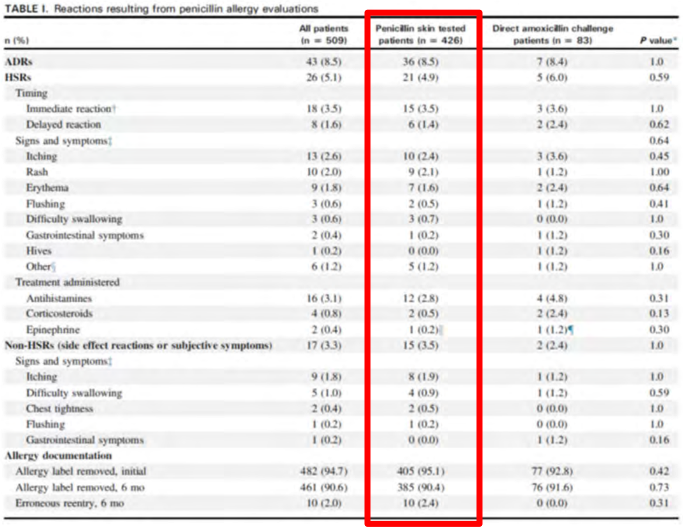
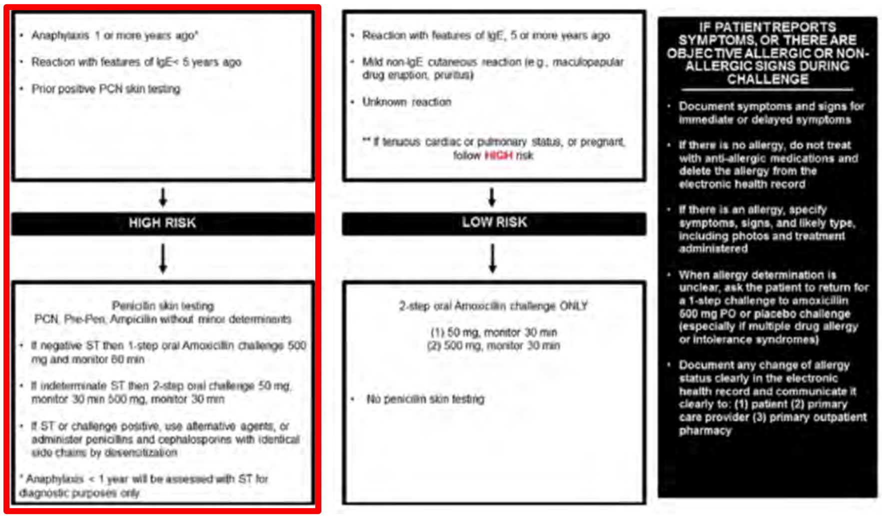


TABLE I. Reactions resulting from penicillin allergy evaluations

n (%)	All patients (n = 509)	Penicillin skin tested patients (n = 426)	Direct amoxicillin challenge patients (n = 83)	*P* value*
ADRs	43 (8.5)	36 (8.5)	7 (8.4)	1.0
HSRs	26 (5.1)	21 (4.9)	5 (6.0)	0.59
Timing				
Immediate reaction†	18 (3.5)	15 (3.5)	3 (3.6)	1.0
Delayed reaction	8 (1.6)	6 (1.4)	2 (2.4)	0.62
Signs and symptoms‡				0.64
Itching	13 (2.6)	10 (2.4)	3 (3.6)	0.45
Rash	10 (2.0)	9 (2.1)	1 (1.2)	1.00
Erythema	9 (1.8)	7 (1.6)	2 (2.4)	0.64
Flushing	3 (0.6)	2 (0.5)	1 (1.2)	0.41
Difficulty swallowing	3 (0.6)	3 (0.7)	0 (0.0)	1.0
Gastrointestinal symptoms	2 (0.4)	1 (0.2)	1 (1.2)	0.30
Hives	1 (0.2)	0 (0.0)	1 (1.2)	0.16
Other§	6 (1.2)	5 (1.2)	1 (1.2)	1.0
Treatment administered				
Antihistamines	16 (3.1)	12 (2.8)	4 (4.8)	0.31
Corticosteroids	4 (0.8)	2 (0.5)	2 (2.4)	0.13
Epinephrine	2 (0.4)	1 (0.2)‖	1 (1.2)¶	0.30
Non-HSRs (side effect reactions or subjective symptoms)	17 (3.3)	15 (3.5)	2 (2.4)	1.0
Signs and symptoms‡				
Itching	9 (1.8)	8 (1.9)	1 (1.2)	1.0
Difficulty swallowing	5 (1.0)	4 (0.9)	1 (1.2)	0.59
Chest tightness	2 (0.4)	2 (0.5)	0 (0.0)	1.0
Flushing	1 (0.2)	1 (0.2)	0 (0.0)	1.0
Gastrointestinal symptoms	1 (0.2)	0 (0.0)	1 (1.2)	0.16
Allergy documentation				
Allergy label removed, initial	482 (94.7)	405 (95.1)	77 (92.8)	0.42
Allergy label removed, 6 mo	461 (90.6)	385 (90.4)	76 (91.6)	0.73
Erroneous reentry, 6 mo	10 (2.0)	10 (2.4)	0 (0.0)	0.31

Blumenthal et al, J Allergy Clin Immunol Pract 2019.

Penicillin Pathway



- Anaphylaxis 1 or more years ago*
- Reaction with features of IgE< 5 years ago
- Prior positive PCN skin testing

HIGH RISK

Penicillin skin testing
PCN, Pre-Pen, Ampicilin without minor determinants

- If negative ST then 1-step oral Amoxicillin challenge 500 mg and monitor 60 min
- If indeterminate ST then 2-step oral challenge 50 mg, monitor 30 min 500 mg, monitor 30 min
- If ST or challenge positive, use alternative agents, or administer penicillins and cephalosporins with identical side chains by desensitization

* Anaphylaxis < 1 year will be assessed with ST for diagnostic purposes only

- Reaction with features of IgE, 5 or more years ago
- Mild non-IgE cutaneous reaction (e.g., maculopapular drug eruption, pruritus)
- Unknown reaction

** If tenuous cardiac or pulmonary status, or pregnant, follow HIGH risk

LOW RISK

2-step oral Amoxicillin challenge ONLY

(1) 50 mg, monitor 30 min
(2) 500 mg, monitor 30 min

- No penicillin skin testing

IF PATIENT REPORTS SYMPTOMS, OR THERE ARE OBJECTIVE ALLERGIC OR NON-ALLERGIC SIGNS DURING CHALLENGE

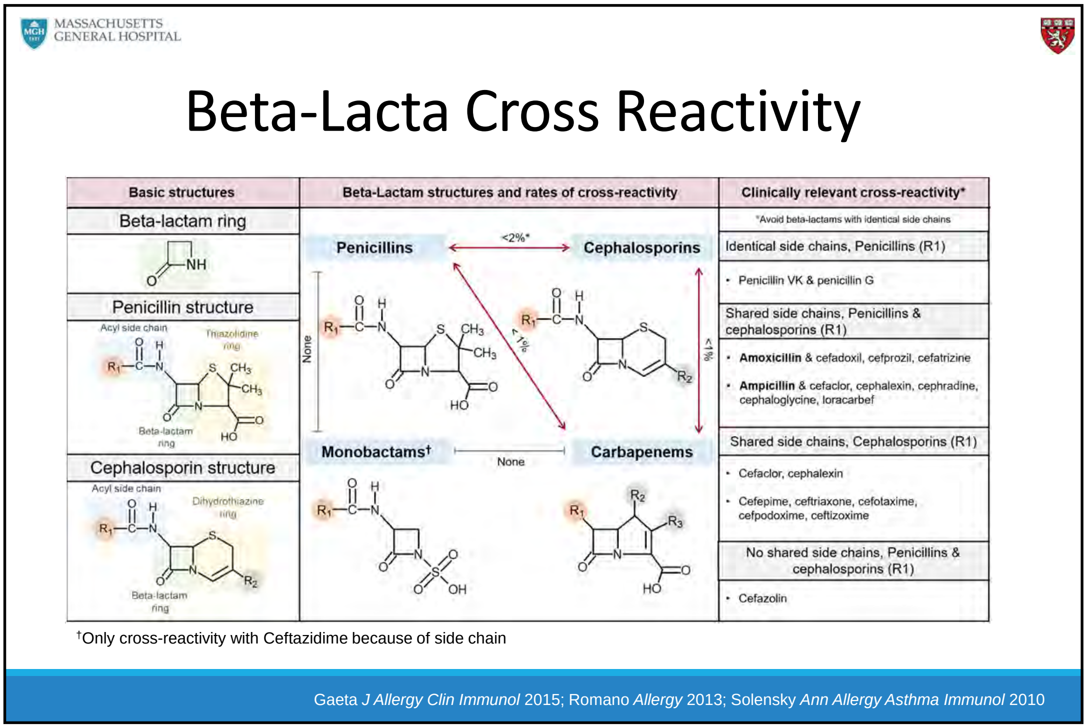
- Document symptoms and signs for immediate or delayed symptoms
- If there is no allergy, do not treat with anti-allergic medications and delete the allergy from the electronic health record
- If there is an allergy, specify symptoms, signs, and likely type, including photos and treatment administered
- When allergy determination is unclear, ask the patient to return for a 1-step challenge to amoxicillin 500 mg PO or placebo challenge (especially if multiple drug allergy or intolerance syndromes)
- Document any change of allergy status clearly in the electronic health record and communicate it clearly to: (1) patient (2) primary care provider (3) primary outpatient pharmacy

Blumenthal et al, J Allergy Clin Immunol Pract 2019.

Case 2: Cephalosporin Use in Penicillin Allergy

28 year old female with a history of amoxicillin allergy in high school with hives and shortness of breath admitted to the inpatient setting with pyelonephritis.

The team would like to use ceftriaxone. What should they do?



Beta-Lacta Cross Reactivity

Basic structures

Beta-Lactam structures and rates of cross-reactivity

Clinically relevant cross-reactivity*

*Avoid beta-lactams with identical side chains

Identical side chains, Penicillins (R1)

- Penicillin VK & penicillin G

Shared side chains, Penicillins & cephalosporins (R1)

- **Amoxicillin** & cefadoxil, cefprozil, cefatrizine
- **Ampicillin** & cefaclor, cephalexin, cephradine, cephaloglycine, loracarbef

Shared side chains, Cephalosporins (R1)

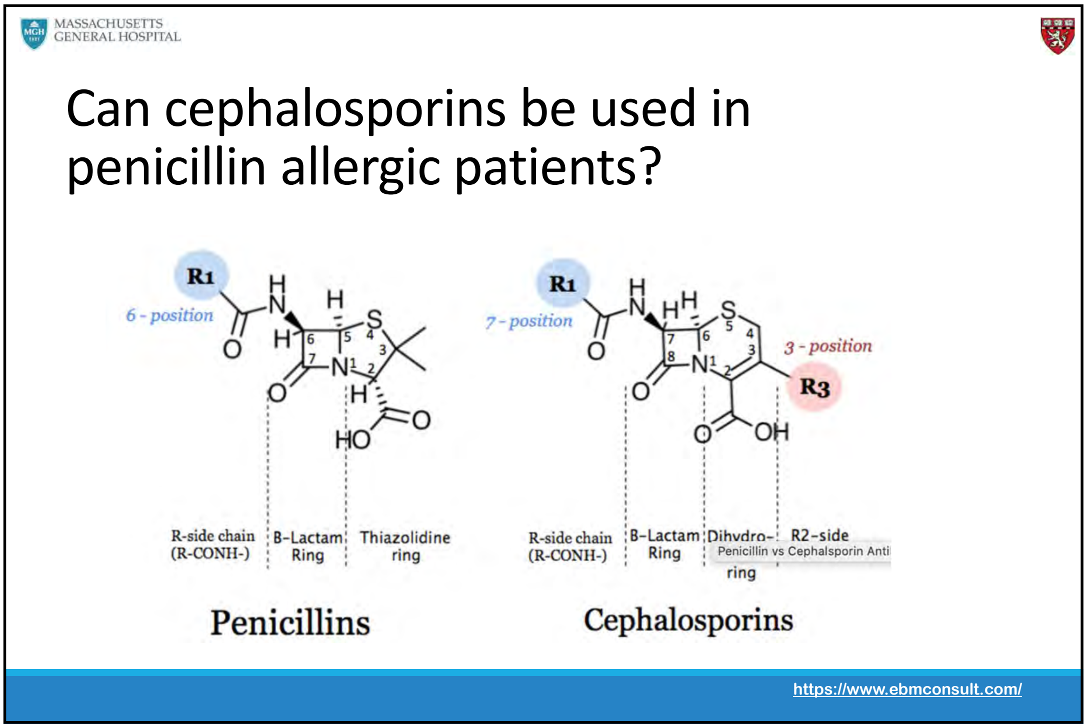
- Cefaclor, cephalexin
- Cefepime, ceftriaxone, cefotaxime, cefpodoxime, ceftizoxime

No shared side chains, Penicillins & cephalosporins (R1)

- Cefazolin

†Only cross-reactivity with Ceftazidime because of side chain

Gaeta *J Allergy Clin Immunol* 2015; Romano *Allergy* 2013; Solensky *Ann Allergy Asthma Immunol* 2010



Can cephalosporins be used in penicillin allergic patients?

https://www.ebmconsult.com/

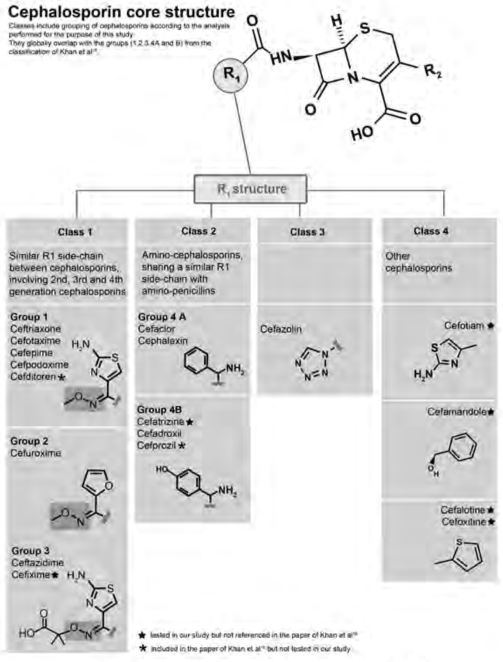


FIGURE 1. Classification of cephalosporins. Adapted from Khan et al.

Can cephalosporins be used in penicillin allergic patients?

Touati N et al, J Allergy Clin Imunol Pract 2021.

MASSACHUSETTS GENERAL HOSPITAL

Can cephalosporins be used in penicillin allergic patients?

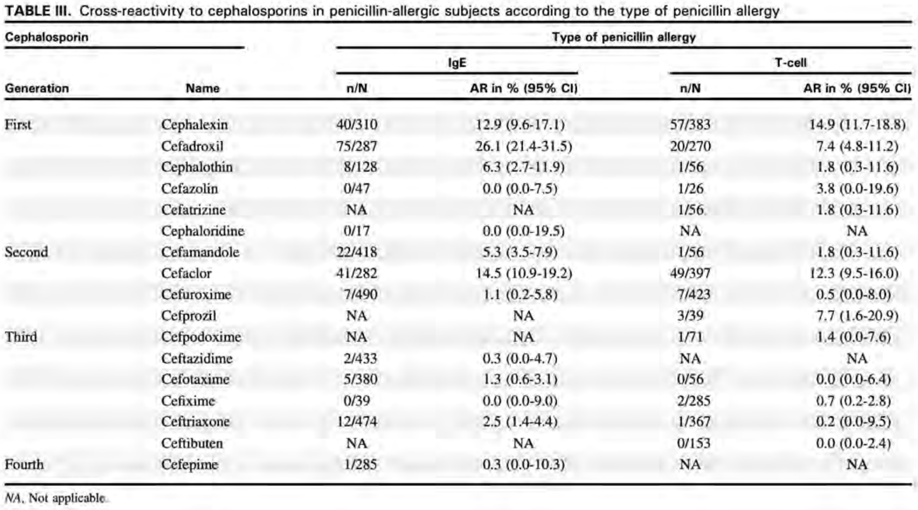


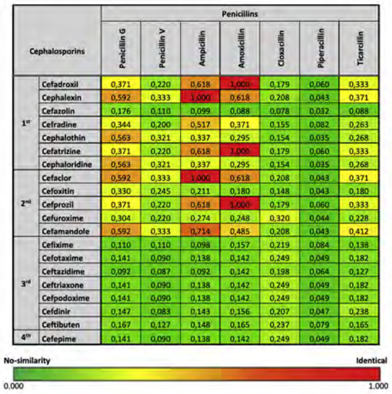
TABLE III. Cross-reactivity to cephalosporins in penicillin-allergic subjects according to the type of penicillin allergy

Cephalosporin		Type of penicillin allergy			
		IgE		T-cell	
Generation	Name	n/N	AR in % (95% CI)	n/N	AR in % (95% CI)
First	Cephalexin	40/310	12.9 (9.6-17.1)	57/383	14.9 (11.7-18.8)
	Cefadroxil	75/287	26.1 (21.4-31.5)	20/270	7.4 (4.8-11.2)
	Cephalothin	8/128	6.3 (2.7-11.9)	1/56	1.8 (0.3-11.6)
	Cefazolin	0/47	0.0 (0.0-7.5)	1/26	3.8 (0.0-19.6)
	Cefatrizine	NA	NA	1/56	1.8 (0.3-11.6)
	Cephaloridine	0/17	0.0 (0.0-19.5)	NA	NA
Second	Cefamandole	22/418	5.3 (3.5-7.9)	1/56	1.8 (0.3-11.6)
	Cefaclor	41/282	14.5 (10.9-19.2)	49/397	12.3 (9.5-16.0)
	Cefuroxime	7/490	1.1 (0.2-5.8)	7/423	0.5 (0.0-8.0)
	Cefprozil	NA	NA	3/39	7.7 (1.6-20.9)
Third	Cefpodoxime	NA	NA	1/71	1.4 (0.0-7.6)
	Ceftazidime	2/433	0.3 (0.0-4.7)	NA	NA
	Cefotaxime	5/380	1.3 (0.6-3.1)	0/56	0.0 (0.0-6.4)
	Cefixime	0/39	0.0 (0.0-9.0)	2/285	0.7 (0.2-2.8)
	Ceftriaxone	12/474	2.5 (1.4-4.4)	1/367	0.2 (0.0-9.5)
	Ceftibuten	NA	NA	0/153	0.0 (0.0-2.4)
Fourth	Cefepime	1/285	0.3 (0.0-10.3)	NA	NA

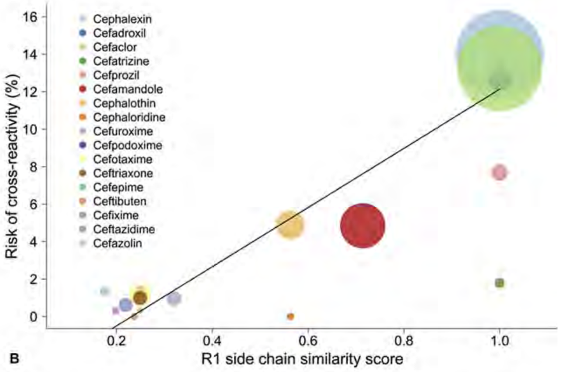
NA, Not applicable.

Picard et al, J Allergy Clin Immunol Pract 2019.

Can cephalosporins be used in penicillin allergic patients?

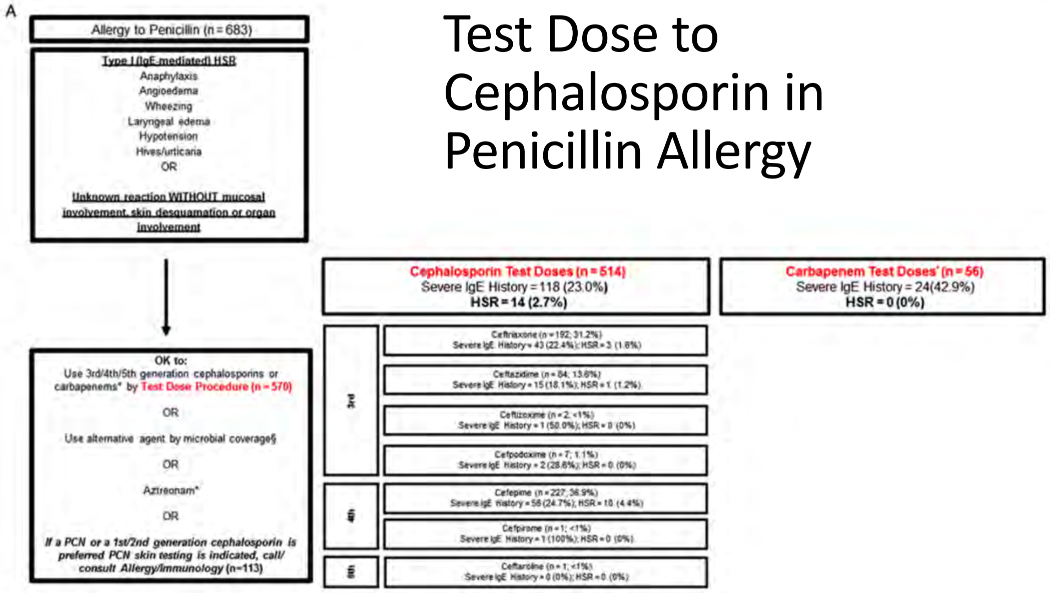


Cephalosporins		Penicillins						
		Penicillin G	Penicillin V	Ampicillin	Amoxicillin	Cloxacillin	Piperacillin	Ticarcillin
1st	Cefadroxil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephalexin	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefazolin	0,176	0,110	0,099	0,088	0,078	0,032	0,088
	Cefradine	0,344	0,200	0,517	0,371	0,155	0,082	0,263
	Cephalothin	0,563	0,321	0,337	0,295	0,154	0,035	0,268
	Cefatrizine	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cephaloridine	0,563	0,321	0,337	0,295	0,154	0,035	0,268
2nd	Cefaclor	0,592	0,333	1,000	0,618	0,208	0,043	0,371
	Cefoxitin	0,330	0,245	0,211	0,180	0,148	0,043	0,180
	Cefprozil	0,371	0,220	0,618	1,000	0,179	0,060	0,333
	Cefuroxime	0,304	0,220	0,274	0,248	0,320	0,044	0,228
	Cefamandole	0,592	0,333	0,714	0,485	0,208	0,043	0,412
3rd	Cefixime	0,110	0,110	0,098	0,157	0,219	0,084	0,138
	Cefotaxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Ceftazidime	0,092	0,087	0,092	0,142	0,198	0,064	0,127
	Ceftriaxone	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefpodoxime	0,141	0,090	0,138	0,142	0,249	0,049	0,182
	Cefdinir	0,147	0,083	0,143	0,156	0,207	0,047	0,238
	Ceftibuten	0,167	0,127	0,148	0,165	0,237	0,079	0,165
4th	Cefepime	0,141	0,090	0,138	0,142	0,249	0,049	0,182



Picard et al, J Allergy Clin Immunol Pract 2019.

Test Dose to Cephalosporin in Penicillin Allergy



A

Allergy to Penicillin (n = 683)

Type I (IgE-mediated) HSR
Anaphylaxis
Angioedema
Wheezing
Laryngeal edema
Hypotension
Hives/urticaria
OR
Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

OK to:
Use 3rd/4th/5th generation cephalosporins or carbapenems* by Test Dose Procedure (n = 570)
OR
Use alternative agent by microbial coverage§
OR
Aztreonam*
OR
If a PCN or a 1st/2nd generation cephalosporin is preferred PCN skin testing is indicated, call/ consult Allergy/Immunology (n=113)

Cephalosporin Test Doses (n = 514)
Severe IgE History = 118 (23.0%)
HSR = 14 (2.7%)

Carbapenem Test Doses* (n = 56)
Severe IgE History = 24(42.9%)
HSR = 0 (0%)

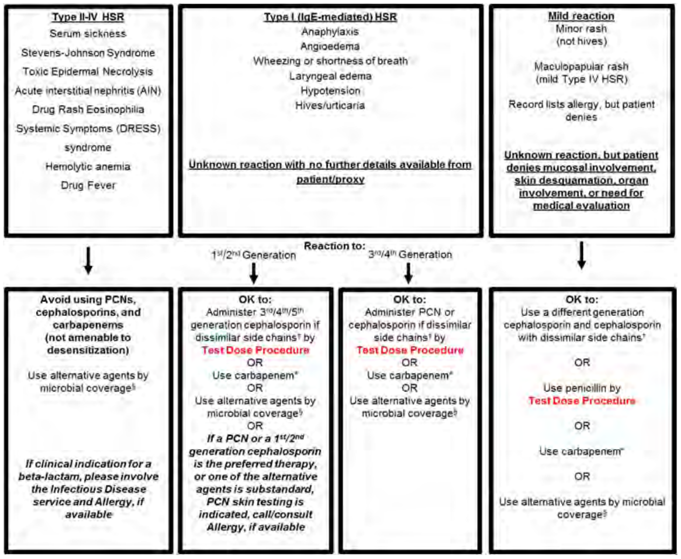
3rd
Ceftriaxone (n = 192; 31.2%)
Severe IgE History = 43 (22.4%); HSR = 3 (1.6%)
Ceftazidime (n = 84; 13.6%)
Severe IgE History = 15 (18.1%); HSR = 1 (1.2%)
Ceftizoxime (n = 2; <1%)
Severe IgE History = 1 (50.0%); HSR = 0 (0%)
Cefpodoxime (n = 7; 1.1%)
Severe IgE History = 2 (28.6%); HSR = 0 (0%)

4th
Cefepime (n = 227; 36.9%)
Severe IgE History = 56 (24.7%); HSR = 10 (4.4%)
Cefpirome (n = 1; <1%)
Severe IgE History = 1 (100%); HSR = 0 (0%)

5th
Ceftaroline (n = 1; <1%)
Severe IgE History = 0 (0%); HSR = 0 (0%)

Blumenthal et al, Infect Control Hosp Epidemiol 2019

Cephalosporin Allergy Pathway



Type II-IV HSR
Serum sickness
Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis
Acute interstitial nephritis (AIN)
Drug Rash Eosinophilia
Systemic Symptoms (DRESS)
syndrome
Hemolytic anemia
Drug Fever

Type I (IgE-mediated) HSR
Anaphylaxis
Angioedema
Wheezing or shortness of breath
Laryngeal edema
Hypotension
Hives/urticaria

Unknown reaction with no further details available from patient/proxy

Mild reaction
Minor rash
(not hives)

Maculopapular rash
(mild Type IV HSR)

Record lists allergy, but patient denies

Unknown reaction, but patient denies mucosal involvement, skin desquamation, organ involvement, or need for medical evaluation

Reaction to:
1st/2nd Generation
3rd/4th Generation

Avoid using PCNs, cephalosporins, and carbapenems (not amenable to desensitization)

Use alternative agents by microbial coverage§

If clinical indication for a beta-lactam, please involve the Infectious Disease service and Allergy, if available

OK to:
Administer 3rd/4th/5th generation cephalosporin if dissimilar side chains† by
Test Dose Procedure
OR
Use carbapenem*
OR
Use alternative agents by microbial coverage§
OR
If a PCN or a 1st/2nd generation cephalosporin is the preferred therapy, or one of the alternative agents is substandard, PCN skin testing is indicated, call/consult Allergy, if available

OK to:
Administer PCN or cephalosporin if dissimilar side chains† by
Test Dose Procedure
OR
Use carbapenem*
OR
Use alternative agents by microbial coverage§

OK to:
Use a different generation cephalosporin and cephalosporin with dissimilar side chains†

OR

Use penicillin by
Test Dose Procedure

OR

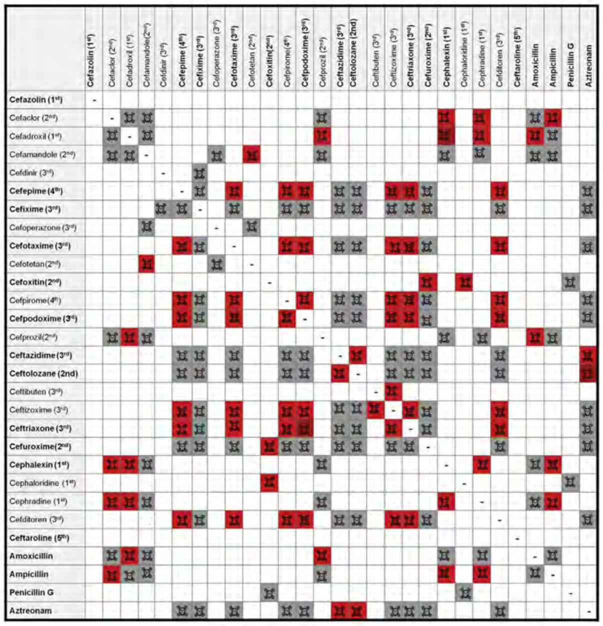
Use carbapenem*

OR

Use alternative agents by microbial coverage§

Blumenthal et al, J Allergy Clin Immunol Pract 2017.

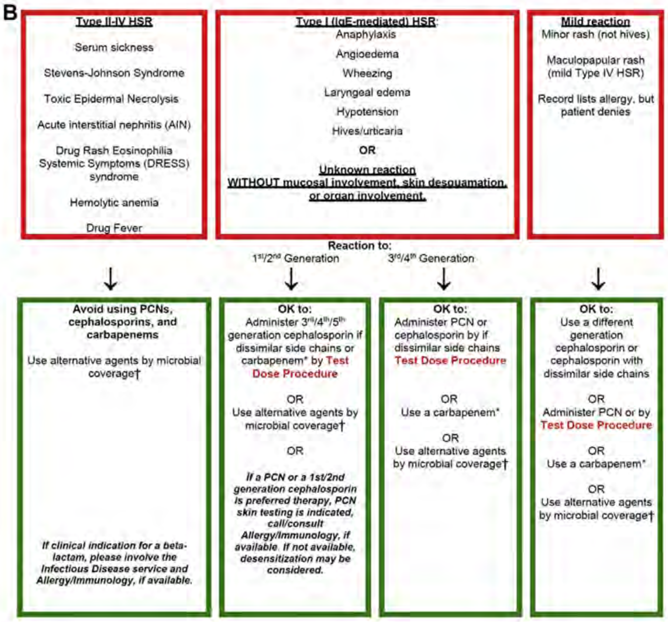
Cephalosporin Cross-Reactivity



	Cefazolin (1st)	Cefaclor (2nd)	Cefadroxil (1st)	Cefamandole(2nd)	Cefdinir (3rd)	Cefepime (4th)	Cefixime (3rd)	Cefoperazone (3rd)	Cefotaxime (3rd)	Cefotetan (2nd)	Cefoxitin(2nd)	Cefpirome(4th)	Cefpodoxime (3rd)	Cefprozil (2nd)	Ceftazidime (3rd)	Ceftolozane (2nd)	Ceftibuten (3rd)	Ceftizoxime (3rd)	Ceftriaxone (3rd)	Cefuroxime (2nd)	Cephalexin (1st)	Cephaloridine (1st)	Cephradine (1st)	Cefditoren (3rd)	Ceftaroline (5th)	Amoxicillin	Ampicillin	Penicillin G	Aztreonam
Cefazolin (1st)	-																												
Cefaclor (2nd)		-	▨	▨										▨							🟥		🟥			▨	🟥		
Cefadroxil (1st)		▨	-	▨										🟥							🟥		🟥			🟥	▨		
Cefamandole (2nd)		▨	▨	-				▨		🟥				▨							▨		▨			▨	▨		
Cefdinir (3rd)					-		▨																						
Cefepime (4th)						-	▨		🟥			🟥	🟥		▨	▨		🟥	🟥	▨				🟥					▨
Cefixime (3rd)					▨	▨	-		▨			▨	▨		▨	▨		▨	▨	▨				▨					▨
Cefoperazone (3rd)				▨				-		▨																			
Cefotaxime (3rd)						🟥	▨		-			🟥	🟥		▨	▨		🟥	🟥	▨				🟥					▨
Cefotetan(2nd)				🟥				▨		-																			
Cefoxitin(2nd)											-									🟥		🟥						▨	
Cefpirome(4th)						🟥	▨		🟥			-	🟥		▨	▨		🟥	🟥	▨				🟥					▨
Cefpodoxime (3rd)						🟥	▨		🟥			🟥	-		▨	▨		🟥	🟥	▨				🟥					▨
Cefprozil(2nd)		▨	🟥	▨										-							▨		▨			🟥	▨		
Ceftazidime (3rd)						▨	▨		▨			▨	▨		-	🟥		▨	▨	▨				▨					🟥
Ceftolozane (2nd)						▨	▨		▨			▨	▨		🟥	-		▨	▨	▨				▨					🟥
Ceftibuten (3rd)																	-	🟥											
Ceftizoxime (3rd)						🟥	▨		🟥			🟥	🟥		▨	▨	🟥	-	🟥	▨				🟥					▨
Ceftriaxone (3rd)						🟥	▨		🟥			🟥	🟥		▨	▨		🟥	-	▨				🟥					▨
Cefuroxime(2nd)						▨	▨		▨		🟥	▨	▨		▨	▨		▨	▨	-				▨					▨
Cephalexin (1st)		🟥	🟥	▨										▨							-		🟥			▨	🟥		
Cephaloridine (1st)											🟥											-						▨	
Cephradine (1st)		🟥	🟥	▨										▨							🟥		-			▨	🟥		
Cefditoren (3rd)						🟥	▨		🟥			🟥	🟥		▨	▨		🟥	🟥	▨				-					▨
Ceftaroline (5th)																									-				
Amoxicillin		▨	🟥	▨										🟥							▨		▨			-	▨		
Ampicillin		🟥	▨	▨										▨							🟥		🟥			▨	-		
Penicillin G											▨											▨						-	
Aztreonam						▨	▨		▨			▨	▨		🟥	🟥		▨	▨	▨				▨					-

Blumenthal et al, J Allergy Clin Immunol Pract 2017.

What about patients with cephalosporin allergy?



B

Type II-IV HSR
Serum sickness
Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis
Acute interstitial nephritis (AIN)
Drug Rash Eosinophilia Systemic Symptoms (DRESS) syndrome
Hemolytic anemia
Drug Fever

Type I (IgE-mediated) HSR:
Anaphylaxis
Angioedema
Wheezing
Laryngeal edema
Hypotension
Hives/urticaria
OR
Unknown reaction
WITHOUT mucosal involvement, skin desquamation, or organ involvement.

Mild reaction
Minor rash (not hives)
Maculopapular rash (mild Type IV HSR)
Record lists allergy, but patient denies

Reaction to:
1st/2nd Generation
3rd/4th Generation

Avoid using PCNs, cephalosporins, and carbapenems
Use alternative agents by microbial coverage†
If clinical indication for a beta-lactam, please involve the Infectious Disease service and Allergy/Immunology, if available.

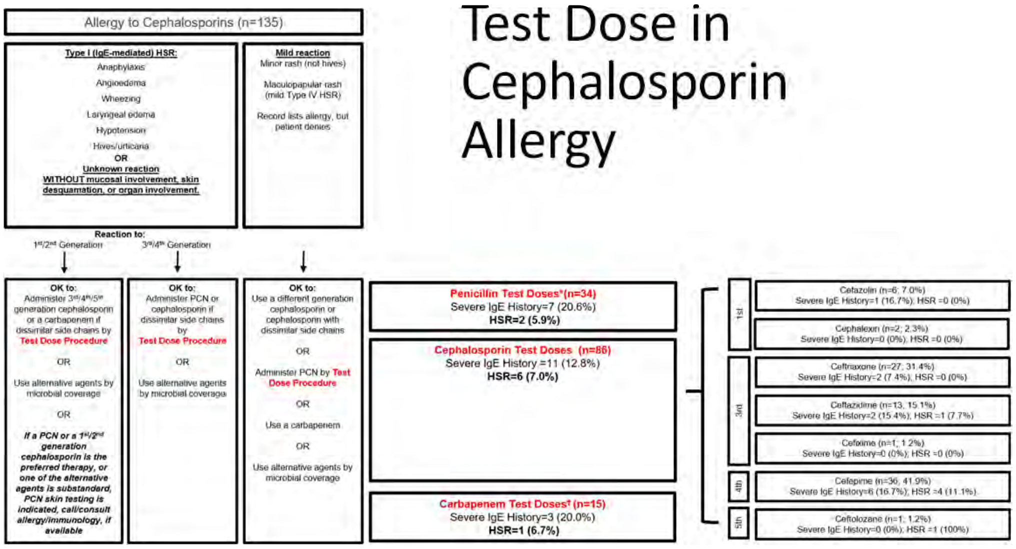
OK to:
Administer 3rd/4th/5th generation cephalosporin if dissimilar side chains or carbapenem* by **Test Dose Procedure**
OR
Use alternative agents by microbial coverage†
OR
If a PCN or a 1st/2nd generation cephalosporin is preferred therapy, PCN skin testing is indicated, call/consult Allergy/Immunology, if available. If not available, desensitization may be considered.

OK to:
Administer PCN or cephalosporin by if dissimilar side chains **Test Dose Procedure**
OR
Use a carbapenem*
OR
Use alternative agents by microbial coverage†

OK to:
Use a different generation cephalosporin or cephalosporin with dissimilar side chains
OR
Administer PCN or by **Test Dose Procedure**
OR
Use a carbapenem*
OR
Use alternative agents by microbial coverage†

Blumenthal et al, J Allergy Clin Immunol Pract 2017.

Test Dose in Cephalosporin Allergy



Allergy to Cephalosporins (n=135)

Type I (IgE-mediated) HSR:
Anaphylaxis
Angioedema
Wheezing
Laryngeal edema
Hypotension
Hives/urticaria
OR
Unknown reaction
WITHOUT mucosal involvement, skin desquamation, or organ involvement.

Mild reaction
Minor rash (not hives)
Maculopapular rash (mild Type IV HSR)
Record lists allergy, but patient denies

Reaction to:
1st/2nd Generation
3rd/4th Generation

OK to:
Administer 3rd/4th/5th generation cephalosporin or a carbapenem if dissimilar side chains by **Test Dose Procedure**
OR
Use alternative agents by microbial coverage
OR
If a PCN or a 1st/2nd generation cephalosporin is the preferred therapy, or one of the alternative agents is substandard, PCN skin testing is indicated, call/consult allergy/immunology, if available

OK to:
Administer PCN or cephalosporin if dissimilar side chains by **Test Dose Procedure**
OR
Use alternative agents by microbial coverage

OK to:
Use a different generation cephalosporin or cephalosporin with dissimilar side chains
OR
Administer PCN by **Test Dose Procedure**
OR
Use a carbapenem
OR
Use alternative agents by microbial coverage

Penicillin Test Doses*(n=34)
Severe IgE History=7 (20.6%)
HSR=2 (5.9%)

Cephalosporin Test Doses (n=86)
Severe IgE History =11 (12.8%)
HSR=6 (7.0%)

Carbapenem Test Doses† (n=15)
Severe IgE History=3 (20.0%)
HSR=1 (6.7%)

1st	Cefazolin (n=6; 7.0%) Severe IgE History=1 (16.7%); HSR =0 (0%)
	Cephalexin (n=2; 2.3%) Severe IgE History=0 (0%); HSR =0 (0%)
3rd	Ceftriaxone (n=27; 31.4%) Severe IgE History=2 (7.4%); HSR =0 (0%)
	Ceftazidime (n=13; 15.1%) Severe IgE History=2 (15.4%); HSR =1 (7.7%)
	Cefixime (n=1; 1.2%) Severe IgE History=0 (0%); HSR =0 (0%)
4th	Cefepime (n=36; 41.9%) Severe IgE History=6 (16.7%); HSR =4 (11.1%)
5th	Ceftolozane (n=1; 1.2%) Severe IgE History=0 (0%); HSR =1 (100%)

Blumenthal et al, Infect Control Hosp Epidemiol 2019

Test Dose Procedure

- Tolerance of the test dose and full dose: Patient is not allergic to the agent administered

- Update patient's allergies in EHR:
  - If agent was a related agent (e.g., ceftriaxone administered in PCN-allergic patient), only update "comments" to include what was tolerated
  - If agent was the same agent as the recorded allergy (e.g., PCN administered in a PCN-allergic patient), remove the allergy from the allergy list
- Patient does not require a test dose procedure to the same antibiotic in the future

---

Case 3: Sulfonamide Hypersensitivity

A 35 year old female reports rash after taking trimethoprim/sulfamethoxazole as a teenager for a UTI.

Is she still allergic?

She is going hiking at Machu Pichu next month and wants to know if she can take acetazolamide even though it is a sulfa medication.

Sulfonamide Hypersensitivity

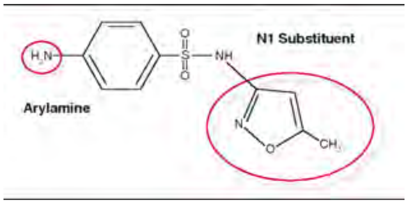
Common cause of drug reactions

Immediate IgE-mediated reactions

Benign T-cell-mediated rashes
- Most common

Severe cutaneous adverse reactions (SCARs)
- Stevens-Johnson syndrome (SJS)/Toxic epidermal necrolysis (TEN)
- Drug reaction eosinophilia systemic symptoms (DRESS)

Sulfonamide Hypersensitivity



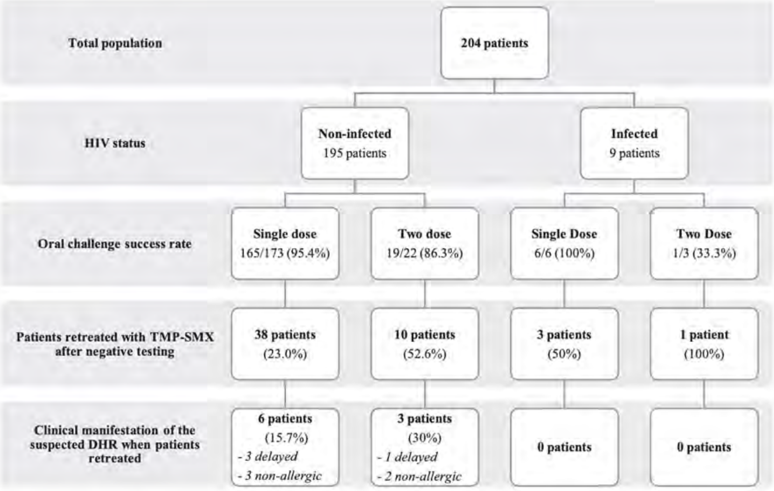
IgE-mediated reactions: Antibodies to N1 group

Non-IgE mediated reactions: Due to N4 arylamine group

Sulfonamide Hypersensitivity

		Cotrimoxazole	Normal Saline	Histamine
Step 1	Epicutaneous (Greer pick)	80 mg/ml		(6 mg/ml)
Step 2	Intradermal	0.08 mg/ml		(0.1 mg/ml)
Step 3	Intradermal	0.8 mg/ml		

Sulfonamide Hypersensitivity



Total population

204 patients

HIV status

Non-infected
195 patients

Infected
9 patients

Oral challenge success rate

Single dose
165/173 (95.4%)

Two dose
19/22 (86.3%)

Single Dose
6/6 (100%)

Two Dose
1/3 (33.3%)

Patients retreated with TMP-SMX after negative testing

38 patients
(23.0%)

10 patients
(52.6%)

3 patients
(50%)

1 patient
(100%)

Clinical manifestation of the suspected DHR when patients retreated

6 patients
(15.7%)
- *3 delayed*
- *3 non-allergic*

3 patients
(30%)
- *1 delayed*
- *2 non-allergic*

0 patients

0 patients

History of immediate, non-severe delayed or unknown TMP-SMX or unspecified sulfa antibiotic allergy

Krantz et al, J Allergy Clin Immunol Pract 2019.

Sulfonamide Hypersensitivity

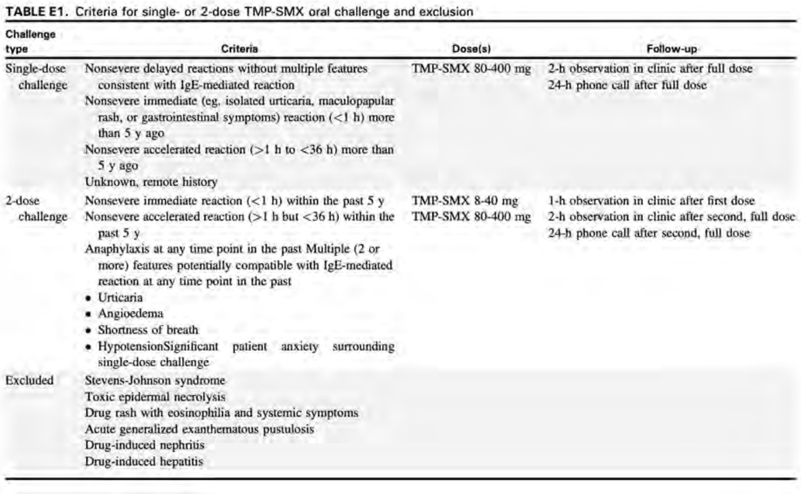
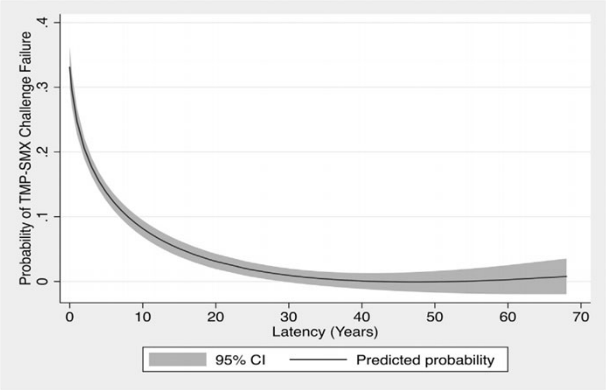


TABLE E1. Criteria for single- or 2-dose TMP-SMX oral challenge and exclusion

Challenge type	Criteria	Dose(s)	Follow-up
Single-dose challenge	Nonsevere delayed reactions without multiple features consistent with IgE-mediated reaction Nonsevere immediate (eg, isolated urticaria, maculopapular rash, or gastrointestinal symptoms) reaction (<1 h) more than 5 y ago Nonsevere accelerated reaction (>1 h to <36 h) more than 5 y ago Unknown, remote history	TMP-SMX 80-400 mg	2-h observation in clinic after full dose 24-h phone call after full dose
2-dose challenge	Nonsevere immediate reaction (<1 h) within the past 5 y Nonsevere accelerated reaction (>1 h but <36 h) within the past 5 y Anaphylaxis at any time point in the past Multiple (2 or more) features potentially compatible with IgE-mediated reaction at any time point in the past • Urticaria • Angioedema • Shortness of breath • HypotensionSignificant patient anxiety surrounding single-dose challenge	TMP-SMX 8-40 mg TMP-SMX 80-400 mg	1-h observation in clinic after first dose 2-h observation in clinic after second, full dose 24-h phone call after second, full dose
Excluded	Stevens-Johnson syndrome Toxic epidermal necrolysis Drug rash with eosinophilia and systemic symptoms Acute generalized exanthematous pustulosis Drug-induced nephritis Drug-induced hepatitis		

Krantz et al, J Allergy Clin Immunol Pract 2019.

Sulfonamide Hypersensitivity



Time since index reaction associated with reduced risk of challenge failure

Krantz et al, J Allergy Clin Immunol Pract 2019.

Do Sulfonamide Antibiotics and Non-Antibiotics Cross-React?

>20,000 patients

Prescription for sulfonamide antibiotic → **Prescription for non-antibiotic sulfonamide**

5% reported allergic reaction

Patients who *were* allergic to sulfonamide antibiotics at higher risk for reactions to non-antibiotic sulfonamides (1.6% vs. 9.9%)

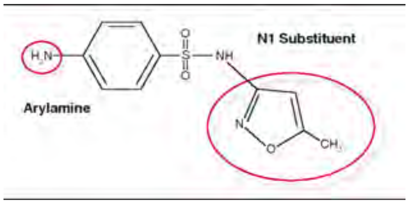
- Risk of penicillin reaction was 2% among patients ***without*** reaction to sulfonamide antibiotics and 14% among patients ***with*** reactions to sulfonamide antibiotics

Stroml et al, NEJM 2003.

Do Sulfonamide Antibiotics and Non-Antibiotics Cross-React?

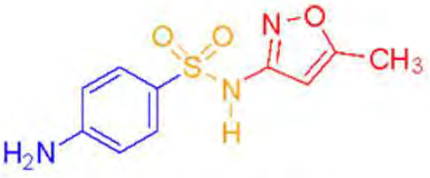
Patients with sulfonamide antibiotic allergy can receive non-antibiotic sulfa containing medications

- Allergy to N1 and N4 portions of sulfonamide antibiotics
- Not present in non-antibiotic sulfonamides



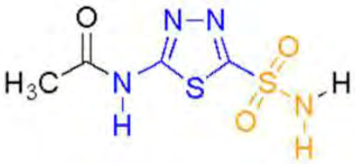
Do Sulfonamide Antibiotics and Non-Antibiotics Cross-React?

ANTIMICROBIAL SULFONAMIDES (HIGH RISK OF CROSS-REACTIVITY)



Sulfamethoxazole

NONANTIMICROBIAL SULFONAMIDES (LOW RISK OF CROSS-REACTIVITY)

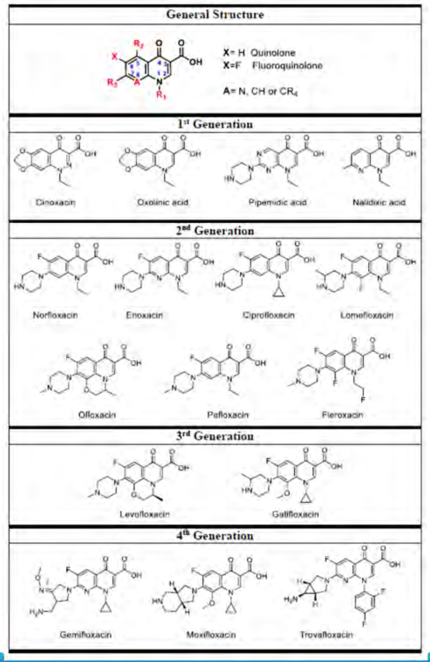


Acetazolamide

Case #5: Quinolones

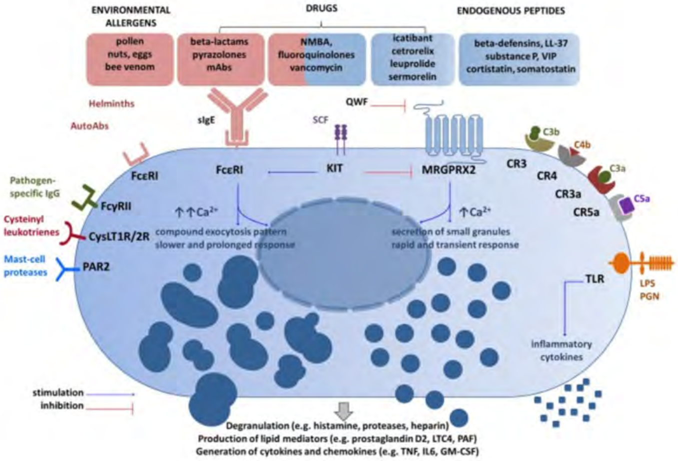
62 year old male treated with levofloxacin and metronidazole for diverticultis.

About 30 minutes after taking the levofloxacin, he develops itching and hives and then feels like his chest is tight. He take 50mg of Benadryl and symptoms improve over the next hour.



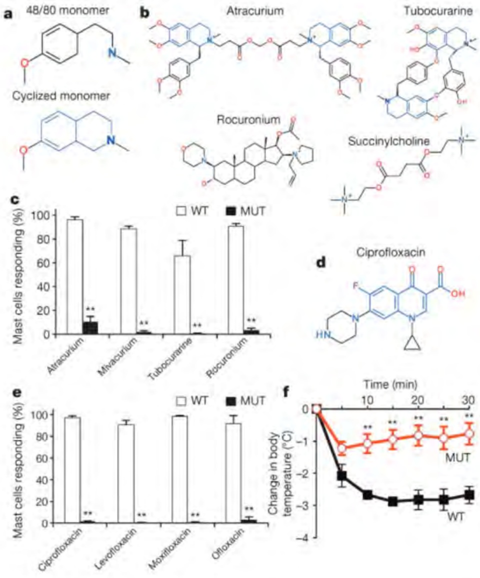
Are hypersensitivity reactions to quinolones IgE-mediated?

Are hypersentivity reactions to quinolones IgE-mediated?



Porebski et al, Front Immunol 2018.

Quinolones directly activate MRGPRX2



Porebski et al, Front Immunol 2018.

Skin testing to quinolones

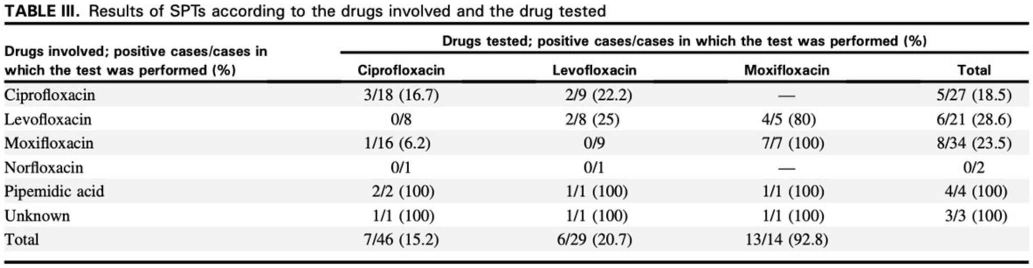


TABLE III. Results of SPTs according to the drugs involved and the drug tested

Drugs involved; positive cases/cases in which the test was performed (%)	Drugs tested; positive cases/cases in which the test was performed (%)			
	Ciprofloxacin	Levofloxacin	Moxifloxacin	Total
Ciprofloxacin	3/18 (16.7)	2/9 (22.2)	—	5/27 (18.5)
Levofloxacin	0/8	2/8 (25)	4/5 (80)	6/21 (28.6)
Moxifloxacin	1/16 (6.2)	0/9	7/7 (100)	8/34 (23.5)
Norfloxacin	0/1	0/1	—	0/2
Pipemidic acid	2/2 (100)	1/1 (100)	1/1 (100)	4/4 (100)
Unknown	1/1 (100)	1/1 (100)	1/1 (100)	3/3 (100)
Total	7/46 (15.2)	6/29 (20.7)	13/14 (92.8)	

Porebski et al, Front Immunol 2018.

Drug Provocation Testing

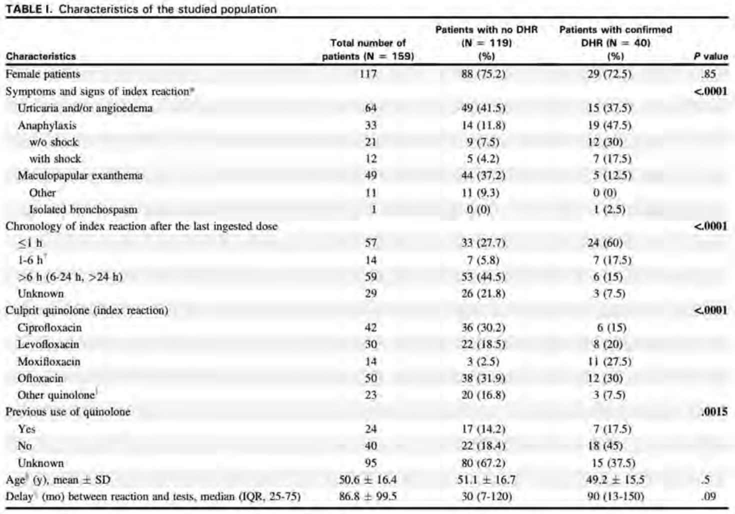
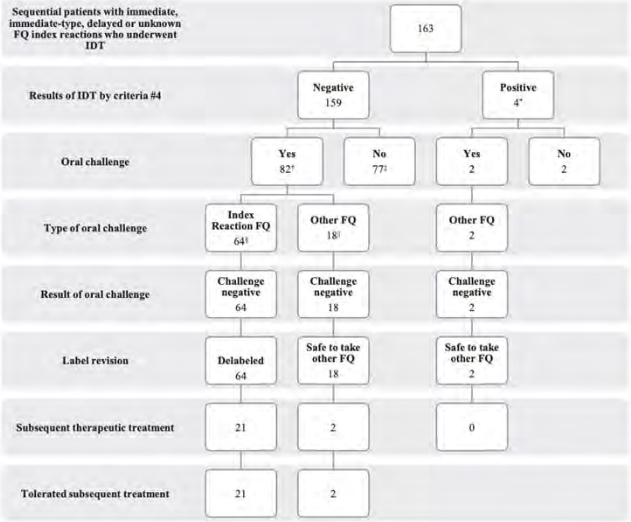


TABLE I. Characteristics of the studied population

Characteristics	Total number of patients (N = 159)	Patients with no DHR (N = 119) (%)	Patients with confirmed DHR (N = 40) (%)	P value
Female patients	117	88 (75.2)	29 (72.5)	.85
Symptoms and signs of index reaction[*]				**<.0001**
Urticaria and/or angioedema	64	49 (41.5)	15 (37.5)	
Anaphylaxis	33	14 (11.8)	19 (47.5)	
w/o shock	21	9 (7.5)	12 (30)	
with shock	12	5 (4.2)	7 (17.5)	
Maculopapular exanthema	49	44 (37.2)	5 (12.5)	
Other	11	11 (9.3)	0 (0)	
Isolated bronchospasm	1	0 (0)	1 (2.5)	
Chronology of index reaction after the last ingested dose				**<.0001**
≤1 h	57	33 (27.7)	24 (60)	
1-6 h[†]	14	7 (5.8)	7 (17.5)	
>6 h (6-24 h, >24 h)	59	53 (44.5)	6 (15)	
Unknown	29	26 (21.8)	3 (7.5)	
Culprit quinolone (index reaction)				**<.0001**
Ciprofloxacin	42	36 (30.2)	6 (15)	
Levofloxacin	30	22 (18.5)	8 (20)	
Moxifloxacin	14	3 (2.5)	11 (27.5)	
Ofloxacin	50	38 (31.9)	12 (30)	
Other quinolone[‡]	23	20 (16.8)	3 (7.5)	
Previous use of quinolone				**.0015**
Yes	24	17 (14.2)	7 (17.5)	
No	40	22 (18.4)	18 (45)	
Unknown	95	80 (67.2)	15 (37.5)	
Age[§] (y), mean ± SD	50.6 ± 16.4	51.1 ± 16.7	49.2 ± 15.5	.5
Delay[‖] (mo) between reaction and tests, median (IQR, 25-75)	86.8 ± 99.5	30 (7-120)	90 (13-150)	.09

Chiriac et al, J Allergy Clin Immunol Pract 2021.

Drug Provocation Testing



Positive IDT result: specific FQ flare at 0.025 mg/mL > to histamine flare, specific FQ flare > to 5 mm at 0.005 mg/mL, and no flare > to 5 mm for either of the other 2 FQs at 0.005 mg/mL

Krantz et al, J Allergy Clin Immunol Pract 2021.

Drug Provocation Testing

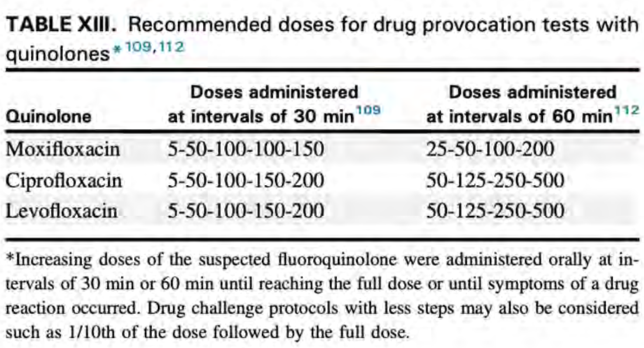
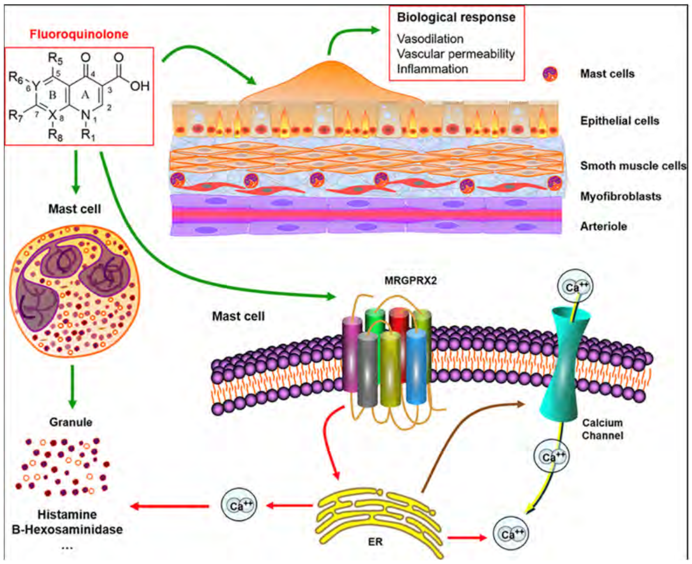


TABLE XIII. Recommended doses for drug provocation tests with quinolones*[109,112]

Quinolone	Doses administered at intervals of 30 min[109]	Doses administered at intervals of 60 min[112]
Moxifloxacin	5-50-100-100-150	25-50-100-200
Ciprofloxacin	5-50-100-150-200	50-125-250-500
Levofloxacin	5-50-100-150-200	50-125-250-500

*Increasing doses of the suspected fluoroquinolone were administered orally at intervals of 30 min or 60 min until reaching the full dose or until symptoms of a drug reaction occurred. Drug challenge protocols with less steps may also be considered such as 1/10th of the dose followed by the full dose.

Broyles et al, J Allergy Clin Immunol Pract 2020.



Liu et al, Int Immunopharmacol 2019.

Summary

- Documented penicillin allergy evaluation is associated with surgical site infections, increased rate of C diff, MRSA, adverse events, and cost
  - Allergy evaluation allows for reintroduction in most people
- Cephalosporin cross-reactivity is based on side chains and can often be used safely in penicillin-allergic patients

Summary

- For patients with a non-severe immediate or delayed history of sulfa allergy, direct oral challenge with trimethoprim-sulfamethoxazole is a safe and efficacious procedure
- Quinolones can directly activate mast cells via MRGPRX2 and skin testing is often falsely positive
  - Drug provocation testing is important in quinolone allergy evaluation

PAAA

Pennsylvania Allergy & Asthma Association

Microbiome's Impact on Immune Function

Ian Myles, MD, MPH

Friday, June 25, 2021
9:30 a.m. - 10:15 a.m.

The Microbiome's Impact on Immune Function

CDR IAN A MYLES, MD/MPH

PAAAI MEETING 2020

National Institute of Allergy and Infectious Diseases

Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

How to we characterize the microbiome?

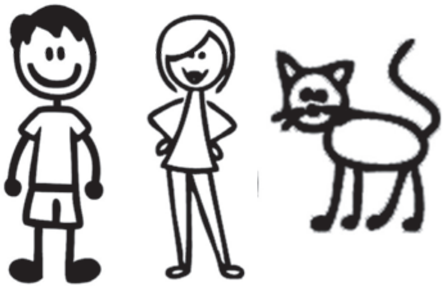
Kingdom:	Animalia			
Phylum:	Chordata			
Class:	Mammalia			Actinopterygii
Order:	Primates	Carnivora		Cypriniformes
Family:	Hominidae	Canidae	Felidae	Cyprinidae
Genus:	Homo	Canis	Felis	Carassius
Species:	Homo sapien	C. lupus	F. silvestris	C. auratus

Cochrane

Genetic similarities between:

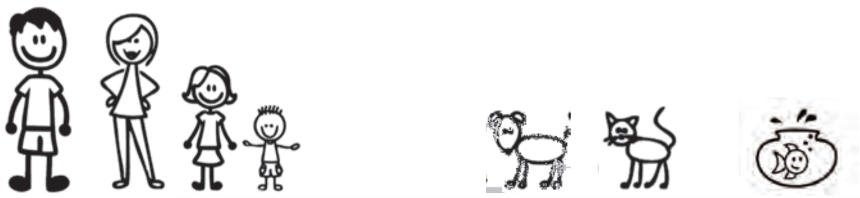
Any two *Homo sapiens*:

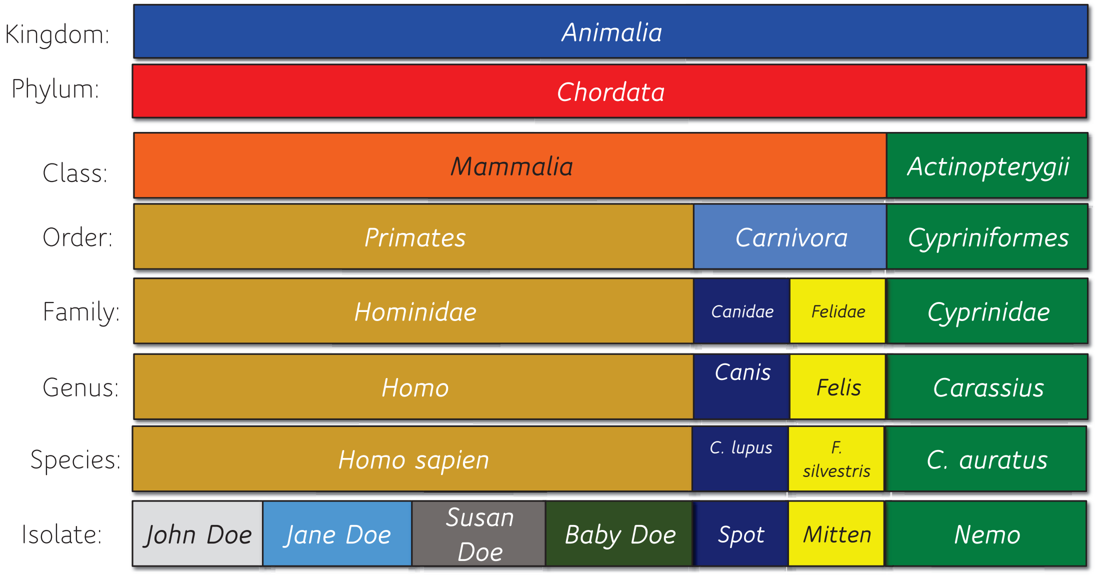
- 99.9%



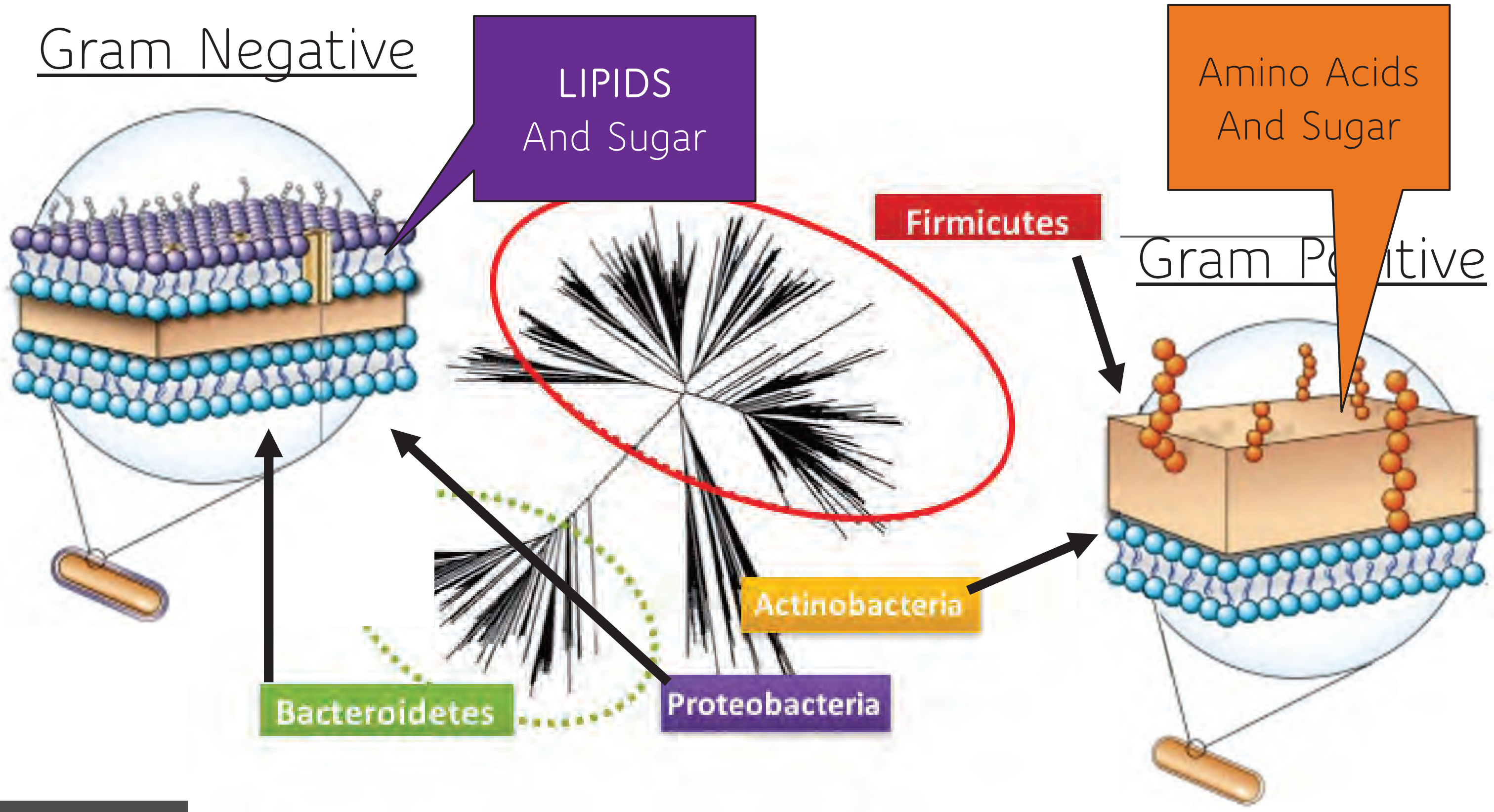
Any two *Lactobacillus acidophilus*:

- At least 90%





Kingdom:	*Animalia*						
Phylum:	*Chordata*						
Class:	*Mammalia*						*Actinopterygii*
Order:	*Primates*				*Carnivora*		*Cypriniformes*
Family:	*Hominidae*				*Canidae*	*Felidae*	*Cyprinidae*
Genus:	*Homo*				*Canis*	*Felis*	*Carassius*
Species:	*Homo sapien*				*C. lupus*	*F. silvestris*	*C. auratus*
Isolate:	*John Doe*	*Jane Doe*	*Susan Doe*	*Baby Doe*	*Spot*	*Mitten*	*Nemo*



Gram Negative

LIPIDS
And Sugar

Firmicutes

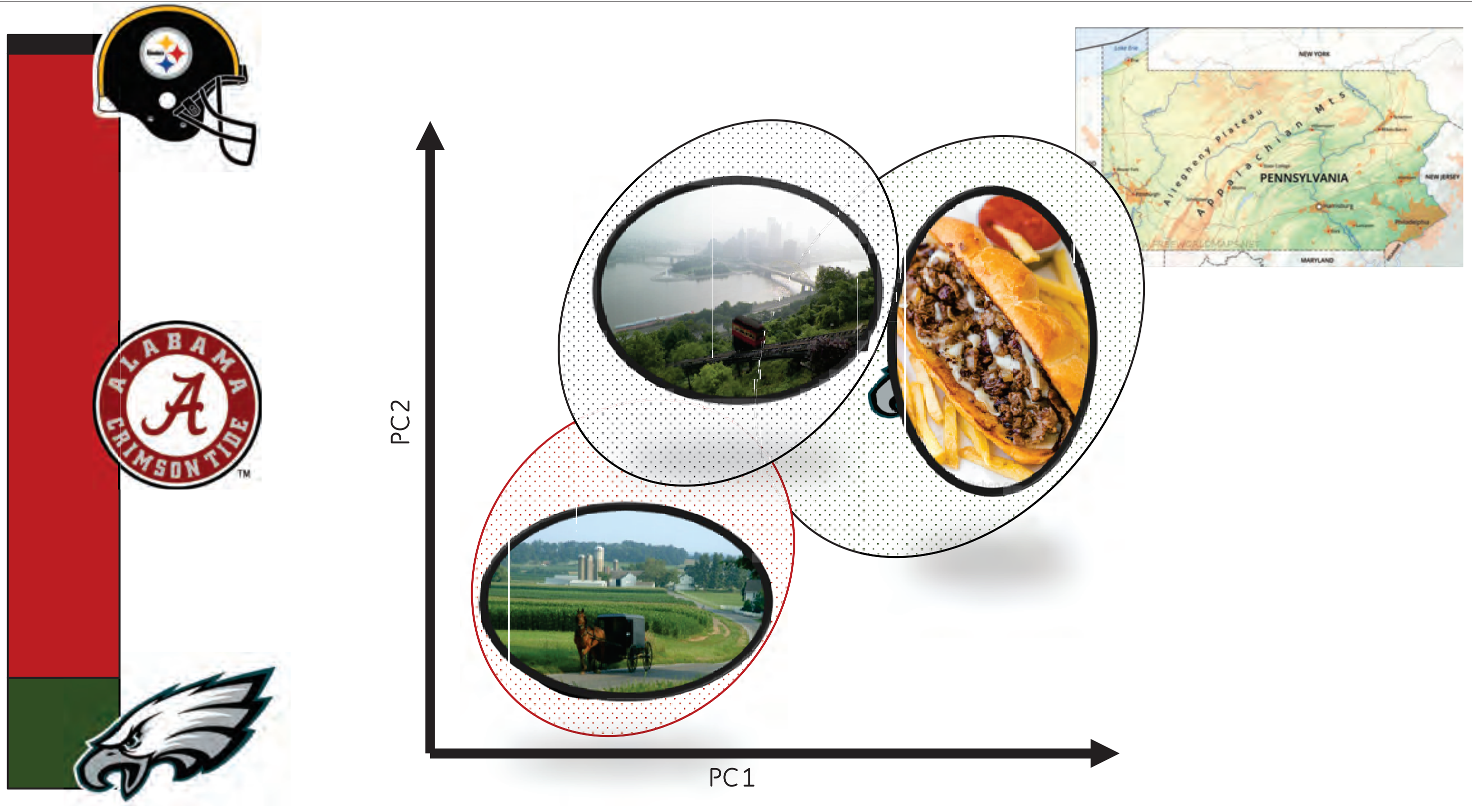
Amino Acids
And Sugar

Gram Po itive

Actinobacteria

Proteobacteria

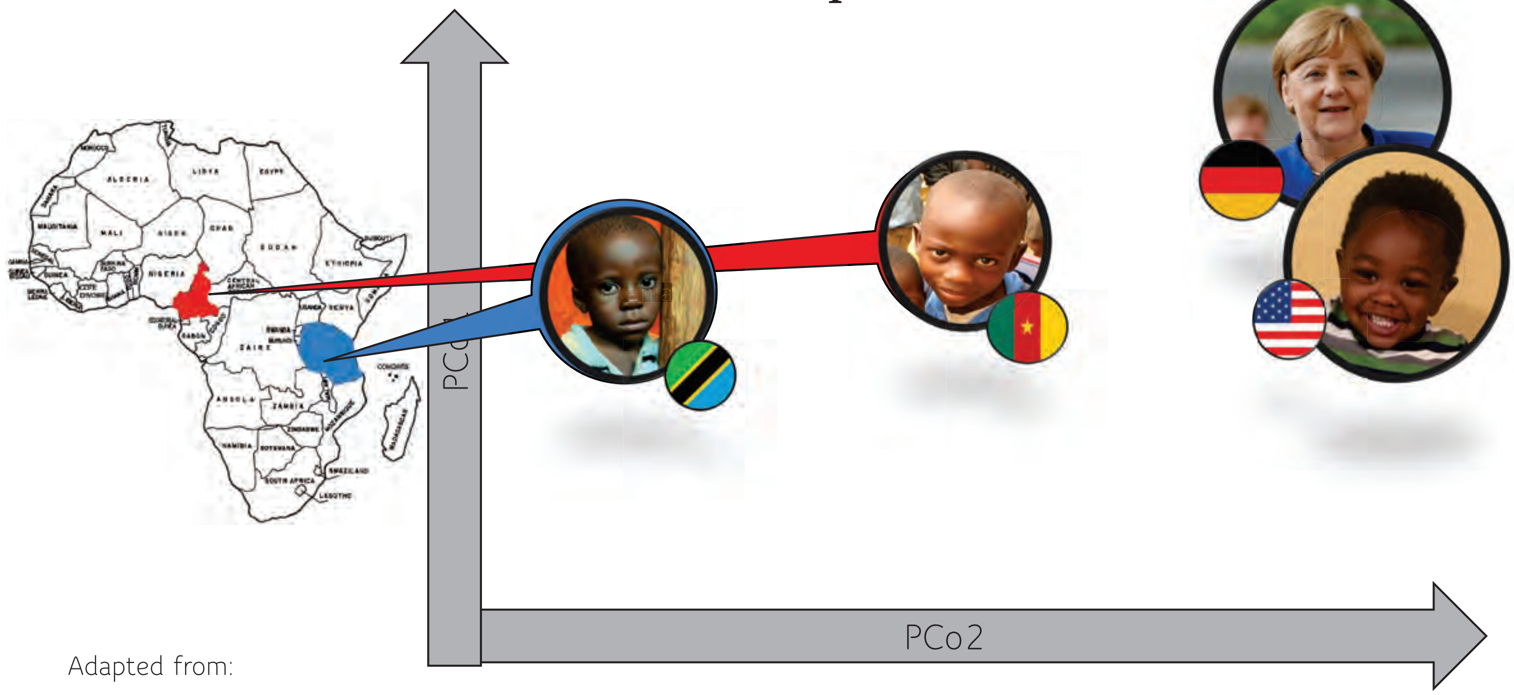
Bacteroidetes



Microbiome = Exposome

Smits *et al.*, *Science* **357**, 802–806 (2017) 25 August 2017

The Microbiome Is a Marker for Environmental Exposure!



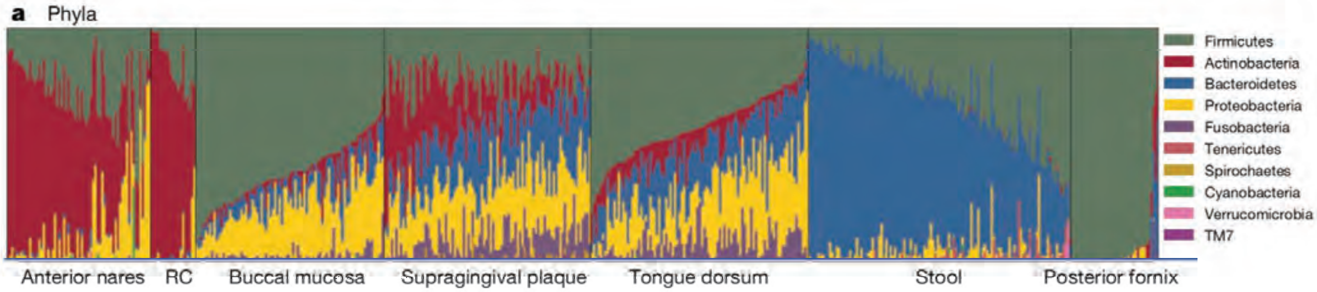
Adapted from:

Smits *et al.*, *Science* **357**, 802–806 (2017) 25 August 2017

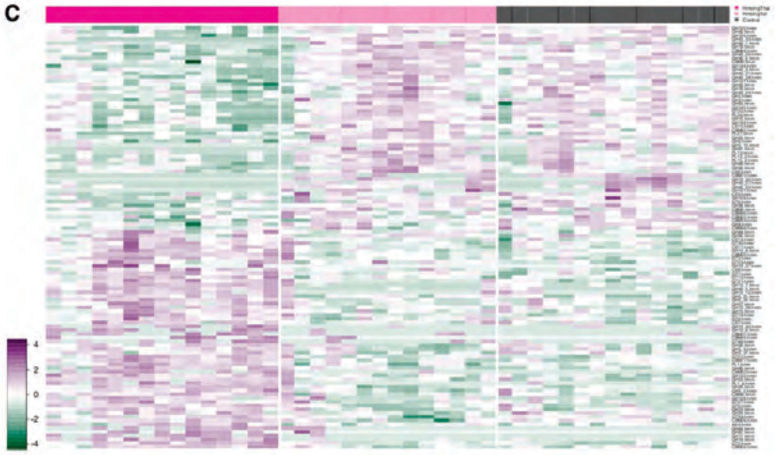
Function over speciation

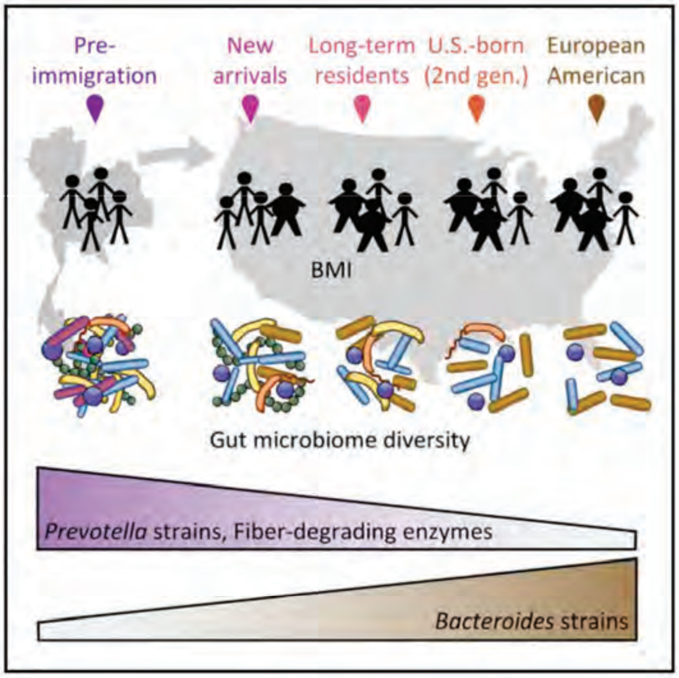
ARTICLE

Structure, function and diversity of the healthy human microbiome



Microbiome Westernizes in function before speciation





Cell

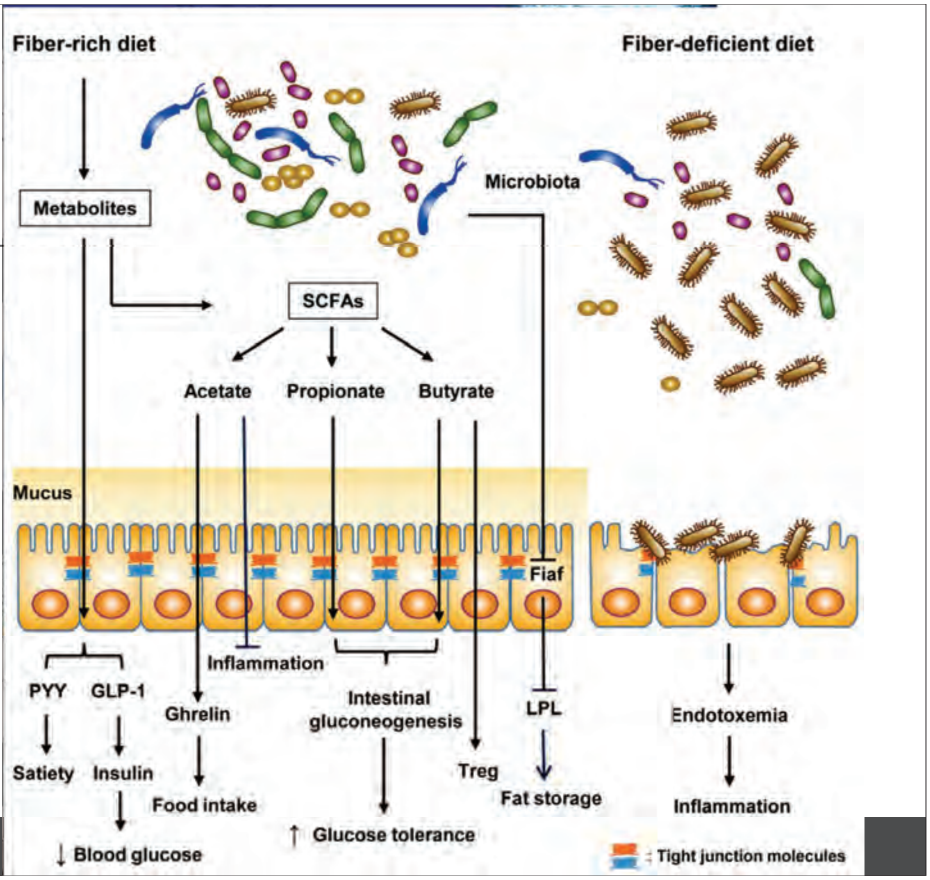
Article

US Immigration Westernizes the Human Gut Microbiome

Microbiome and Cellular immunity

Gut commensals protect intestinal lining, product SCFA

Yonsei Medical Journal
YMJ
pISSN 0513-5796 • eISSN 1976-2437
Open Access, Peer-reviewed, Monthly
eymj.org



Short chain fatty acids (SCFA) drive dendritic cells towards Treg induction


Brief Reviews

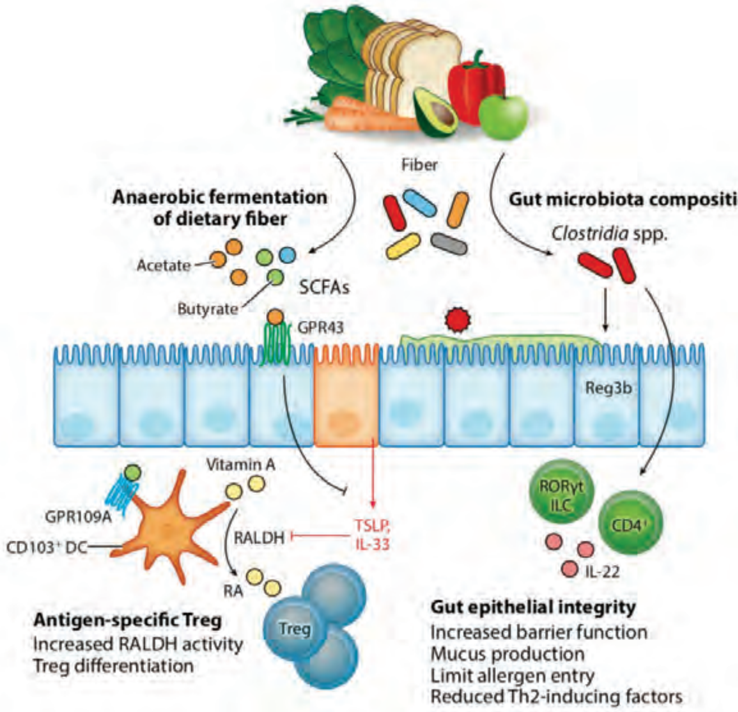
The Journal of Immunology

The Influence of the Microbiome on Allergic Sensitization to Food

Catherine H. Plunkett* and Cathryn R. Nagler*,†

Metabolite-Sensing G Protein–Coupled Receptors—Facilitators of Diet-Related Immune Regulation

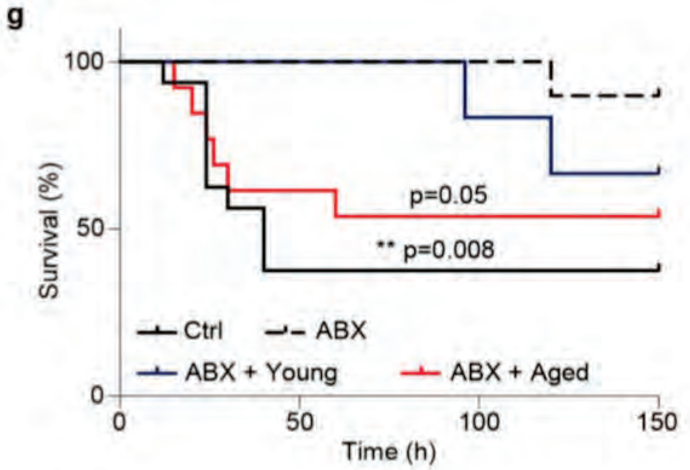
Jian K. Tan,[1] Craig McKenzie,[1] Eliana Mariño,[1,2] Laurence Macia,[1,2,3,4] and Charles R. Mackay[1]



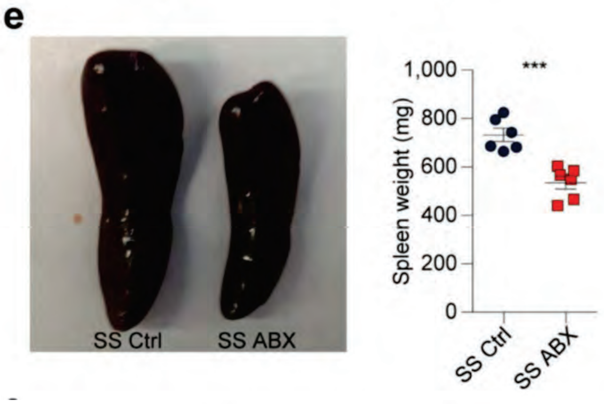
Antigen-specific Treg
Increased RALDH activity
Treg differentiation

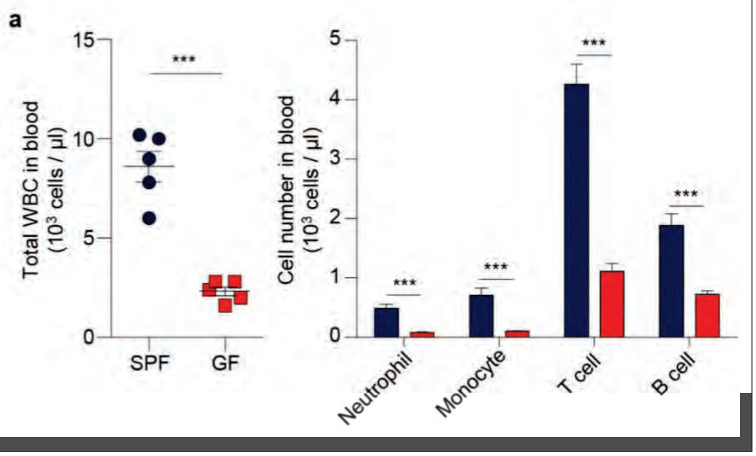
Gut epithelial integrity
Increased barrier function
Mucus production
Limit allergen entry
Reduced Th2-inducing factors

SCFA induce bone marrow immune cell production, protect neutrophils from aging

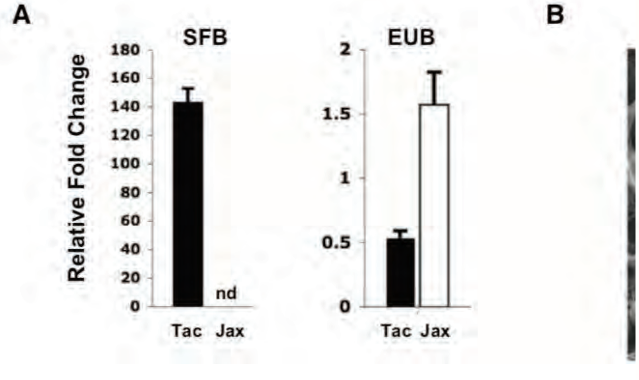


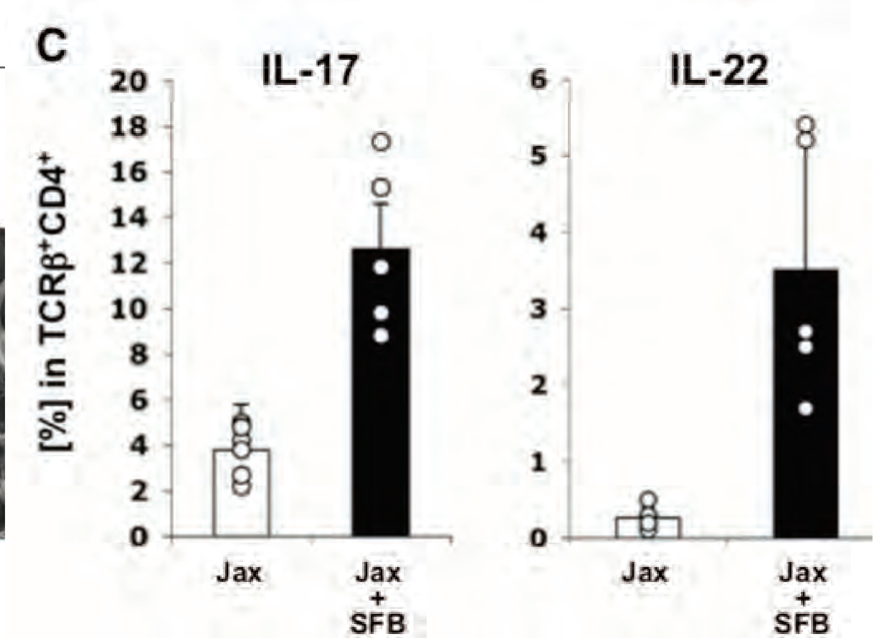
Endotoxemia Challenge





Gut microbiome dictates Th17 differentiation in mice

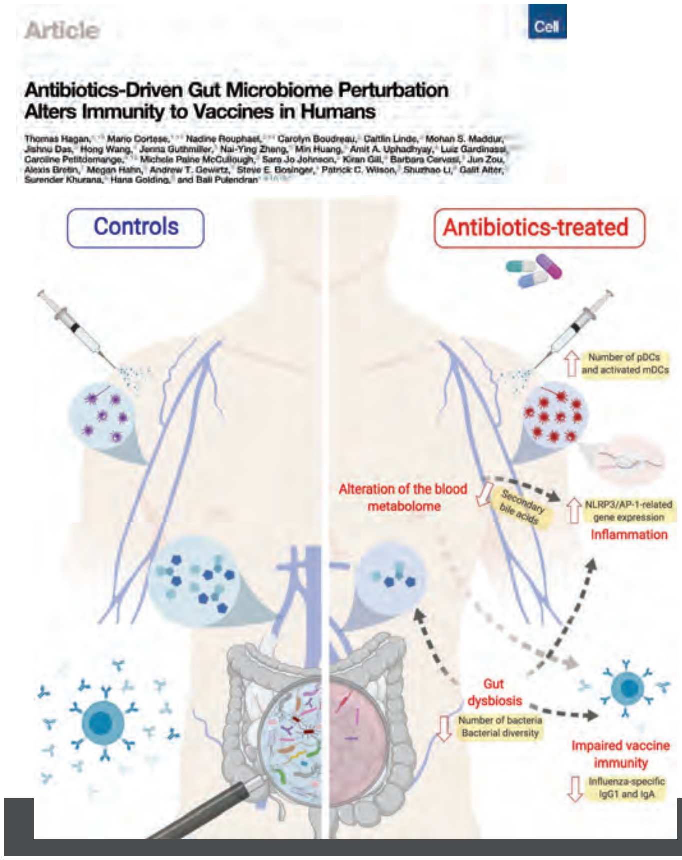




Induction of Intestinal Th17 Cells by Segmented Filamentous Bacteria

Ivaylo I. Ivanov,[1,10] Koji Atarashi,[3,10] Nicolas Manel,[1,11] Eoin L. Brodie,[4,11] Tatsuichiro Shima,[7,11] Ulas Karaoz,[4] Dongguang Wei,[5] Katherine C. Goldfarb,[4] Clark A. Santee,[4] Susan V. Lynch,[6] Takeshi Tanoue,[3] Akemi Imaoka,[7] Kikuji Itoh,[8] Kiyoshi Takeda,[3] Yoshinori Umesaki,[7] Kenya Honda,[3,9,*] and Dan R. Littman[1,2,*]

Microbiome and humoral immunity

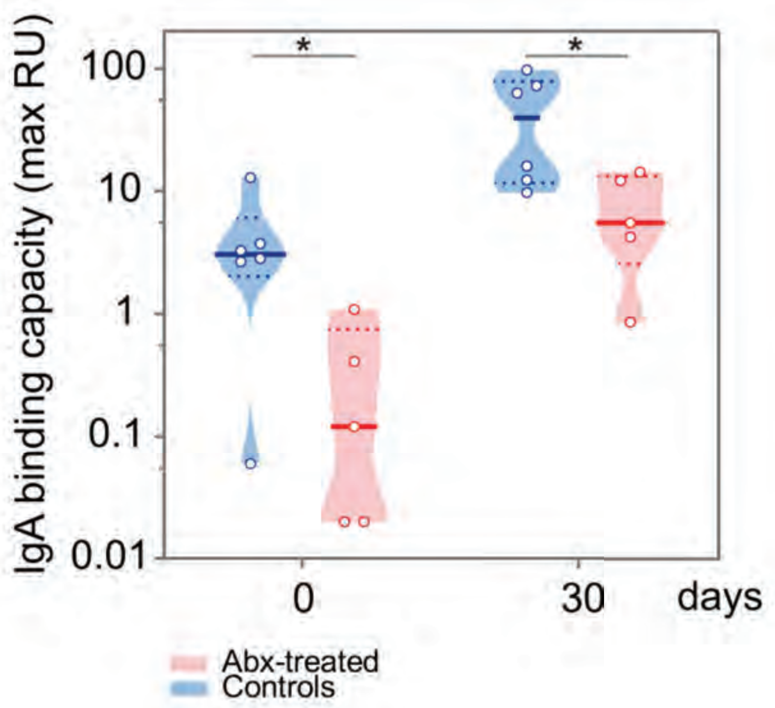


Article

Cell

Antibiotics-Driven Gut Microbiome Perturbation Alters Immunity to Vaccines in Humans

Thomas Hagan, Mario Cortese, Nadine Rouphael, Carolyn Boudreau, Caitlin Linde, Mohan S. Maddur, Jishnu Das, Hong Wang, Jenna Guthmiller, Nai-Ying Zheng, Min Huang, Amit A. Uphadhyay, Luiz Gardinassi, Caroline Petitdemange, Michele Paine McCullough, Sara Jo Johnson, Kiran Gill, Barbara Cervasi, Jun Zou, Alexis Bretin, Megan Hahn, Andrew T. Gewirtz, Steve E. Bosinger, Patrick C. Wilson, Shuzhao Li, Galit Alter, Surender Khurana, Hana Golding, and Bali Pulendran



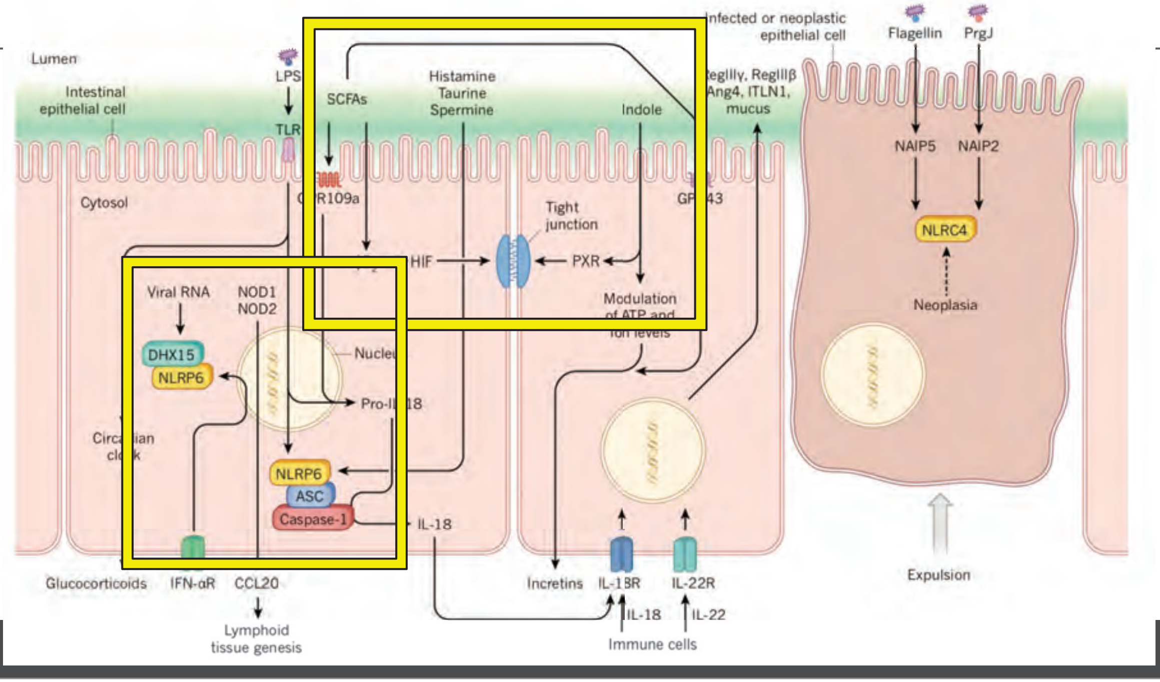
Microbiome and innate immunity

REVIEW

doi:10.1038/nature18847

The microbiome and innate immunity

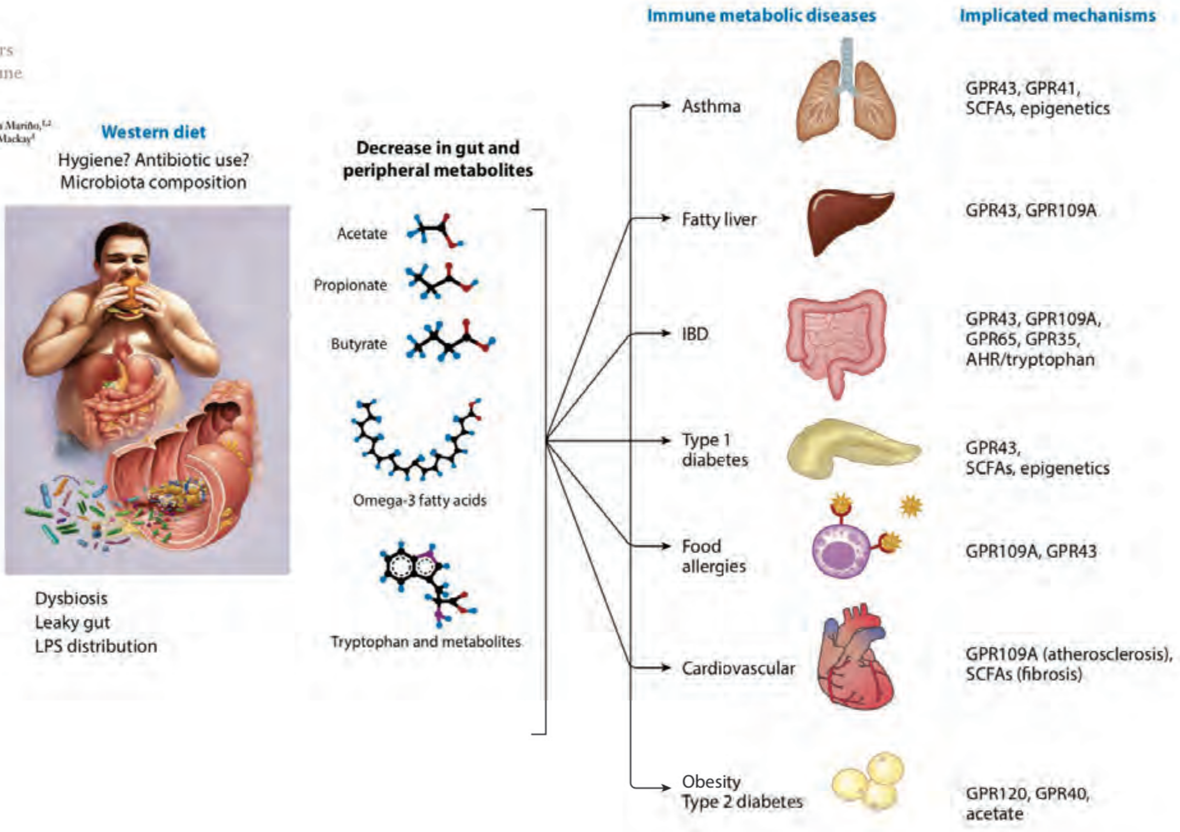
Christoph A. Thaiss, Niv Zmora, Maayan Levy & Eran Elinav



Microbiome and disease states

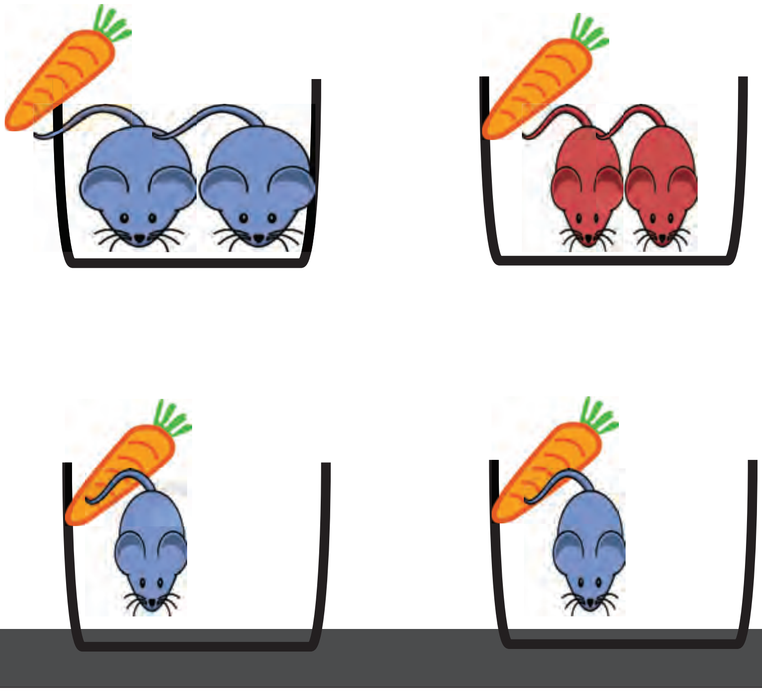
Metabolite-Sensing G Protein–Coupled Receptors—Facilitators of Diet-Related Immune Regulation

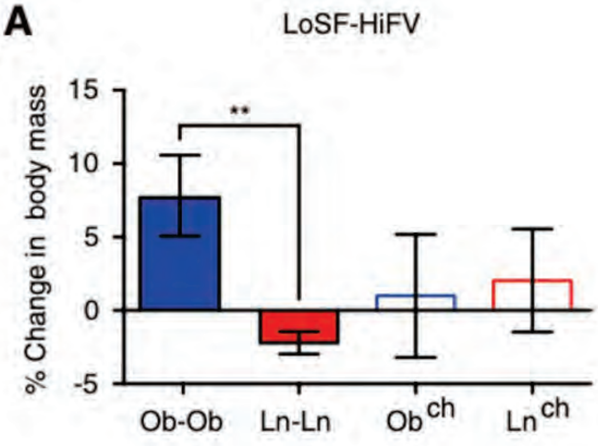
Jian K. Tan,[1] Craig McKenzie,[1] Eliana Mariño,[1,2] Laurence Macia,[1,2,3,4] and Charles R. Mackay[1]



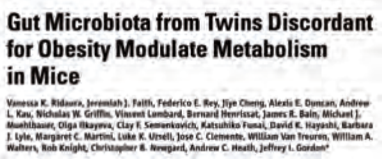
Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

Vanessa K. Ridaura, Jeremiah J. Faith, Federico E. Rey, Jiye Cheng, Alexis E. Duncan, Andrew L. Kau, Nicholas W. Griffin, Vincent Lombard, Bernard Henrissat, James R. Bain, Michael J. Muehlbauer, Olga Ilkayeva, Clay F. Semenkovich, Katsuhiko Funai, David K. Hayashi, Barbara J. Lyle, Margaret C. Martini, Luke K. Ursell, Jose C. Clemente, William Van Treuren, William A. Walters, Rob Knight, Christopher B. Newgard, Andrew C. Heath, Jeffrey I. Gordon*



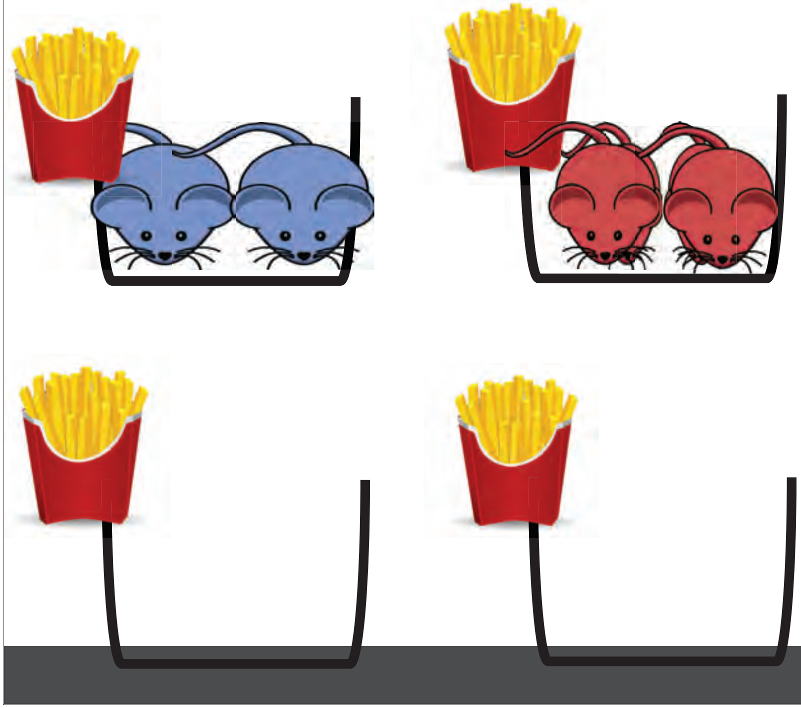


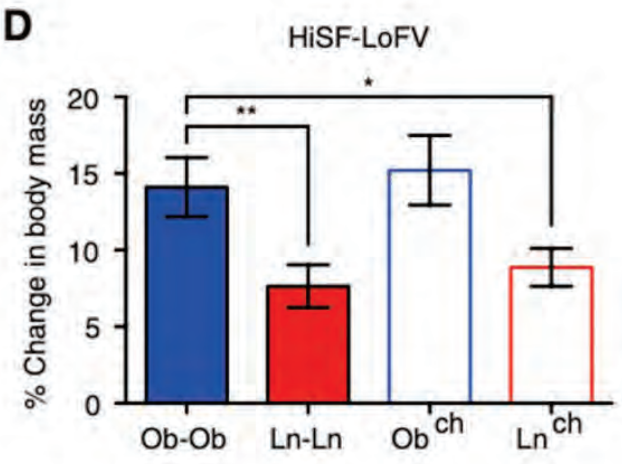
www.sciencemag.org SCIENCE VOL 341 6 SEPTEMBER 2013



Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

Vanessa K. Ridaura, Jeremiah J. Faith, Federico E. Rey, Jiye Cheng, Alexis E. Duncan, Andrew L. Kau, Nicholas W. Griffin, Vincent Lombard, Bernard Henrissat, James R. Bain, Michael J. Muehlbauer, Olga Ilkayeva, Clay F. Semenkovich, Katsuhiko Funai, David K. Hayashi, Barbara J. Lyle, Margaret C. Martini, Luke K. Ursell, Jose C. Clemente, William Van Treuren, William A. Walters, Rob Knight, Christopher B. Newgard, Andrew C. Heath, Jeffrey I. Gordon*





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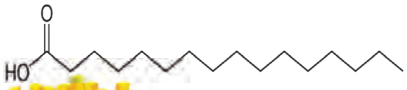
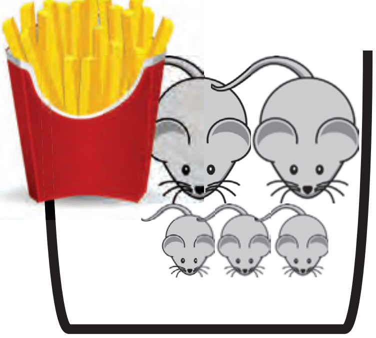
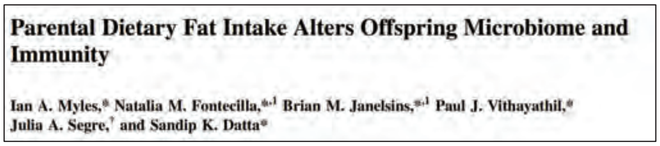




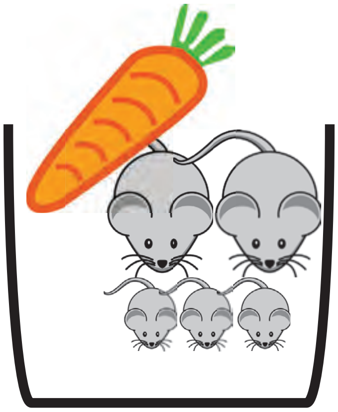


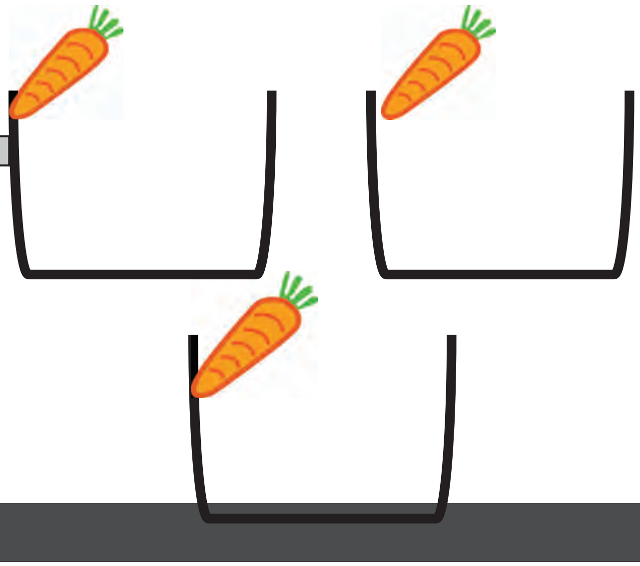
Parental Dietary Fat Intake Alters Offspring Microbiome and Immunity

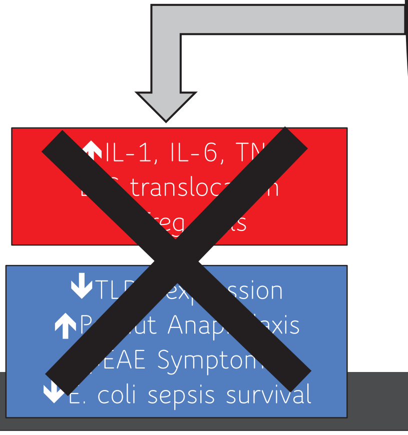
Ian A. Myles,* Natalia M. Fontecilla,*[1] Brian M. Janelsins,*[1] Paul J. Vithayathil,* Julia A. Segre,† and Sandip K. Datta*

Effects of Parental Omega-3 Fatty Acid Intake on Offspring Microbiome and Immunity

Ian A. Myles*, Nathan B. Pincus†, Natalia M. Fontecilla†, Sandip K. Datta



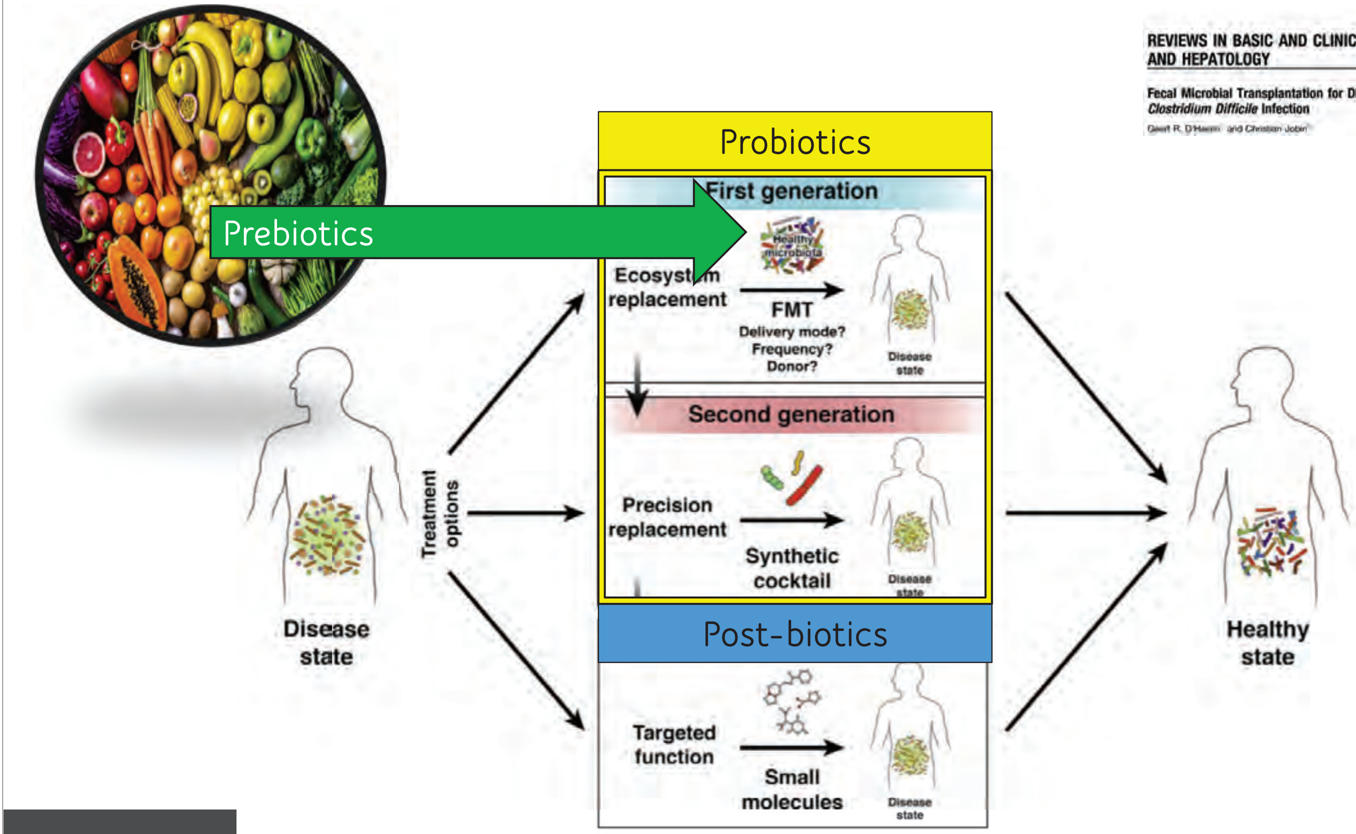




~~↑IL-1, IL-6, TN~~
~~translocat n~~
~~reg ts~~

~~↓TL ex ssion~~
~~↑P ut Anap axis~~
~~EAE Sympton~~
~~↓E. coli sepsis survival~~

Microbiome as therapy



Probiotics

Prebiotics

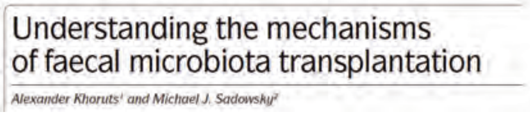
Post-biotics

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

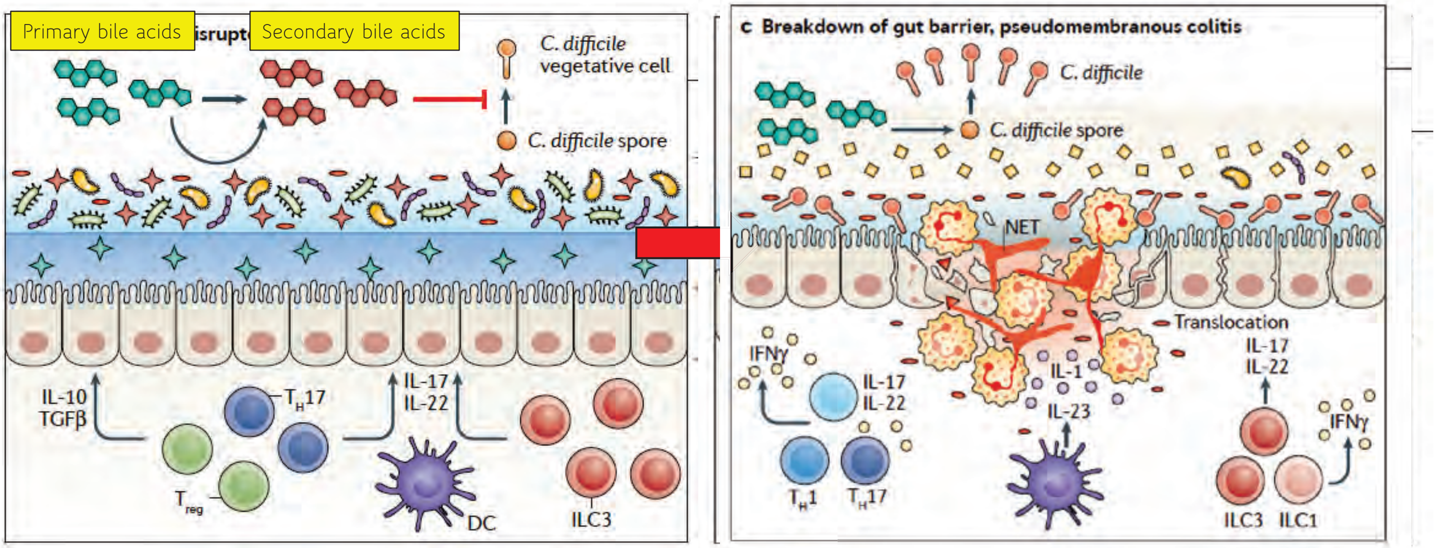
Fecal Microbial Transplantation for Diseases Beyond Recurrent *Clostridium Difficile* Infection

Geert R. D'Haens and Christian Jobin

Commensal-derived secondary bile acids protect against C. diff


Understanding the mechanisms of faecal microbiota transplantation

Alexander Khoruts[1] and Michael J. Sadowsky[2]

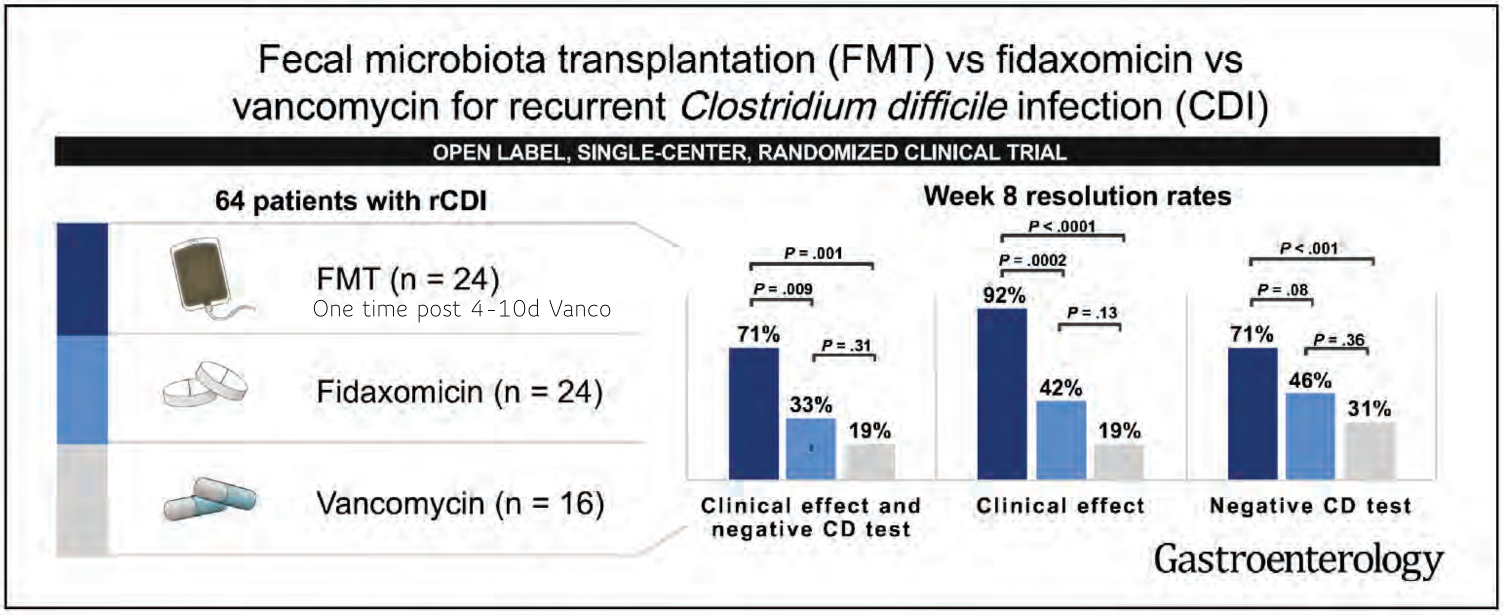


NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY VOLUME 13 | SEPTEMBER 2016 | 511

FMT improves rCDI outcomes


Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent *Clostridium difficile* Infection

Christian Lodberg Hvas,[1] Simon Mark Dahl Jørgensen,[1] Søren Peter Jørgensen,[1] Merete Storgaard,[2] Lars Lemming,[3] Mette Mejlby Hansen,[1] Christian Erikstrup,[4] and Jens Frederik Dahlerup[1]


Fecal microbiota transplantation (FMT) vs fidaxomicin vs vancomycin for recurrent *Clostridium difficile* infection (CDI)

OPEN LABEL, SINGLE-CENTER, RANDOMIZED CLINICAL TRIAL

64 patients with rCDI

- FMT (n = 24)
  One time post 4-10d Vanco
- Fidaxomicin (n = 24)
- Vancomycin (n = 16)

Week 8 resolution rates

Gastroenterology 2019;156:1324–1332

American Journal of Clinical Dermatology (2019) 20:367–377
https://doi.org/10.1007/s40257-018-0404-3

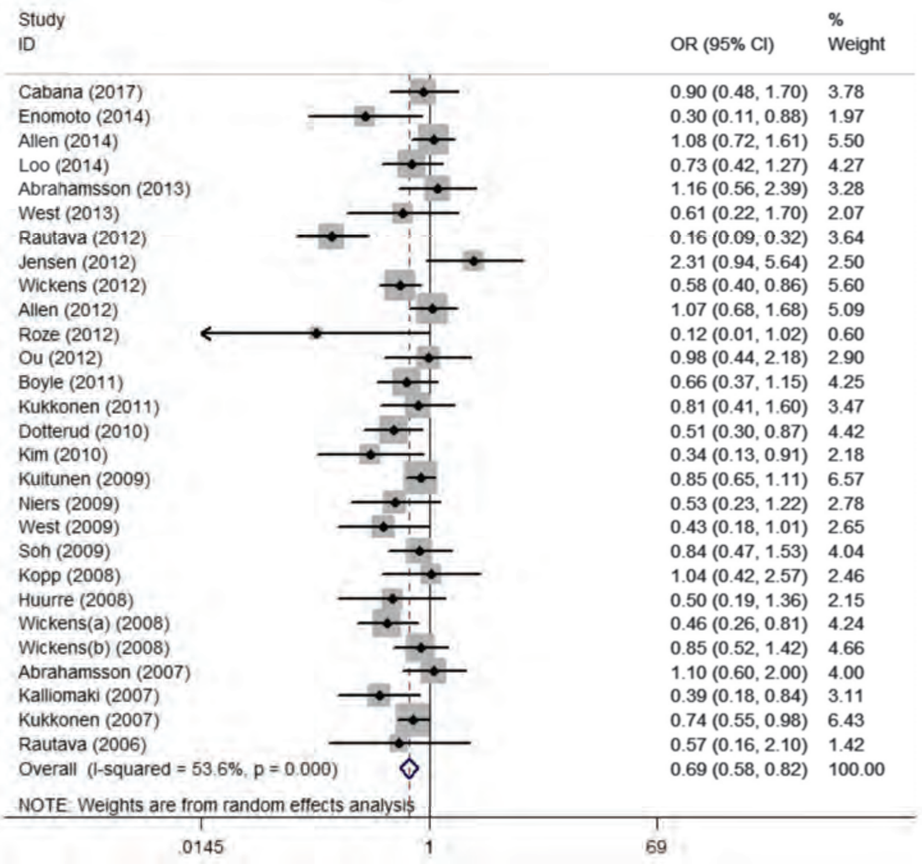
SYSTEMATIC REVIEW

Probiotic Supplementation for Prevention of Atopic Dermatitis in Infants and Children: A Systematic Review and Meta-analysis

Lin Li[1] · Zhen Han[1] · Xiaoping Niu[1] · Guozheng Zhang[1] · Yuliang Jia[1] · Shunguo Zhang[1] · Chiyi He[1]

- Probiotics during both pre-natal and post-natal period protect against eczema in meta-analysis.
- Variable by strain and inclusion criteria

- *B. bifidum BGN4 + B. lactis AD011 + L. acidophilus AD031*
- *LGG + L. acidophilus + B. breve 12*
- *L. rhamnosus HN001 + B. lactis HN019*
- *L. rhamnosus HN001 + B. longum 999 + L. paracaset ST11*
- *B. breve M16V + B. longum BB536*



Study ID	OR (95% CI)	% Weight
Cabana (2017)	0.90 (0.48, 1.70)	3.78
Enomoto (2014)	0.30 (0.11, 0.88)	1.97
Allen (2014)	1.08 (0.72, 1.61)	5.50
Loo (2014)	0.73 (0.42, 1.27)	4.27
Abrahamsson (2013)	1.16 (0.56, 2.39)	3.28
West (2013)	0.61 (0.22, 1.70)	2.07
Rautava (2012)	0.16 (0.09, 0.32)	3.64
Jensen (2012)	2.31 (0.94, 5.64)	2.50
Wickens (2012)	0.58 (0.40, 0.86)	5.60
Allen (2012)	1.07 (0.68, 1.68)	5.09
Roze (2012)	0.12 (0.01, 1.02)	0.60
Ou (2012)	0.98 (0.44, 2.18)	2.90
Boyle (2011)	0.66 (0.37, 1.15)	4.25
Kukkonen (2011)	0.81 (0.41, 1.60)	3.47
Dotterud (2010)	0.51 (0.30, 0.87)	4.42
Kim (2010)	0.34 (0.13, 0.91)	2.18
Kuitunen (2009)	0.85 (0.65, 1.11)	6.57
Niers (2009)	0.53 (0.23, 1.22)	2.78
West (2009)	0.43 (0.18, 1.01)	2.65
Soh (2009)	0.84 (0.47, 1.53)	4.04
Kopp (2008)	1.04 (0.42, 2.57)	2.46
Huurre (2008)	0.50 (0.19, 1.36)	2.15
Wickens(a) (2008)	0.46 (0.26, 0.81)	4.24
Wickens(b) (2008)	0.85 (0.52, 1.42)	4.66
Abrahamsson (2007)	1.10 (0.60, 2.00)	4.00
Kalliomaki (2007)	0.39 (0.18, 0.84)	3.11
Kukkonen (2007)	0.74 (0.55, 0.98)	6.43
Rautava (2006)	0.57 (0.16, 2.10)	1.42
Overall (I-squared = 53.6%, p = 0.000)	0.69 (0.58, 0.82)	100.00

NOTE: Weights are from random effects analysis

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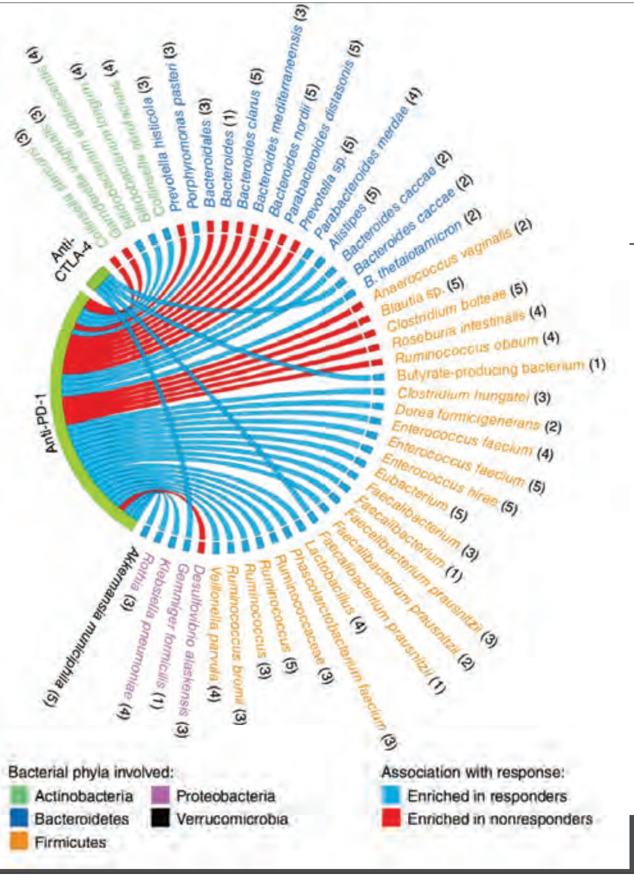
nature medicine | FOCUS | REVIEW ARTICLE

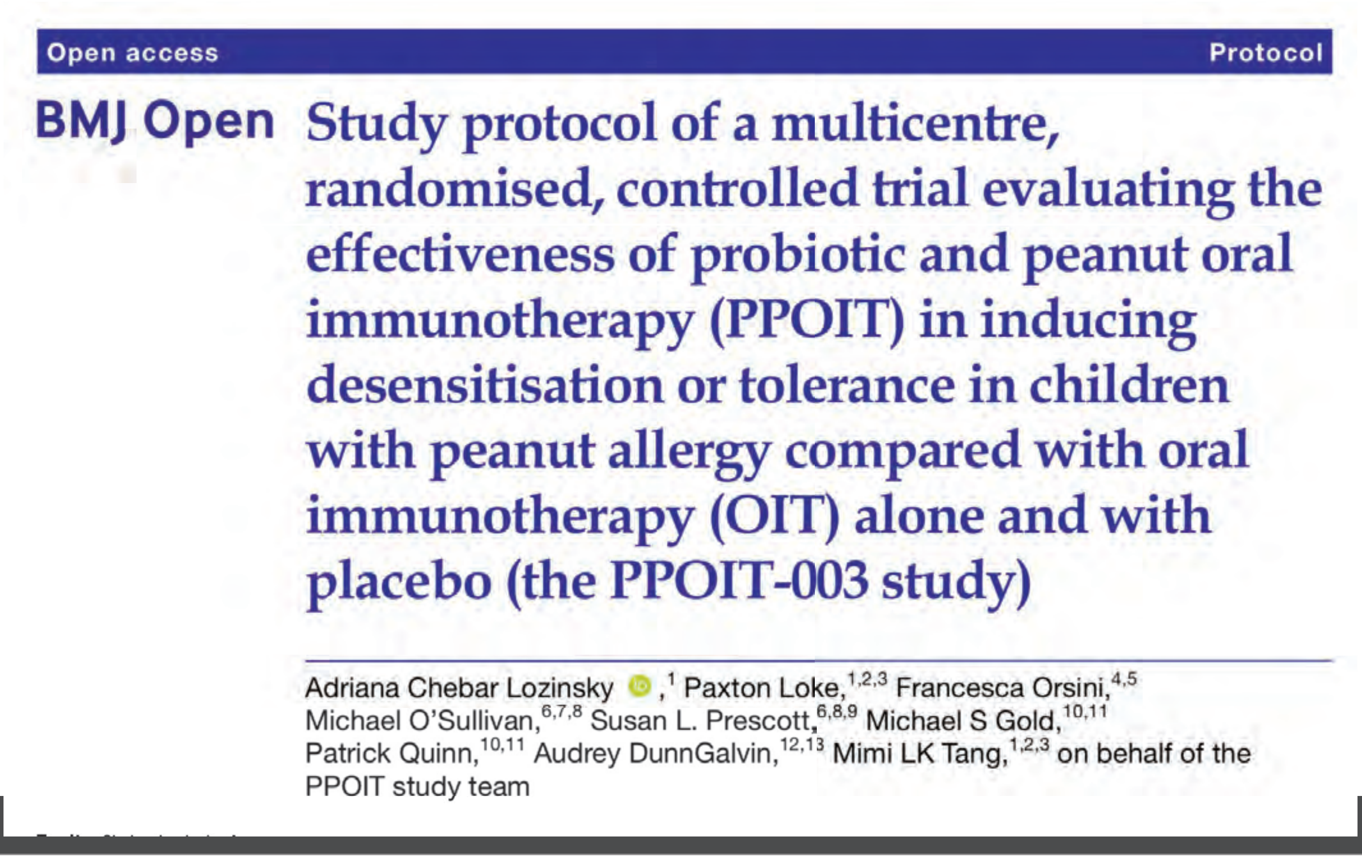
The microbiome, cancer, and cancer therapy

Beth A. Helmink[1], M. A. Wadud Khan[1], Amanda Hermann[1], Vancheswaran Gopalakrishnan[1,2] and Jennifer A. Wargo[1,2,3]*

Gut microbiome can predict outcome to cancer treatment.

Co-treatment with probiotics studies underway.





Open access Protocol

BMJ Open

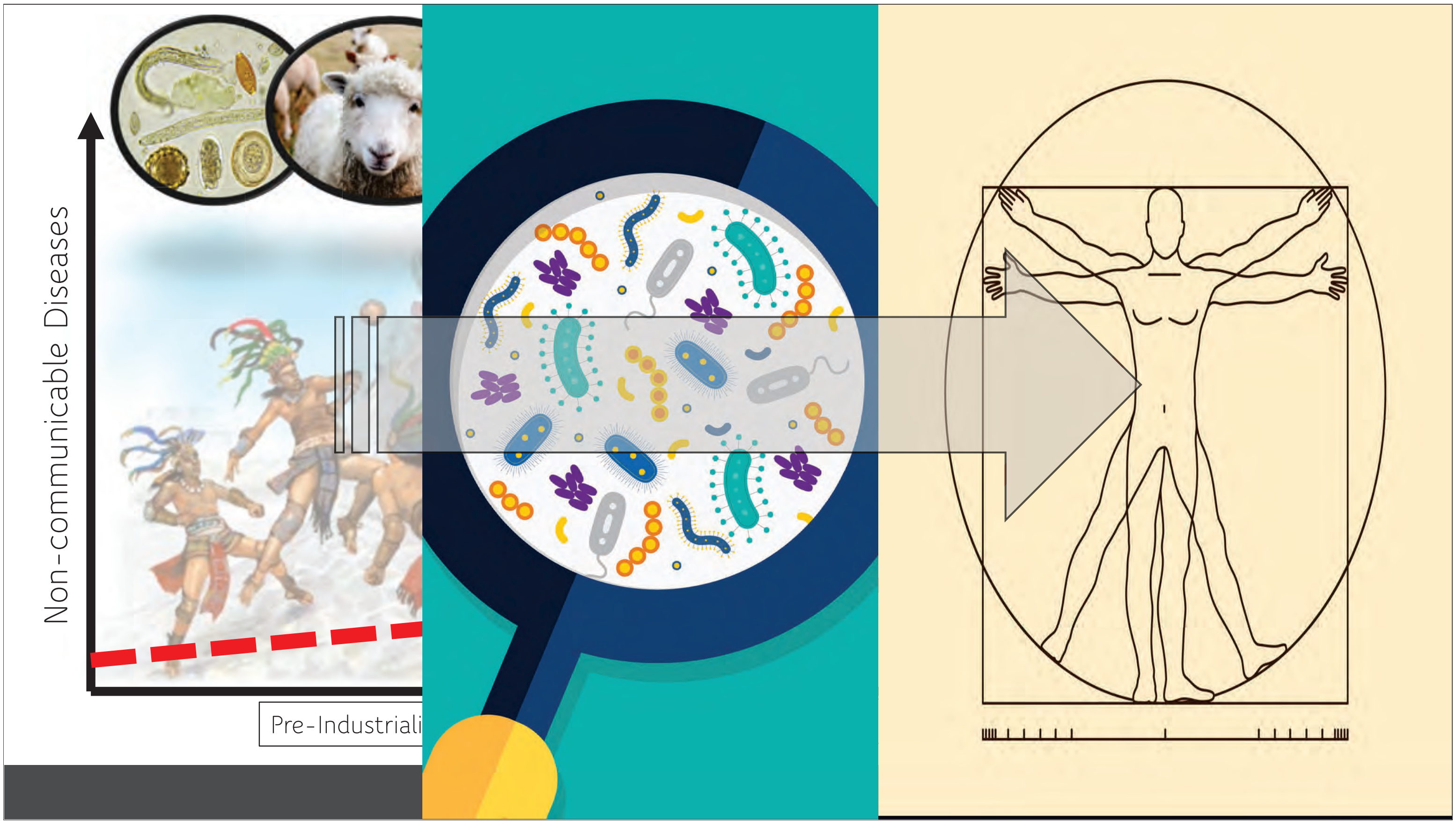
Study protocol of a multicentre, randomised, controlled trial evaluating the effectiveness of probiotic and peanut oral immunotherapy (PPOIT) in inducing desensitisation or tolerance in children with peanut allergy compared with oral immunotherapy (OIT) alone and with placebo (the PPOIT-003 study)

Adriana Chebar Lozinsky,[1] Paxton Loke,[1,2,3] Francesca Orsini,[4,5] Michael O'Sullivan,[6,7,8] Susan L. Prescott,[6,8,9] Michael S Gold,[10,11] Patrick Quinn,[10,11] Audrey DunnGalvin,[12,13] Mimi LK Tang,[1,2,3] on behalf of the PPOIT study team

---

Major take home points

- The field had moved from species based to function based assessment of the microbiome
  - Bacterial behavior is far more fluid than bacterial speciation
- Gut microbes are the best studied: assist in all aspects of immune function
- Microbiome is therapeutic target for disease states
- A healthy microbiome must be sustained with healthy diet (sorry!)


Non-communicable Diseases
Pre-Industriali

PAAA

Pennsylvania Allergy & Asthma Association

Drug Allergy Pearls in the Inpatient Setting

Rebecca Saff, MD, PhD

Friday, June 25, 2021
10:45 a.m. - 11:30 a.m.

Drug Allergy Pearls in the Inpatient Setting

Rebecca Saff, MD, PhD
Division of Rheumatology, Allergy & Immunology
Massachusetts General Hospital
Boston, MA

Disclosures

None

Objectives

- Discuss how to the evaluate and manage patients with drug hypersensitivity reactions
- Discuss diagnostic strategies of drug allergy (including skin testing, desensitization, drug challenge) and understand when each is appropriate
- Review specific drug allergy scenarios for penicillin, NSAIDs, and chemotherapy

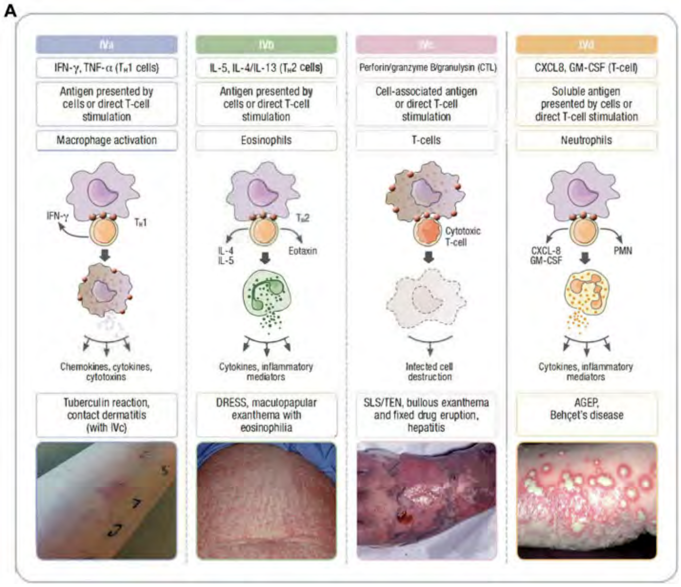
---

Case 1: Delayed hypersensitivity reaction

42 year old female underwent liver transplant. Course complicated by fever, treated with multiple antibiotics including vancomycin, piperacillin-tazobactam, ceftriaxone, metronidazole.

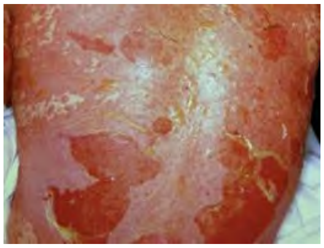
Three weeks into hospitalization she develops fever and rash and the team would like to know which antibiotic was the culprit.

Delayed Hypersensitivity Reaction



Phillips EJ et al. J Allergy Clin Immunol 2019.

Clinical Manifestations of T cell Mediated Reactions



SJS/TEN:
Fever
Blistering lesions
Involvement of multiple mucous membranes
Skin necrosis (Nikolsky sign)

DRESS:
Fever
Lymphadenopathy
Rash >50% body surface area
Organ involvement (liver, kidney)

Peter JG et al. J Allergy Clin Immunol Prac 2017: 547-563.

Clinical Manifestations of T cell Mediated Reactions

AGEP:
Fever
Pustular Rash
Neutrophilic leukocytosis

Fixed Drug Eruption:
Single of multifocal
Flat or bullous
Hyperpigment with healing

Peter JG et al. J Allergy Clin Immunol Prac 2017: 547-563.

Evaluation of Medication Reactions

Consider timing and characteristics

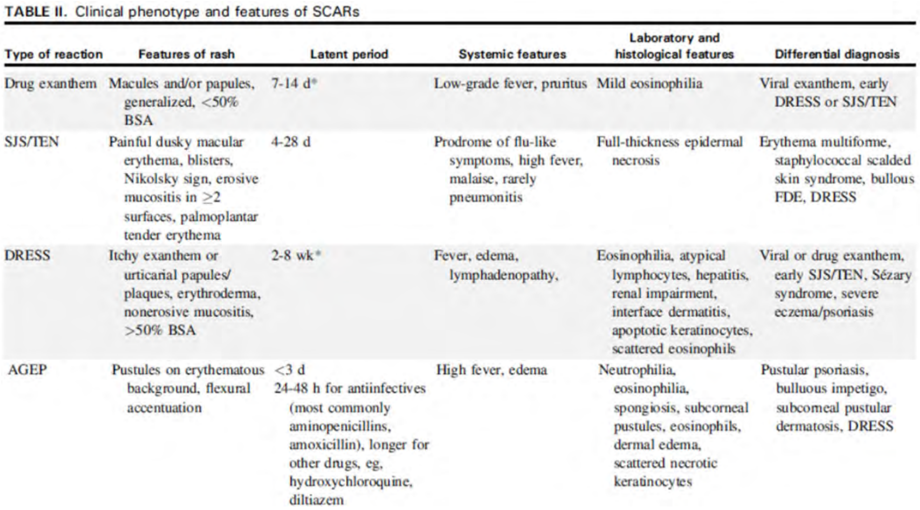


TABLE II. Clinical phenotype and features of SCARs

Type of reaction	Features of rash	Latent period	Systemic features	Laboratory and histological features	Differential diagnosis
Drug exanthem	Macules and/or papules, generalized, <50% BSA	7-14 d*	Low-grade fever, pruritus	Mild eosinophilia	Viral exanthem, early DRESS or SJS/TEN
SJS/TEN	Painful dusky macular erythema, blisters, Nikolsky sign, erosive mucositis in ≥2 surfaces, palmoplantar tender erythema	4-28 d	Prodrome of flu-like symptoms, high fever, malaise, rarely pneumonitis	Full-thickness epidermal necrosis	Erythema multiforme, staphylococcal scalded skin syndrome, bullous FDE, DRESS
DRESS	Itchy exanthem or urticarial papules/plaques, erythroderma, nonerosive mucositis, >50% BSA	2-8 wk*	Fever, edema, lymphadenopathy,	Eosinophilia, atypical lymphocytes, hepatitis, renal impairment, interface dermatitis, apoptotic keratinocytes, scattered eosinophils	Viral or drug exanthem, early SJS/TEN, Sézary syndrome, severe eczema/psoriasis
AGEP	Pustules on erythematous background, flexural accentuation	<3 d 24-48 h for antiinfectives (most commonly aminopenicillins, amoxicillin), longer for other drugs, eg, hydroxychloroquine, diltiazem	High fever, edema	Neutrophilia, eosinophilia, spongiosis, subcorneal pustules, eosinophils, dermal edema, scattered necrotic keratinocytes	Pustular psoriasis, bullous impetigo, subcorneal pustular dermatosis, DRESS

Peter et al, J Allergy Clin Immunol Pract 2017.

Consider most likely culprit

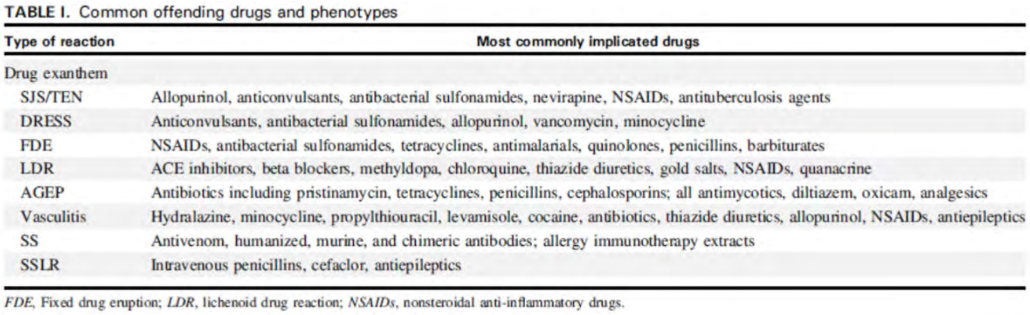


TABLE I. Common offending drugs and phenotypes

Type of reaction	Most commonly implicated drugs
Drug exanthem	
SJS/TEN	Allopurinol, anticonvulsants, antibacterial sulfonamides, nevirapine, NSAIDs, antituberculosis agents
DRESS	Anticonvulsants, antibacterial sulfonamides, allopurinol, vancomycin, minocycline
FDE	NSAIDs, antibacterial sulfonamides, tetracyclines, antimalarials, quinolones, penicillins, barbiturates
LDR	ACE inhibitors, beta blockers, methyldopa, chloroquine, thiazide diuretics, gold salts, NSAIDs, quanacrine
AGEP	Antibiotics including pristinamycin, tetracyclines, penicillins, cephalosporins; all antimycotics, diltiazem, oxicam, analgesics
Vasculitis	Hydralazine, minocycline, propylthiouracil, levamisole, cocaine, antibiotics, thiazide diuretics, allopurinol, NSAIDs, antiepileptics
SS	Antivenom, humanized, murine, and chimeric antibodies; allergy immunotherapy extracts
SSLR	Intravenous penicillins, cefaclor, antiepileptics

FDE, Fixed drug eruption; *LDR*, lichenoid drug reaction; *NSAIDs*, nonsteroidal anti-inflammatory drugs.

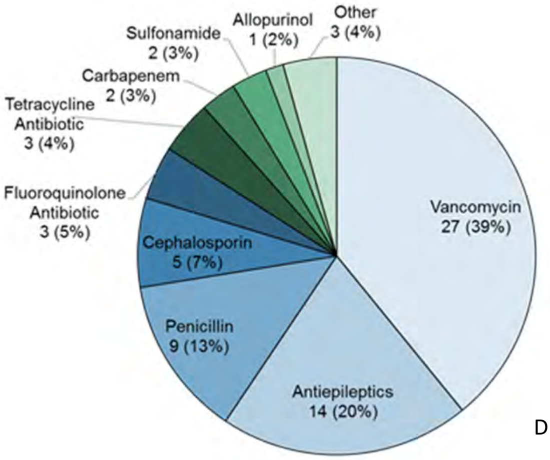
Peter et al, J Allergy Clin Immunol Pract 2017.

DRESS Syndrome

- High mortality (5-40%)
- Clinical criteria, AEC > 1500/mL, rash, and systemic involvement (fever, LAD, hepatitis, nephritis)
- Anticonvulsants, antimicrobials, sulfasalazine, NSAIDs, ACE inhibitors, Beta blockers, dapsone, allopurinol, azathioprine, diltiazem, methimazole, dobutamine

Kardaun *Br J Dermatol* 2007

Causes of DRESS



DRESS Syndrome cohort (n=69)

Wolfson et al, J Allergy Clin Immunol Pract 2019.

HLA Association with DRESS

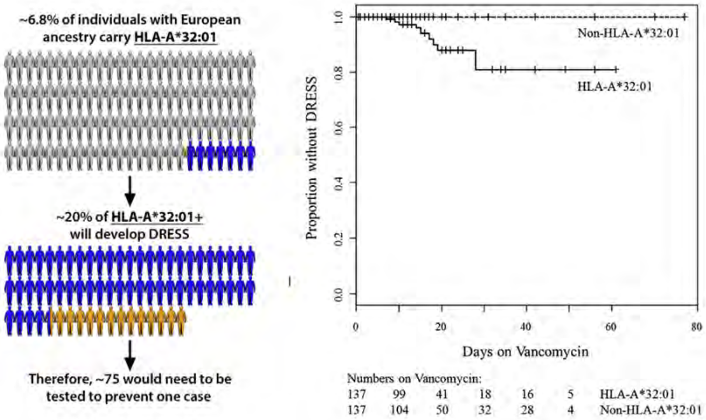
TABLE I. HLA associations with delayed immunologically mediated ADR and implications for translation

Drug phenotype	HLA allele	HLA risk allele prevalence	Disease prevalence	OR	NPV	PPV	NNT	Current use as screening test
Abacavir hypersensitivity syndrome[2,7,8]	B*57:01	5% to 8% European ancestry <1% African/Asia 2.5% African American	8% (3% true HSR and 2% to 7% false-positive diagnosis	960	100% for patch test confirmed	55%	13	Routine in HIV clinical practice in developed world
Allopurinol SJS/TEN and DRESS/DIHS[2,9,10]	B*58:01	9% to 11% Han Chinese 1% to 6% European ancestry†	1/250-1/1000	580	100% (Han Chinese, Southeast Asian)[‖]	3%	250	Selectively used‡
Carbamazepine SJS/TEN[2,11]	B*15:02†,§	10% to 15% Han Chinese <1% Koreans, Japanese <0.1% European ancestry	1% to 4% (Han Chinese)	>1000	100% (Han Chinese, East Asian)	3%	1000	Routine in many Southeast Asian countries
Dapsone DRESS/DHIS[2,12]	B*13:01	2% to 20% Chinese 28% Papuans/Australian Aboriginals 0% European/African 1.5% Japanese <2% African and African American	1% to 4% Han Chinese	20	99.8% (Han Chinese, East Asian)	7.8%	84	Screening programs implemented in China and Southeast Asia, where leprosy is prevalent
Flucloxacillin[13]	B*57:01	5% to 8% European ancestry <1% African/Asia 2.5% African American	8.5/100,000	81	99.99	0.14%	13,819	No

Phillips EJ et al. J Allergy Clin Immunol 2019.

HLA Association with DRESS

HLA-A*32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms



~6.8% of individuals with European ancestry carry HLA-A*32:01

~20% of HLA-A*32:01+ will develop DRESS

Therefore, ~75 would need to be tested to prevent one case

Numbers on Vancomycin:						
137	99	41	18	16	5	HLA-A*32:01
137	104	50	32	28	4	Non-HLA-A*32:01

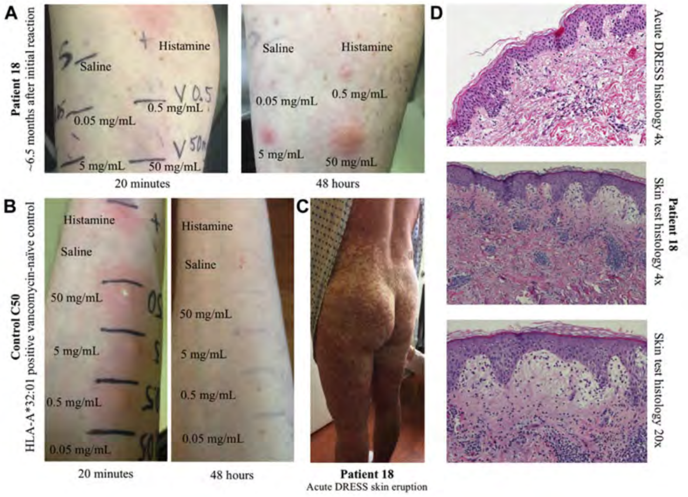
Konvinse KC et al, J Allergy Clin Immunol 2019.

Testing: What to Test and When to Test?

Type of Reaction	Utility of Delayed Read Skin Testing
Drug Exanthem ("maculopapular rash")	Patch or Intradermal
Abacavir hypersensitivity	Patch
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Patch or intradermal
Stevens-Johnson Syndrome Toxic Epidermal Necrolysis (SJS) Toxic epidermal necrolysis (TEN)	Patch or no testing
Acute generalized exanthematous pustulosis	Patch or intradermal
Drug-induced liver disease (DILI) or Drug-induced interstitial nephritis	No
Vasculitis	Not Usually
Fixed Drug Eruption	Intralesional Patch or intradermal

Adapted from Phillips et al, *JACI In Pr* 2018.

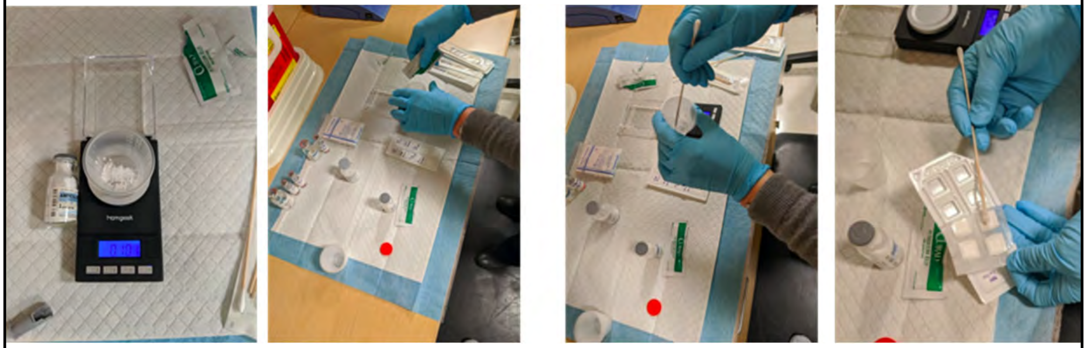
Intradermal Testing



Konvinse KC et al, J Allergy Clin Immunol 2019.

Patch Testing

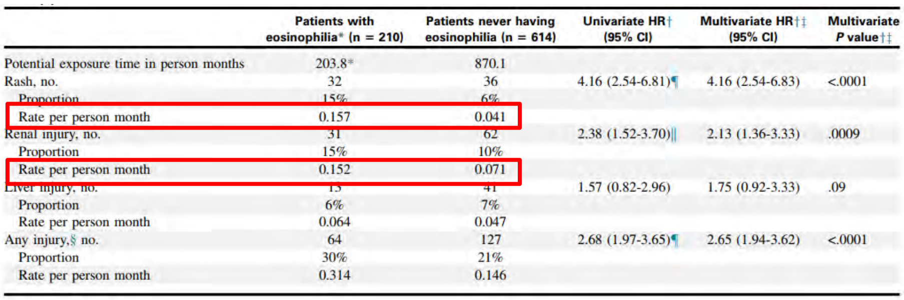
- Patients must have intact and non-inflamed skin for patch testing
- Can remain on almost all drugs including beta-blockers and anti-histamines
  - Patients should be preferably off steroids for 1 month or on < 20 mg of prednisone equivalent
  - There is no standardized positive control for delayed intradermal testing or patch testing
  - If a negative test occurs on steroids or any other immunosuppressive, patch testing or delayed intradermal testing should be repeated off steroids



Case 2: A case of eosinophilia

60 year old female with diabetic food ulcer develops eosinophilia while on vancomycin. Absolute eosinophil count of 980 with no rash, normal liver function, and normal kidney function. Should the antibiotic be changed?

Peripheral Blood Eosinophilia and Relationship to Hypersensitivity Reactions

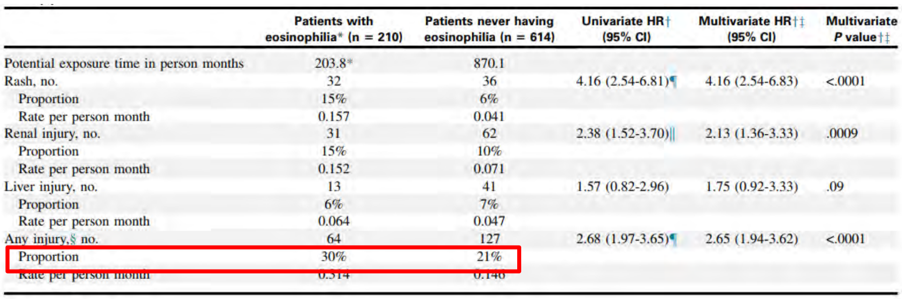


	Patients with eosinophilia* (n = 210)	Patients never having eosinophilia (n = 614)	Univariate HR† (95% CI)	Multivariate HR†‡ (95% CI)	Multivariate P value†‡
Potential exposure time in person months	203.8*	870.1			
Rash, no.	32	36	4.16 (2.54-6.81)¶	4.16 (2.54-6.83)	<.0001
Proportion	15%	6%			
Rate per person month	0.157	0.041			
Renal injury, no.	31	62	2.38 (1.52-3.70)‖	2.13 (1.36-3.33)	.0009
Proportion	15%	10%			
Rate per person month	0.152	0.071			
Liver injury, no.	13	41	1.57 (0.82-2.96)	1.75 (0.92-3.33)	.09
Proportion	6%	7%			
Rate per person month	0.064	0.047			
Any injury,§ no.	64	127	2.68 (1.97-3.65)¶	2.65 (1.94-3.62)	<.0001
Proportion	30%	21%			
Rate per person month	0.314	0.146			

Patients with eosinophilia are 4 times as likely to have rash and twice as likely to have renal injury as patients without eosinophilia

Blumenthal et al, *JACI* 2015.

Peripheral Blood Eosinophilia and Relationship to Hypersensitivity Reactions



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Renal injury, no.	31	62	2.38 (1.52-3.70)‖	2.13 (1.36-3.33)	.0009
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Rate per person month	0.152	0.071			
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Proportion	30%	21%			
Rate per person month	0.314	0.146			

Only 30% will develop any symptoms, so can continue antibiotics with close monitoring

Blumenthal et al, *JACI* 2015.

Case 3: Aspirin Hypersensitivity

A 62 year old patient reports hives after taking ibuprofen 20 years ago. He was told to avoid all ASA and NSAIDs and has only been using Tylenol.

He was admitted with chest pain and is going to the cath lab. The team calls as they would like to give him aspirin.

NSAID Hypersensitivity: Classification

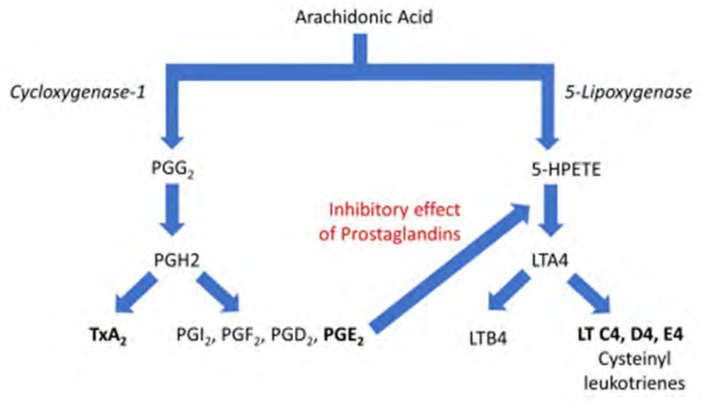
1. Rhinitis and asthma induced by NSAIDs
2. Chronic urticaria or angioedema aggravated by NSAIDs
3. Urticaria or angioedema induced by multiple NSAIDs
4. Single NSAID-induced reactions
5. Delayed NSAID reactions

Classification of NSAID Reactions

	Underlying Disease	Cross-Reactivity with other NSAIDs	First exposure reaction	Timing of reaction	Able to desensitize?
NSAID-induced rhinitis and asthma	AERD	Yes	Yes	Typically 1-3 hours	Yes
NSAID-exacerbated urticaria/angioedema	CIU	Yes	Yes	Typically 1-4 hours	No
NSAID-induced urticaria/angioedema	None	Yes	Yes	Varies from minutes to hours	Yes
Single NSAID-induced reactions	None	No	No	Immediate (minutes)	Yes
Delayed NSAID reactions	None	No	No	>24 hours	No

Adapted from Gollapudi RR et al, JAMA 2004

COX Inhibition in NSAID Reactions



Gnanenthiran et al, Am Heart J. 2018.

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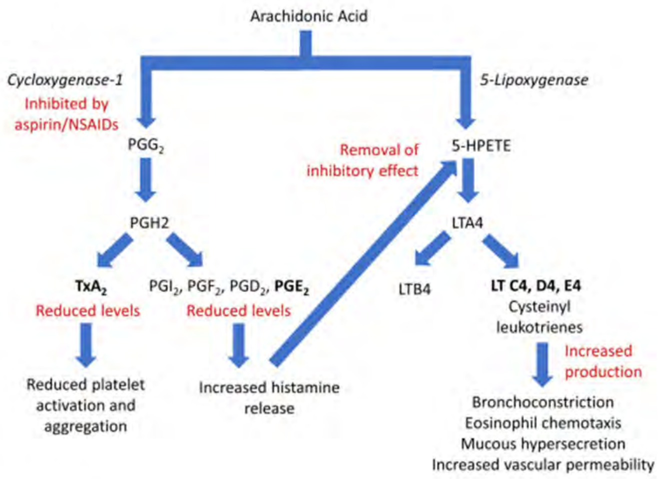
COX Inhibition in NSAID Reactions



Arachidonic Acid

Cycloxygenase-1

Inhibited by aspirin/NSAIDs

PGG_2

PGH2

TxA_2

Reduced levels

Reduced platelet activation and aggregation

PGI_2, PGF_2, PGD_2, **PGE_2**

Reduced levels

Increased histamine release

Removal of inhibitory effect

5-Lipoxygenase

5-HPETE

LTA4

LTB4

LT C4, D4, E4

Cysteinyl leukotrienes

Increased production

Bronchoconstriction
Eosinophil chemotaxis
Mucous hypersecretion
Increased vascular permeability

Gnanenthiran et al, Am Heart J 2018.

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Is this a class or drug-specific reaction?

Can we consider aspirin test dose?

NSAIDs: Similar Chemical Structures

Group	Drugs
Salicylic acid derivates	Aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfalazine, olsalazine
Para-aminophenol derivates	Acetaminophen
Indol and indene acetic acids	Indomethacin, sulindac, etodolac
Heteroaryl acetic acid	Tolmetin, diclofenac, ketorolac
Arylpropionic acid	Ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin
Anthranilic acid (fenamates)	Mefenamic acid, meclofenamic acid
Enolic acid	Oxicams (piroxicam, tenoxicam), pyrazolidinediones (phenylbutazone, oxyfentathrazone)
Alkalones	Nabumetone
Pyrazolic derivates	Antipyrine, aminopyrine, dipyrone

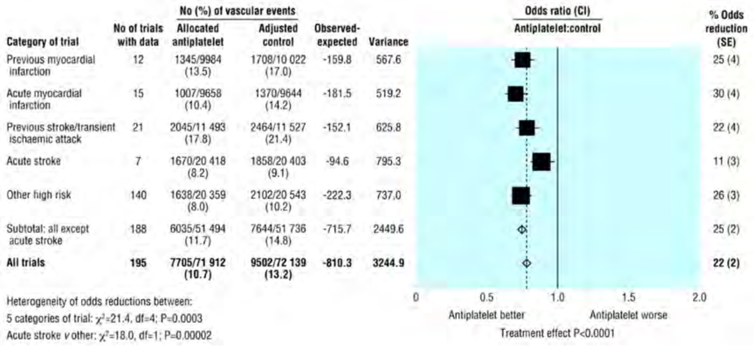
Not unusual to develop an HSR even after years of symptom-free use

Sanchez-Borges at al, Pharmaceuticals 2010.
Kowalski et al, Immunol Allergy Clin N Am 2013.

Aspirin Allergy in CAD Patient

Aspirin significantly reduces cardiovascular events

Guidelines recommend aspirin therapy indefinitely for patients with CAD unless there is a clear contraindication (active bleeding, major coagulopathy, true aspirin allergy)



Category of trial	No of trials with data	No (%) of vascular events Allocated antiplatelet	No (%) of vascular events Adjusted control	Observed-expected	Variance	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6	25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2	30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8	22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3	11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6	25 (2)
All trials	**195**	**7705/71 912 (10.7)**	**9502/72 139 (13.2)**	**-810.3**	**3244.9**	**22 (2)**

Heterogeneity of odds reductions between:
5 categories of trial: χ^2=21.4, df=4; P=0.0003
Acute stroke *v* other: χ^2=18.0, df=1; P=0.00002

Feng et al, Ann Allergy Asthma Immunol 2013.

NSAID Adverse Reactions are Common

- 1.5-3.5% of the general population
    - < 20% of reactions with hypersensitivity by history
- Evidence for reported NSAID allergy as a risk factor for poor outcomes
- No skin testing available
    - Reliance on clinical history +/- drug challenge
- No standardized challenge protocols

Blumental et al, J Allergy Clin Immunol Pract 2017.
Li et al, J Allergy Clin Immunol 2020.

Safety of Aspirin Challenge/Test Dose

In an evaluation of 30 patients with a history of “aspirin allergy”, all but 2 had negative challenges to aspirin

In a study of 275 patients with a history of NSAID hypersensitivity, 214 (77.8%) patients tolerated the suspected NSAID

Viola et al, Clin Exp Allergy 2011.
Woessner et al, Immunol Allergy Clin North Am 2013.

2-step NSAID oral challenge

	No Reaction	Immediate Reaction	Delayed Reaction	Total
Aspirin	114	15	3	132
Ibuprofen	52	6	2	60
Naproxen	8	1	1	10
Other NSAID*	2	1	0	3
Total	176 (85.9%)	23 (11.2%)	6 (2.9%)	205 (100%)

86% of patients had no reaction
62.5% with reactions occurred at >60 minutes

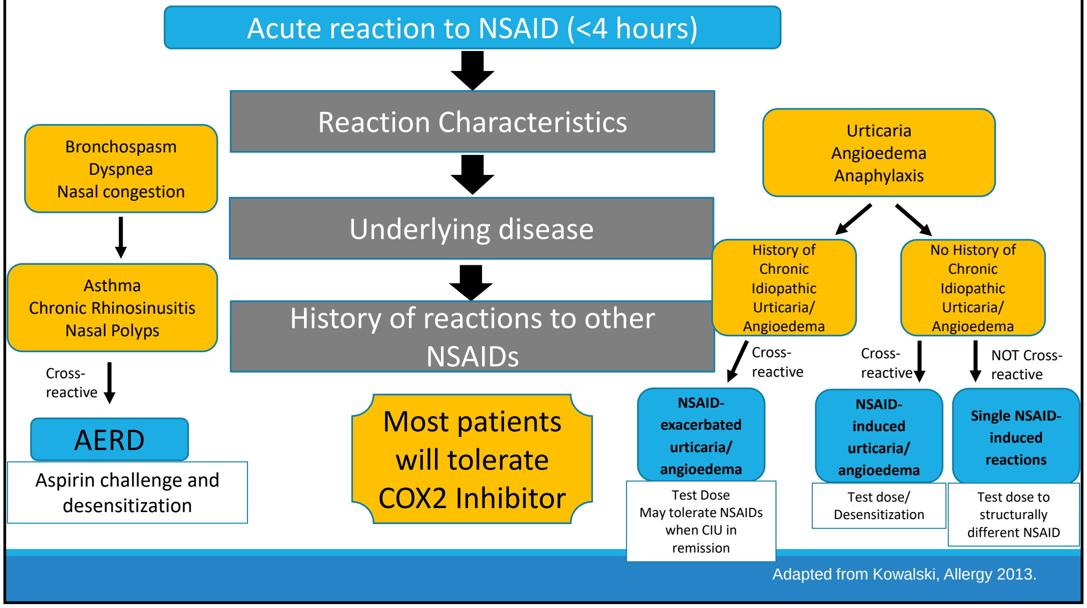
Li et al, AAAAI oral abstract 2021.

Proposed NSAID Drug Challenge Outpatient Protocol (non-AERD)	
Step 1	1/10-1/4 dose*, 60 min observation
Step 2	Remainder of dose, 120 min observation

Vitals +/- spirometry prior to each step, and after challenge complete.
Repeat at onset of any symptoms of a reaction.
*depending on specific oral medication dose availability

Li et al, AAAAI oral abstract 2021.

Evaluation of NSAID Hypersensitivity



Acute reaction to NSAID (<4 hours)

Reaction Characteristics

Underlying disease

History of reactions to other NSAIDs

Bronchospasm
Dyspnea
Nasal congestion

Asthma
Chronic Rhinosinusitis
Nasal Polyps

Cross-reactive

AERD

Aspirin challenge and desensitization

Most patients will tolerate COX2 Inhibitor

Urticaria
Angioedema
Anaphylaxis

History of Chronic Idiopathic Urticaria/ Angioedema

Cross-reactive

NSAID-exacerbated urticaria/ angioedema

Test Dose
May tolerate NSAIDs when CIU in remission

No History of Chronic Idiopathic Urticaria/ Angioedema

Cross-reactive

NSAID-induced urticaria/ angioedema

Test dose/ Desensitization

NOT Cross-reactive

Single NSAID-induced reactions

Test dose to structurally different NSAID

Adapted from Kowalski, Allergy 2013.

Aspirin Desensitization

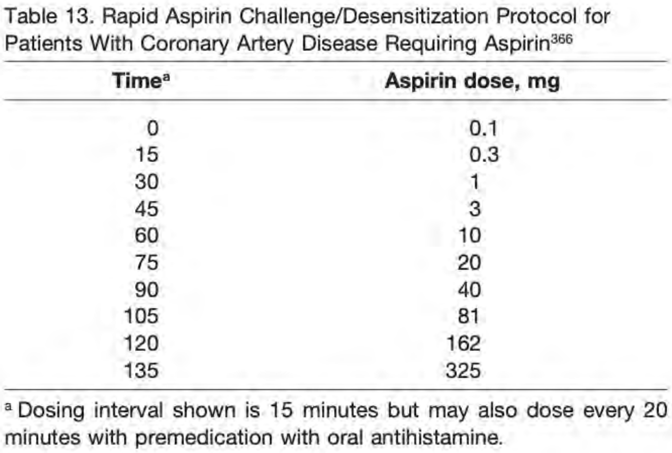


Table 13. Rapid Aspirin Challenge/Desensitization Protocol for Patients With Coronary Artery Disease Requiring Aspirin[366]

Time[a]	Aspirin dose, mg
0	0.1
15	0.3
30	1
45	3
60	10
75	20
90	40
105	81
120	162
135	325

[a] Dosing interval shown is 15 minutes but may also dose every 20 minutes with premedication with oral antihistamine.

Joint Task Force on Practice Parameters, Ann Allergy Asthma Immunol 2010.

Aspirin Desensitization

330 patients with a self-reported history of ASA sensitivity and presenting with either an ACS or known/suspected CAD

History of:
- Mucocutaneous reactions in 246 patients (74.5%)
    - Urticaria in 177 patients (53.6%)
    - Angioedema in 69 patients (20.9%)
- Respiratory sensitivity (asthma and rhinitis and broncospasm) in 65 patients (19.7%)
- Anaphylaxis in 19 patients (5.8%)

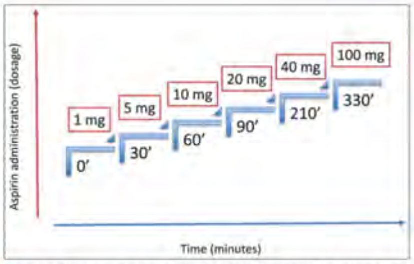


Figure. Rapid aspirin desensitization protocol. Six sequential doses of aspirin (1, 5, 10, 20, 40, and 100 mg) administered orally for 5.5 h.

Rossini et al. Circ Cardiovasc Interv 2017.

Aspirin Desensitization

- Successful in 315 patients (95.4%)
    - Including history of anaphylaxis
- 15 patients (4.6%) failed
    - 10 with history of urticaria and angioedema
    - 5 with history of respiratory reaction (asthma, dyspnea, or bronchospasm)

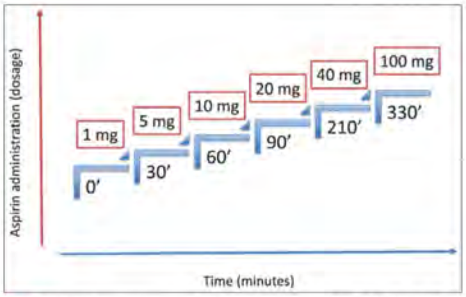


Figure. Rapid aspirin desensitization protocol. Six sequential doses of aspirin (1, 5, 10, 20, 40, and 100 mg) administered orally for 5.5 h.

Rossini et al. Circ Cardiovasc Interv 2017.

Case 5: Chemotherapy Reaction

A 54 year old female recently diagnosed with recurrent ovarian cancer.

She had previously been treated with 6 cycles of carboplatin and gemzar.

On her second cycle (8th lifetime dose), within minutes of starting the infusion, she developed bilateral palmar pruritus, erythema, chest tightness and hypotension.

Her infusion was stopped and she was treated with IV diphenhydramine and steroids.

Her symptoms improved after 30 minutes.

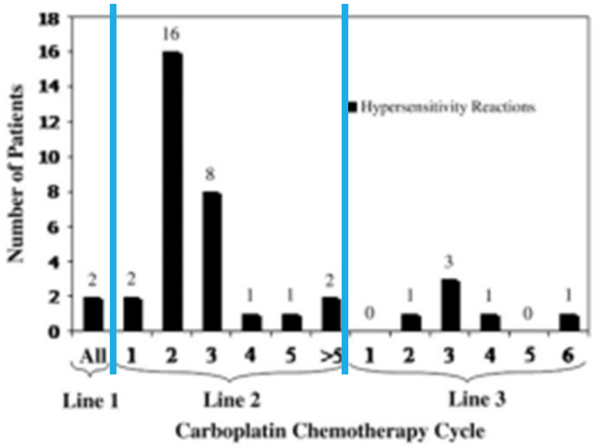
Did this patient have a hypersensitivity reaction to carboplatin?

Classic Symptoms of Hypersensitivity Reactions

Immediate reactions	N	Percent
Oropharynx	6	15.8
Throat tightness	5	13.2
Tongue swelling	2	5.3
Cardiovascular	11	28.9
Tachycardia/bradycardia	3	7.9
Blood pressure alterations	4	10.5
Chest pain	1	2.6
Dizzy/lightheaded	4	10.5
Pulmonary	11	28.9
Chest tightness	3	7.9
Shortness of breath	5	13.2
Cough	1	2.6
Nasal symptoms	5	13.2
Gastrointestinal	14	36.8
Nausea/vomiting	14	36.8
Genitourinary	2	5.3
Urethral burning	2	5.3
Cutaneous	30	78.9
Erythema/flushing	23	60.5
Pruritus	21	55.3
Urticaria	5	13.2
Palmar erythema	19	50.0
Delayed reactions		
Cutaneous	3	7.9
Rash	1	2.6
Pruritus	2	5.3
Erythema	1	2.6
Combined cutaneous reactions	33	86.8

Hesterberg et.al, J Allergy Clin Immunol 2009

Timing of Initial Hypersensitivity Reaction



Hesterberg et al, J Allergy Clin Immunol 2009.

Was this a HSR to Carboplatin?

Bilateral palmar pruritus, erythema, chest tightness and hypotension

Classic symptoms of a hypersensitivity reaction to carboplatin

Hypersensitivity reaction occurred during second cycle of her second course (8th lifetime dose) of carboplatin

Timing is typical of hypersensitivity reaction to carboplatin

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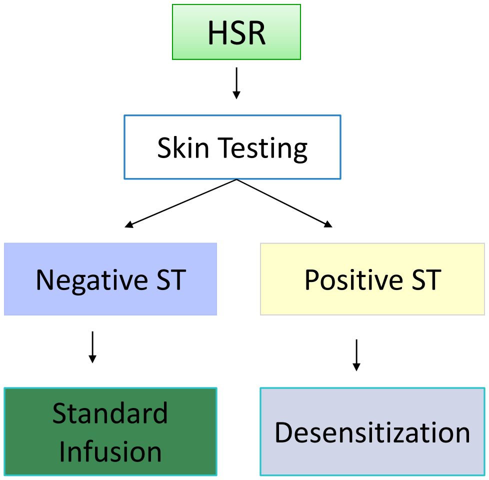
Is there a role for skin testing?



Skin testing well-validated

- 98-99% positive predictive value

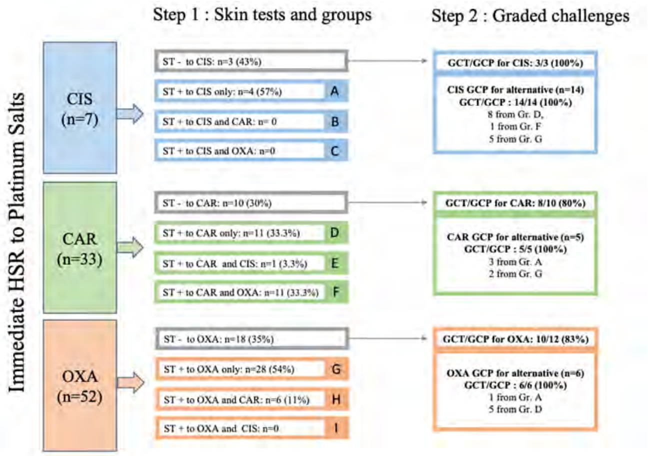
False negative rates as high as 8.5%

Zanotti et al, J Clin Oncol 2001.
Gomez et al, Int J Gynecol Cancer 2009.

Carboplatin Skin Testing

		Carboplatin
Step 1	**Epicutaneous** (Greer pick)	10 mg/ml
Step 2	**Intradermal**	0.1 mg/ml
Step 3	**Intradermal**	1 mg/ml
Step 4	**Intradermal**	5 mg/ml

Negative predictive value of skin testing



Immediate HSR to Platinum Salts

Step 1 : Skin tests and groups

CIS (n=7)
- ST - to CIS: n=3 (43%)
- ST + to CIS only: n=4 (57%) A
- ST + to CIS and CAR: n= 0 B
- ST + to CIS and OXA: n=0 C

CAR (n=33)
- ST - to CAR: n=10 (30%)
- ST + to CAR only: n=11 (33.3%) D
- ST + to CAR and CIS: n=1 (3.3%) E
- ST + to CAR and OXA: n=11 (33.3%) F

OXA (n=52)
- ST - to OXA: n=18 (35%)
- ST + to OXA only: n=28 (54%) G
- ST + to OXA and CAR: n=6 (11%) H
- ST + to OXA and CIS: n=0 I

Step 2 : Graded challenges

GCT/GCP for CIS: 3/3 (100%)

CIS GCP for alternative (n=14)
GCT/GCP : 14/14 (100%)
8 from Gr. D,
1 from Gr. F
5 from Gr. G

GCT/GCP for CAR: 8/10 (80%)

CAR GCP for alternative (n=5)
GCT/GCP : 5/5 (100%)
3 from Gr. A
2 from Gr. G

GCT/GCP for OXA: 10/12 (83%)

OXA GCP for alternative (n=6)
GCT/GCP : 6/6 (100%)
1 from Gr. A
5 from Gr. D

Risk of false negative if less than 14 days after reaction

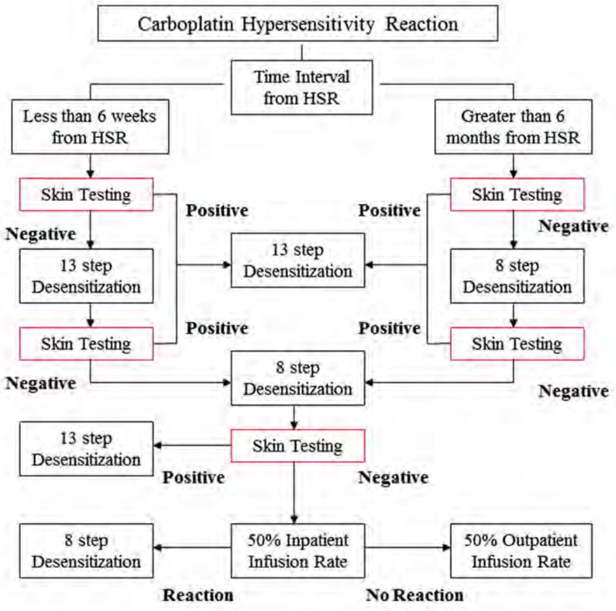
Pradelli et al, J Allergy Clin Immunol Pract 2020.

Risk of future reactions

- Can have false negative initially after reaction
  - Initial desensitization followed by repeat skin testing helps to confirm true negative

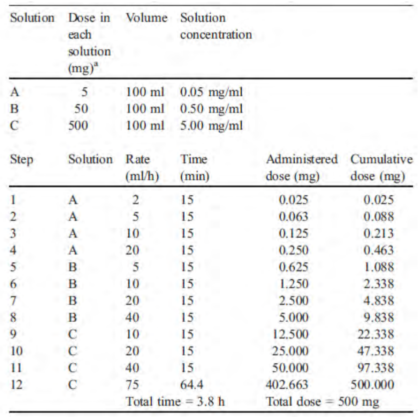
- Negative testing **does not** mean patient will not develop reaction in the future
  - Patient has same risk of developing reaction as average patient on future treatments
  - Overall incidence of hypersensitivity reactions is 12%

False Negative Carboplatin Testing



Patil et al, J Allergy Clin Immunol 2012.
Lax et al. J Allergy Clin Immunol Pract 2015.

Carboplatin Desensitization is Safe and Effective



Solution	Dose in each solution (mg)^{a}	Volume	Solution concentration
A	5	100 ml	0.05 mg/ml
B	50	100 ml	0.50 mg/ml
C	500	100 ml	5.00 mg/ml

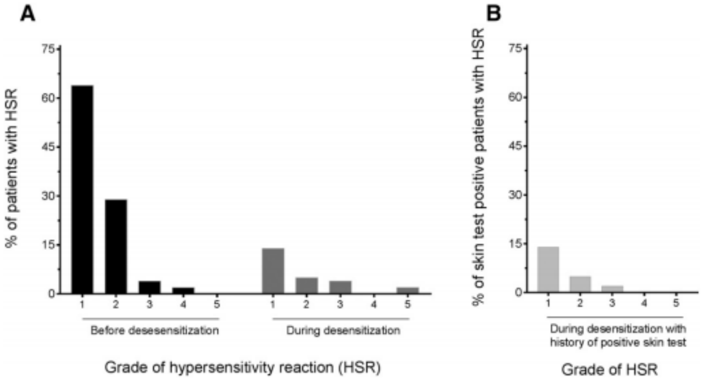
Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	A	2	15	0.025	0.025
2	A	5	15	0.063	0.088
3	A	10	15	0.125	0.213
4	A	20	15	0.250	0.463
5	B	5	15	0.625	1.088
6	B	10	15	1.250	2.338
7	B	20	15	2.500	4.838
8	B	40	15	5.000	9.838
9	C	10	15	12.500	22.338
10	C	20	15	25.000	47.338
11	C	40	15	50.000	97.338
12	C	75	64.4	402.663	500.000
		Total time = 3.8 h		Total dose = 500 mg	

- >1000 successful desensitizations at MGH and BWH
  - Majority tolerated without any reactions

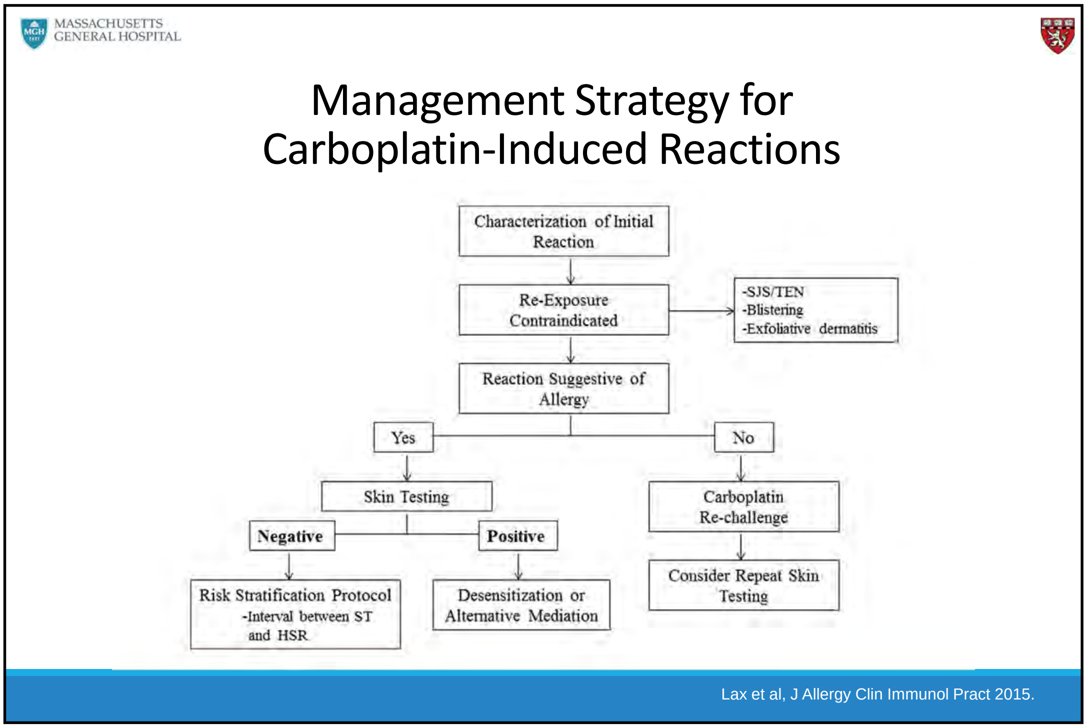
Lee et al. Gynecol Oncol 2004; Lee et al. Gynecol Oncol 2005; Castells et al. J Allergy Clin Immunol 2008; Hesterberg et al. J Allergy Clin Immunol 2009.

Carboplatin Desensitization is Safe and Effective

129 patients underwent carboplatin desensitization and completed a total of 788 cycles



Altwerger et al, Gyn Onc 2017.



Management Strategy for Carboplatin-Induced Reactions

Characterization of Initial Reaction

Re-Exposure Contraindicated

-SJS/TEN
-Blistering
-Exfoliative dermatitis

Reaction Suggestive of Allergy

Yes

No

Skin Testing

Negative

Positive

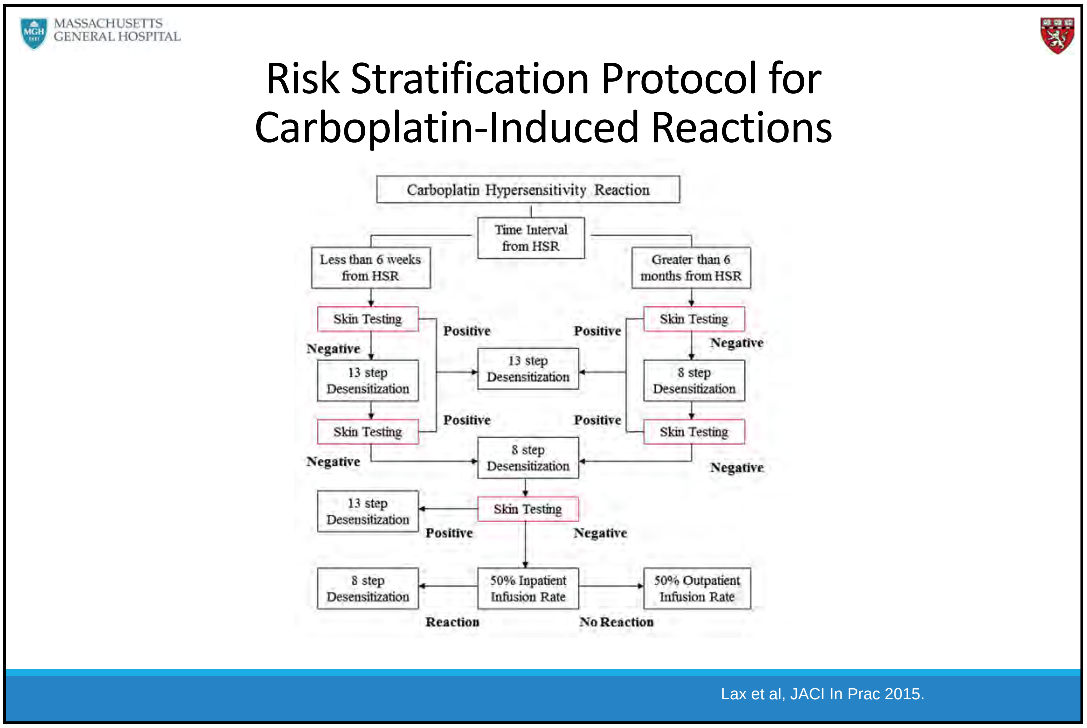
Risk Stratification Protocol
-Interval between ST and HSR

Desensitization or Alternative Mediation

Carboplatin Re-challenge

Consider Repeat Skin Testing

Lax et al, J Allergy Clin Immunol Pract 2015.



Risk Stratification Protocol for Carboplatin-Induced Reactions

Carboplatin Hypersensitivity Reaction

Time Interval from HSR

Less than 6 weeks from HSR

Greater than 6 months from HSR

Skin Testing

Positive

Positive

Skin Testing

Negative

13 step Desensitization

Negative

8 step Desensitization

13 step Desensitization

Positive

Positive

Skin Testing

Skin Testing

8 step Desensitization

Negative

Negative

13 step Desensitization

Skin Testing

Positive

Negative

8 step Desensitization

50% Inpatient Infusion Rate

50% Outpatient Infusion Rate

Reaction

No Reaction

Lax et al, JACI In Prac 2015.

Desensitization

- Patients with reaction history consistent with IgE-mediated reaction
  - Recent, severe reaction
  - Positive skin testing
- Patient too acutely ill to tolerate anaphylaxis
- Indicated when there is not equivalent alternative treatment

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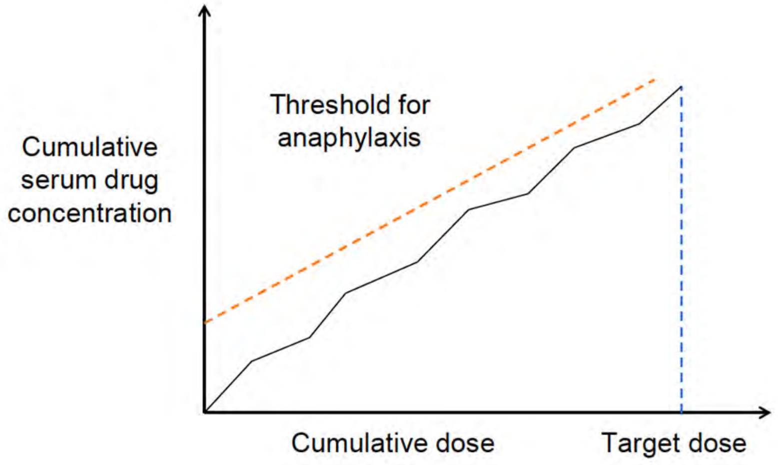
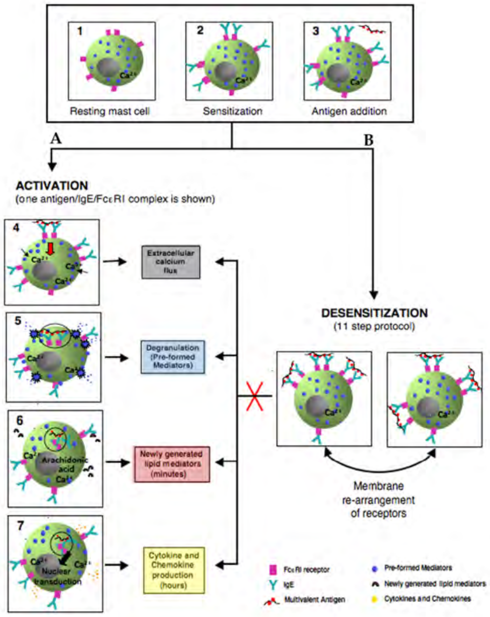
Desensitization





Vecillas Sánchez et al, Int J Mol Sci 2017.

Safety of Desensitization

TABLE IIC. Severity of the breakthrough reactions during the RDDs through consecutive years

Year	Desensitization reaction grade				Total
	0	1	2	3	
2007	236 (66%)	81 (23%)	18 (5%)	23 (6%)	358
2008	341 (67%)	126 (25%)	20 (4%)	23 (5%)	510
2009	434 (77%)	104 (18%)	15 (3%)	14 (2%)	567
2010	594 (80%)	107 (14%)	16 (2%)	25 (3%)	742
Total	1605	418	69	85	2177

RDD, Rapid drug desensitization.
Percentages represent the fraction of patients in a given year who experienced a desensitization breakthrough reaction (grade 0-3), and sum to 100% by rows.

Sloane et al. J Allergy Clin Immunol Prac 2016.

Case #5: Chemotherapy

72 year old male recently diagnosed with Non-Hodgkin's Lymphoma, started on Rituximab therapy

About one hour after starting his **first infusion**, he developed fever, chills and back pain

Infusion was stopped and he received IV diphenhydramine and ranitidine and symptoms resolved within 35 minutes

Was this a hypersensitivity reaction to Rituximab?

Hypersensitivity to Biologics

Increased use of biologics has resulted in increase in hypersensitivity reactions

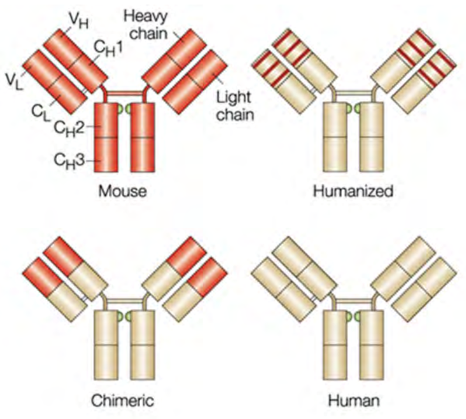
All biologics have potential to cause reaction

- Composition: Degree of humanization is important
- Administration: Typically given episodically
- Interactions with other medications

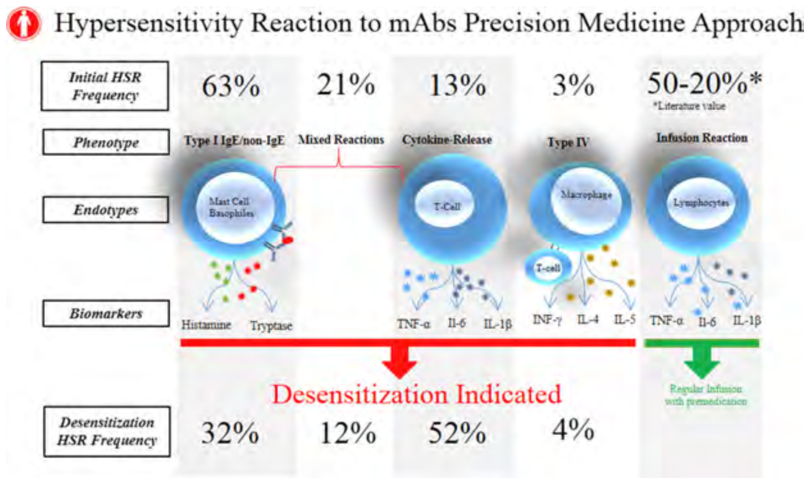
Composition of Biologicals

Increasing reactivity

- Murine
- Chimeric
- Humanized
- Human



Types of Hypersensitivity Reactions to Biologics



Isabwe et al, J All Clin Immunol 2018.

Types of Hypersensitivity Reactions to Biologics

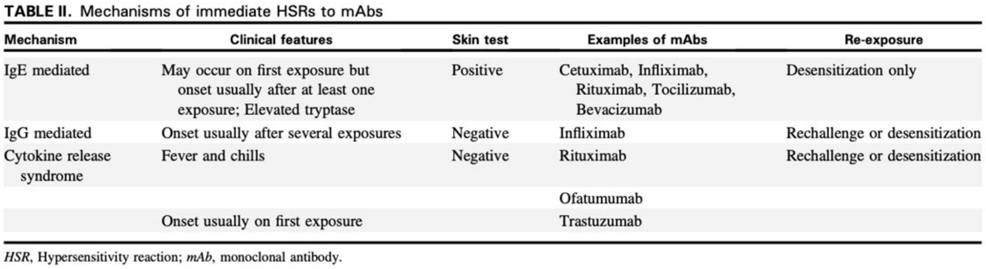


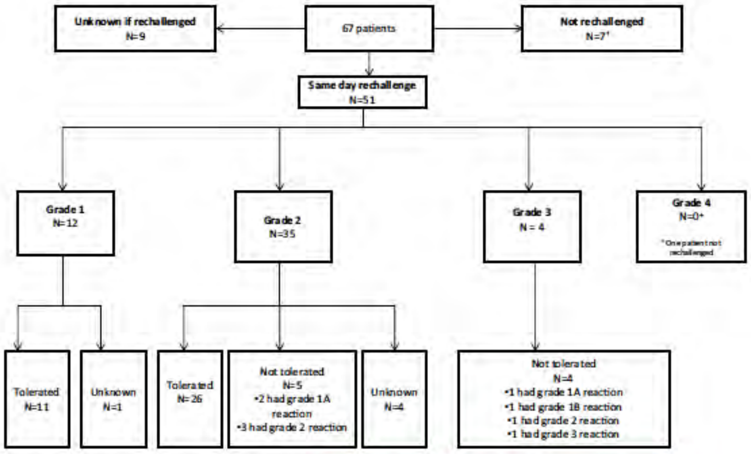
TABLE II. Mechanisms of immediate HSRs to mAbs

Mechanism	Clinical features	Skin test	Examples of mAbs	Re-exposure
IgE mediated	May occur on first exposure but onset usually after at least one exposure; Elevated tryptase	Positive	Cetuximab, Infliximab, Rituximab, Tocilizumab, Bevacizumab	Desensitization only
IgG mediated	Onset usually after several exposures	Negative	Infliximab	Rechallenge or desensitization
Cytokine release syndrome	Fever and chills	Negative	Rituximab	Rechallenge or desensitization
			Ofatumumab	
	Onset usually on first exposure		Trastuzumab	

HSR, Hypersensitivity reaction; *mAb*, monoclonal antibody.

Picard et al, J All Clin Immunol 2017.

Infusion reactions



Unknown if rechallenged
N=9

67 patients

Not rechallenged
N=7†

Same day rechallenge
N=51

Grade 1
N=12

Grade 2
N=35

Grade 3
N = 4

Grade 4
N=0*
*One patient not rechallenged

Tolerated
N=11

Unknown
N=1

Tolerated
N=26

Not tolerated
N=5
- 2 had grade 1A reaction
- 3 had grade 2 reaction

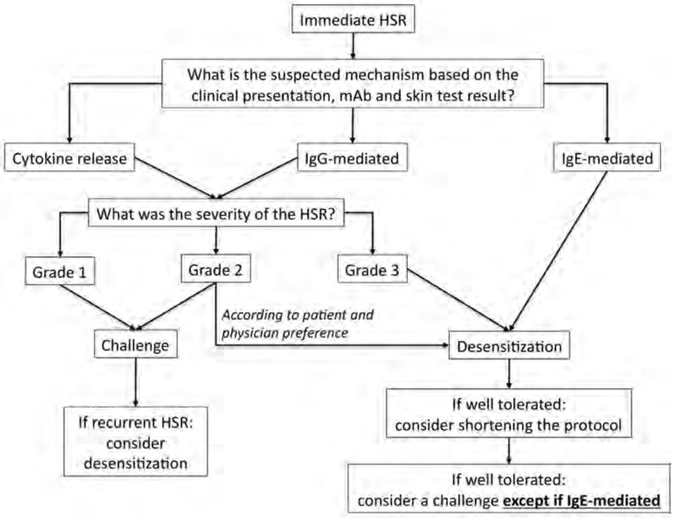
Unknown
N=4

Not tolerated
N=4
- 1 had grade 1A reaction
- 1 had grade 1B reaction
- 1 had grade 2 reaction
- 1 had grade 3 reaction

*Rechallenge at our institution is 50% standard infusion rate
†Among these patients: 2 had Grade 1B, 4 had Grade 2, 1 had Grade 4

Levin AS et al, J All Clin Immunol Pract 2017.

Immediate Hypersensitivity Reactions



Immediate HSR

What is the suspected mechanism based on the clinical presentation, mAb and skin test result?

Cytokine release

IgG-mediated

IgE-mediated

What was the severity of the HSR?

Grade 1

Grade 2

Grade 3

Challenge

According to patient and physician preference

Desensitization

If recurrent HSR: consider desensitization

If well tolerated: consider shortening the protocol

If well tolerated: consider a challenge **except if IgE-mediated**

Picard et al, J All Clin Immunol 2017.

Evaluation of Hypersensitivity Reaction to Biologic Agent

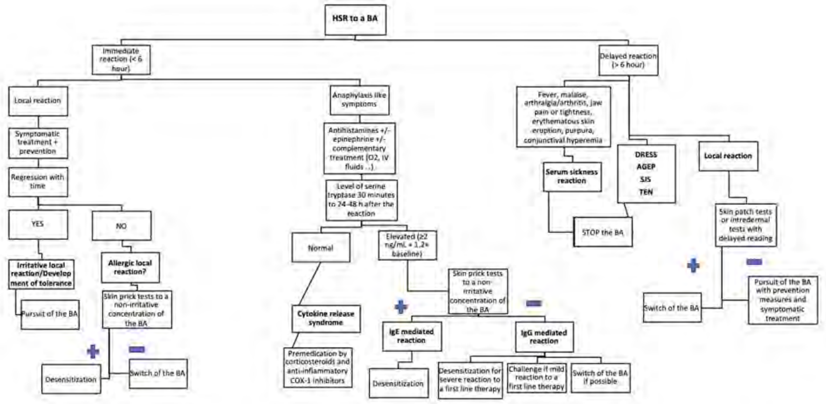


FIGURE E1. Decision tree proposal for the management of hypersensitivity reactions due to biological agents. *AGEP,* Acute generalized exanthematous pustulosis; *BA*, biological agents; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *HSR*, hypersensitivity reaction; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

Barakat L et al, J Allergy Clin Immunol Pract 2021.

Rituximab Skin Testing

TABLE VII. Rituximab skin test results and desensitization outcome

Skin test status	No. of patients	n (%) of patients with reaction	No. of desensitizations	n (%) of desensitizations with reactions
IST+*	5	3 (60)*	32	10 (31)†
IST−†	13	9 (69)*	115	32 (28)†
Total	18	12 (67)	147	42 (29)

*Initial skin test positive.
†Initial skin test negative.

TABLE VIII. Serum tryptase level during desensitizations

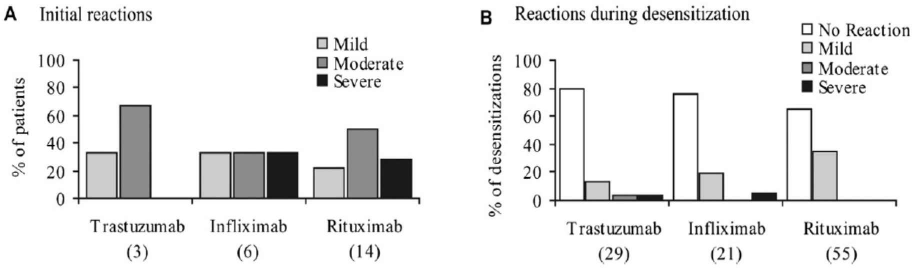
Serum tryptase level	With HSRs* (including mast cell disorder†)	Uncomplicated* (including mast cell disorder†)	Total* (including mast cell disorder†)
Tryptase level elevated	6 (19)	1 (15)	7 (34)
Tryptase level normal	23 (24)	30 (30)	53 (54)
Total	29 (43)	31 (45)	60 (88)
%	21% (44%)	3% (33%)	*P* value .036

*Excluding a patient with mast cell disorder.
†Including a patient with mast cell disorder.

Wong et al, JACI In Prac 2017.

Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment

Patrick J. Brennan, MD, PhD,* Tito Rodriguez Bouza, MD,* F. Ida Hsu, MD, David E. Sloane, MD, and Mariana C. Castells, MD, PhD *Boston, Mass*



Brennan et al, JACI 2009.

Rituximab Desensitization

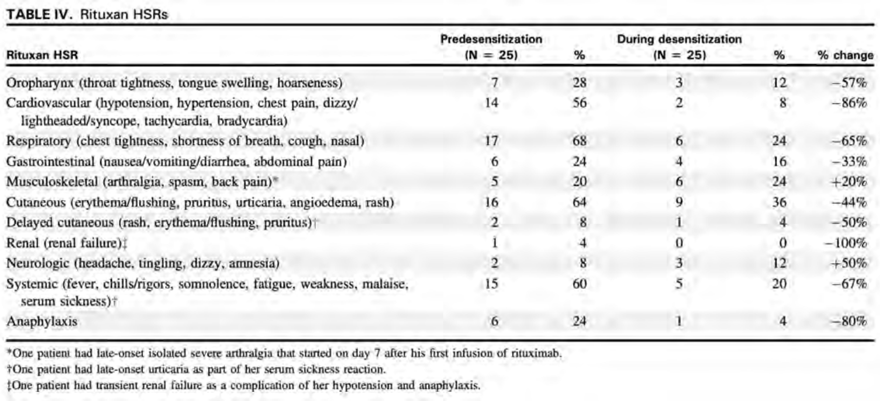


TABLE IV. Rituxan HSRs

Rituxan HSR	Predesensitization (N = 25)	%	During desensitization (N = 25)	%	% change
Oropharynx (throat tightness, tongue swelling, hoarseness)	7	28	3	12	−57%
Cardiovascular (hypotension, hypertension, chest pain, dizzy/ lightheaded/syncope, tachycardia, bradycardia)	14	56	2	8	−86%
Respiratory (chest tightness, shortness of breath, cough, nasal)	17	68	6	24	−65%
Gastrointestinal (nausea/vomiting/diarrhea, abdominal pain)	6	24	4	16	−33%
Musculoskeletal (arthralgia, spasm, back pain)*	5	20	6	24	+20%
Cutaneous (erythema/flushing, pruritus, urticaria, angioedema, rash)	16	64	9	36	−44%
Delayed cutaneous (rash, erythema/flushing, pruritus)†	2	8	1	4	−50%
Renal (renal failure)‡	1	4	0	0	−100%
Neurologic (headache, tingling, dizzy, amnesia)	2	8	3	12	+50%
Systemic (fever, chills/rigors, somnolence, fatigue, weakness, malaise, serum sickness)†	15	60	5	20	−67%
Anaphylaxis	6	24	1	4	−80%

*One patient had late-onset isolated severe arthralgia that started on day 7 after his first infusion of rituximab.
†One patient had late-onset urticaria as part of her serum sickness reaction.
‡One patient had transient renal failure as a complication of her hypotension and anaphylaxis.

Wong et al, JACI In Prac 2017.

Summary

- Classification of the hypersensitivity reaction can determine best course of evaluation
  - Timing and characteristics can help to identify culprits
  - There is strong association with HLA in DRESS
  - Delayed intradermal and Patch testing can be helpful
- Asymptomatic peripheral eosinophilia with medications must be monitored but may not develop other complications

Summary

- Aspirin test dose important in the evaluation of aspirin hypersensitivity
  - If test dose is positive or patient unstable, consider desensitization
- Skin testing can be helpful in platinum hypersensitivity and desensitization can allow patients to remain on 1st line treatment
- Hypersensitivity reactions to biologics are common
  - Consider type of reaction to determine whether premedication and rechallenge or desensitization

MASSACHUSETTS
GENERAL HOSPITAL

PAAA

Pennsylvania Allergy & Asthma Association

Advances in Atopic Dermatitis

Ian A Myles, MD, MPH

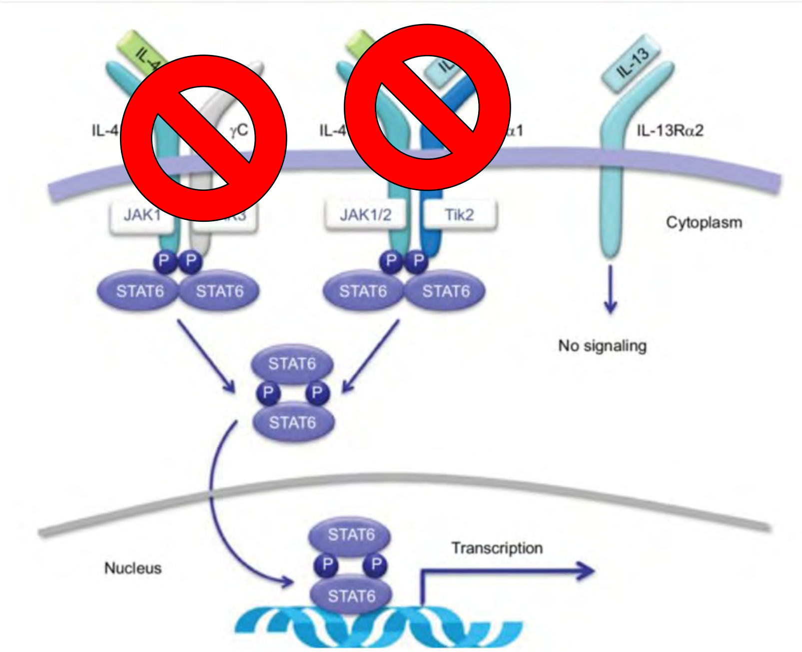
Friday, June 25, 2021
8 a.m. - 8:45 a.m.

Advances in Atopic Dermatitis

CDR Ian A Myles, MD/MPH

Disclosures

- Speaker holds the patent to *R. mucosa* treatment
- R. mucosa is currently licensed by Forte Bioscience

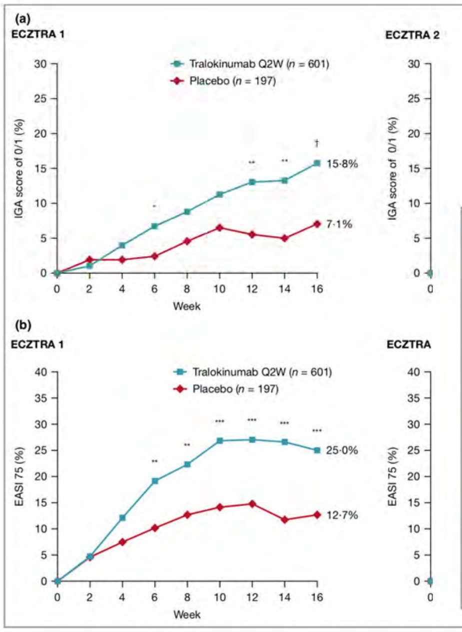



CLINICAL TRIAL

BJD
British Journal of Dermatology

Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2)*

A. Wollenberg[1] A. Blauvelt,[2] E. Guttman-Yassky,[3] M. Worm,[4] C. Lynde,[5,6] J.-P. Lacour,[7] L. Spelman,[8,9] N. Katoh,[10] H. Saeki,[11] Y. Poulin,[12] A. Lesiak,[13] L. Kircik,[14,15] S.H. Cho,[16] P. Herranz,[17] M.J. Cork,[18] K. Peris,[19] L.A. Steffensen,[20] B. Bang,[20] A. Kuznetsova,[20] T.N. Jensen,[20] M.L. Østerdal,[20] E.L. Simpson[21] and on behalf of the ECZTRA 1 and ECZTRA 2 study investigators

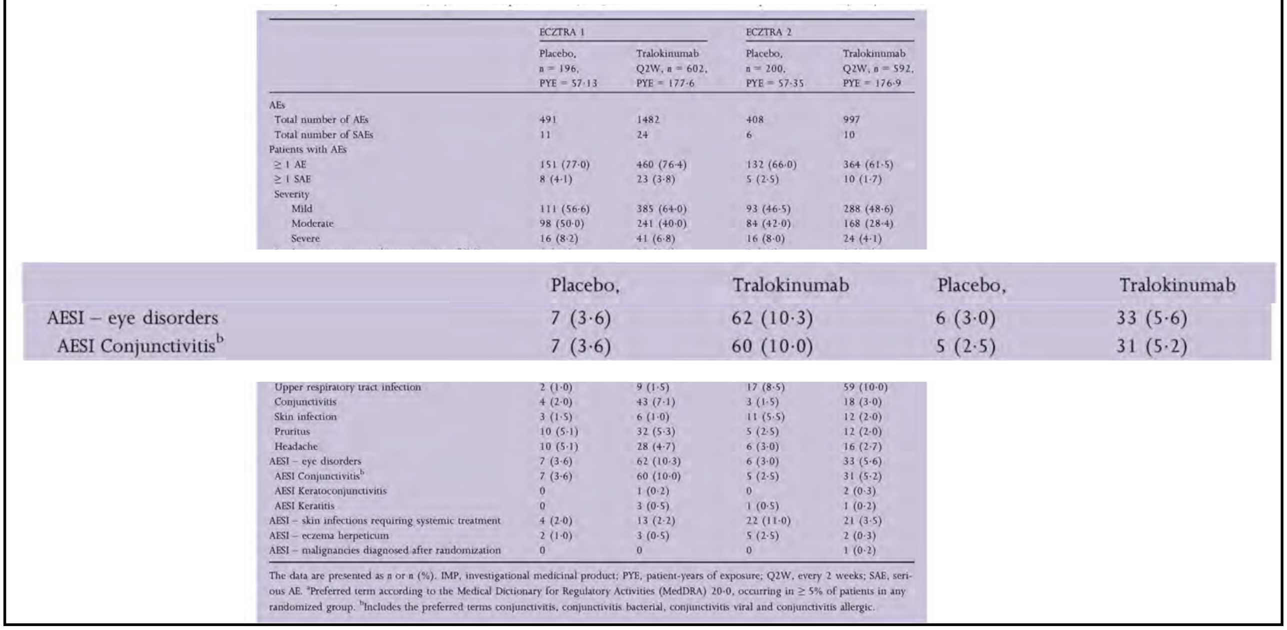



Week 0
IGA score of 4
EASI score of 31.9
Worst daily pruritus NRS score of 8

Week 8
IGA score of 1
EASI score of 4.3
Worst daily pruritus NRS score of 3

Week 16
IGA score of 2
EASI score of 3.6
Worst daily pruritus NRS score of 3

Treatment associated with conjunctivitis

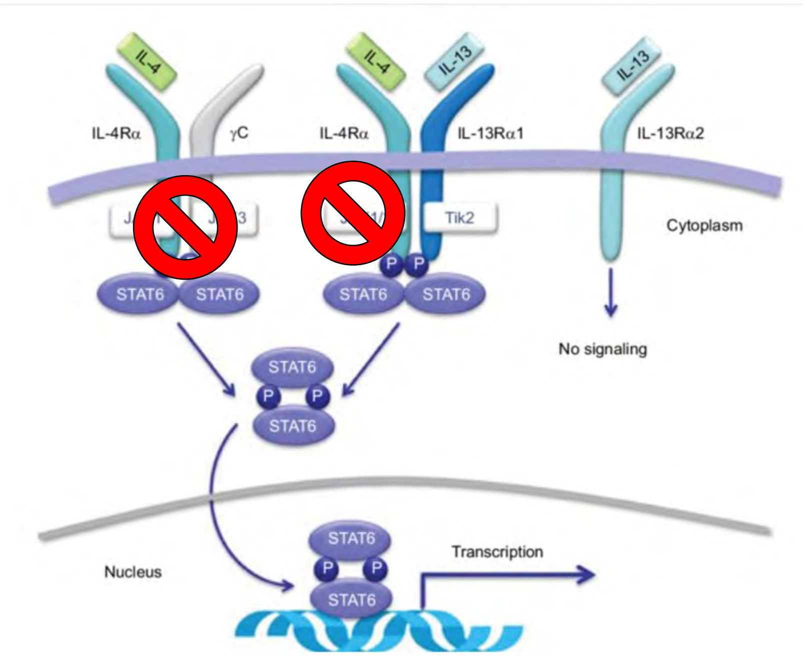


	ECZTRA 1		ECZTRA 2	
	Placebo, n = 196, PYE = 57·13	Tralokinumab Q2W, n = 602, PYE = 177·6	Placebo, n = 200, PYE = 57·35	Tralokinumab Q2W, n = 592, PYE = 176·9
AEs				
Total number of AEs	491	1482	408	997
Total number of SAEs	11	24	6	10
Patients with AEs				
≥ 1 AE	151 (77·0)	460 (76·4)	132 (66·0)	364 (61·5)
≥ 1 SAE	8 (4·1)	23 (3·8)	5 (2·5)	10 (1·7)
Severity				
Mild	111 (56·6)	385 (64·0)	93 (46·5)	288 (48·6)
Moderate	98 (50·0)	241 (40·0)	84 (42·0)	168 (28·4)
Severe	16 (8·2)	41 (6·8)	16 (8·0)	24 (4·1)

	Placebo,	Tralokinumab	Placebo,	Tralokinumab
AESI – eye disorders	7 (3·6)	62 (10·3)	6 (3·0)	33 (5·6)
AESI Conjunctivitis[b]	7 (3·6)	60 (10·0)	5 (2·5)	31 (5·2)

Upper respiratory tract infection	2 (1·0)	9 (1·5)	17 (8·5)	59 (10·0)
Conjunctivitis	4 (2·0)	43 (7·1)	3 (1·5)	18 (3·0)
Skin infection	3 (1·5)	6 (1·0)	11 (5·5)	12 (2·0)
Pruritus	10 (5·1)	32 (5·3)	5 (2·5)	12 (2·0)
Headache	10 (5·1)	28 (4·7)	6 (3·0)	16 (2·7)
AESI – eye disorders	7 (3·6)	62 (10·3)	6 (3·0)	33 (5·6)
AESI Conjunctivitis[b]	7 (3·6)	60 (10·0)	5 (2·5)	31 (5·2)
AESI Keratoconjunctivitis	0	1 (0·2)	0	2 (0·3)
AESI Keratitis	0	3 (0·5)	1 (0·5)	1 (0·2)
AESI – skin infections requiring systemic treatment	4 (2·0)	13 (2·2)	22 (11·0)	21 (3·5)
AESI – eczema herpeticum	2 (1·0)	3 (0·5)	5 (2·5)	2 (0·3)
AESI – malignancies diagnosed after randomization	0	0	0	1 (0·2)

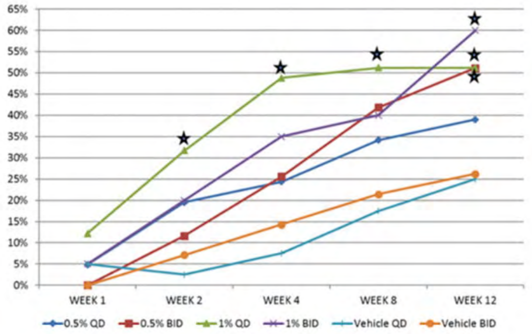
The data are presented as *n* or *n* (%). IMP, investigational medicinal product; PYE, patient-years of exposure; Q2W, every 2 weeks; SAE, serious AE. [a]Preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) 20·0, occurring in ≥ 5% of patients in any randomized group. [b]Includes the preferred terms conjunctivitis, conjunctivitis bacterial, conjunctivitis viral and conjunctivitis allergic.



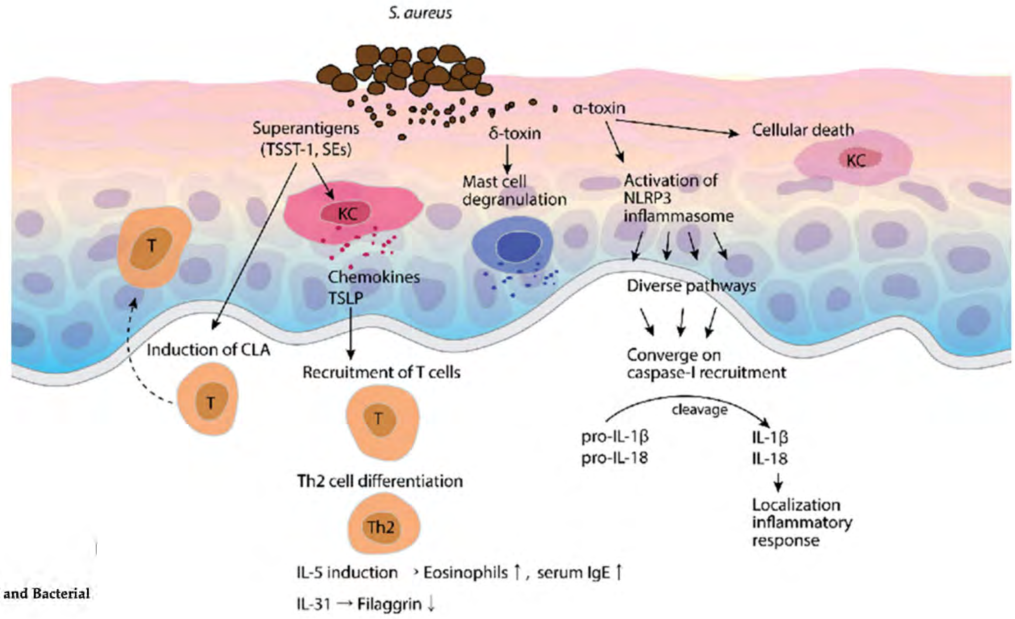
A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis

Johnny Peppers, PhD,[a] Amy S. Paller, MD,[b] Tomoko Maeda-Chubachi, MD, PhD,[c]
Sterling Wu, PhD,[d] Kevin Robbins, BSc, LLM,[d] Kelly Gallagher, MS,[d] and John E. Kraus, MD, PhD[c]
Raleigh, Morrisville, and Research Triangle Park, North Carolina; Chicago, Illinois; and Collegeville, Pennsylvania

- Tapinarof associated with enhanced EASI75



S. aureus contributes to AD pathology



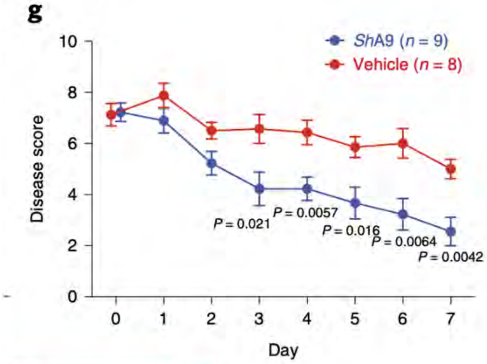
toxins

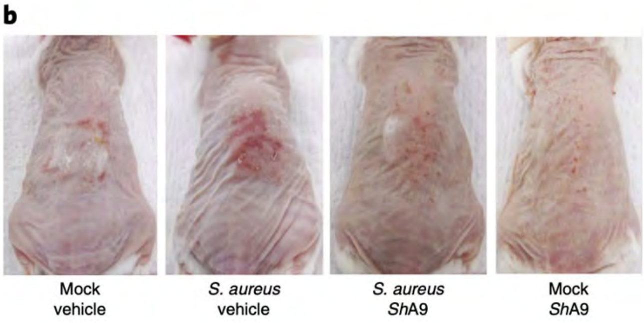
Review

The Pathogenetic Effect of Natural and Bacterial Toxins on Atopic Dermatitis

Kyung-Duck Park[1], Sok Cheon Pak[2] and Kwan-Kyu Park[3,*]

S. hominus treatment improves outcomes in mouse models of *S. aureus* dermatitis





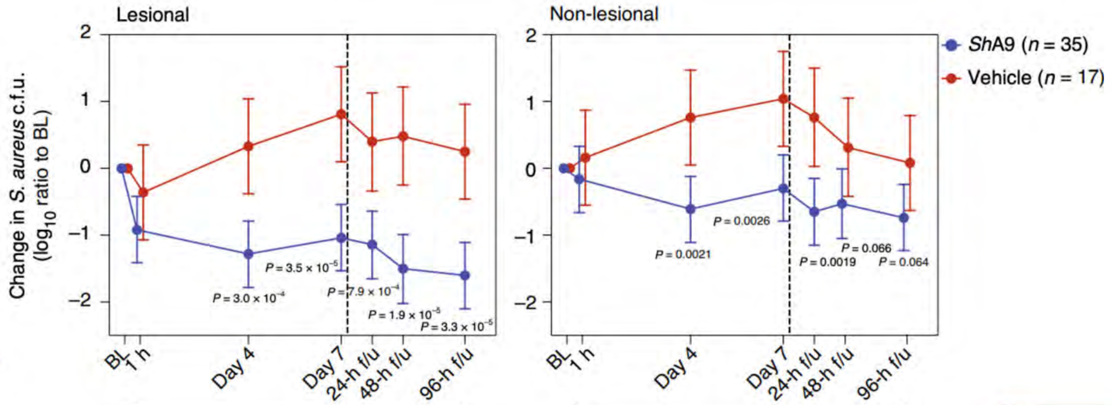

ARTICLES

nature medicine

Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase 1 randomized clinical trial

Teruaki Nakatsuji, Tissa R. Hata, Yun Tong, Joyce Y. Cheng, Faiza Shafiq, Anna M. Butcher, Secilia S. Salem, Samantha L. Brinton, Amanda K. Rudman Spergel, Keli Johnson, Brett Jepson, Agustin Calatroni, Gloria David, Marco Ramirez-Gama, Patricia Taylor, Donald Y. M. Leung and Richard L. Gallo

Sh9 reduces *S. aureus* burden in patients

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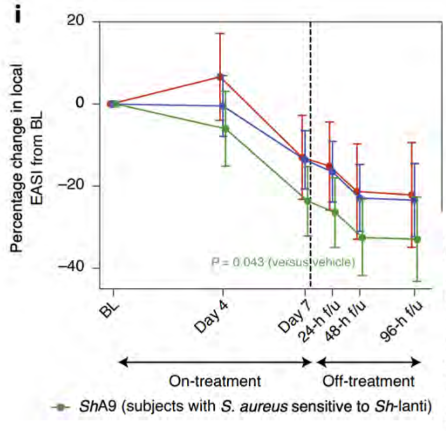

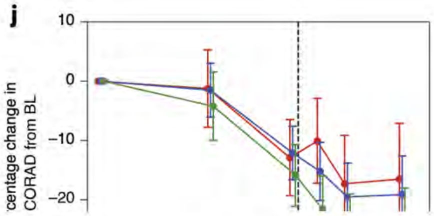

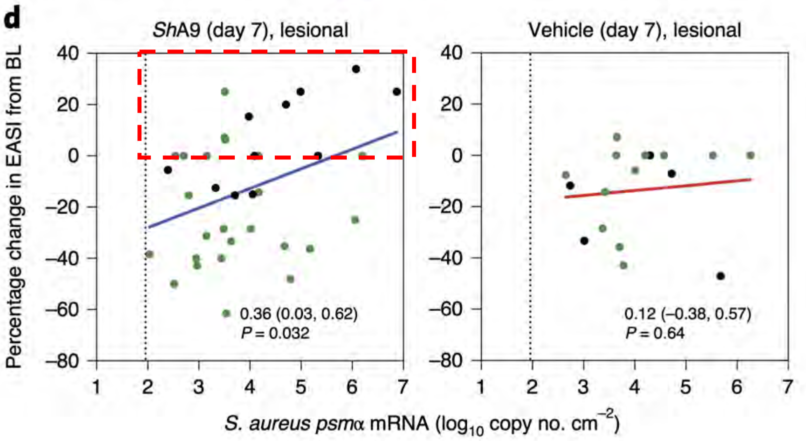


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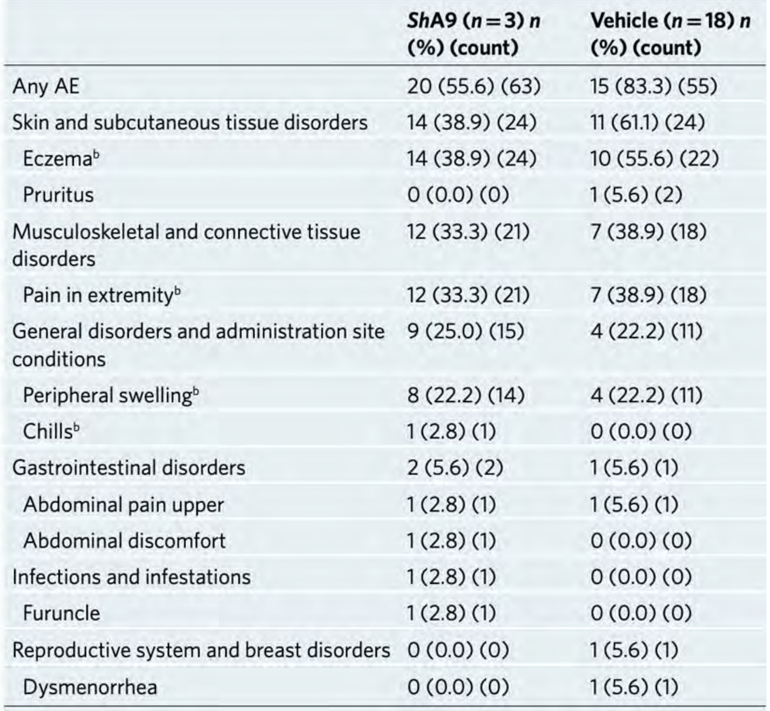
Teruaki Nakatsuji[1], Tissa R. Hata[1], Yun Tong[1], Joyce Y. Cheng[1], Faiza Shafiq[1], Anna M. Butcher[1], Secilia S. Salem[1], Samantha L. Brinton[1], Amanda K. Rudman Spergel[2], Keli Johnson[3], Brett Jepson[3], Agustin Calatroni[3], Gloria David[3], Marco Ramirez-Gama[4], Patricia Taylor[4], Donald Y. M. Leung[4] and Richard L. Gallo[1]



	*Sh*A9 (*n* = 3) *n* (%) (count)	Vehicle (*n* = 18) *n* (%) (count)
Any AE	20 (55.6) (63)	15 (83.3) (55)
Skin and subcutaneous tissue disorders	14 (38.9) (24)	11 (61.1) (24)
Eczema[b]	14 (38.9) (24)	10 (55.6) (22)
Pruritus	0 (0.0) (0)	1 (5.6) (2)
Musculoskeletal and connective tissue disorders	12 (33.3) (21)	7 (38.9) (18)
Pain in extremity[b]	12 (33.3) (21)	7 (38.9) (18)
General disorders and administration site conditions	9 (25.0) (15)	4 (22.2) (11)
Peripheral swelling[b]	8 (22.2) (14)	4 (22.2) (11)
Chills[b]	1 (2.8) (1)	0 (0.0) (0)
Gastrointestinal disorders	2 (5.6) (2)	1 (5.6) (1)
Abdominal pain upper	1 (2.8) (1)	1 (5.6) (1)
Abdominal discomfort	1 (2.8) (1)	0 (0.0) (0)
Infections and infestations	1 (2.8) (1)	0 (0.0) (0)
Furuncle	1 (2.8) (1)	0 (0.0) (0)
Reproductive system and breast disorders	0 (0.0) (0)	1 (5.6) (1)
Dysmenorrhea	0 (0.0) (0)	1 (5.6) (1)


ARTICLES

nature medicine

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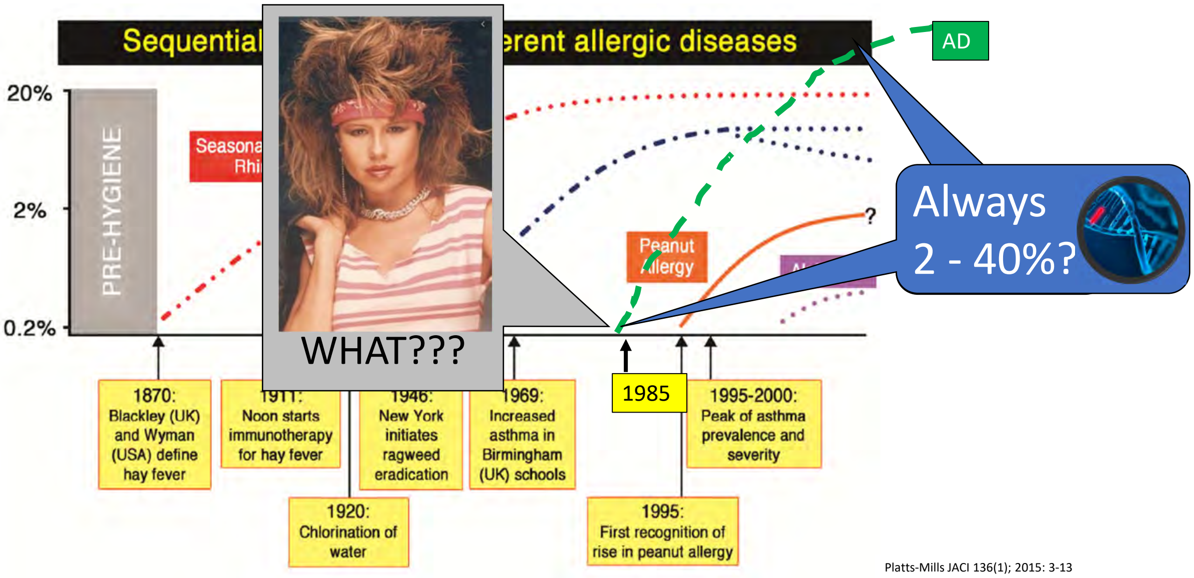
Teruaki Nakatsuji[1], Tissa R. Hata[1], Yun Tong[1], Joyce Y. Cheng[1], Faiza Shafiq[1], Anna M. Butcher[1], Secilia S. Salem[1], Samantha L. Brinton[1], Amanda K. Rudman Spergel[2], Keli Johnson[3], Brett Jepson[3], Agustin Calatroni[3], Gloria David[3], Marco Ramirez-Gama[4], Patricia Taylor[4], Donald Y. M. Leung[4] and Richard L. Gallo[1]

Allergies: Ancient Disease but Modern Pandemic



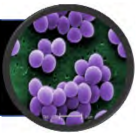
Platts-Mills JACI 136(1); 2015: 3-13
Latvala et al. BMJ 330 (2005) 1186
Henderson, et al. JACI. 2008;121:872-7

↓↓↓Sphingolipids, Ceramides, & Phospholipids

Modulate Immunity

Govern AMP production

Inhibit Staph



Enhance Barrier

Park et al; Biomol Ther (2013);

Distribution of AD

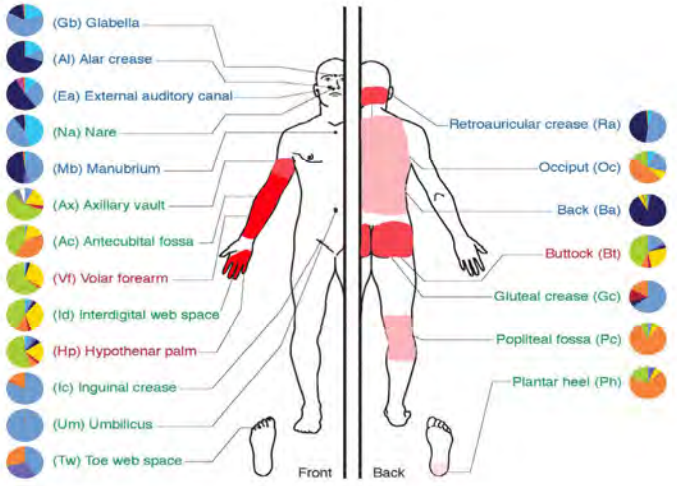
Journal of Investigative Dermatology (2012), Volume 132

Distribution of Gram-negative Bacteria

JID75

Skin Microbiome: Looking Back to Move Forward

Heidi H. Kong[1] and Julia A. Segre[2]



Sequence Program,[5,7] Patrick R. Murray,[6] Maria L. Turner,[1] and Julia A. Segre[2,8]

Overview of Atopic Derm:

- Primarily environmental disorder
- Baseline defects in sphingolipid pathway
  - May be upstream of other dysfunctions
- Significant overlap with distribution of Gram negative bacteria
- Could Gram Negative's sphingolipid production contribute to AD?

Do Bacteria make sphingolipids?

Google Search I'm Feeling Lucky

Myles *et al. BMC Microbiology* (2016) 16:60
DOI 10.1186/s12866-016-0684-9

BMC Microbiology

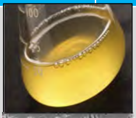
METHODOLOGY ARTICLE Open Access

A method for culturing Gram-negative skin microbiota

Ian A. Myles[1*], Jensen D. Reckhow[1†], Kelli W. Williams[1†], Inka Sastalla[1], Karen M. Frank[2] and Sandip K. Datta[1]

Scientific classification

Kingdom:	Bacteria
Phylum:	Proteobacteria
Class:	Alphaproteobacteria
Order:	Rhodospirillales
Family:	Acetobacteraceae
Genus:	Roseomonas

Pre-clinical evaluations	 HV	 AD
Barrier dysfunction 	⬇	⬆
Staphylococcus aureus growth 	⬇	⬆
Immune function 	⬆	⬇
Mouse Model	⬆	⬇

JCI insight

RESEARCH ARTICLE

Transplantation of human skin microbiota in models of atopic dermatitis

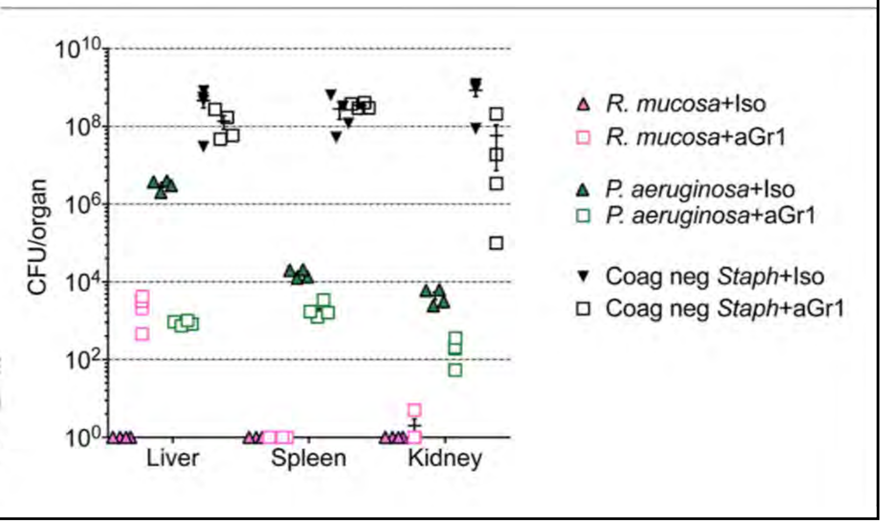
Ian A. Myles,[1] Kelli W. Williams,[1] Jensen D. Reckhow,[1] Momodou L. Jammeh,[1] Nathan B. Pincus,[1] Inka Sastalla,[1] Danial Saleem,[1] Kelly D. Stone,[2] and Sandip K. Datta[1]

R. mucosa does not generate tissue infection in wild type mice

frontiers in Cellular and Infection Microbiology

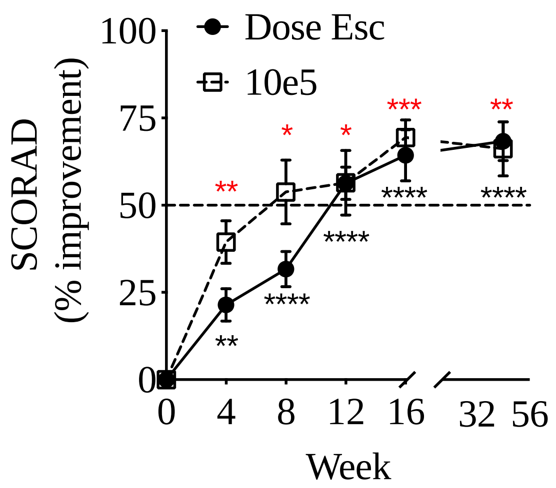
Differing Virulence of Healthy Skin Commensals in Mouse Models of Infection

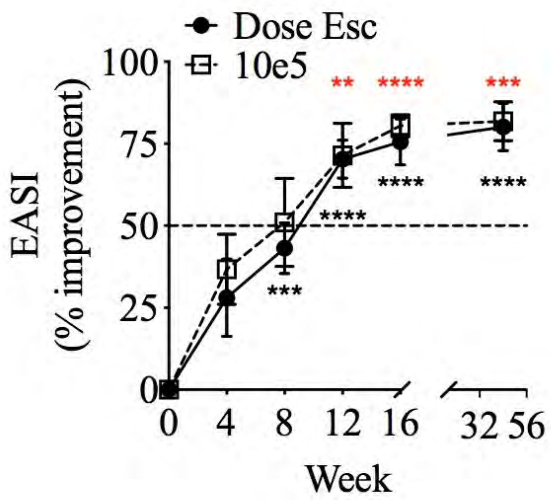
Ian A. Myles, Ian N. Moore, Carlo R. Castillo and Sandip K. Datta



BACTERiAD I/II

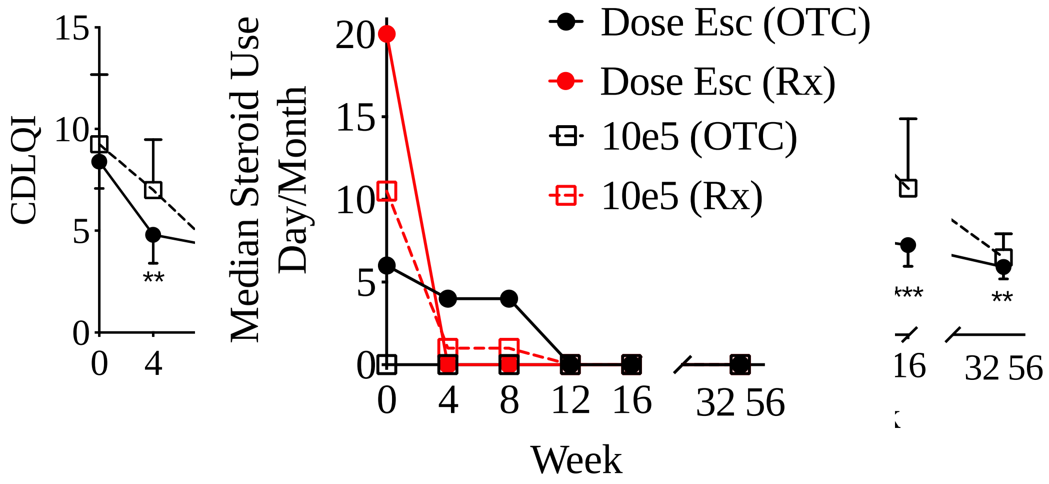
R. mucosa treatment improved outcomes in AD



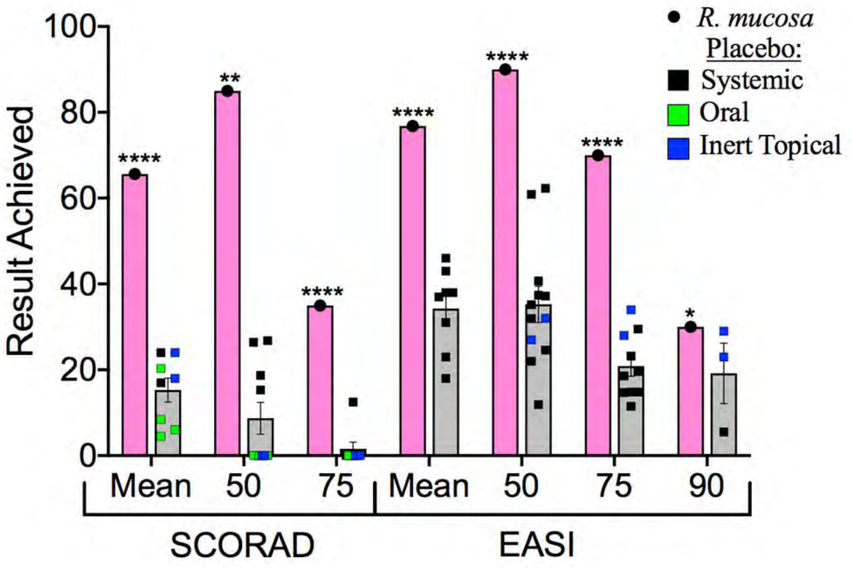


Treatment associated with improvement in adjunct markers of AD


Therapeutic responses to *Roseomonas mucosa* in atopic dermatitis may involve lipid-mediated TNF-related epithelial repair



R. mucosa treatment is significantly superior to reported placebo results



Snast et al, Am J Clin Dermatol. 2018
Lee, et al, JACI. 2008
Fishbein, J Ped Nursing. 2019


Therapeutic responses to *Roseomonas mucosa* in atopic dermatitis may involve lipid-mediated TNF-related epithelial repair

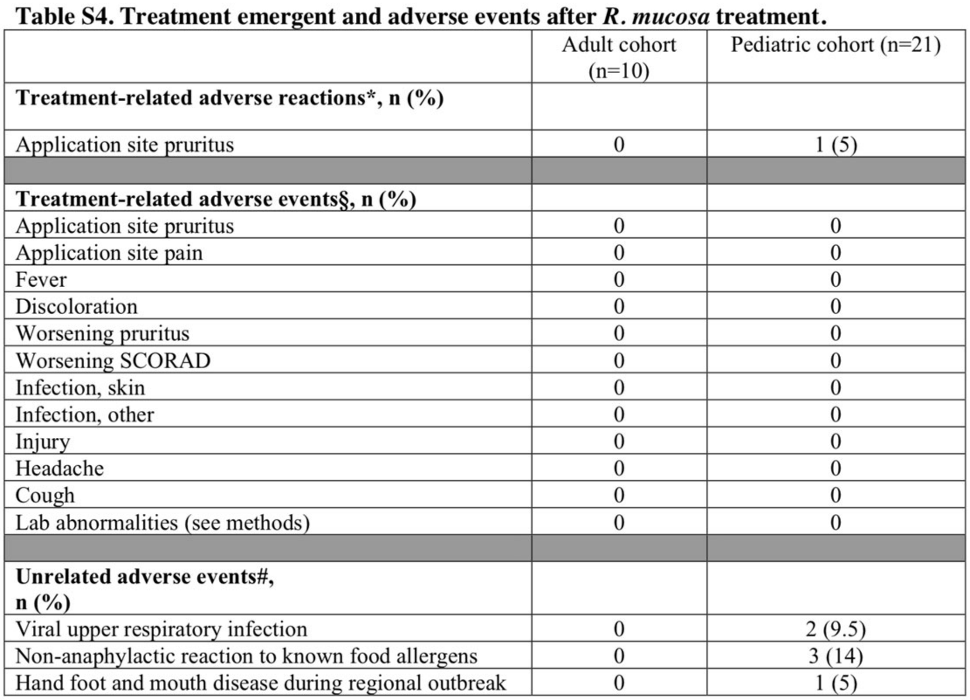
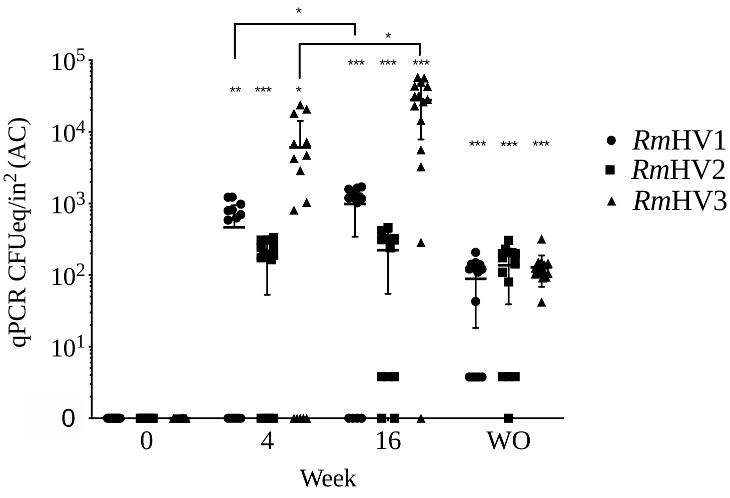
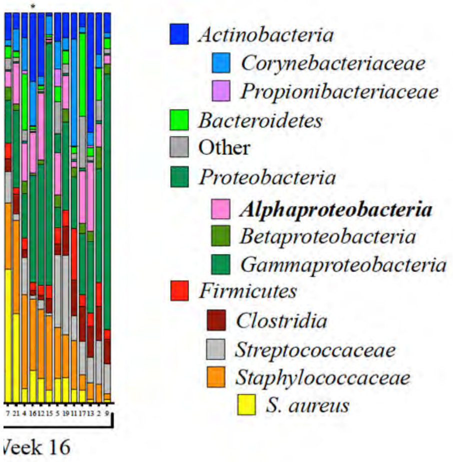


Table S4. Treatment emergent and adverse events after *R. mucosa* treatment.

	Adult cohort (n=10)	Pediatric cohort (n=21)
Treatment-related adverse reactions*, n (%)		
Application site pruritus	0	1 (5)
Treatment-related adverse events§, n (%)		
Application site pruritus	0	0
Application site pain	0	0
Fever	0	0
Discoloration	0	0
Worsening pruritus	0	0
Worsening SCORAD	0	0
Infection, skin	0	0
Infection, other	0	0
Injury	0	0
Headache	0	0
Cough	0	0
Lab abnormalities (see methods)	0	0
Unrelated adverse events#, n (%)		
Viral upper respiratory infection	0	2 (9.5)
Non-anaphylactic reaction to known food allergens	0	3 (14)
Hand foot and mouth disease during regional outbreak	0	1 (5)

R. mucosa treatment enhanced microbiome diversity; colonization






SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

ATOPIC DERMATITIS

Therapeutic responses to *Roseomonas mucosa* in atopic dermatitis may involve lipid-mediated TNF-related epithelial repair

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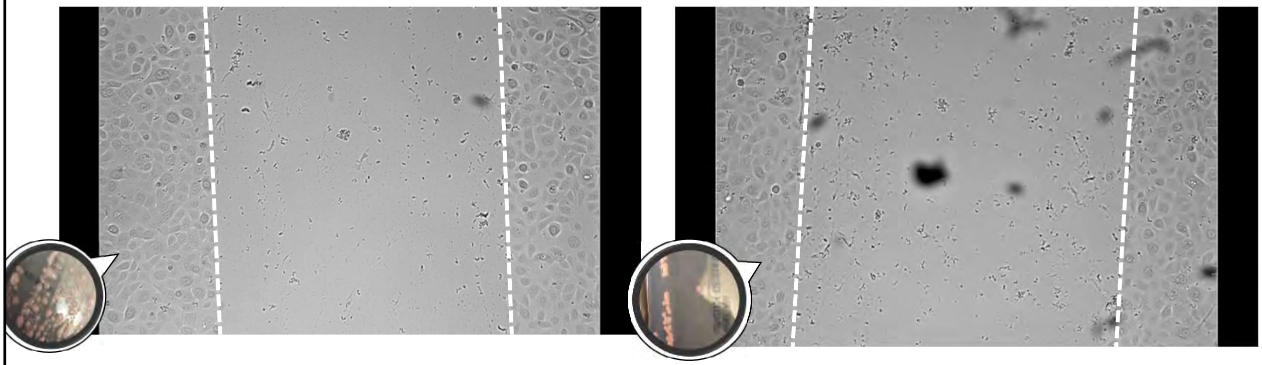
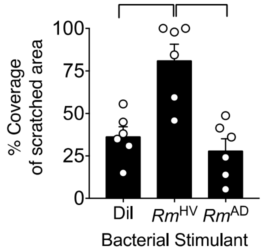
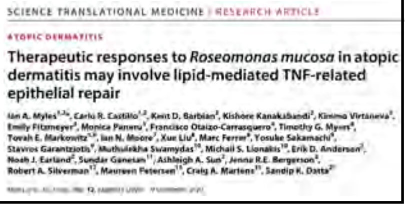
Models Used: Scratch Assay and MC903 Mouse AD-like dermatitis



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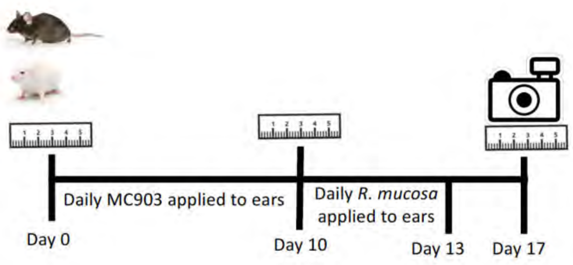
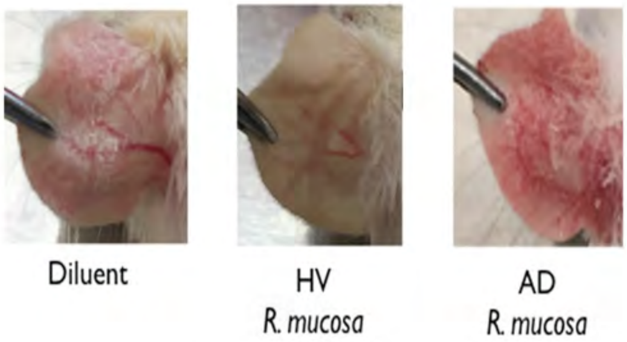
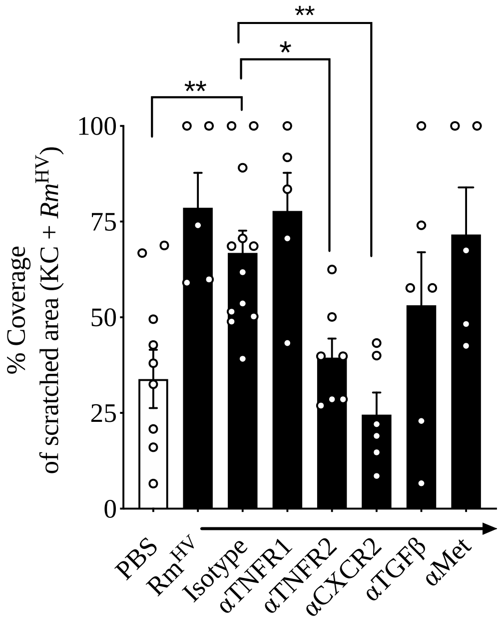
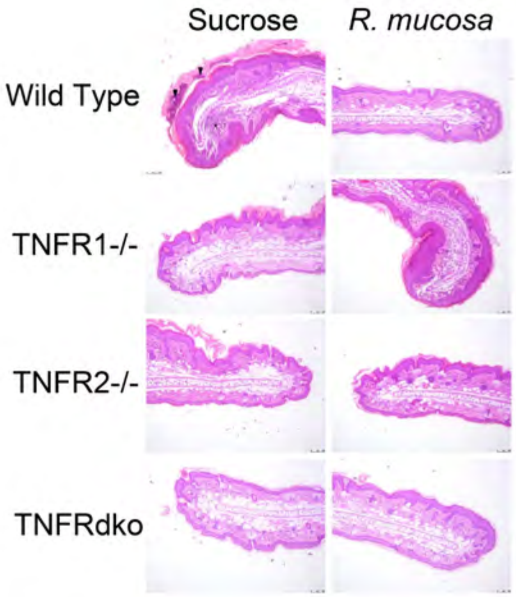
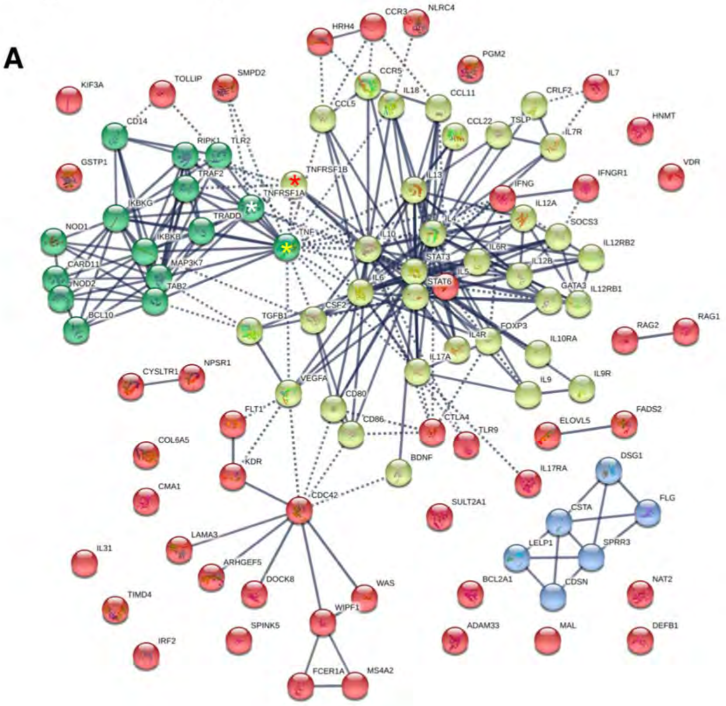








Alleles associated with AD cluster around TNF

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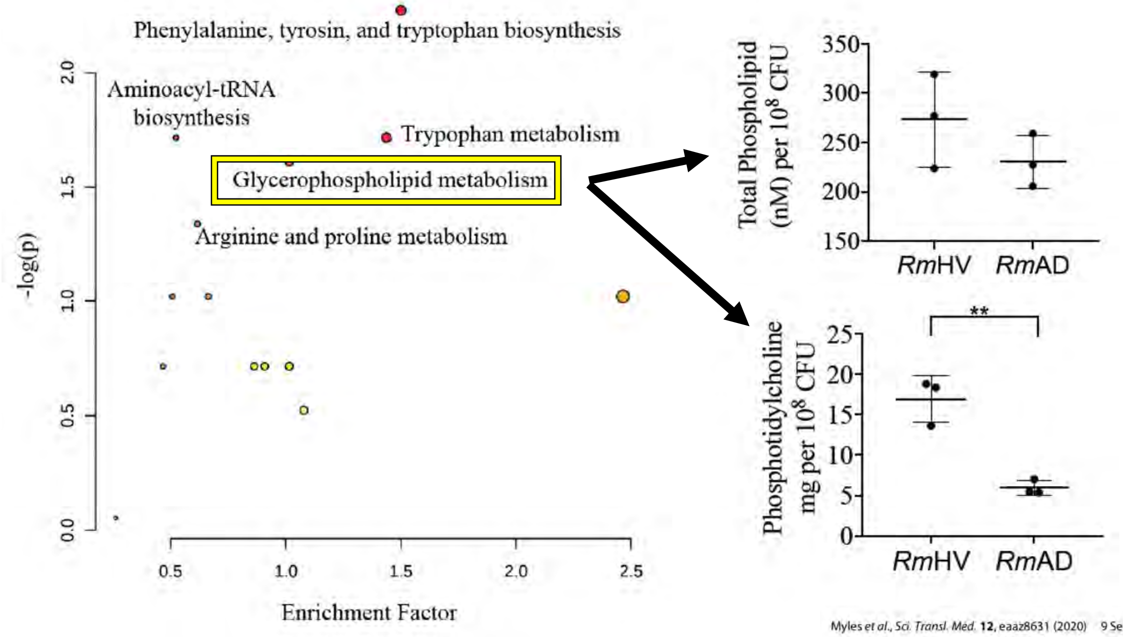
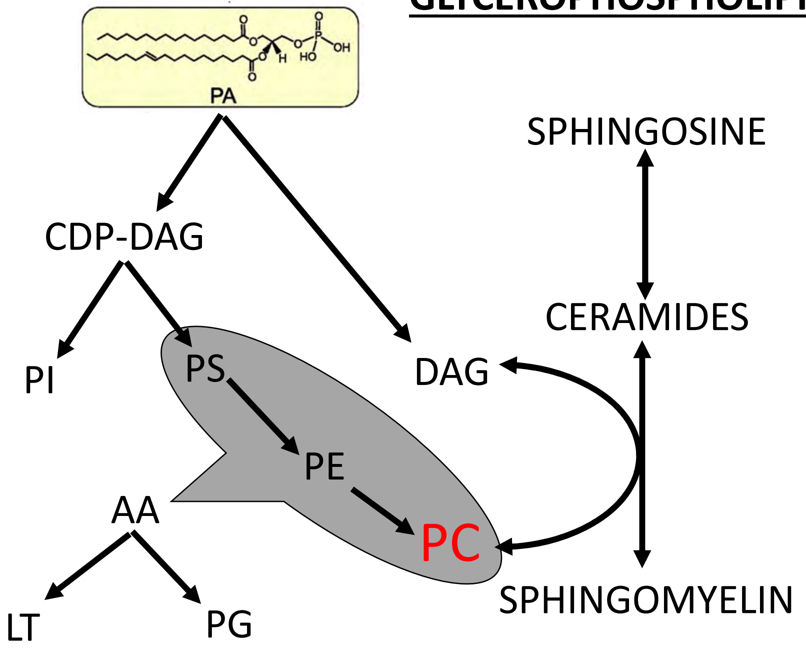
Metabolomic Comparison Between RmHV and RmAD



Myles et al., *Sci. Transl. Med.* **12**, eaaz8631 (2020) 9 September 2020

GLYCEROPHOSPHOLIPID PATHWAY



PA

CDP-DAG

PI

PS

PE

PC

DAG

AA

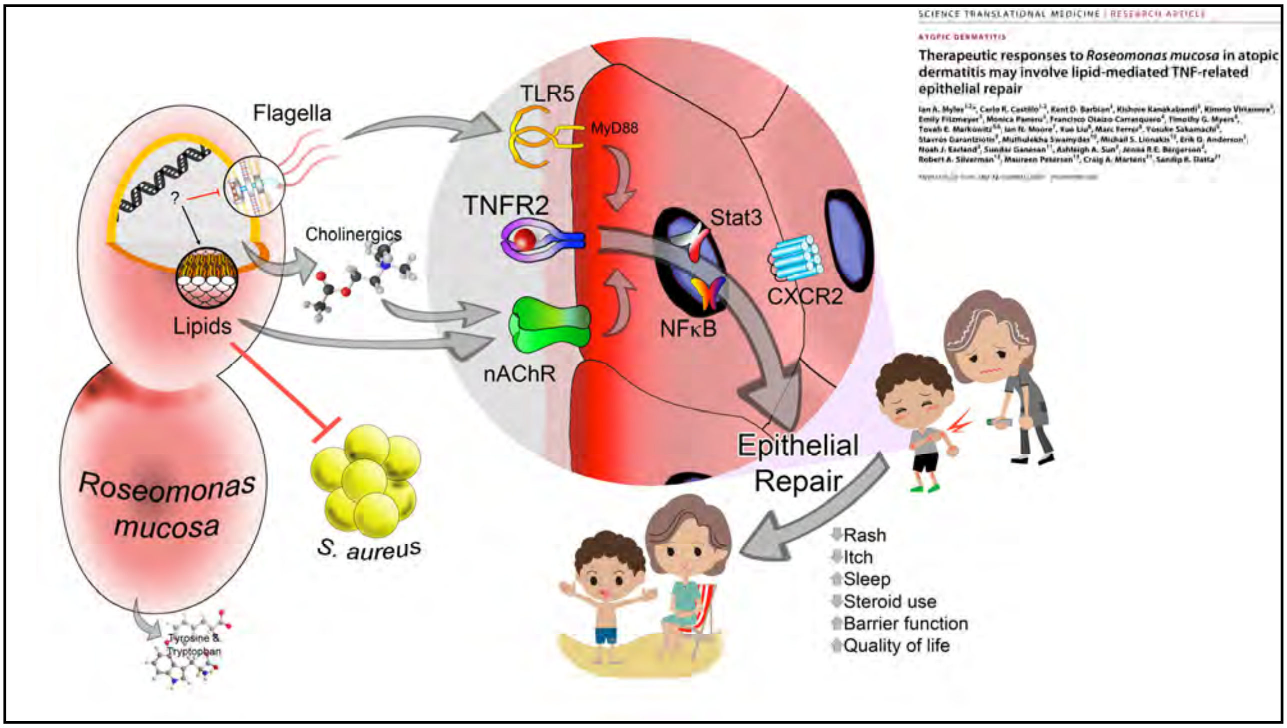
LT

PG

SPHINGOSINE

CERAMIDES

SPHINGOMYELIN



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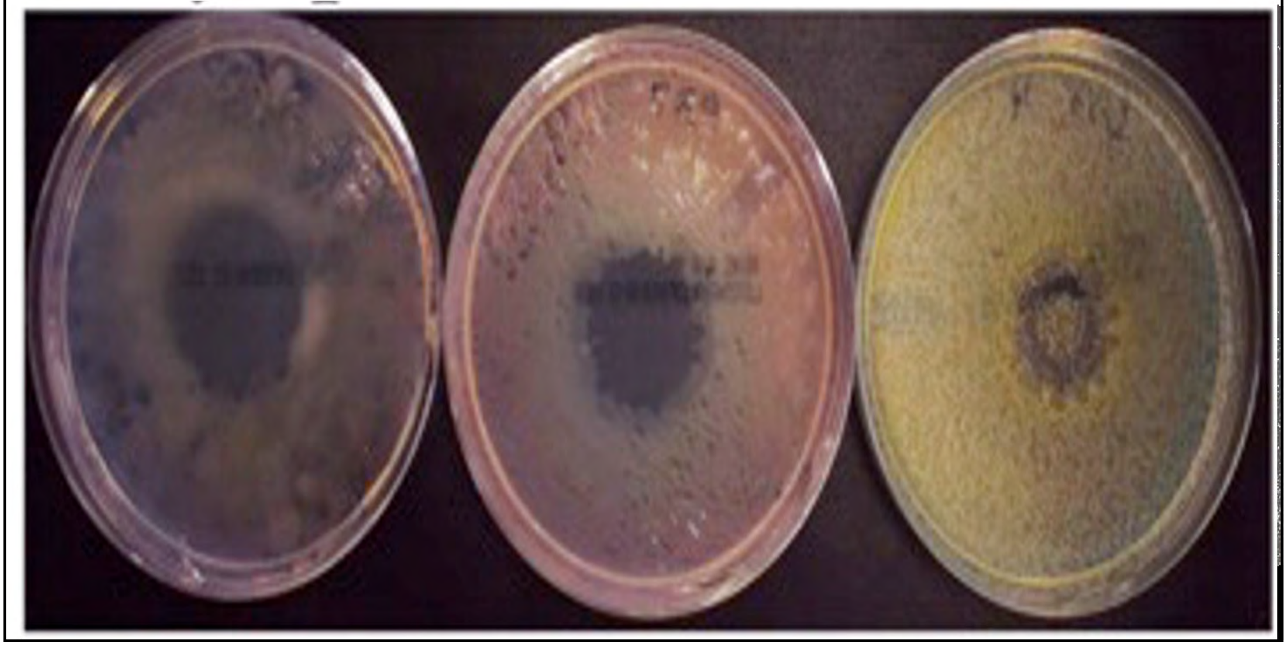
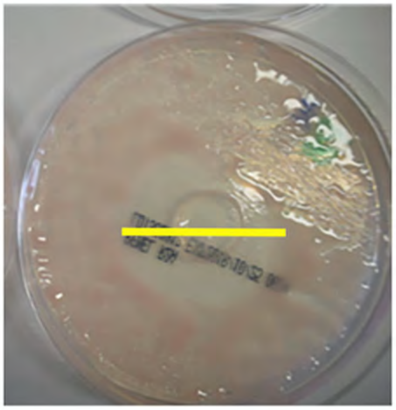
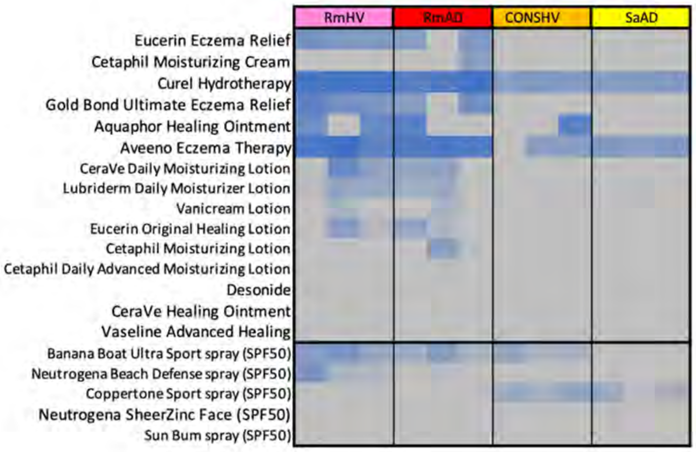
The world is awash in antibiotics



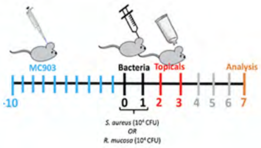
Challenged commensal bacteria with topical products



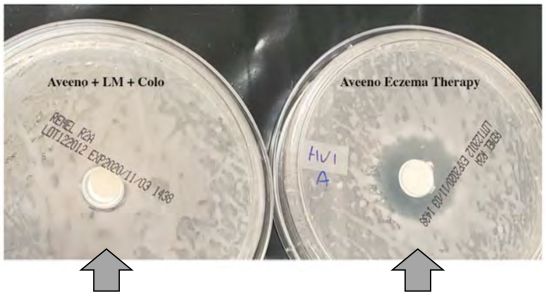


- Products varied but many inhibited the growth of common bacteria
    - RmHV = *Roseomonas* from healthy volunteers; RmAD = *Roseomonas* from patients with atopic derm; CONSHV = Coagulase negative *Staph*. from health volunteers; SaAD = *Staph aureus* from patients with AD.

Mixed ingredients to find a pre-biotic combination



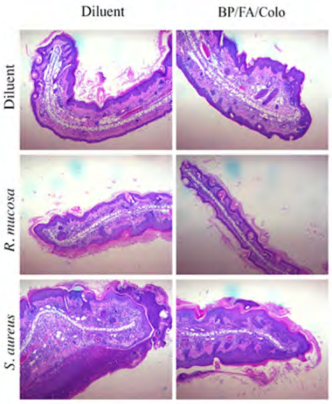
On a culture plate:



Aveeno with our mix

Aveeno off the shelf

In Mice:



Combo alone did not change outcome

Combo enhanced *R. mucosa* treatment

Ccombo partly reversed *S. aureus* harms

PAAA
Pennsylvania Allergy & Asthma Association

Diagnosis and Management of Food Allergy in a Breast-Fed Infant

Kirsi Järvinen-Seppo, MD, PhD

Friday, June 25, 2021
12:15 a.m. - 1:00 p.m.

PAAA does not have permission to share slides

Pennsylvania Allergy & Asthma Association

PRESENTATIONS FOR SATURDAY, JUNE 26, 2021

Severe Asthma in the Age of Phenotyping
Sally Wenzel, MD

Mast Cell Disorders
Lawrence Schwartz, MD, PhD

Annual Business Meeting
Allyson Larkin, PAAA President

Mayer A. Green, MD Allergy Foundation Lecture:
The Brave New Biologic World of Asthma
Sally Wenzel, MD

Biomarkers for Systematic Anaphylaxis
Lawrence Schwartz, MD, PhD

The Role of OIT in Food Allergy Management
Hugh Windom, MD

Getting Started with Food OIT
Hugh Windom, MD

PAAA

Pennsylvania Allergy & Asthma Association

Severe Asthma in the Age of Phenotyping

Sally Wentzel, MD

Saturday, June 26, 2021
8:00 a.m. - 8:45 a.m.

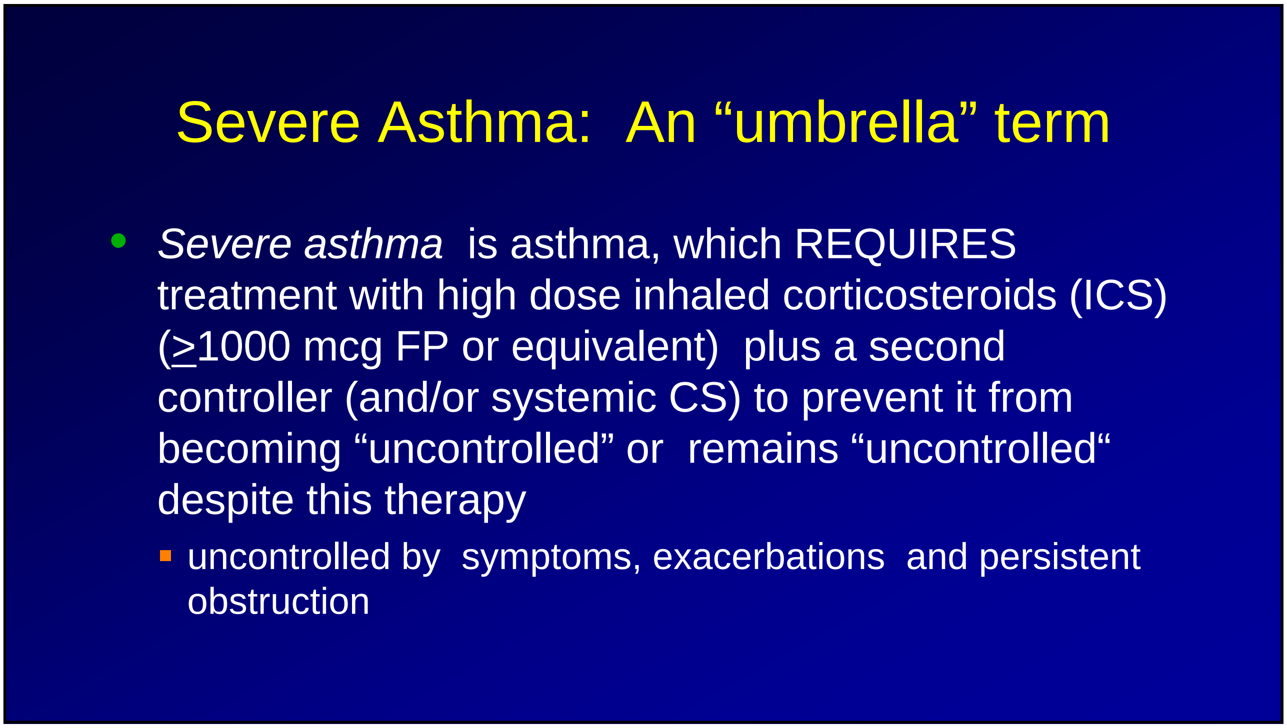
Severe Asthma in the Age of Phenotyping

Sally Wenzel, MD
Professor of Medicine and Immunology
Chair, Dept of Environmental and Occupational health

The University of Pittsburgh
Asthma Institute
@UPMC and the University of Pittsburgh School of Medicine

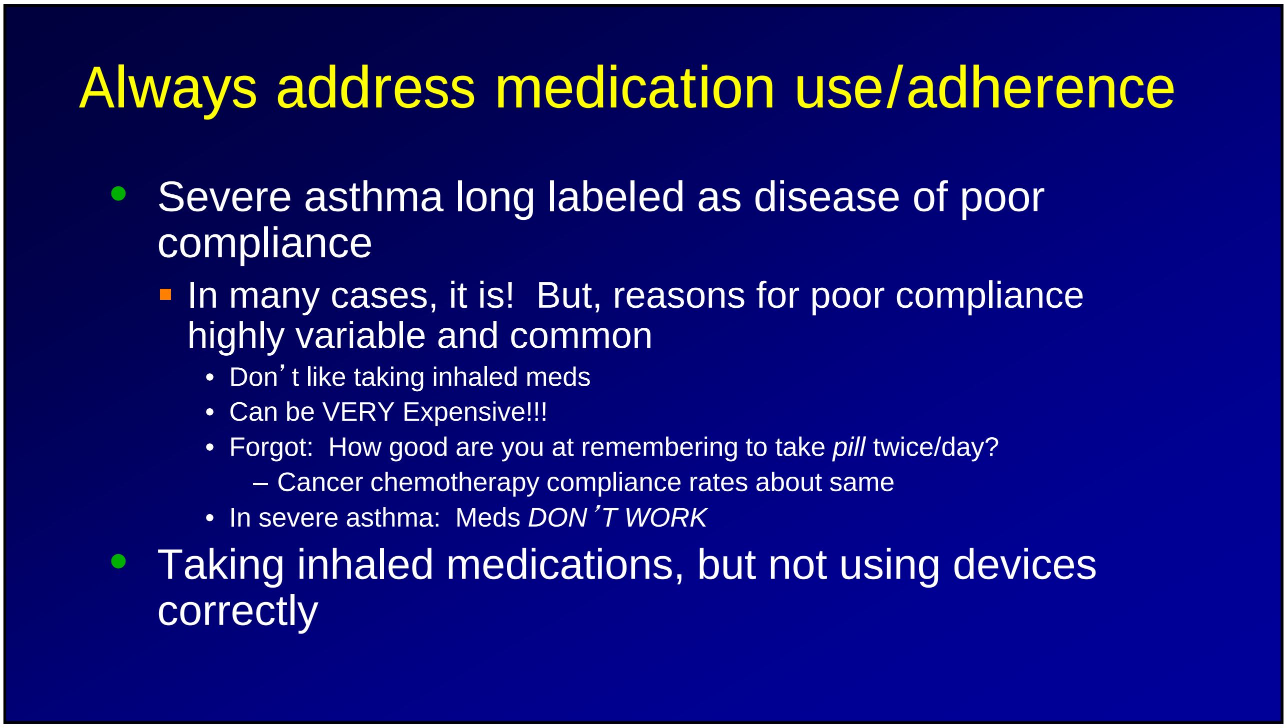
Declaration of COI

- Research funding: AstraZeneca, Teva, Sanofi-Genzyme,
- Consulting: AstraZeneca, Sanofi-Genzyme, Novartis, GSK



Severe Asthma: An "umbrella" term

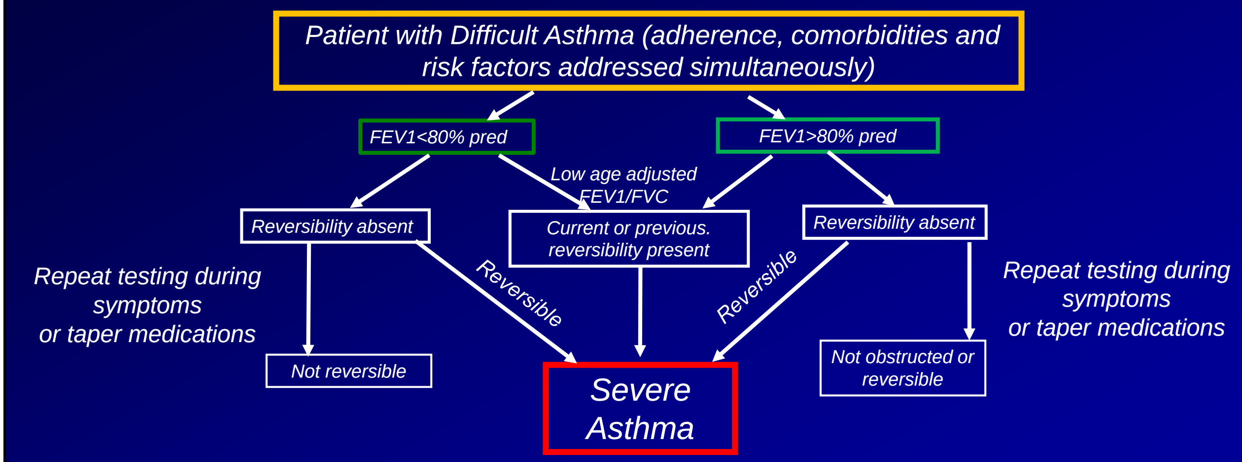
- *Severe asthma* is asthma, which REQUIRES treatment with high dose inhaled corticosteroids (ICS) ($\geq$1000 mcg FP or equivalent) plus a second controller (and/or systemic CS) to prevent it from becoming "uncontrolled" or remains "uncontrolled" despite this therapy
  - uncontrolled by symptoms, exacerbations and persistent obstruction



Always address medication use/adherence

- Severe asthma long labeled as disease of poor compliance
  - In many cases, it is! But, reasons for poor compliance highly variable and common
    - Don't like taking inhaled meds
    - Can be VERY Expensive!!!
    - Forgot: How good are you at remembering to take *pill* twice/day?
      - Cancer chemotherapy compliance rates about same
    - In severe asthma: Meds *DON'T WORK*
- Taking inhaled medications, but not using devices correctly

Approaching Difficult Asthma



Patient with Difficult Asthma (adherence, comorbidities and risk factors addressed simultaneously)

FEV1<80% pred

FEV1>80% pred

Low age adjusted FEV1/FVC

Reversibility absent

Current or previous. reversibility present

Reversibility absent

Repeat testing during symptoms or taper medications

Reversible

Reversible

Repeat testing during symptoms or taper medications

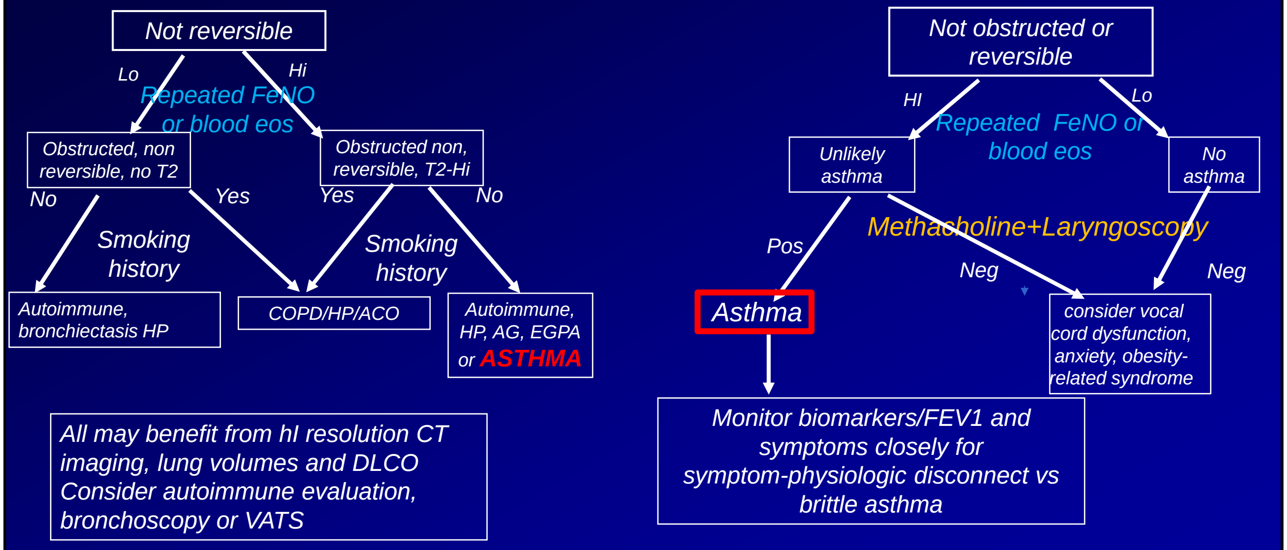
Not reversible

Severe Asthma

Not obstructed or reversible

Wenzel, S AJRCCM 2021

And then what ?



Not reversible

Lo

Hi

Repeated FeNO or blood eos

Obstructed, non reversible, no T2

Obstructed non, reversible, T2-Hi

No

Yes

Yes

No

Smoking history

Smoking history

Autoimmune, bronchiectasis HP

COPD/HP/ACO

Autoimmune, HP, AG, EGPA or **ASTHMA**

All may benefit from hI resolution CT imaging, lung volumes and DLCO Consider autoimmune evaluation, bronchoscopy or VATS

Not obstructed or reversible

HI

Lo

Repeated FeNO or blood eos

Unlikely asthma

No asthma

Methacholine+Laryngoscopy

Pos

Neg

Neg

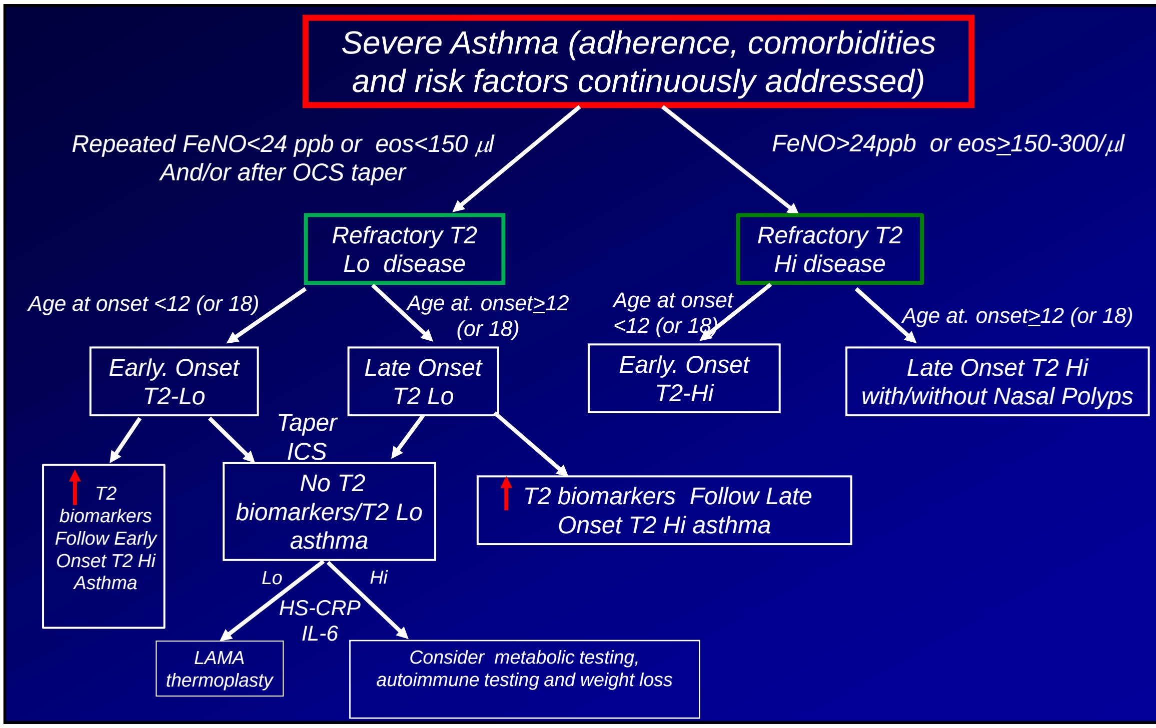
Asthma

consider vocal cord dysfunction, anxiety, obesity-related syndrome

Monitor biomarkers/FEV1 and symptoms closely for symptom-physiologic disconnect vs brittle asthma

2021: Emergence of Molecular Phenotypes

- Identification of clinical/molecular **characteristics**:
  - Non-specific individual signs, symptoms, outcomes
    - eg: Obesity, exacerbation-prone, fixed obstruction, eosinophilic
    - Do not, alone, give insight into underlying causes
  - Genes or mRNA/protein expression
- Incorporation of *multiple related clinical/hereditary or molecular characteristics* identifies a **phenotype**
- Merging of both *clinical and molecular characteristics* defines a **Molecular Phenotype**
  - Enhanced by responses to targeted therapies



Severe Asthma (adherence, comorbidities and risk factors continuously addressed)

Repeated FeNO<24 ppb or eos<150 µl
And/or after OCS taper

FeNO>24ppb or eos≥150-300/µl

Refractory T2 Lo disease

Refractory T2 Hi disease

Age at onset <12 (or 18)

Age at. onset≥12 (or 18)

Age at onset <12 (or 18)

Age at. onset≥12 (or 18)

Early. Onset T2-Lo

Late Onset T2 Lo

Early. Onset T2-Hi

Late Onset T2 Hi with/without Nasal Polyps

Taper ICS

↑ T2 biomarkers Follow Early Onset T2 Hi Asthma

No T2 biomarkers/T2 Lo asthma

↑ T2 biomarkers Follow Late Onset T2 Hi asthma

Lo

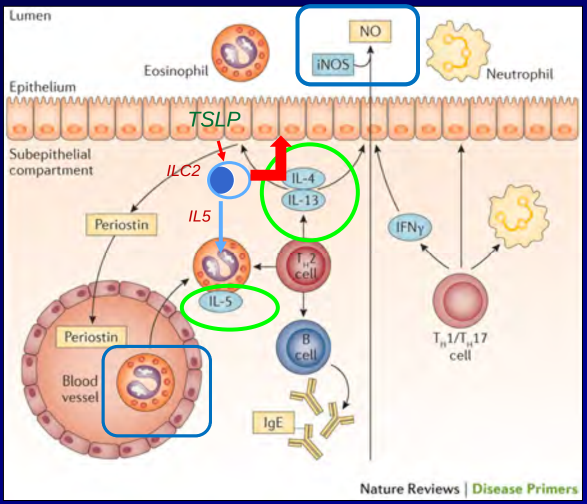
Hi

HS-CRP IL-6

LAMA thermoplasty

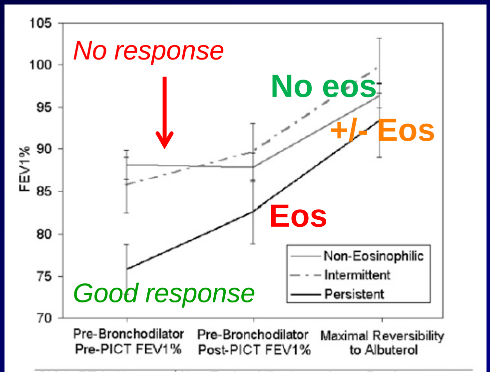
Consider metabolic testing, autoimmune testing and weight loss

”Type-2” inflammation: Identifying available biomarkers



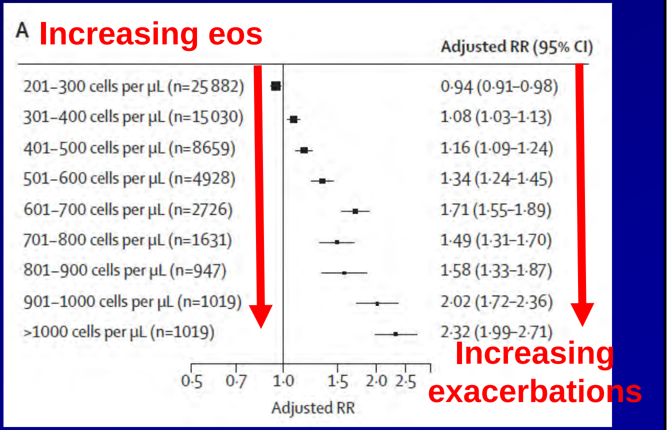
Holgate, S. T. Wenzel, S et al. (2015) Asthma
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.25

Eosinophils: Predict response to CS treatment and exacerbation risk



%Δ in FEV_1 (L)	Non-Eosinophilic	Intermittent	Persistent	p
Pre- to Post-PICT	-0.2%	4.7%	8.6%	0.001
Post-PICT to Max Rev	10.1%	12.1%	13.5%	0.32

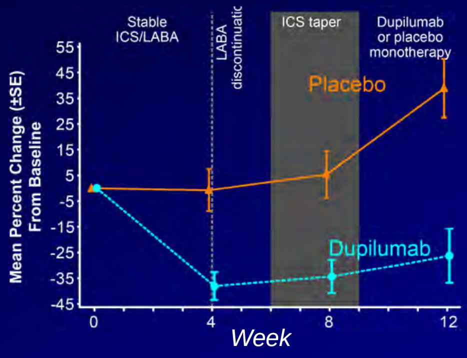
McGrath AJRCCM 2012



Price DB, Lancet Resp Med 2015

Much *less* helpful when patients treated with systemic CSs

Fraction Exhaled NO (FeNO)



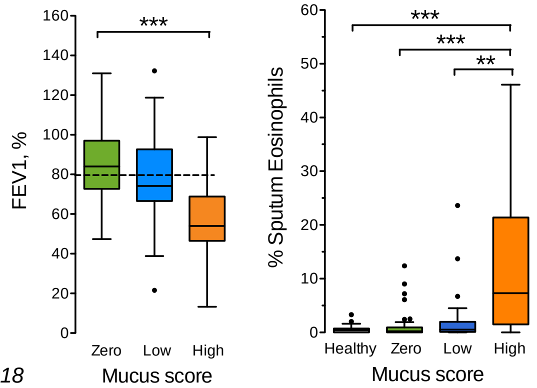
Correlation of FeNO with FEV_1
at Week 12: r = -0.408 P = 0.009

Wenzel N Engl J Med 2013

- Generated by *epithelial* iNOS
    - Upregulated by IL-4/13
- High levels seen across spectrum of asthma severity
    - High likelihood of systemic CS dependent disease *Wysocki et al JACI 2011, Wu W JACI 2013*
- Induced by IL-4/13 in epithelial cells
    - *Both predicts response to IL-4R directed therapy and responds (declines) with treatment*

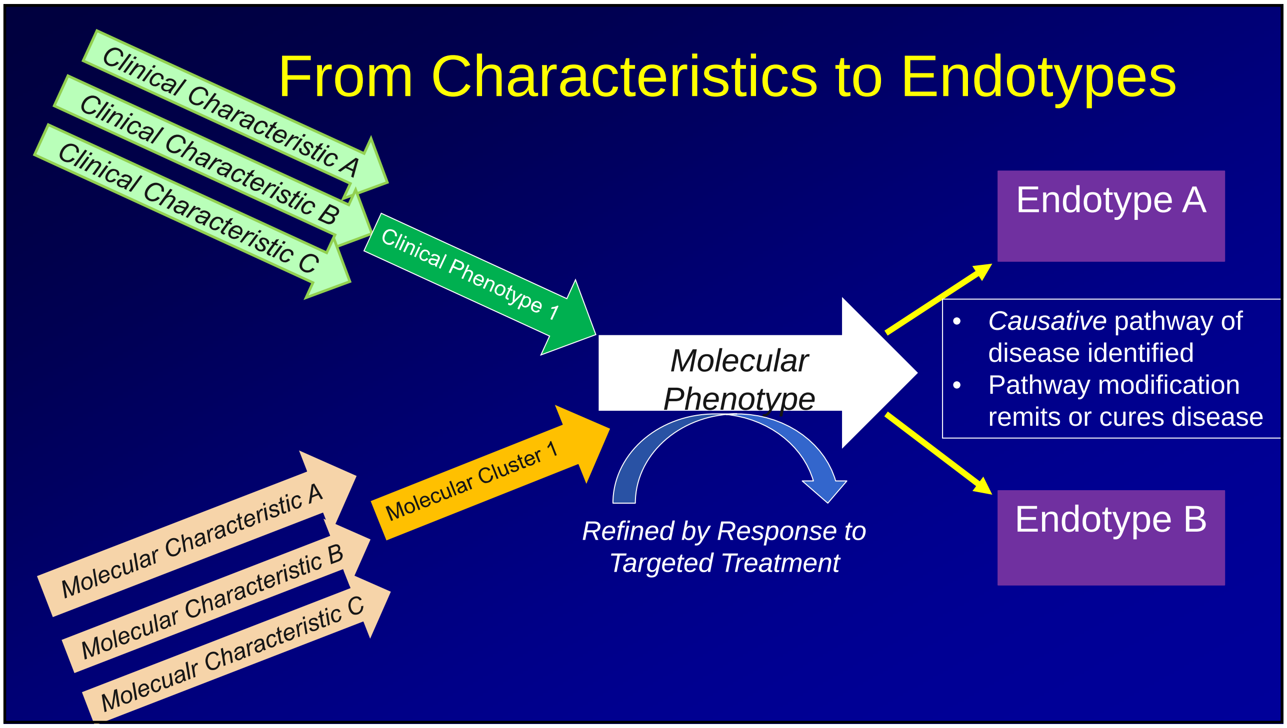
CT-imaging supports role of T2/eos to mucus and worsening FEV1

Dunican E…Fahy J J Clin Invest 2018



Interventional studies needed to confirm role of T2 cytokines

From Characteristics to Endotypes



Clinical Characteristic A

Clinical Characteristic B

Clinical Characteristic C

Clinical Phenotype 1

Molecular Characteristic A

Molecular Characteristic B

Molecualr Characteristic C

Molecular Cluster 1

Molecular Phenotype

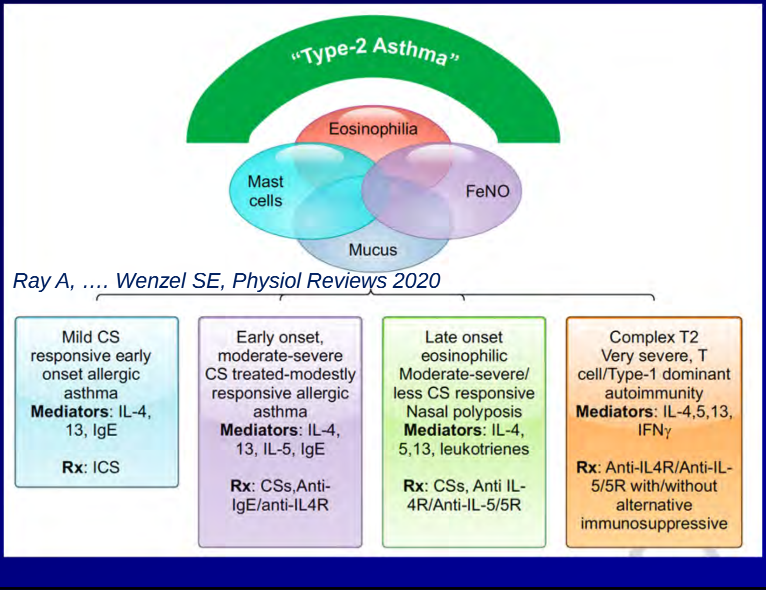
Refined by Response to Targeted Treatment

Endotype A

- *Causative* pathway of disease identified
- Pathway modification remits or cures disease

Endotype B

2021: Type-2 Hi Molecular Phenotypes

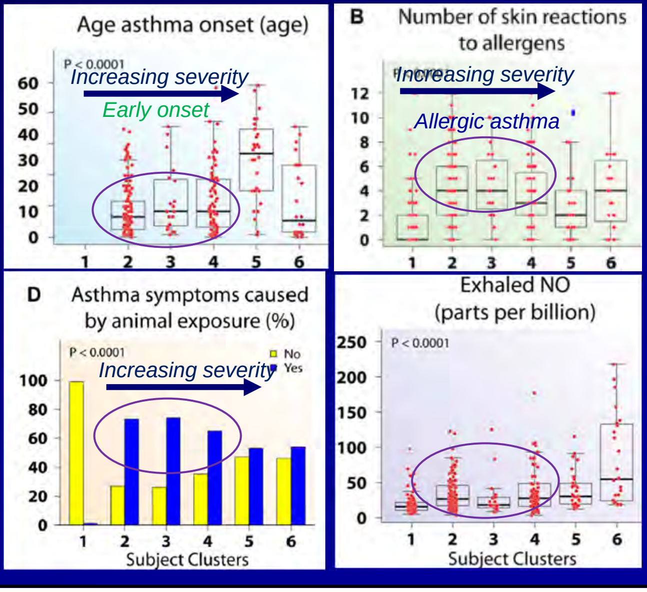


Ray A, …. Wenzel SE, Physiol Reviews 2020

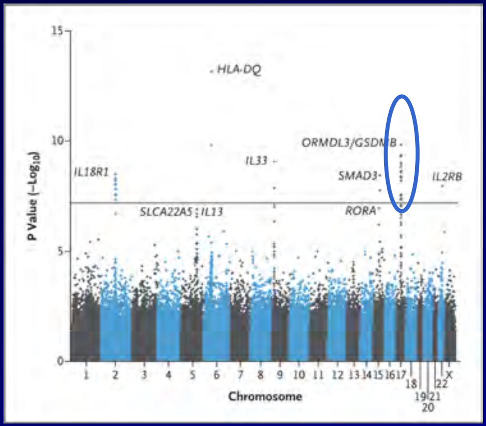
Mild CS responsive early onset allergic asthma **Mediators**: IL-4, 13, IgE **Rx**: ICS	Early onset, moderate-severe CS treated-modestly responsive allergic asthma **Mediators**: IL-4, 13, IL-5, IgE **Rx**: CSs,Anti-IgE/anti-IL4R	Late onset eosinophilic Moderate-severe/ less CS responsive Nasal polyposis **Mediators**: IL-4, 5,13, leukotrienes **Rx**: CSs, Anti IL-4R/Anti-IL-5/5R	Complex T2 Very severe, T cell/Type-1 dominant autoimmunity **Mediators**: IL-4,5,13, IFNγ **Rx**: Anti-IL4R/Anti-IL-5/5R with/without alternative immunosuppressive

Allergic/early onset asthma most prominent T2 Hi

- SARP clusters show importance of age at onset
  Moore W et al AJRCCM 2010, Wu W et al JACI 2014
  - 2nd was analysis of >350 patients from SARP
- Three clusters of early onset allergic asthma (#2-4) of worsening severity
  - Early onset allergic disease
    - associated with milder asthma
    - *modest T2-biomarker elevations*
    - strongest family history



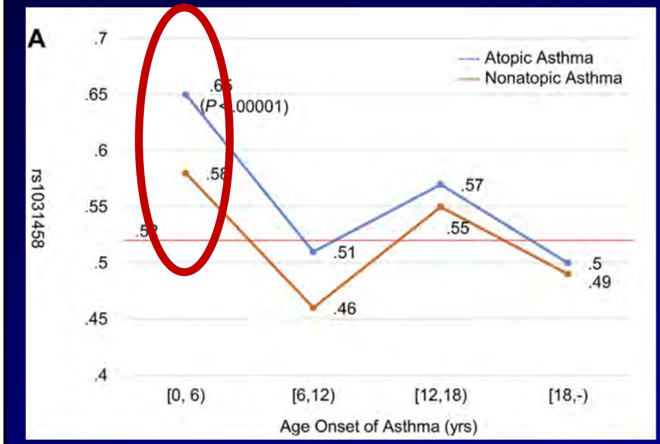
Studies consistently support genetic contribution to early onset asthma (EOA)



Moffatt MF et al. A Large Scale Consortium-Based Genomewide Association Study of Asthma N Engl J Med 2010;363:1211-1221

- CHILDHOOD onset asthma --- strong associations with genetic loci
- Highest p-values for any region were in 17q12-21
  - Consistently identified across most all subsequent studies
  - SNPs in GSDMB and ORMDL3 remain most associated with asthma
  - Little to no overlap of allergy-related genes and asthma-related genes

Genetics and EOA

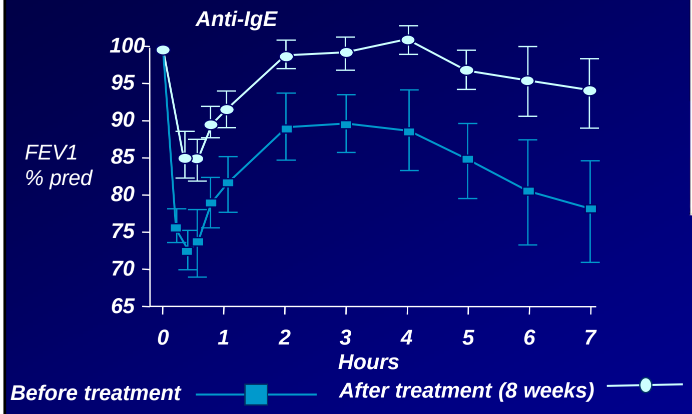


- GSDMB risk alleles more common in early onset asthma and greater severity
  - GSDMB expression regulated by its SNPs
- Promoter contains IRF binding sites, consistent with viral relationships
  - Enhanced by Type-1 interferons suggesting its importance in viral-intersection with EOA

Li X, Christenson et al J Allergy Clin Immunol March 2021

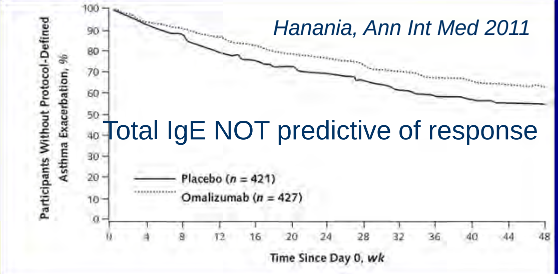
Integrating biologics to define phenotypes: Allergy/IgE

Blocks allergic responses in mild asthma



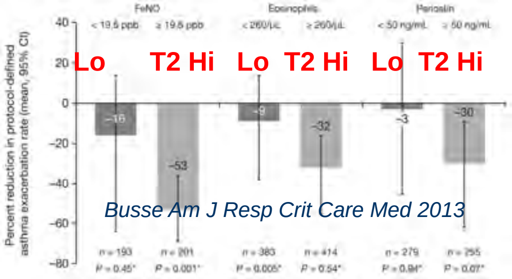
Fahy JV, et al. Am J Respir Crit Care Med. 1997 .

Severe allergic asthma

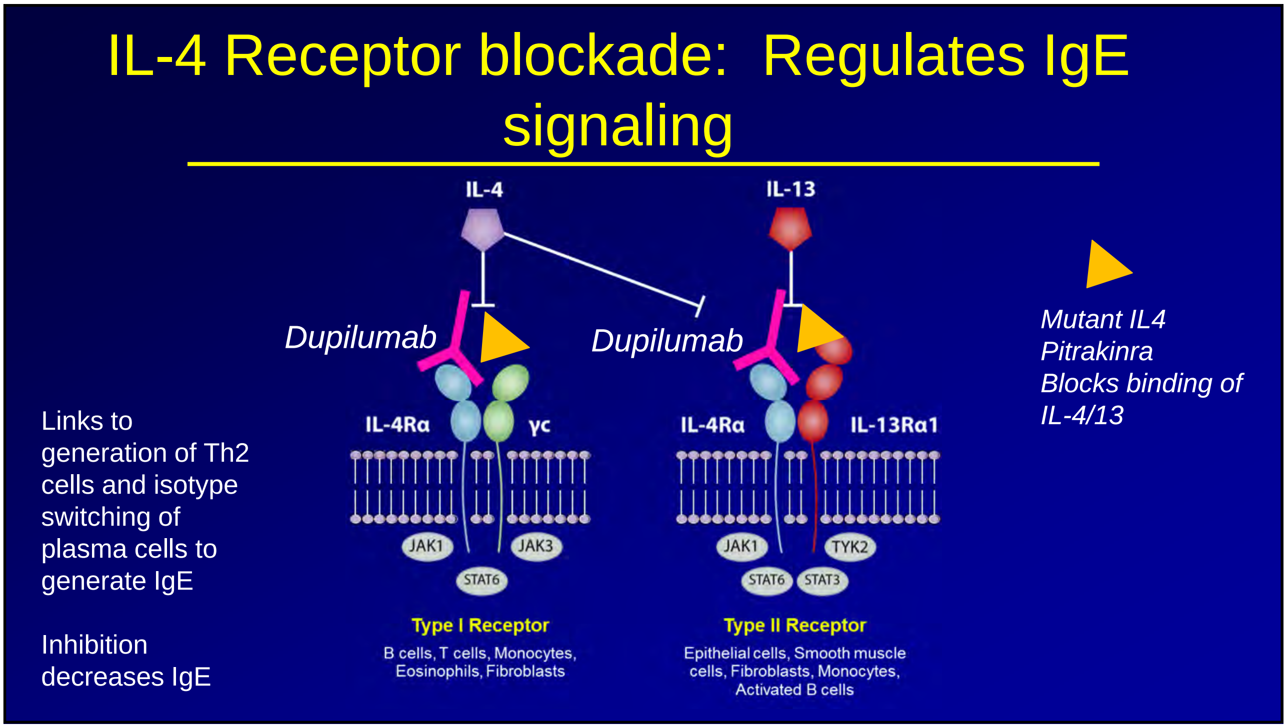


Hanania, Ann Int Med 2011

Total IgE NOT predictive of response



Busse Am J Resp Crit Care Med 2013

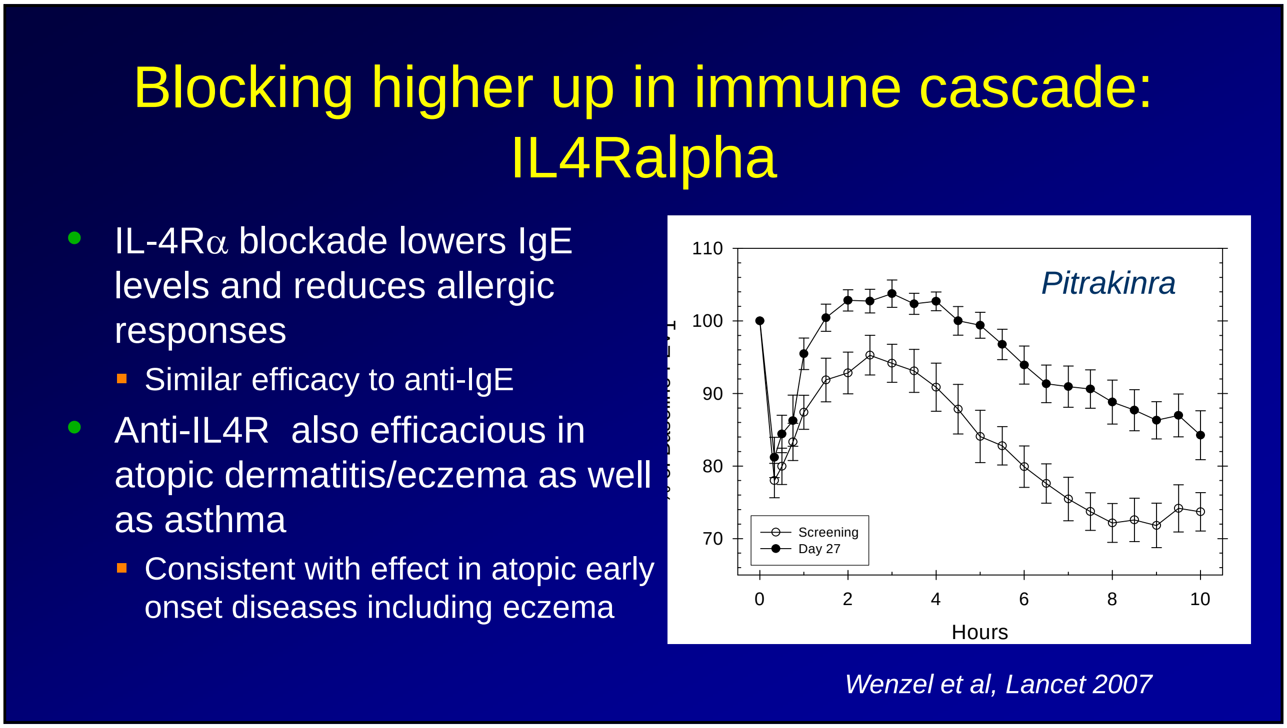


IL-4 Receptor blockade: Regulates IgE signaling

Links to generation of Th2 cells and isotype switching of plasma cells to generate IgE

Inhibition decreases IgE

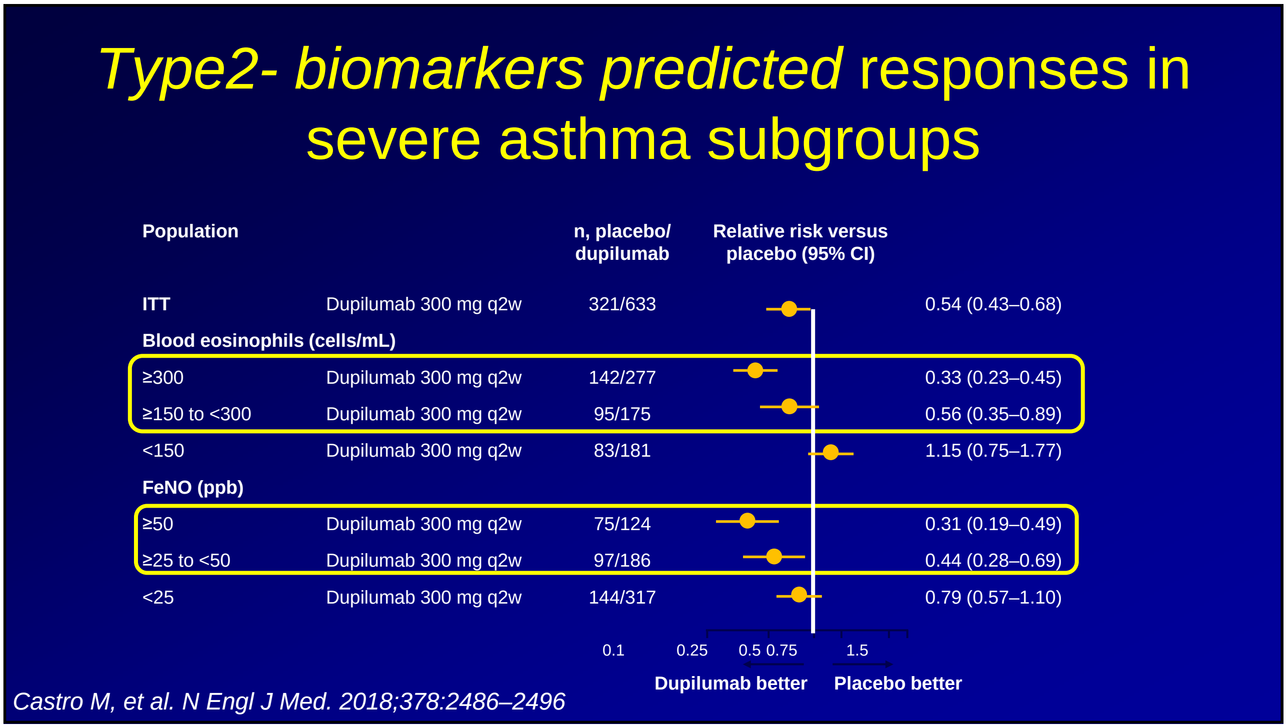
Mutant IL4
Pitrakinra
Blocks binding of IL-4/13



Blocking higher up in immune cascade: IL4Ralpha

- IL-4Rα blockade lowers IgE levels and reduces allergic responses
  - Similar efficacy to anti-IgE
- Anti-IL4R also efficacious in atopic dermatitis/eczema as well as asthma
  - Consistent with effect in atopic early onset diseases including eczema

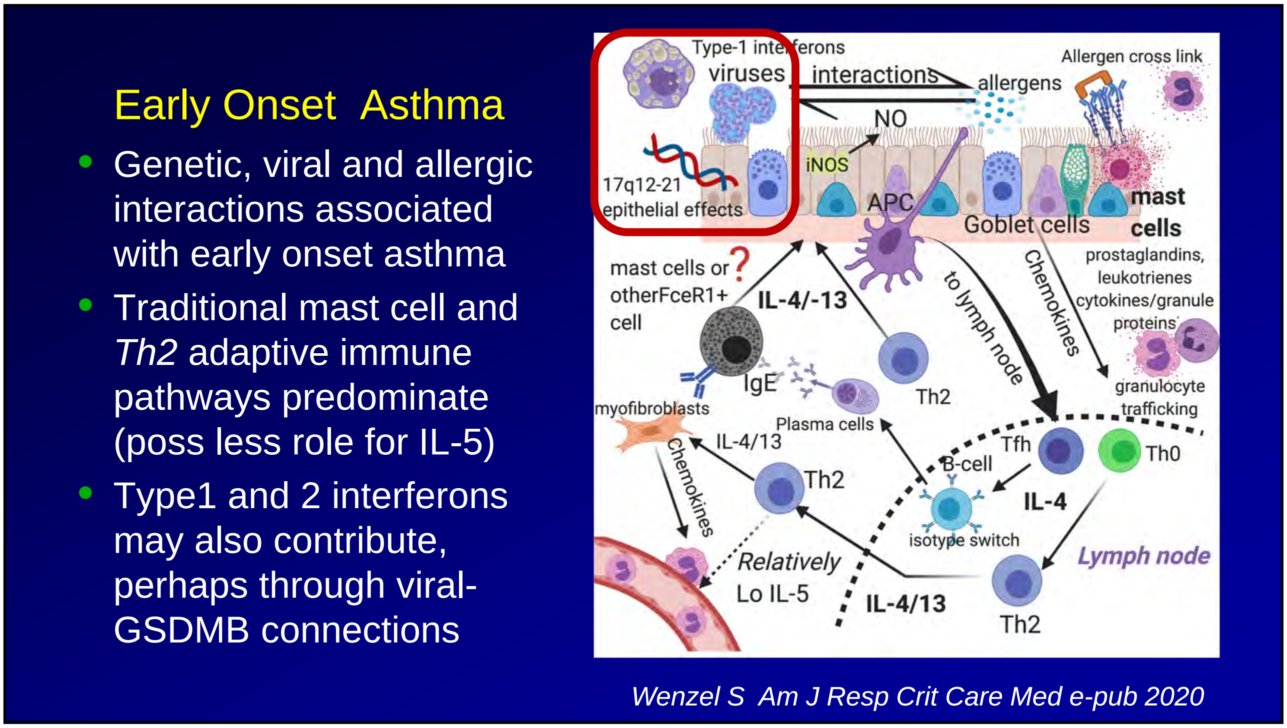
Wenzel et al, Lancet 2007



Type2- biomarkers predicted responses in severe asthma subgroups

Population		**n, placebo/ dupilumab**	**Relative risk versus placebo (95% CI)**
ITT	Dupilumab 300 mg q2w	321/633	0.54 (0.43–0.68)
Blood eosinophils (cells/mL)			
≥300	Dupilumab 300 mg q2w	142/277	0.33 (0.23–0.45)
≥150 to <300	Dupilumab 300 mg q2w	95/175	0.56 (0.35–0.89)
<150	Dupilumab 300 mg q2w	83/181	1.15 (0.75–1.77)
FeNO (ppb)			
≥50	Dupilumab 300 mg q2w	75/124	0.31 (0.19–0.49)
≥25 to <50	Dupilumab 300 mg q2w	97/186	0.44 (0.28–0.69)
<25	Dupilumab 300 mg q2w	144/317	0.79 (0.57–1.10)

Castro M, et al. N Engl J Med. 2018;378:2486–2496



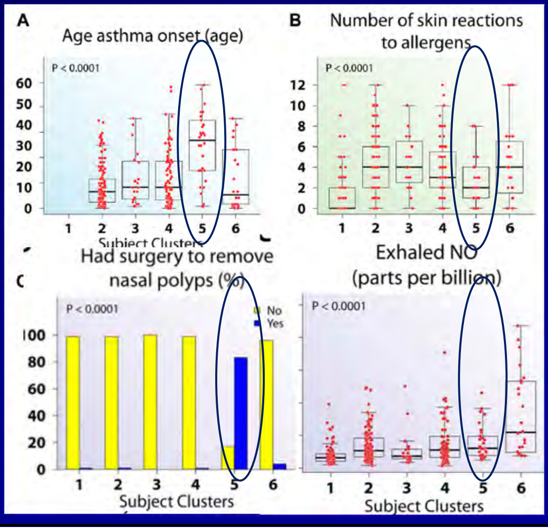
Early Onset Asthma

- Genetic, viral and allergic interactions associated with early onset asthma
- Traditional mast cell and *Th2* adaptive immune pathways predominate (poss less role for IL-5)
- Type1 and 2 interferons may also contribute, perhaps through viral-GSDMB connections

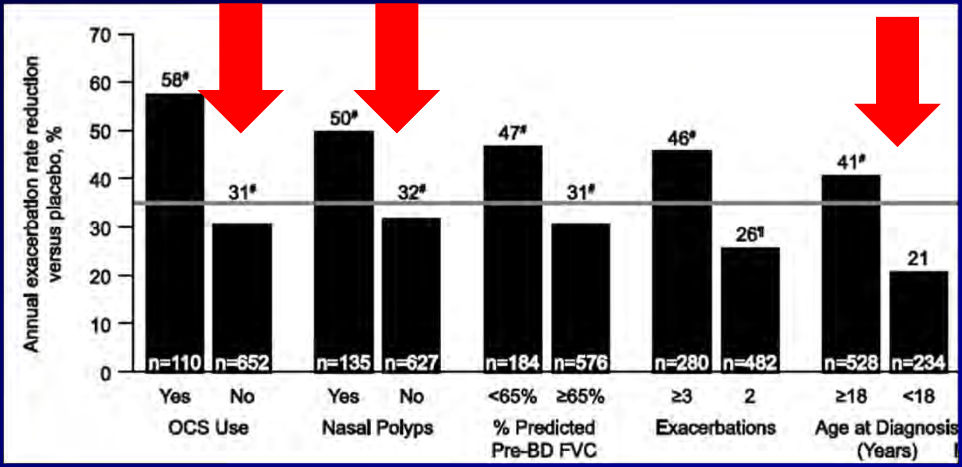
Wenzel S Am J Resp Crit Care Med e-pub 2020

Late onset T2 Hi disease: Nasal polyposis, eosinophilia and severe asthma

- Adult onset cluster easily identified *Wu et al JACI 2011*
  - Nasal polyps most common in adult onset cluster
  - Low allergic responses
  - High eos and FeNO c/w T2 disease
  - Clinically vastly different from early onset asthma



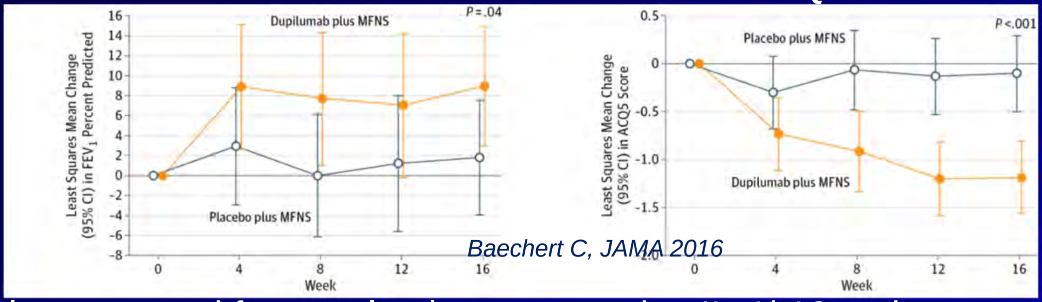
Anti-IL-5/5R therapies *more* effective in severe (OCS dependent), late onset, less allergic, nasal polyp disease



Bleecker E et al Eur Respir J 2018

Anti-IL-4R also works well in late onset/nasal polyp associated disease

FEV1 ***ACQ5***



Baechert C, JAMA 2016

- Also approved for nasal polyps, supporting IL-4/-13 pathway
  - Marked reduction in polyp scores and associated symptoms
  - Suggests association with ILC2 cells (greater IL-5, IL-13 expression stimulated by TSLP?)
  - Dupilumab may also be more effective in late than early onset Castro, *Hanania N, Chest meeting 2019C*

OCS dependent pts: a different phenotype or more of the same?

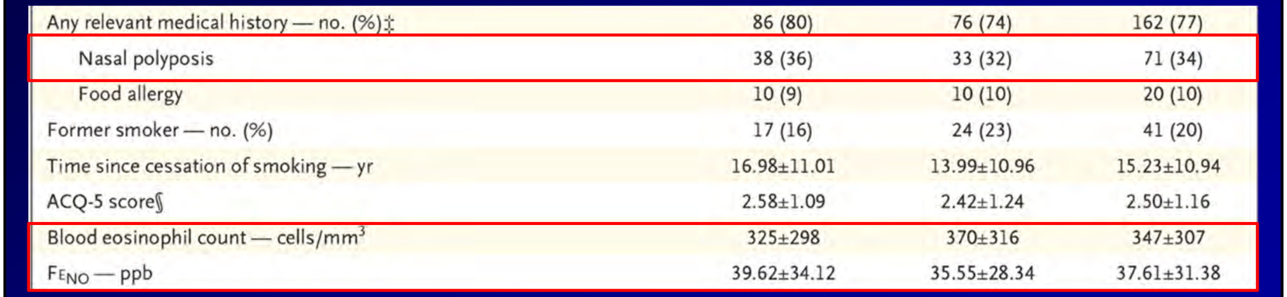
	Placebo N=75	Benra Q4W N=72	Benra Q8W N=73
Pre-BD FEV$_1$ (L), mean (SD)	1.931 (0.662)	1.850 (0.741)	1.754 (0.635)
Pre-BD FEV$_1$ as % of predicted normal (SD)	62.0 (16.5)	57.4 (18.0)	59 (17.9)
Pre-BD FEV$_1$:FVC, (%), mean(SD)	62 (13)	59 (13)	59 (12)
Reversibility, (%), median (%, range)	16.4 (-5.4 to 93.4)	18.2 (-3.0 to 126.0)	22.6 (-3.4 to 88.0)
ACQ-6 score, mean (SD)	2.68 (0.95)	2.59 (1.13)	2.42 (1.21)
AQLQ(S)+12 score, mean (SD)	4.11 (1.07)	4.25 (1.09)	4.44 (1.25)
Total asthma symptom score, mean (SD)	2.43 (0.99)	2.47 (0.99)	2.34 (1.09)
Time since diagnosis, (years), median (range)	10.5 (1.1 to 54.5)	13.3 (1.2 to 52.3)	16.3 (1.3 to 53.0)
Prior year exacerbations, (n), mean (SD)	2.5 (1.8)	2.8 (2.0)	3.1 (2.8)
Nasal polyps, n (%)	28 (37)	22 (31)	20 (27)
Atopy (Phadiatop test), n (%)	37 (49)	29 (40)	29 (40)

- This study recruited an overall poorly controlled, oral glucocorticoid-dependent asthma population

ACQ-6 = Asthma Control Questionnaire-6; AQLQ(S) + 12 = asthma quality of life questionnaire for 12 years and older; Benra = benralizumab; BD = bronchodilator; FEV$_1$ = forced expiratory volume in 1 second; FVC = forced volume capacity; Q4W = every 4 weeks; Q8W = every 8 weeks; SD = standard deviation.

Nair P et al. Supplementary appendix. *N Engl J Med*. 2017.

Dupilumab trial: eosinophils high even without being inclusion criteria

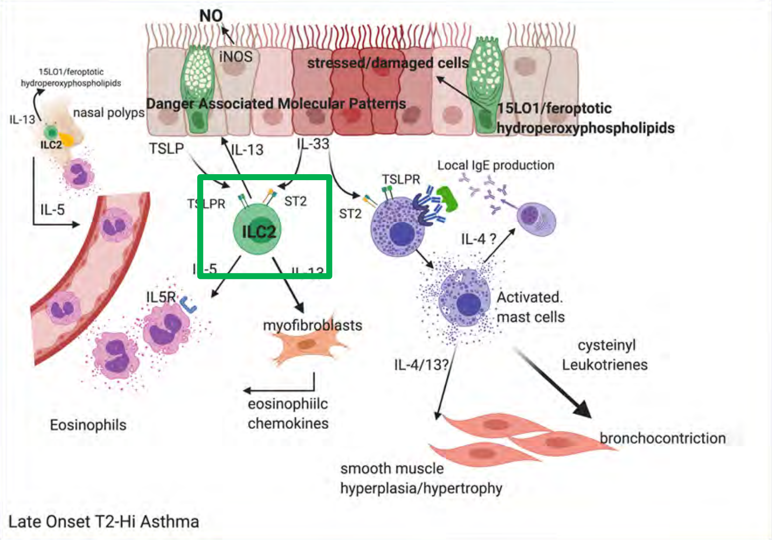


Any relevant medical history — no. (%)‡	86 (80)	76 (74)	162 (77)
Nasal polyposis	38 (36)	33 (32)	71 (34)
Food allergy	10 (9)	10 (10)	20 (10)
Former smoker — no. (%)	17 (16)	24 (23)	41 (20)
Time since cessation of smoking — yr	16.98±11.01	13.99±10.96	15.23±10.94
ACQ-5 score§	2.58±1.09	2.42±1.24	2.50±1.16
Blood eosinophil count — cells/mm^3	325±298	370±316	347±307
F_{ENO} — ppb	39.62±34.12	35.55±28.34	37.61±31.38

Rabe K et al N Engl J Med 2018

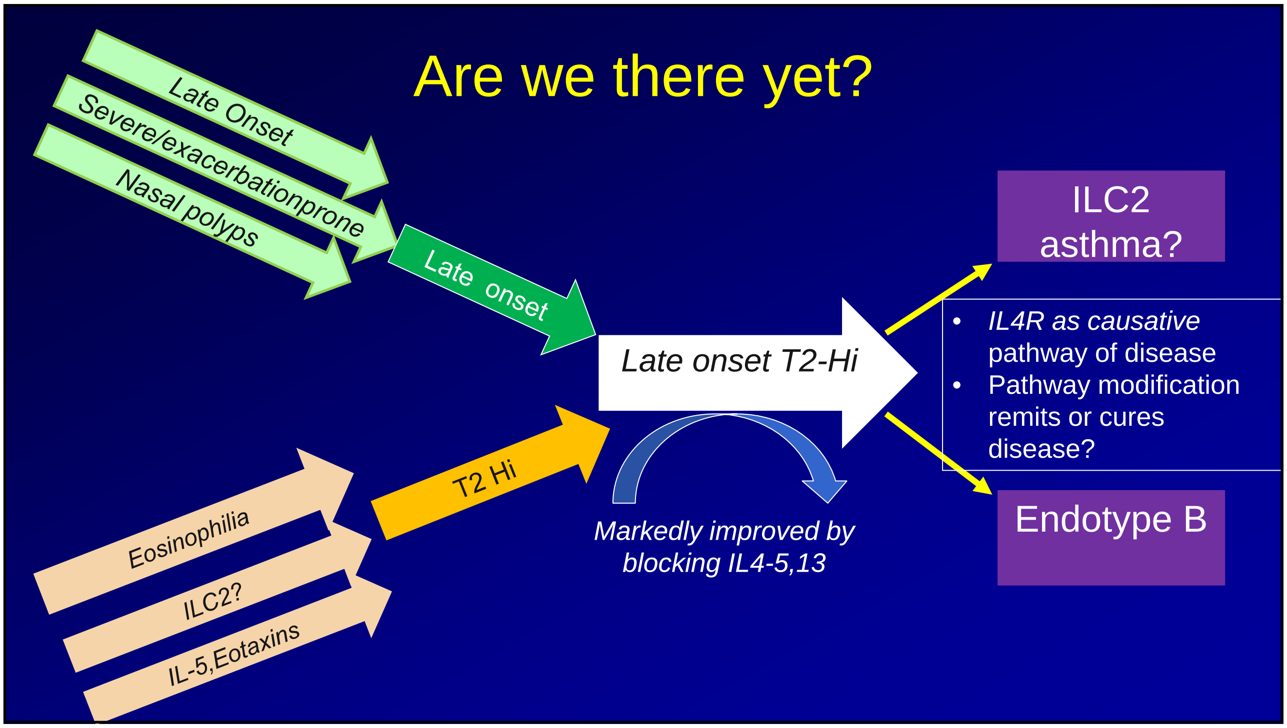
Late Onset T2 Hi severe asthma

- Maybe close to achieving endotype status associated with specific biologic pathway
- Strong association with nasal polyps, possibly ILC2 cells with high IL-5/13 production



Wenzel S Am J Resp Crit Care Med e-pub 2020

Are we there yet?



Late Onset

Severe/exacerbationprone

Nasal polyps

Late onset

Late onset T2-Hi

Eosinophilia

ILC2?

IL-5,Eotaxins

T2 Hi

Markedly improved by blocking IL4-5,13

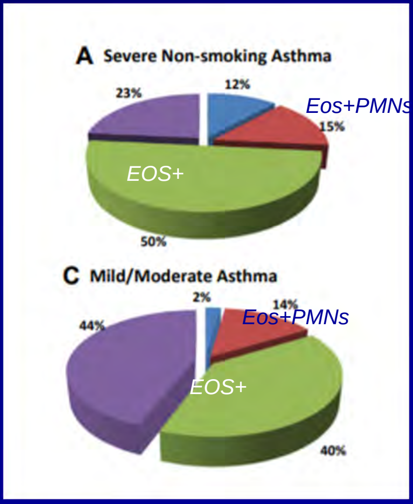
ILC2 asthma?

- *IL4R as causative* pathway of disease
- Pathway modification remits or cures disease?

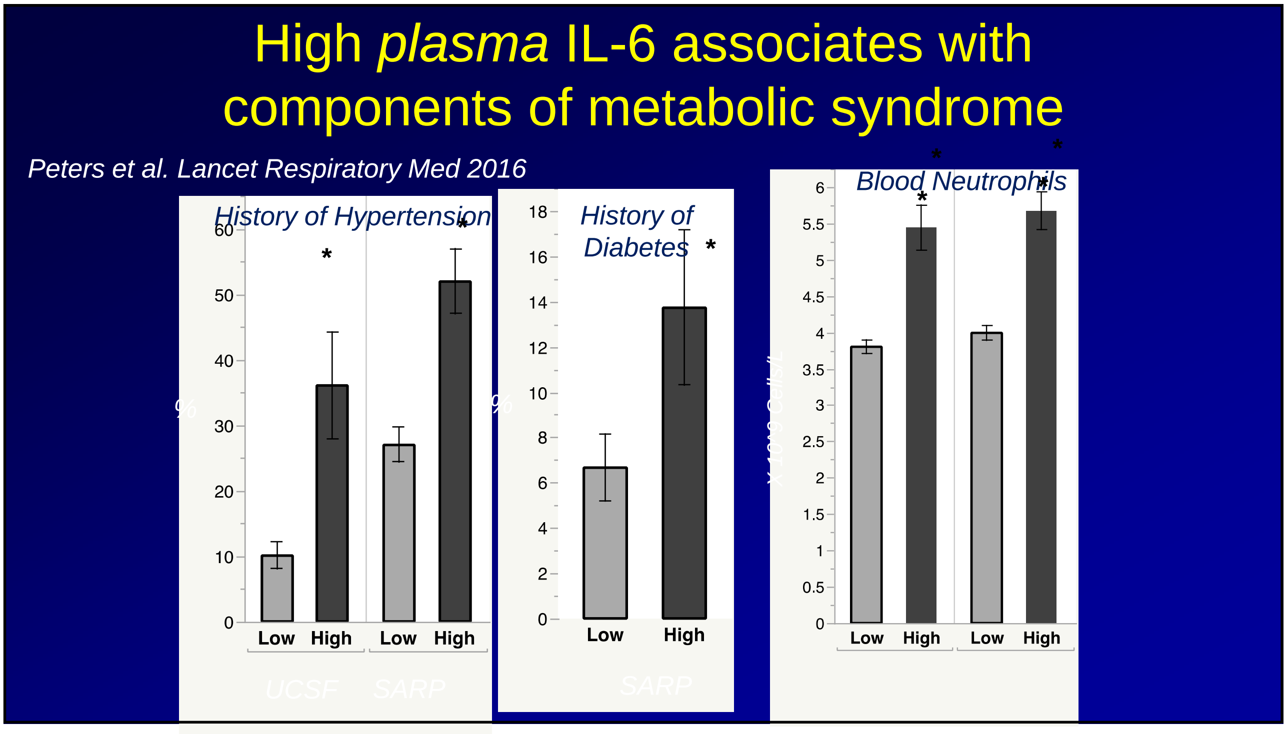
Endotype B

Non-T2 molecular phenotypes: Are we making progress?

- Unclear what % of asthma has no evidence for T2 pathway activation
  - Single sputum from U-BIOPRED suggest 62% “eosinophilic-T2 HI” asthma
  - Repeated FeNO and sputum in SARP suggest 78% T2 Hi
  - May depend on asthma definition and CS doses

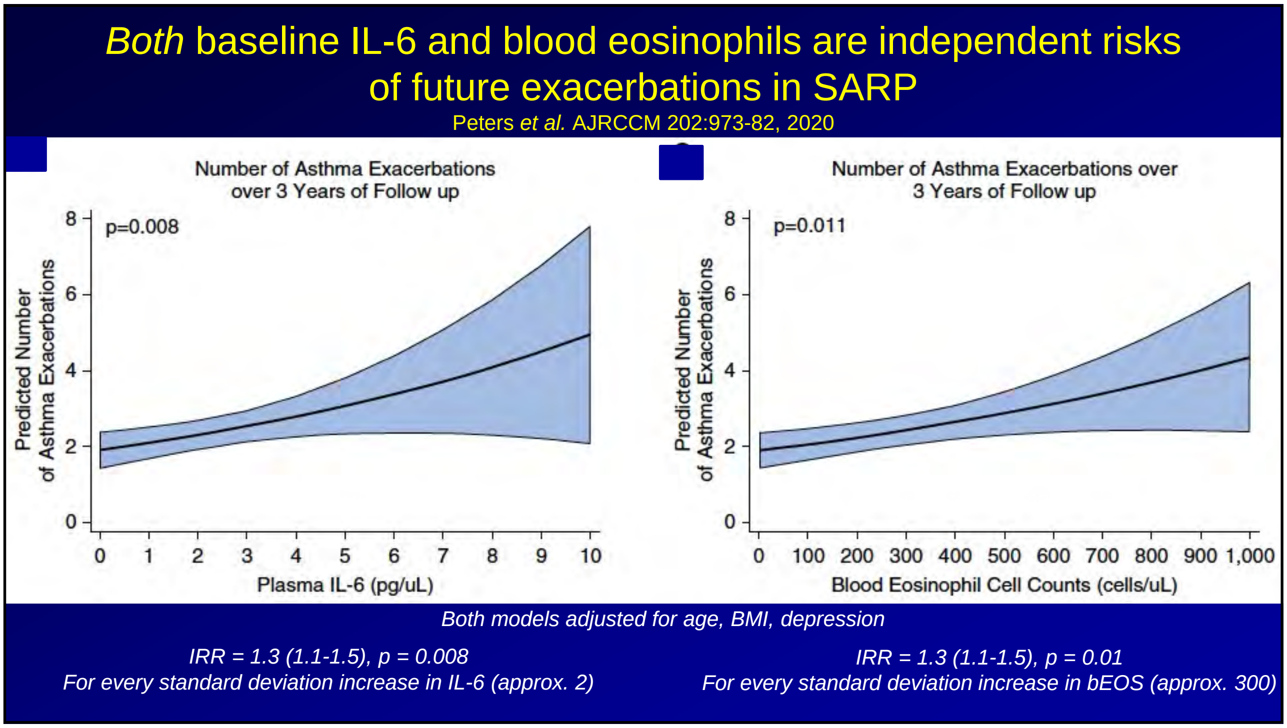


Rossios J Allergy Clin Immunol 2017



High *plasma* IL-6 associates with components of metabolic syndrome

Peters et al. Lancet Respiratory Med 2016



Both baseline IL-6 and blood eosinophils are independent risks of future exacerbations in SARP

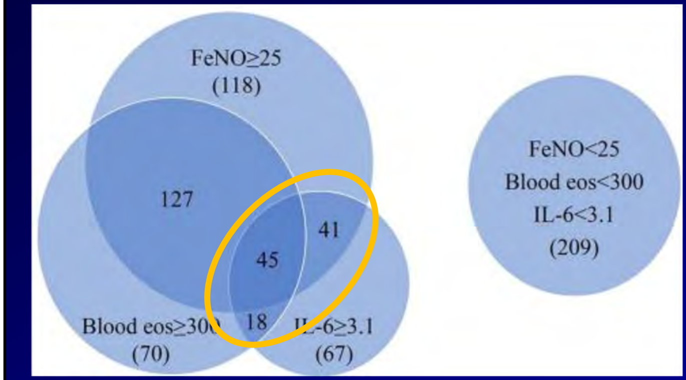
Peters *et al.* AJRCCM 202:973-82, 2020

Both models adjusted for age, BMI, depression

IRR = 1.3 (1.1-1.5), p = 0.008
For every standard deviation increase in IL-6 (approx. 2)

IRR = 1.3 (1.1-1.5), p = 0.01
For every standard deviation increase in bEOS (approx. 300)

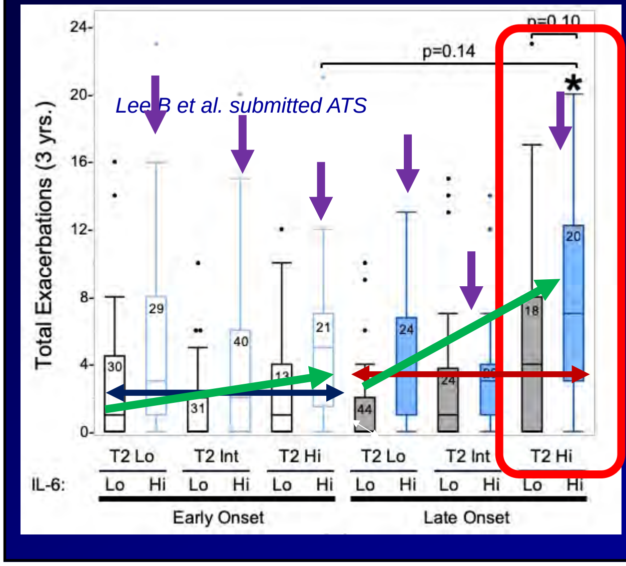
But what if T2 and IL-6 together: Complex immune processes may make more difficult to treat



Li X, Hastie AT, et al J Allergy Clin Immunol 2020

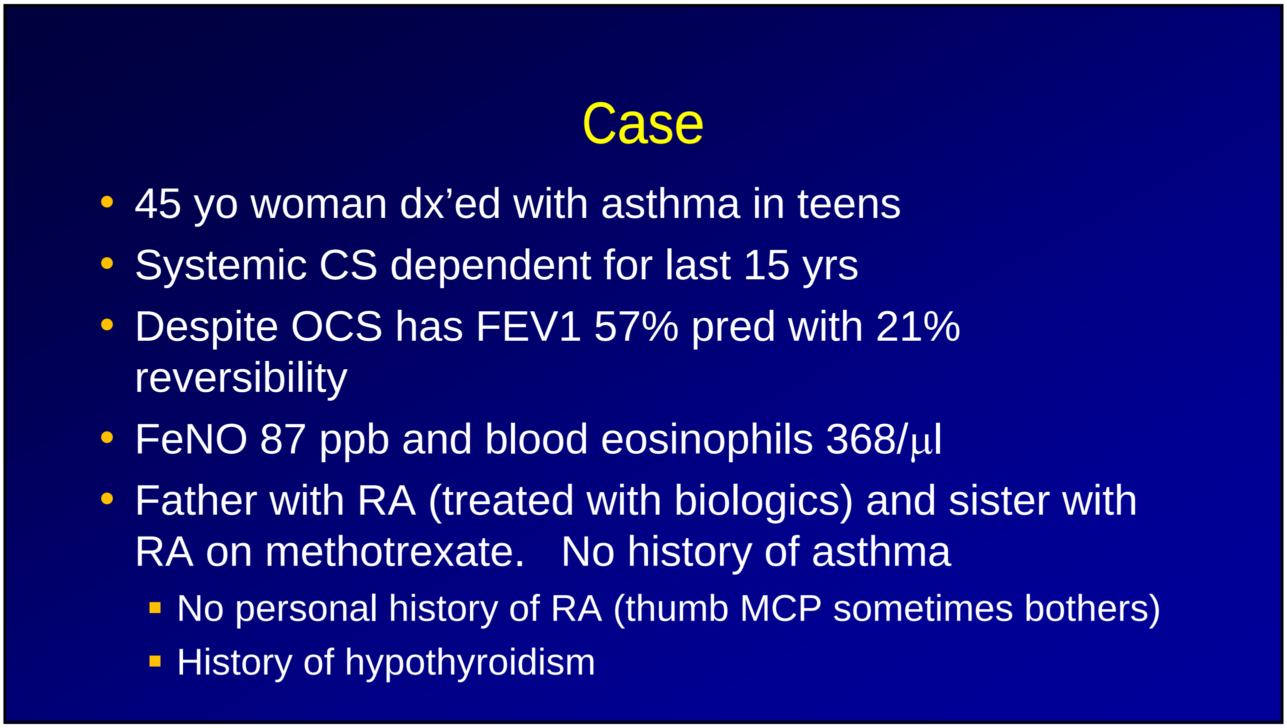
- Although elevated IL-6 levels can be seen in isolation, 61% seen in combination with elevated Type-2 biomarkers
- When both are elevated, and controlling for age at onset, suggests even more severe disease

Combining age at onset, T2 biomarkers and IL-6



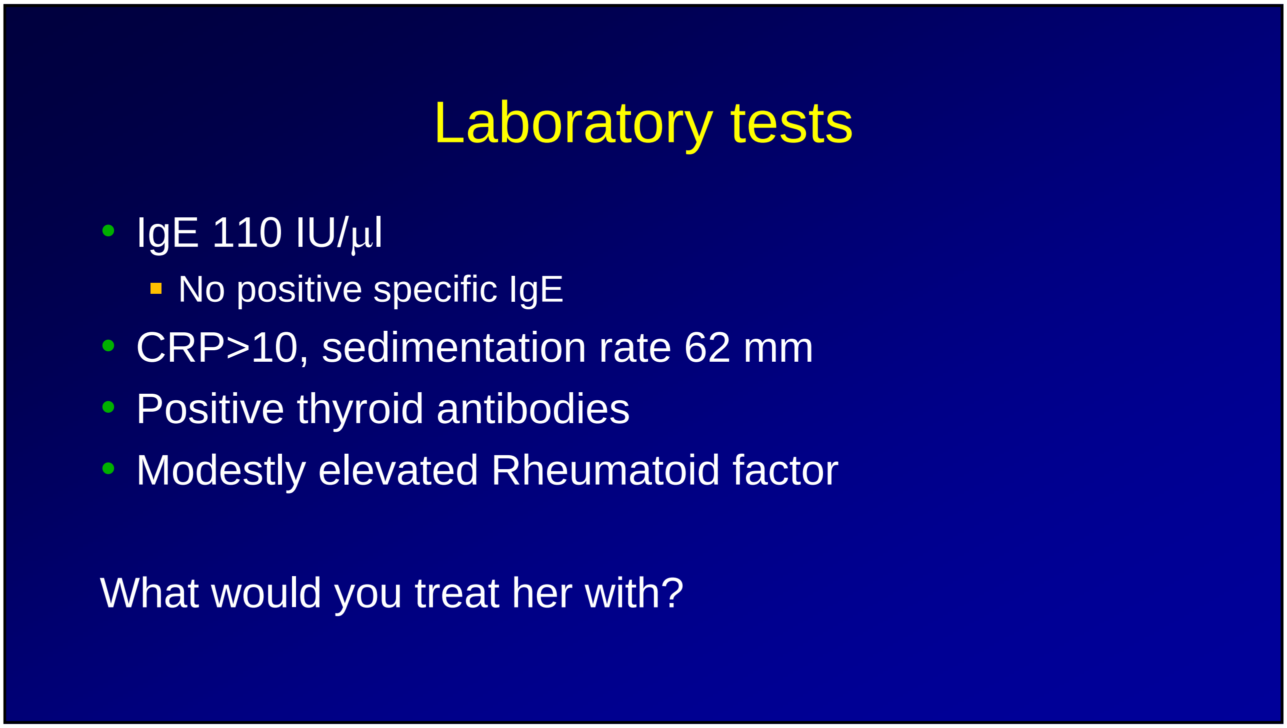
Lee B et al. submitted ATS

- Late onset asthma slightly more exacerbation prone than EOA
- T2 biomarkers (0, 1 or 2) increase exacerbation risk ONLY in LOA
- IL-6 increases exacerbation risk irrespective of T2 status
- But highest risk is in LOA, T2 Hi-IL-6 high group consistent with very complex disease
- Response to single targeted Rx unclear



Case

- 45 yo woman dx’ed with asthma in teens
- Systemic CS dependent for last 15 yrs
- Despite OCS has FEV1 57% pred with 21% reversibility
- FeNO 87 ppb and blood eosinophils 368/μl
- Father with RA (treated with biologics) and sister with RA on methotrexate.   No history of asthma
  - No personal history of RA (thumb MCP sometimes bothers)
  - History of hypothyroidism



Laboratory tests

- IgE 110 IU/μl
  - No positive specific IgE
- CRP>10, sedimentation rate 62 mm
- Positive thyroid antibodies
- Modestly elevated Rheumatoid factor

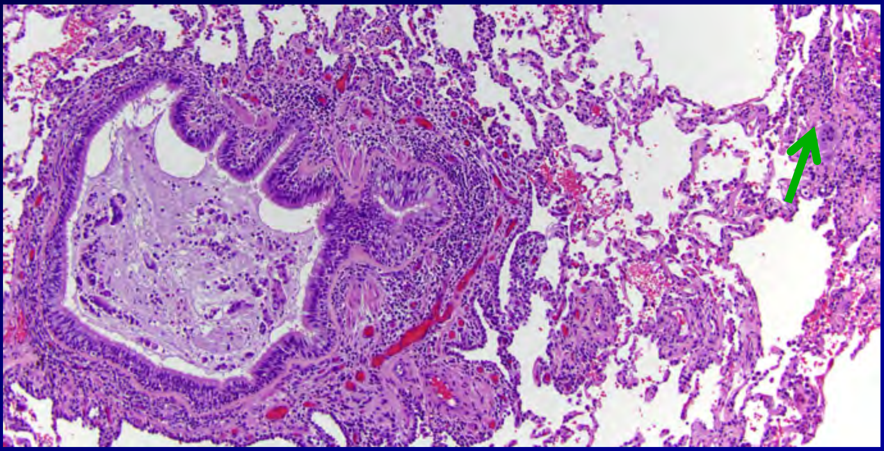
What would you treat her with?

Type- 2 + “asthma”: “Autoimmune”and/or Asthmatic Granulomatosis

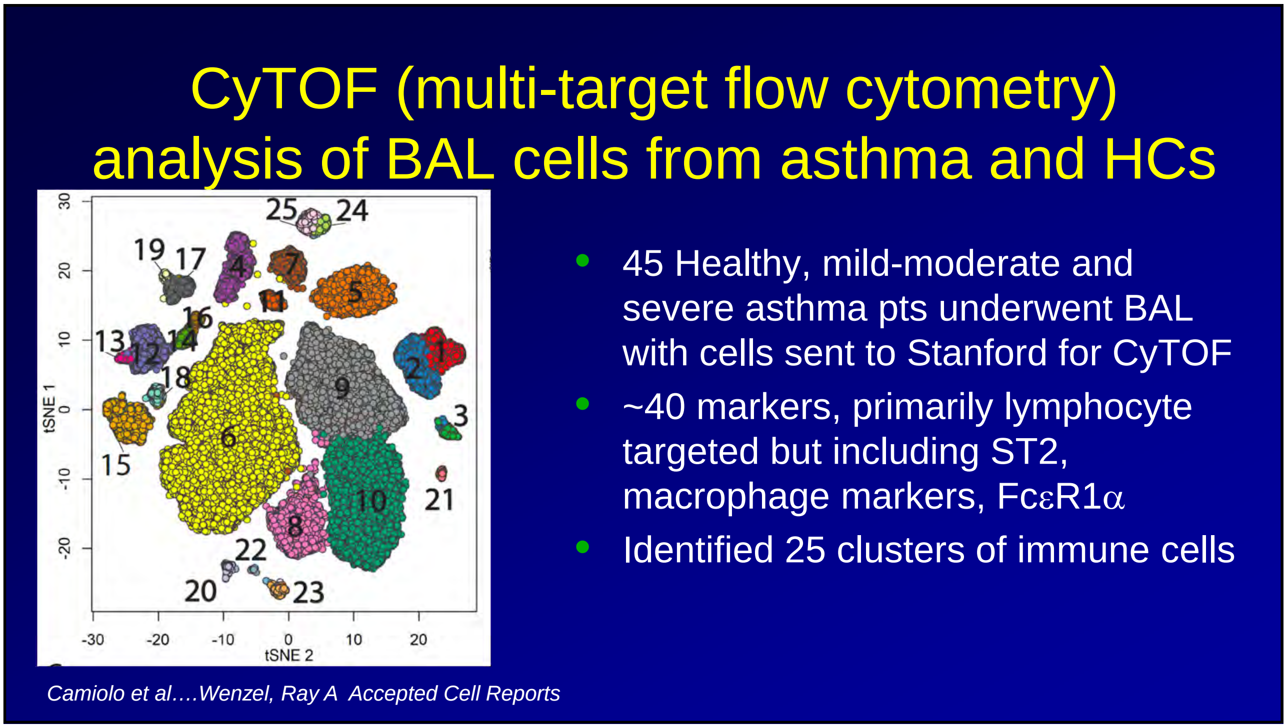
- “severe asthma” pts who meet asthma diagnosis
  - All on systemic corticosteroids
  - Late/adult onset or adult worsening of early onset
  - Often very high FeNO (and blood eos) despite systemic CSs
  - Often associated with family and personal autoimmune history
- Asthmatic granulomatosis identified in ~50%

Wenzel Am J Resp Crit Care Med 2012

Complex immunity: Small airway inflammation and granulomas



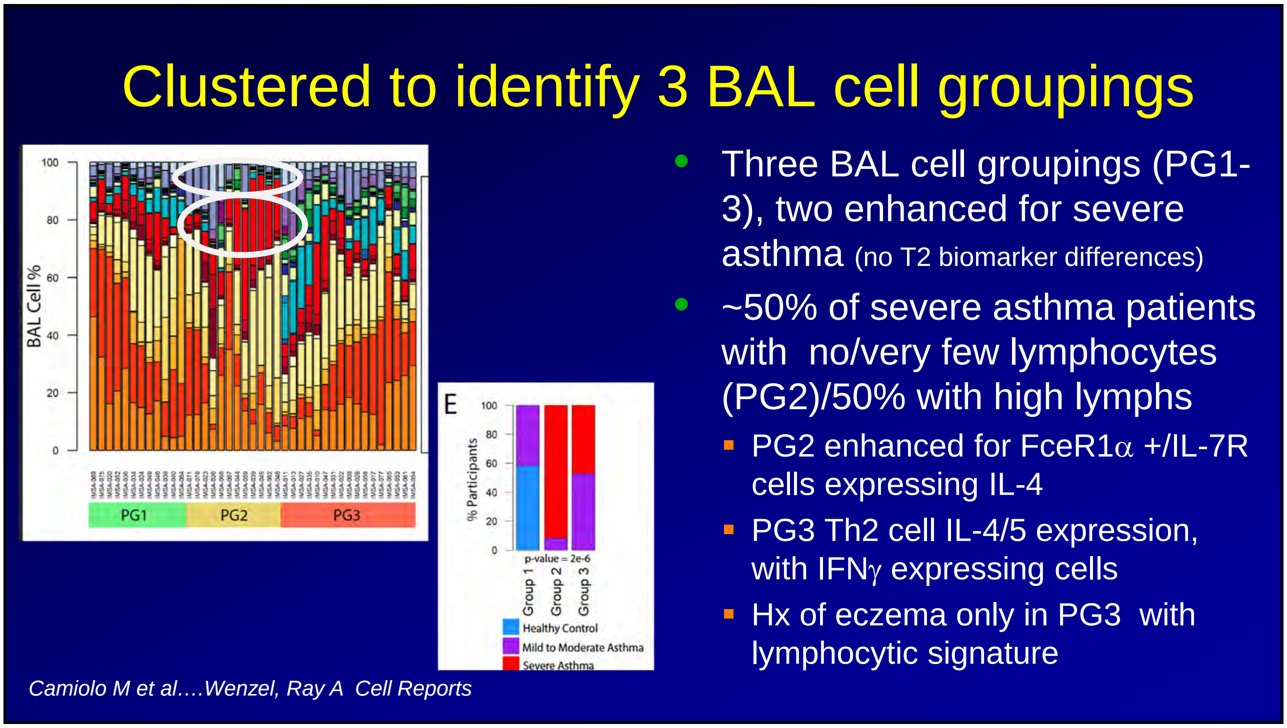
Consider Rx with T2 biologic and alternate immunosuppressive



CyTOF (multi-target flow cytometry) analysis of BAL cells from asthma and HCs

- 45 Healthy, mild-moderate and severe asthma pts underwent BAL with cells sent to Stanford for CyTOF
- ~40 markers, primarily lymphocyte targeted but including ST2, macrophage markers, FcεR1α
- Identified 25 clusters of immune cells

Camiolo et al….Wenzel, Ray A Accepted Cell Reports

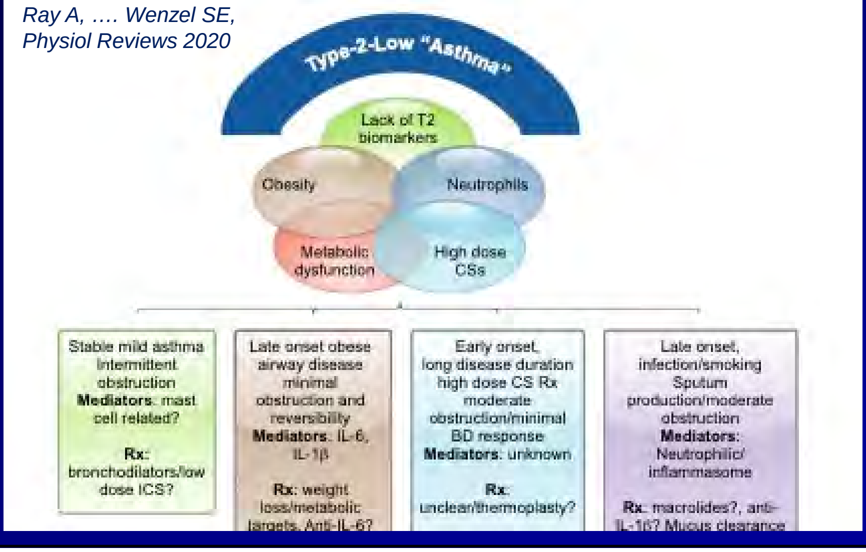


Clustered to identify 3 BAL cell groupings

- Three BAL cell groupings (PG1-3), two enhanced for severe asthma (no T2 biomarker differences)
- ~50% of severe asthma patients with no/very few lymphocytes (PG2)/50% with high lymphs
  - PG2 enhanced for FceR1α +/IL-7R cells expressing IL-4
  - PG3 Th2 cell IL-4/5 expression, with IFNγ expressing cells
  - Hx of eczema only in PG3 with lymphocytic signature

Camiolo M et al….Wenzel, Ray A Cell Reports

The great unknowns: True T2-Lo Asthma



Ray A, …. Wenzel SE,
Physiol Reviews 2020

Conclusions

- Asthma is a complex grouping of clinical-molecular phenotypes
- Severe Asthma consistently associates with T2 Hi asthma
- However, not all Type-2 Hi asthma is alike with variation by age at onset, severity, co-morbid conditions and pathobiologic processes
  - Early onset allergic asthma most common, but also more often NOT severe
  - Late onset–nasal polyp-eosinophilic asthma often severe and close to achieving endotype status
  - Better molecular approaches are needed to identify patients who may benefit from differing targeted approaches

Acknowledgments

- All my colleagues in 21 years of SARP
- Anuradha Ray, Matt Camiolo, Wei Wu (Pitt and CMU)

PAAA

Pennsylvania Allergy & Asthma Association

Mast Cell Disorders

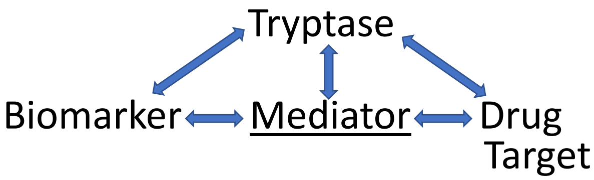
Lawrence Schwartz, MD, PhD

Saturday, June 26, 2021
8:45 a.m. - 9:30 a.m.

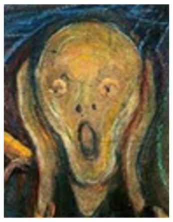
PAAA 2021 Annual Meeting

Mast Cell Disorders

Lawrence B Schwartz, MD, PhD
Virginia Commonwealth University



Disclosure Slide: Lawrence B. Schwartz, MD, PhD



Employment

- VCU/VCUHS

Research Grants

- NIH
- Novartis, GSK, Merck, Dyax-Shire-Takeda, CSL Behring, Deciphera, Blueprint

Consulting

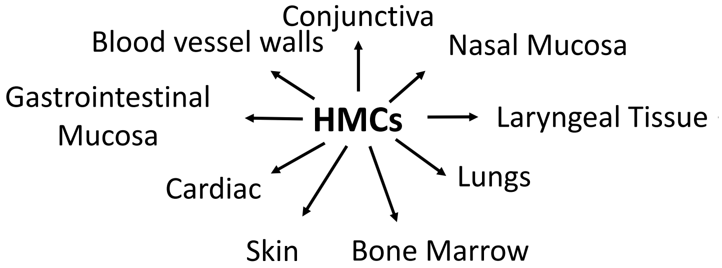
- Genentech, Deciphera, Dyax-Shire-Takeda, CSL Behring, Deciphera, Blueprint, Allakos, Astra-Zeneca, GLG, Celldex

Other Financial Interests

- VCU Royalties/Licensing Fees:
  ThermoFisher-Phadia (tryptase test);
  Millipore, Santa Cruz, BioLegend, Hycult Biotech (mAbs);
  Genentech (tryptase inhibitor)
- Up-To-Date Card (royalties)
- Cecil's Textbook of Medicine Anaphylaxis chapter (royalties)
- NIH Study Section (honoraria)

Human Mast Cells

Reside in Bone Marrow & Peripheral Tissues (not in the circulation)



HMCs

Conjunctiva

Nasal Mucosa

Laryngeal Tissue

Lungs

Bone Marrow

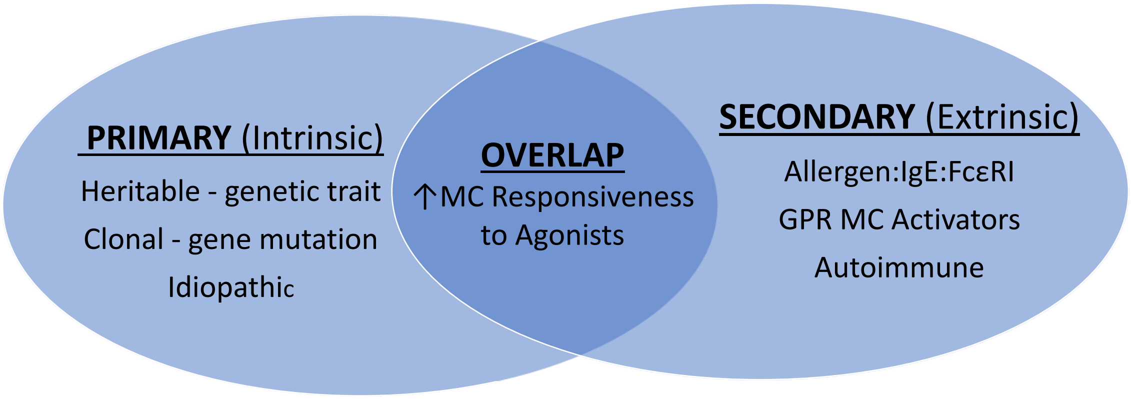
Skin

Cardiac

Gastrointestinal Mucosa

Blood vessel walls

Primary vs Secondary Disorders of Mast Cells



PRIMARY (Intrinsic)

Heritable - genetic trait

Clonal - gene mutation

Idiopathic

OVERLAP

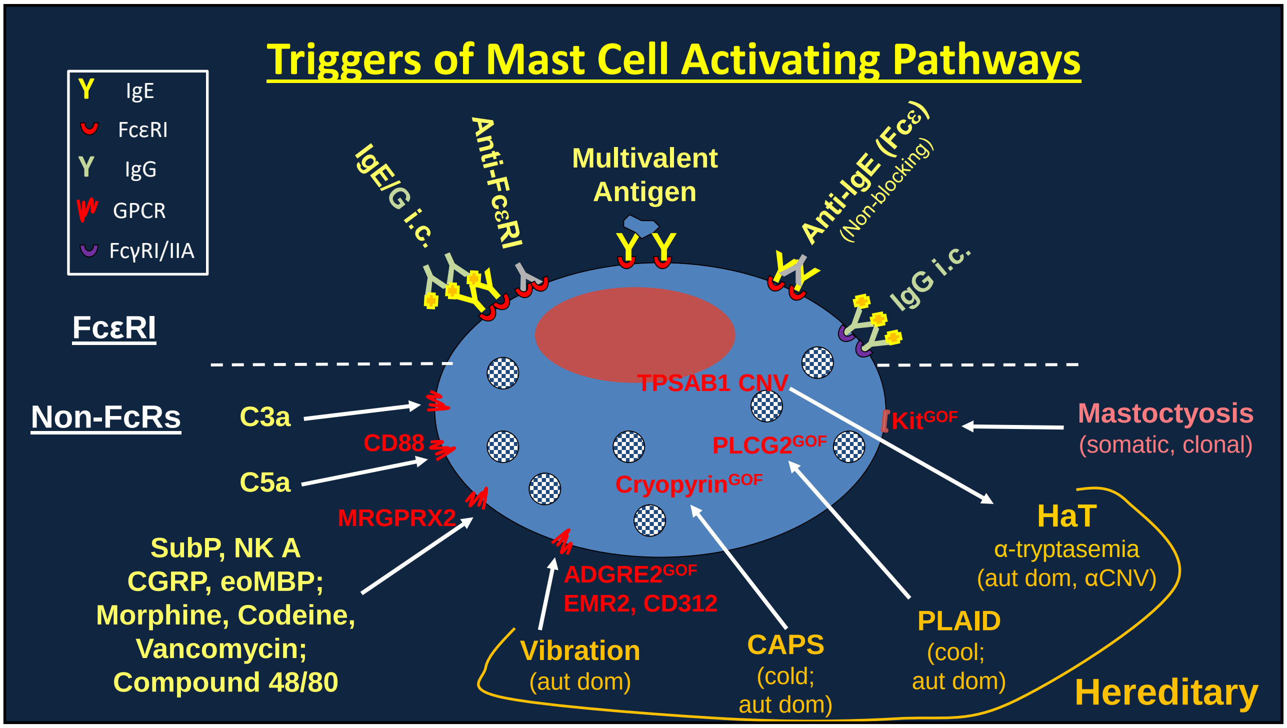
↑MC Responsiveness to Agonists

SECONDARY (Extrinsic)

Allergen:IgE:FcεRI

GPR MC Activators

Autoimmune



Triggers of Mast Cell Activating Pathways

Y IgE
FcεRI
Y IgG
GPCR
FcγRI/IIA

FcεRI

Non-FcRs

IgE/G i.c.

Anti-FcεRI

Multivalent Antigen

Anti-IgE (Fcε)
(Non-blocking)

IgG i.c.

C3a

CD88

C5a

MRGPRX2

SubP, NK A
CGRP, eoMBP;
Morphine, Codeine,
Vancomycin;
Compound 48/80

TPSAB1 CNV

Kit^{GOF}

PLCG2^{GOF}

Cryopyrin^{GOF}

ADGRE2^{GOF}
EMR2, CD312

Mastoctyosis
(somatic, clonal)

HaT
α-tryptasemia
(aut dom, αCNV)

Vibration
(aut dom)

CAPS
(cold;
aut dom)

PLAID
(cool;
aut dom)

Hereditary

Cases of Interest

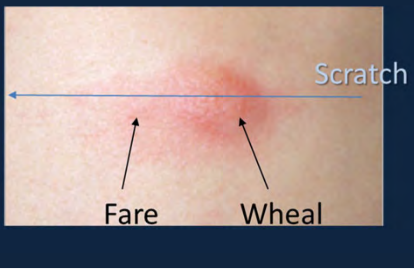
(1) 45 y/o: 3h after eating tuna salad lunch, watery diarrhea & hives → syncope while on commode. PMH: systemic anaphylaxis to wasp sting. FH: negative

(2) 51 y/o F: frequent neurocardiogenic (pre)syncope x33y; EDS (joint hypermobility); IBS ±(flushing or dyspnea), retained primary dentition. FH: 3 of 4 F sibs+, 19 y/o son (presyncope, scoliosis) with overlapping problems (but not 2 younger sons).

Adult Indolent Systemic Mastocytosis: Presenting Scenarios

30 y/o F with pruritic rash

Urticaria pigmentosa with a positive Darier's sign



↑Serum Baseline Tryptase

Prevalence: ~1:100,000 ⇒ ~1:10,000

PB D816V c-kit+

Case 1

45 y/o M: 3h after eating tuna salad lunch, watery diarrhea & hives → syncope while on commode. PMH: systemic anaphylaxis to wasp sting. FH: negative

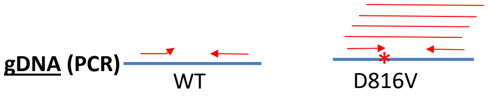
Serum baseline tryptase (sBT) =60 ng/mL (<12) & acute =95 ng/mL (>2+1.2*60=74)

Systemic mastocytosis:
- <u>i) clonal MCs ~</u> somatic Kit^{GOF};
- <u>ii) systemic anaphylaxis</u> (spontaneous/insect sting allergy) ~40-50% prevalence.

Diagnosis of Systemic Mastocytosis (1:10,000 prevalence)
<u>Major Criterion</u>: MC Aggregates (BM bx, >15 MC/hpf)
<u>Minor Criteria</u>: (1)Abnormal MC morphology; (2) Activating c-*KIT* mutation*; (3) CD25^{+} MC; (4) Baseline serum tryptase >20 ng/ml* ***, can be done with peripheral blood*
Diagnosis: 1 major + 1 minor OR ≥3 minor

Valent et al. Leukemia Res 25:603-25, 2001; Schuch & Brockow Immunol Allergy Clin North Am **37**:153-64, 2017

D816V c-kit <u>Allele-Specific</u> PCR in <u>Peripheral Blood</u>



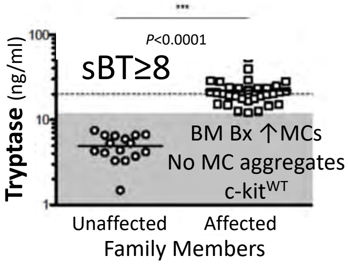
Detection Limit~0.01% (1 in 10,000 cells)
~90% sensitivity adult ISM (with skin lesions > without)

Will not detect other mutations of c-kit - more problematic in children than adults;
mRNA (RT-PCR) low yield (low CD117 expression in circulating progenitors);
Kit gene sequencing low yield (mutation>2-5% of cells).

Kristensen et al. Allergy 72:1737-43, 2017
Kristensen et al. British J Haematol 178:330-2, 2017

<u>Hereditary **α**-Tryptasemia</u> (5-6% prevalence European ancestry)

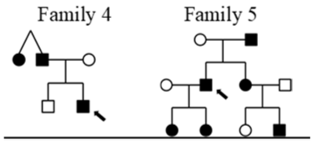
Jon Lyons, MD et al
NIAID, NIH



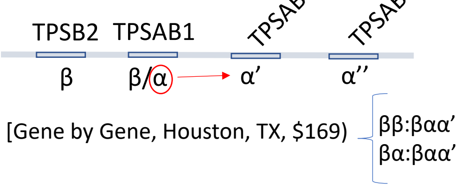
sBT≥8

BM Bx ↑MCs
No MC aggregates
c-kit^{WT}

Autosomal Dominant



TPSAB1 CNV



ββ:ββ
ββ:βα
βα:βα

[Gene by Gene, Houston, TX, $169)

ββ:βαα'
βα:βαα'

Flushing/Pruritus/**Vibratory Urticaria**
Dysautonomia: IBS-C/D, POTS
MSK: EDSIII→arthritis
Retained primary dentition
Anaphylaxis: ↑severity

HaT in 10% severe insect sting systemic anaphylaxis
HaT in 12% systemic mastocytosis
(↑SA from 40-50% in SM to 90% in SM+HaT)
HaT in 17% Idiopathic systemic anaphylaxis

Lyons et al: JACI 133:1471, 2014; Nat Genetics 48:1564, 2016; JACI 147:622, 2020

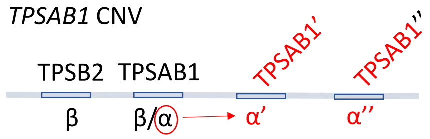
Case 2

51 y/o WF frequent neurocardiogenic (pre)syncope (POTS) x33y; EDS (joint hypermobility); IBS ±(flushing/pruritus or dyspnea). FH: overlapping problems in 3 of 4 F sibs & oldest son (presyncope, scoliosis), but not in younger 2 sons.

sBT = 12 ng/ml
24 h urine 11β-PGF2α, N-methylhistamine, LTE4 = each wnl (no evidence for MCAS)
19y son with sxs: sBT =9.9; two younger sons w/o sxs: sBT=4 and 5 ng/mL
FH & sBT levels c/w Hat

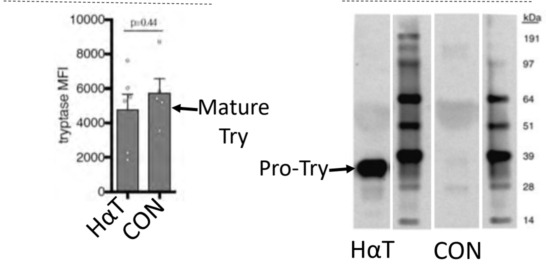
HaT TPSAB1 α-tryptase CNV genotype (GeneByGene $169) in M & older son;
normal genotype in younger sons

How might α-tryptase overexpression account for any clinical features of HaT?

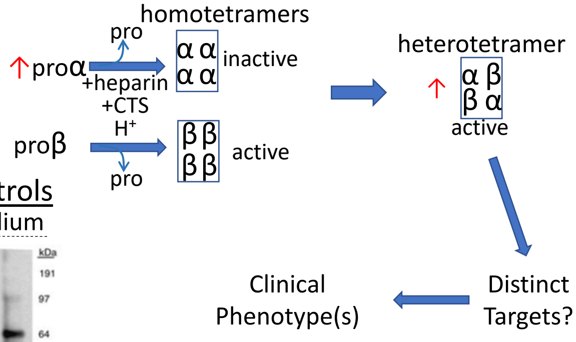

TPSAB1 CNV
TPSB2 TPSAB1
β β/α → α’ α’’

Mast Cells from HαT patients or controls

CellTryptase (flow) WB, MC medium

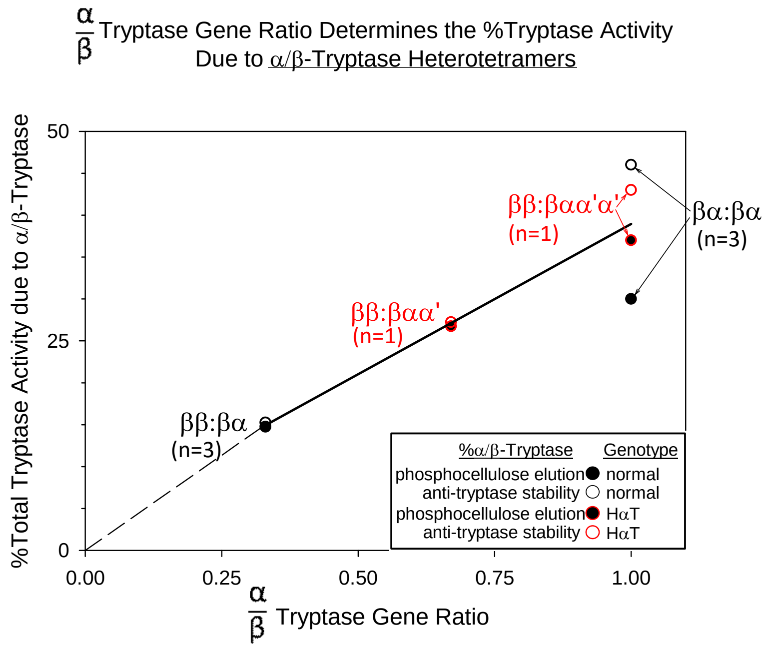


No ↑mature tryptase! ↑Protryptase(s)


↑proα → +heparin +CTS H⁺ → homotetramers α α α α inactive
proβ → β β β β active
pro
pro
→ heterotetramer ↑ α β β α active
→ Distinct Targets? → Clinical Phenotype(s)


Quang Le, PhD

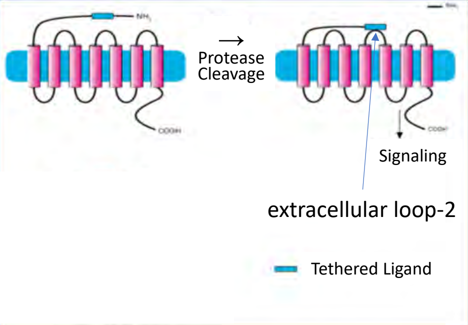
Lyons et al. JACI 133:1471-4, 2014;
Nat Genetics 48:1564-9, 2016;
Le et al J Exp Med 216:2348, 2019



$\frac{\alpha}{\beta}$ Tryptase Gene Ratio Determines the %Tryptase Activity Due to α/β-Tryptase Heterotetramers

Le et al J Exp Med 216:2348, 2019

Protease-Activated Receptor (PAR)-2



PAR2 activation activates:

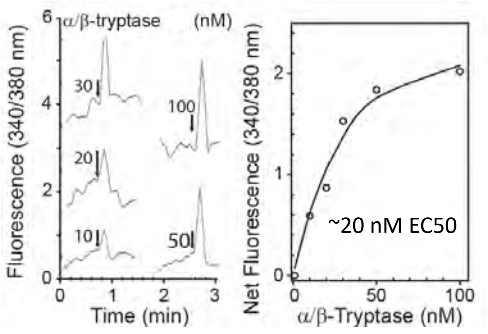
- Smooth muscle: bronchospasm, abdominal cramping
- Neurons: pruritus, hyperalgesia
- Endothelium: vasopermeability
- Epithelium: inflammation

Is PAR2 a target for mast cell tryptase?
Discrepancies in literature with
tissue-derived and rh-tryptase.

No PAR2 activation with α- or β- rhu-tryptases;
No PAR2 activation with tissue-derived tryptase
(ββ:ββ tryptase genotype)
(*Le et al J Exp Med 216:2348, 2019)*

Hypothesis
α/β but not β tryptase activates PAR2

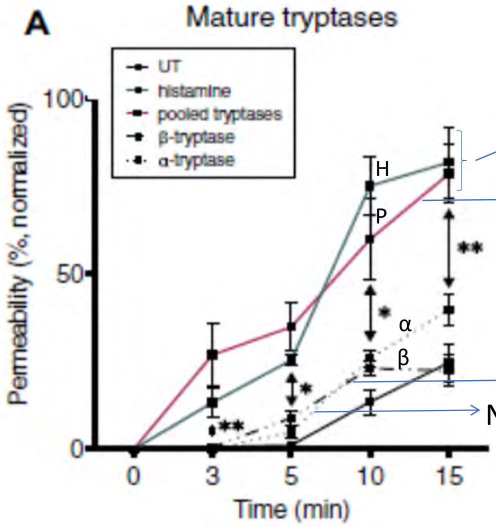
α/β-Tryptase Heterotetramers activate Protease-Activated Receptor-2 on Jurkat cells



Le et al J Exp Med 216:2348, 2019

Pooled mature lung-derived tryptases increase PAR-2–dependent vascular endothelial permeability, but neither α- nor β- homotetrameric tryptases do so

Lyons et al. JACI 147:622-32, 2021



↑Permeability to histamine and pooled lung tryptase

↑Permeability blocked by anti-tryptase mAb inhibitor or by a PAR2-specific peptide inhibitor.

No ↑vasopermeability to α-tryptase

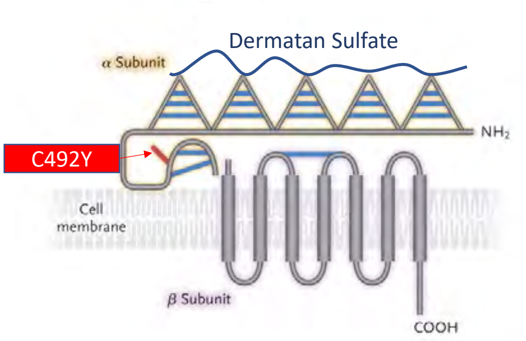
No ↑vasopermeability to β-tryptase

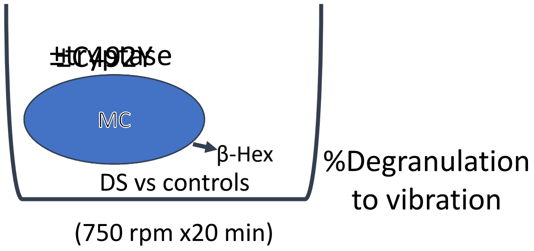
Severe Hereditary Vibratory Urticaria ~ C492Y in Adhesion GPCR (*ADGR-E2*; CD312, EMR2*)*

Boyden SE et al. New Engl J Med 374:656-663, 2016

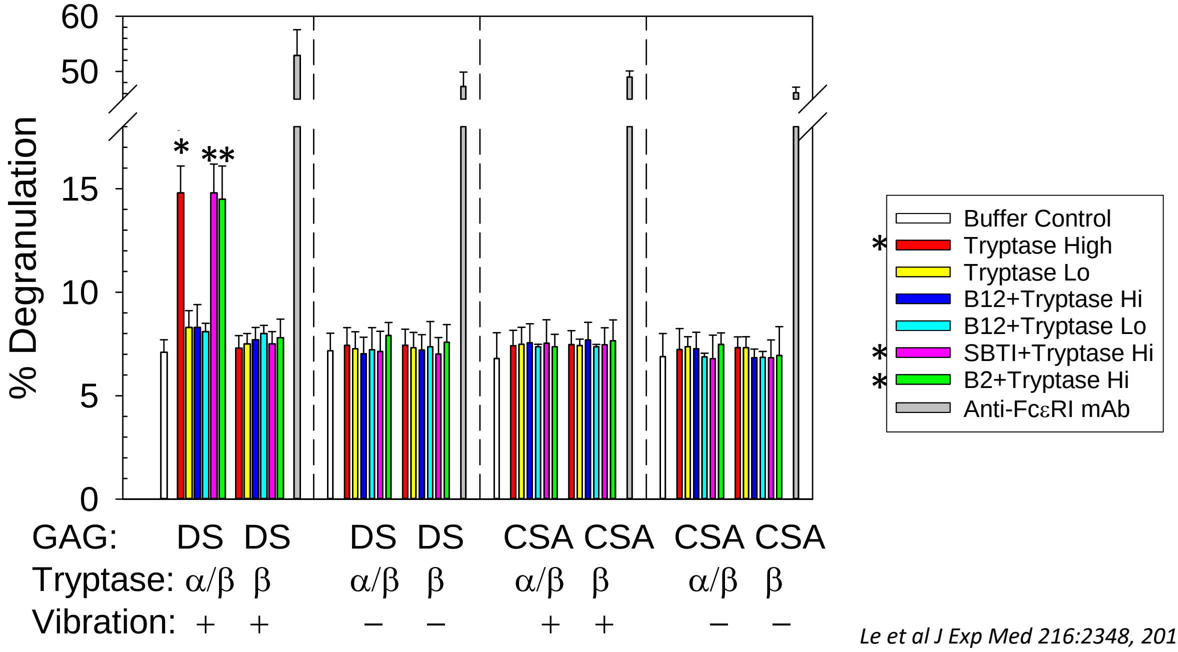
EMR2, noncovalently bound α to β, inhibiting GPCR activity. α also binds to dermatan sulfate; mechanical stress separates α from β, activating GPCR activity.

C492Y permits cleavage → weak α:β binding → persistent separation of α from β → ↑EMR2 activity & MC activation with mechanical stress (Severe Hereditary Vibratory Urticaria.

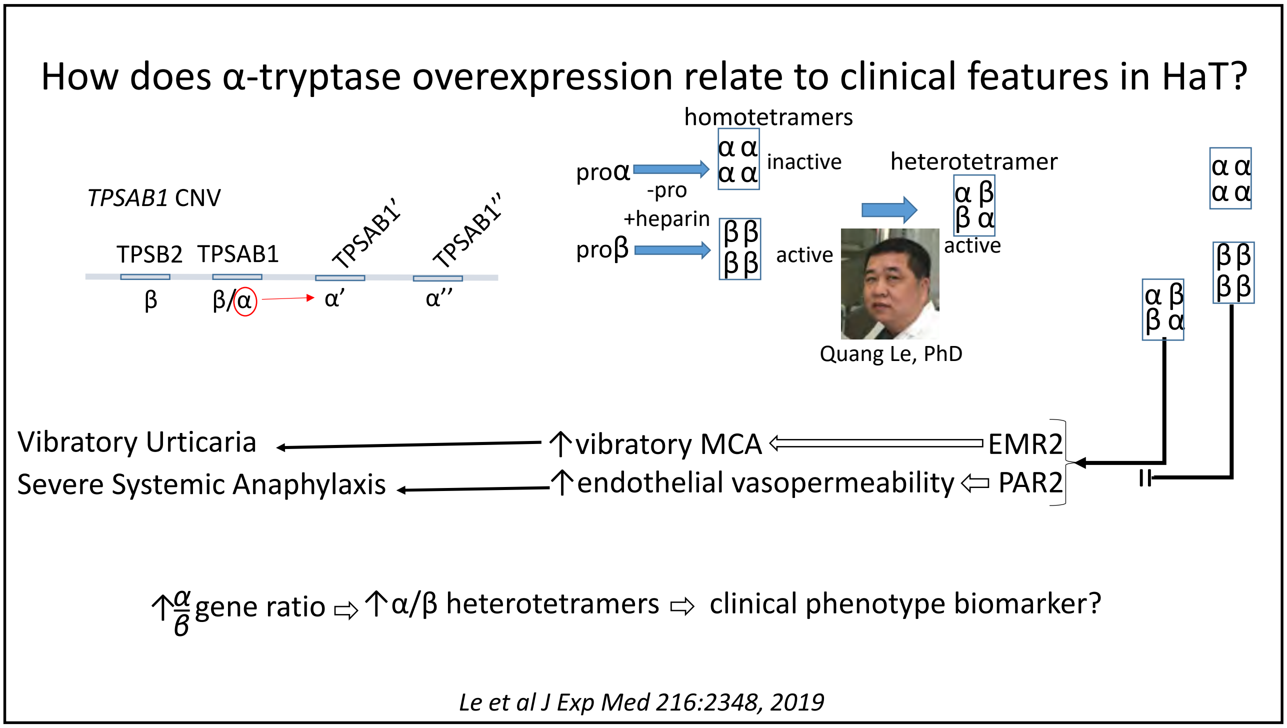




α/β-Tryptase but not β-tryptase makes skin MCs degranulate to vibration



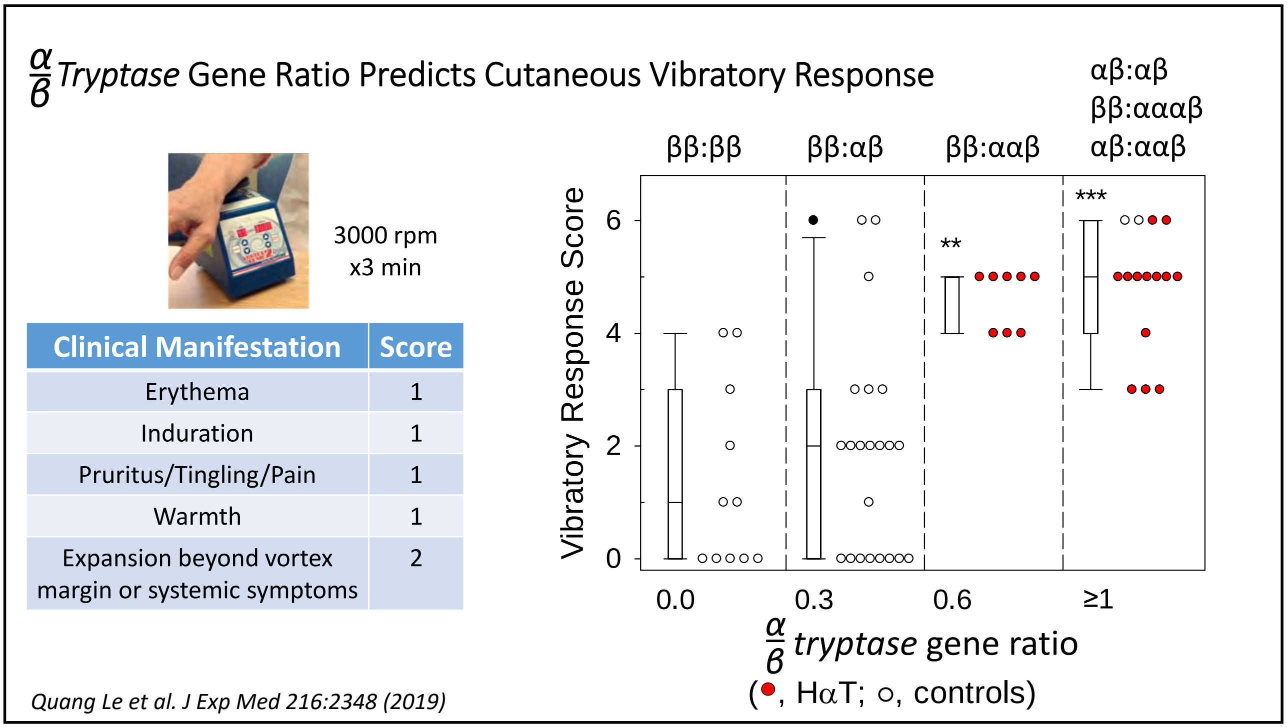
Le et al J Exp Med 216:2348, 2019



How does α-tryptase overexpression relate to clinical features in HaT?

↑$\frac{\alpha}{\beta}$gene ratio ⇨ ↑α/β heterotetramers ⇨ clinical phenotype biomarker?

Le et al J Exp Med 216:2348, 2019



$\frac{\alpha}{\beta}$ *Tryptase* Gene Ratio Predicts Cutaneous Vibratory Response

3000 rpm
x3 min

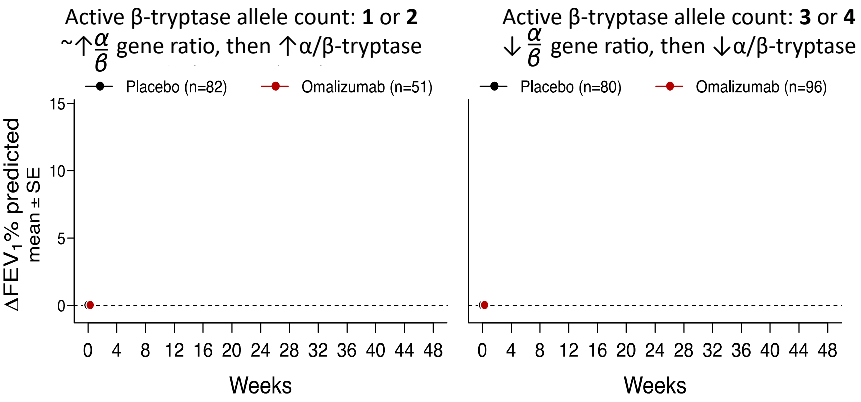
Clinical Manifestation	Score
Erythema	1
Induration	1
Pruritus/Tingling/Pain	1
Warmth	1
Expansion beyond vortex margin or systemic symptoms	2

$\frac{\alpha}{\beta}$ *tryptase* gene ratio
(●, HαT; ○, controls)

Quang Le et al. J Exp Med 216:2348 (2019)

In severe persistent allergic asthmatics (*post hoc* analysis, EXTRA)

↑Response to omalizumab ~ $\uparrow\frac{\alpha}{\beta}$ Tryptase Genotype



Active β-tryptase allele count: **1** or **2**
~$\uparrow\frac{\alpha}{\beta}$ gene ratio, then ↑α/β-tryptase

Active β-tryptase allele count: **3** or **4**
$\downarrow\frac{\alpha}{\beta}$ gene ratio, then ↓α/β-tryptase

(analogous results for reduction in SABA use, and improvements in TASS & asthma QOL)

Hypothesis: α/β-tryptase has a greater impact than β-tryptase on asthma pathogenesis, resulting in a greater clinical impact when MC/Bas degranulation is attenuated by omalizumab.

Maun et al. Cell 179:417-31, 2019

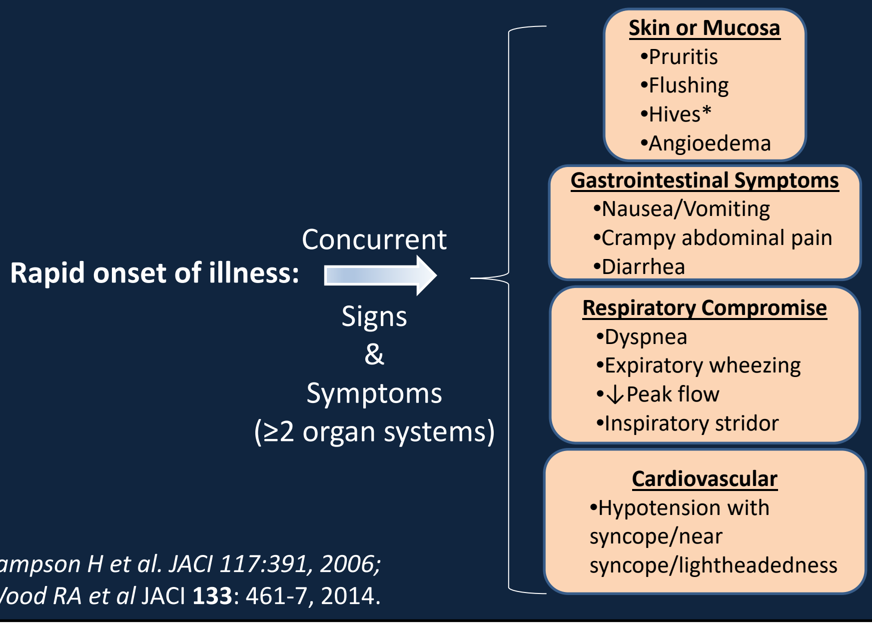
Concluding Comments

1. Primary disorders of mast cells are more common than previously recognized, with hereditary alpha-tryptasemia (HaT) being present in 5% of those with European ancestry, while mastocytosis, a clonal disorder a/w Kit GOF mutations, is present in about 0.01% of adults.
2. HaT led to the discovery of α/β-tryptase heterotetramers that form spontaneously and may contribute to the vibratory urticaria and to severe anaphylaxis associated with HaT.
3. The portion of tryptase activity due to α/β-tryptase corresponds to the α/β gene ratio, a potential biomarker for biologic or pathologic events due to this particular form of tryptase, and under certain circumstances may help predict when inhibiting tryptase activity would provide clinical benefit.

Thanks….

NIH	Genentech	VCU S-Lab
Jon Lyons	Robert Lazarus	Quang Le
Josh Milner	Tangsheng Yi	Yoshi Fukuoka
Dean Metcalfe	Henry Maun	Brant Ward
Andrea Naranjo		Victoria Harlow
Ana Olivera		

Systemic Anaphylaxis in America: Clinical Diagnosis & Prevalence



Rapid onset of illness: Concurrent Signs & Symptoms (≥2 organ systems)

Skin or Mucosa
- Pruritis
- Flushing
- Hives*
- Angioedema

Gastrointestinal Symptoms
- Nausea/Vomiting
- Crampy abdominal pain
- Diarrhea

Respiratory Compromise
- Dyspnea
- Expiratory wheezing
- ↓Peak flow
- Inspiratory stridor

Cardiovascular
- Hypotension with syncope/near syncope/lightheadedness

Adult Prevalence
2 – 8%

Can we be more precise with biomarkers?

Sampson H et al. JACI 117:391, 2006;
Wood RA et al JACI **133**: 461-7, 2014.

Differential Diagnosis of Allergen:IgE:FcεRI-mediated Systemic Anaphylaxis

Pulmonary/Cardiogenic disorders

Vasovagal

Flushing disorders (benign, carcinoid syndrome, neuroendocrine tumors)

Panic attacks, Vocal cord dysfunction

Hereditary/Acquired Angioedema (bradykinin)

Complement activation (C3a, C5a)

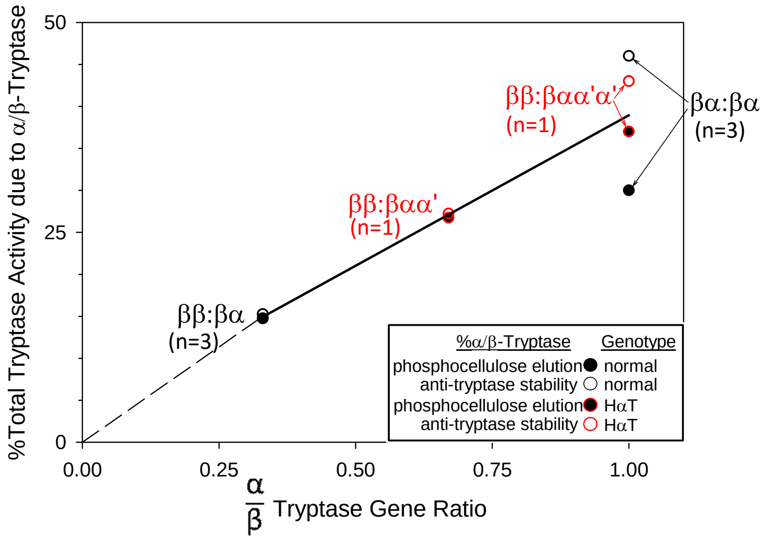
Scombroidosis (ingested histamine)

Other shock syndromes (septic, toxins, …)

1° MCAS: mastocytosis/hereditary α-tryptasemia/idiopathic

Can we be more precise with biomarkers?

$\frac{\alpha}{\beta}$ Tryptase Gene Ratio Determines the %Tryptase Activity Due to α/β-Tryptase Heterotetramers

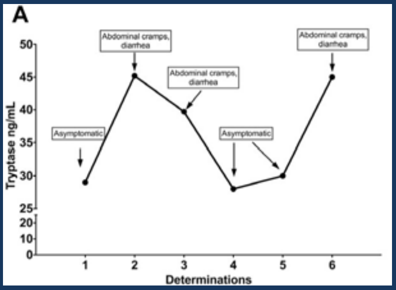


Le et al J Exp Med 216:2348, 2019

Case 2

Adult M: recurrent episodes diarrhea/abdominal cramps, lightheadedness and flushing. Similar symptoms in father, 3|6 sibs and 1|2 children. GI studies & bx wnl.

Acute tryptase levels 40-45, baseline levels 25-30, c/w mast cell activation.



Sabato et al. JACI 134:1448-550, 2014 & J Clin Immunol 38:457-9, 2018.

Elevated baseline tryptase and autosomal dominant pattern of inheritance, c/w newly described Hereditary Alpha-Tryptasemia (HaT)

Pennsylvania Allergy & Asthma Association

Annual Business Meeting

Allyson Larkin, MD—PAAA President

Saturday, June 26, 2021
10:00 a.m. - 10:15 a.m.

Welcome to the
2021
Pennsylvania Allergy & Asthma Association

Annual Business Meeting

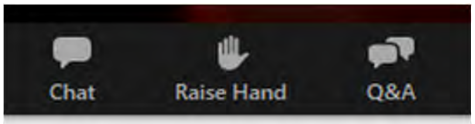
Saturday, June 26, 2021
10:00 AM – 10:15 AM

PAAA
Pennsylvania Allergy & Asthma Association

Meeting Instructions

Enter all questions in the Q&A tab

Use the chat feature to speak with other attendees in the meeting.



If you wish to speak, raise your hand and staff will unmute you.

AGENDA

A. Call to Order (*Allyson Larkin, MD*)

B. Approval of Minutes of June 27, 2020 Annual Business Meeting (*Allyson Larkin, MD*)

C. President's Report (*Allyson Larkin, MD*)

D. Treasurer's Report/Finance Committee (*Robert Zemble, MD*)

E. Committee/Representative Reports
  1) Membership (*Janet Beausoliel*)
  2) Nominating (*Laura Fisher, MD*)
  3) PAERF (*Sarah Henrickson, MD*)
  4) Special Awards *(Janet Beausoleil, MD)*

F. New/Old Business

G. Incoming President's Remarks *(Allyson Larkin, MD)*

H. Adjournment

APPROVAL OF THE MINUTES

June 27, 2021

I. Call to Order – Dr. Laura Fisher, PAAA President, called the meeting to order at 9:45 a.m. Drs. Beausoleil, Becker, DaVeiga, DeFelice, Kalman, Koven, Kravitz, Larkin, Lutzkanin, Shampain and Zemble were present for the meeting.

Dr. Fisher commented on the unprecedented times and expressed her appreciation for the support received from all her colleagues on board, allergists in Pennsylvania and surrounding states, and the local and state medical societies. She asked that PAAA members continue to support and help each other, noting that we are all colleagues, not competitors.

II. Approval of Minutes of June 22, 2019, Annual Business Meeting – On a motion made and seconded, those present voted unanimously via a Zoom Poll to approve the minutes of the 2019 Annual Business Meeting.

III. President's Report – Dr. Fisher thanked everyone for coming to the virtual annual business meeting. She noted that while the business meeting is required by the Bylaws, as it is the site for the annual election of our new leaders, it also provides an annual opportunity for the leadership to touch base and to hear members' concerns and issues.

(Continued on next slide)

Dr. Fisher expressed her appreciation and thanks to Planning Committee and recognized the excellent programming and speakers the committee had assembled for this year's annual meeting. With the safety of members, attendees, and staff being paramount, the Board voted unanimously to suspend the 2020 meeting. The Hotel Hershey graciously worked with PAAA to cancel the meeting without penalty

IV. Treasurer's Report/Finance Committee – Dr. Sigrid Da Veiga reported on the financial statement as of December 2019. She noted that PAAA's total assets were $475,000 compared with $428,000 in the prior year, and total liabilities were approximately $27,000 compared to $24,000 the year before. On a motion made and seconded, those present voted unanimously via a Zoom Poll to accept the financial statement.

V. Report of the Membership Committee – Dr. Stephanie Knapp reported on the membership statistics. She reported that PAAA gained one new member and five new fellows in training over the last year. The current membership stands at 199 dues-paying members. Of those members, 44% have not paid their dues this year, compared to 29% last year. The drop is attributed to the cancellation of the annual meeting which usually motivates members to renew their membership with their annual meeting registration. The Board has agreed to conduct an outreach drive to recoup these nonrenewing members.

(Continued on next slide)

VI. Report of the Nominating Committee - In the absence of Dr. Palumbo, Nominating Committee member Dr. Laura Foster reviewed the slate and called for any nominations from the floor. Hearing none, on a motion made and seconded, those present voted unanimously via a Zoom Poll to accept the slate as presented.

VII. PAERF – Dr. Magee DeFelice reviewed the financial report as of April 2020. She noted that PAAA assets are down by $4000. The drop is attributed to the decline in the PAERF long-term investments. A more recent statement from June indicates that the markets have already started to recover. Dr. DeFelice also reported that PAERF is working on improving donor recognition. In the future, PAERF intends to recognize different levels of donor support (Platinum, Gold, Silver, and Bronze) and to develop additional ways to recognize those who contribute. In closing, Dr. DeFelice thanked all those who have donated to PAERF in the past.

VIII. New/Old Business – There was no new or old business.

IX. President Awards - Dr. Denise Kalman highlighted Dr. Fisher's accomplishments, noting her strong voice for private practitioners and her forward-thinking and decisiveness as PAAA president. She thanked her for serving during this particularly challenging year.

X. Passing of the Gavel – Dr. Fisher passed the mantle of leadership to Dr. Allyson Larkin and expressed complete confidence in her ability to lead PAAA going forward.

XI. Remarks of Incoming President – Dr. Allyson Larkin thanked Dr. Fisher for her leadership and willingness to continue to serve PAAA as its representative to the PAMED Specialty Leadership Cabinet. Dr. Larkin thanked those present for the opportunity to serve. She is looking forward to working with the Board of Regents to make a meaningful impact through every channel and medium available, whether virtual or in-person.

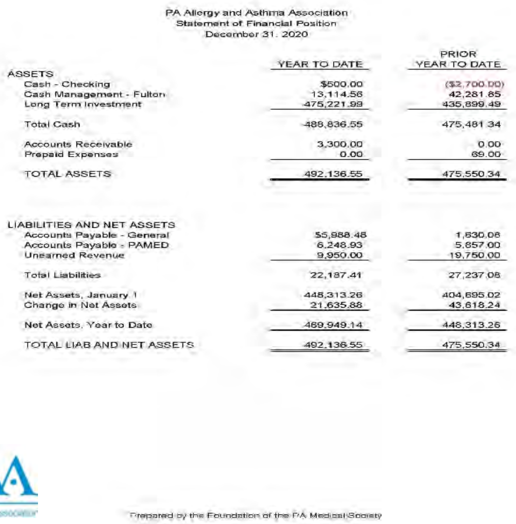
There being no further business, the meeting adjourned at 10:05 a.m.

PRESIDENT’S REPORT

Allyson Larkin, MD

TREASURER'S REPORT

Pennsylvania Allergy and Asthma Association
Statement of Financial Position
December 31, 2020



PA Allergy and Asthma Association
Statement of Financial Position
December 31, 2020

	YEAR TO DATE	PRIOR YEAR TO DATE
ASSETS		
Cash - Checking	$500.00	($2,700.00)
Cash Management - Fulton	13,114.56	42,281.85
Long Term Investment	475,221.99	435,899.49
Total Cash	488,836.55	475,481.34
Accounts Receivable	3,300.00	0.00
Prepaid Expenses	0.00	69.00
TOTAL ASSETS	492,136.55	475,550.34
LIABILITIES AND NET ASSETS		
Accounts Payable - General	55,988.48	1,630.08
Accounts Payable - PAMED	6,248.93	5,857.00
Unearned Revenue	9,950.00	19,750.00
Total Liabilities	22,187.41	27,237.08
Net Assets, January 1	448,313.26	404,695.02
Change in Net Assets	21,635.88	43,618.24
Net Assets, Year to Date	469,949.14	448,313.26
TOTAL LIAB AND NET ASSETS	492,136.55	475,550.34

Prepared by the Foundation of the PA Medical Society

MEMBERSHIP COMMITTEE REPORT

Current Membership	
Active	**161**
Associate	**3**
Corresponding	**9**
Emeritus	**46**
In-training	**17**
Total Members	**236**

New Members Since June 2020

Active
Desha Jordan, MD, FAAP

In Training
Anthony Lacava Jr, MD
Catherine Popadiuk, DO
Sebastian Sylvestre, MD

NOMINATING COMMITTEE REPORT

2021-2022 Board of Regents Nominees

Name	Position
Robert Zemble, MD, Allentown, PA	President-Elect (1-year term)
Gisoo Ghaffari, MD, Hershey, PA	Secretary/Treasurer (1-year term)
Megan Ford, MD, Philadelphia, PA	Member-At-Large (4-year term)
Melanie Ruffner, MD, Ph.D., Philadelphia, PA	Member-At-Large (4-year term)
Magee DeFelice, MD, Philadelphia, PA	Member –At-Large (2-year term)
Catherine Popadiuk, DO, Hershey, PA	FIT (1-year term)

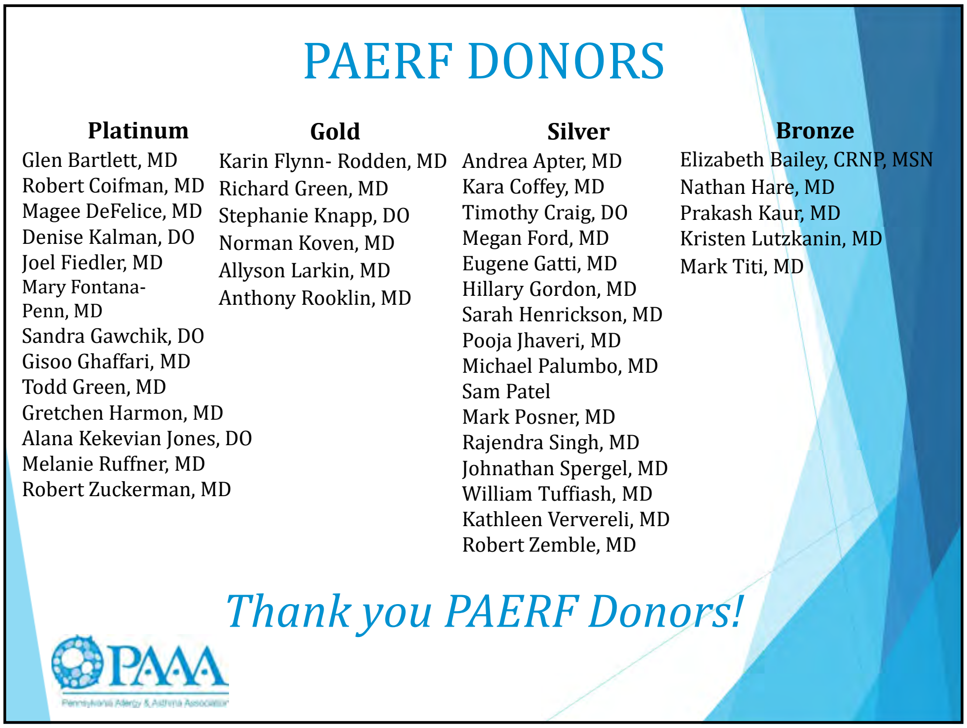
Appointments

Hey Chong, MD, Ph.D.	Program Chair 2022
Magee DeFelice, MD	Assistant Program Chair 2022

PAERF COMMITTEE REPORT

Pennsylvania Allergy Education and Research Fund
Statement of Financial Position May 31, 2021

ASSETS:			
Cash Management - General	7,488.99		
Long-term Investments, at Market	150,768.95		
Total, Cash and Investments		158,257.94	
Accounts Receivable		1,400.00	
Prepaid Expenses		0.00	
TOTAL, ASSETS			***$159,657.94***
LIABILITIES AND NET ASSETS:			
Accounts Payable - General	0.00		
Unearned Revenue	0.00		
Total, Liabilities		0.00	
Net Assets, January 1, 2021	148,574.44		
Change in Net Assets	11,083.50		
Net Assets, May 31, 2021		159,657.94	
TOTAL, LIABILITIES AND NET ASSETS			***$159,657.94***



PAERF DONORS

Platinum

Glen Bartlett, MD
Robert Coifman, MD
Magee DeFelice, MD
Denise Kalman, DO
Joel Fiedler, MD
Mary Fontana-Penn, MD
Sandra Gawchik, DO
Gisoo Ghaffari, MD
Todd Green, MD
Gretchen Harmon, MD
Alana Kekevian Jones, DO
Melanie Ruffner, MD
Robert Zuckerman, MD

Gold

Karin Flynn- Rodden, MD
Richard Green, MD
Stephanie Knapp, DO
Norman Koven, MD
Allyson Larkin, MD
Anthony Rooklin, MD

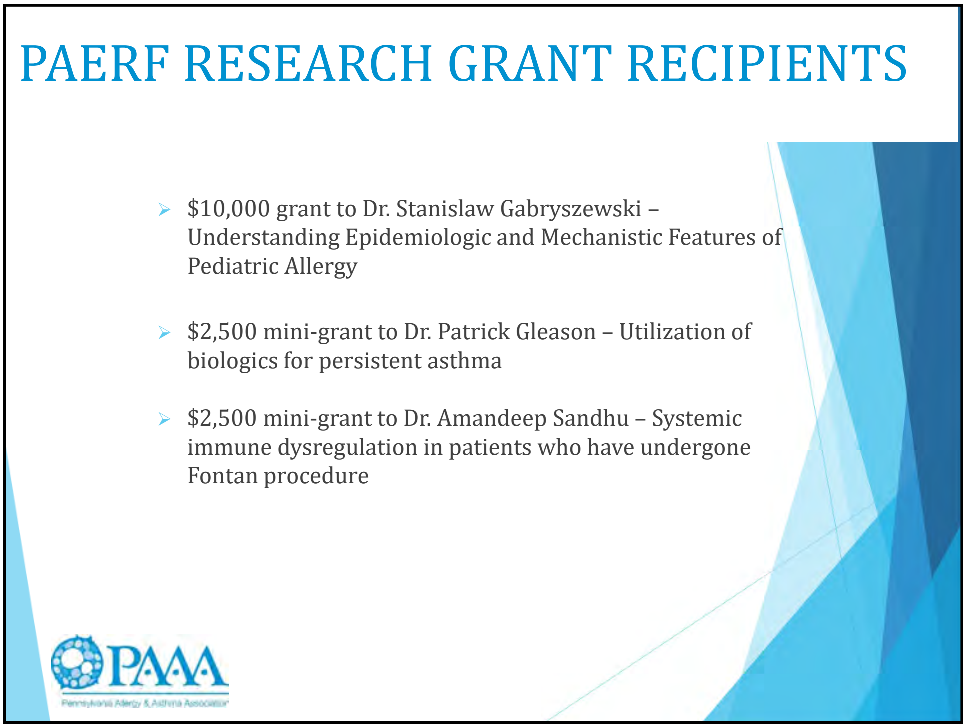
Silver

Andrea Apter, MD
Kara Coffey, MD
Timothy Craig, DO
Megan Ford, MD
Eugene Gatti, MD
Hillary Gordon, MD
Sarah Henrickson, MD
Pooja Jhaveri, MD
Michael Palumbo, MD
Sam Patel
Mark Posner, MD
Rajendra Singh, MD
Johnathan Spergel, MD
William Tuffiash, MD
Kathleen Ververeli, MD
Robert Zemble, MD

Bronze

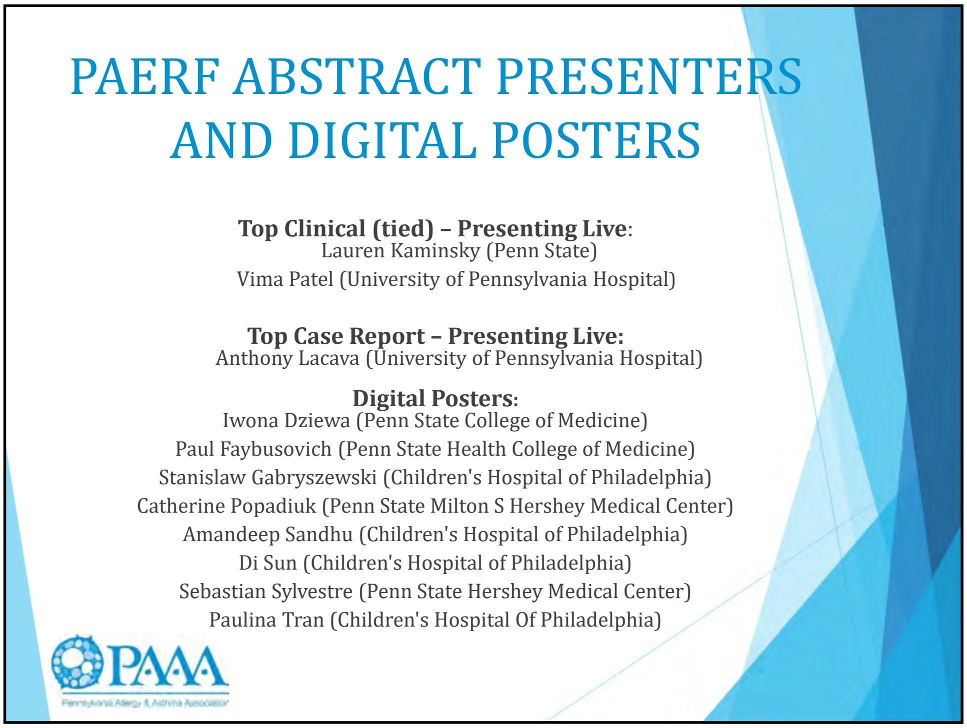
Elizabeth Bailey, CRNP, MSN
Nathan Hare, MD
Prakash Kaur, MD
Kristen Lutzkanin, MD
Mark Titi, MD

Thank you PAERF Donors!



PAERF RESEARCH GRANT RECIPIENTS

- $10,000 grant to Dr. Stanislaw Gabryszewski – Understanding Epidemiologic and Mechanistic Features of Pediatric Allergy
- $2,500 mini-grant to Dr. Patrick Gleason – Utilization of biologics for persistent asthma
- $2,500 mini-grant to Dr. Amandeep Sandhu – Systemic immune dysregulation in patients who have undergone Fontan procedure



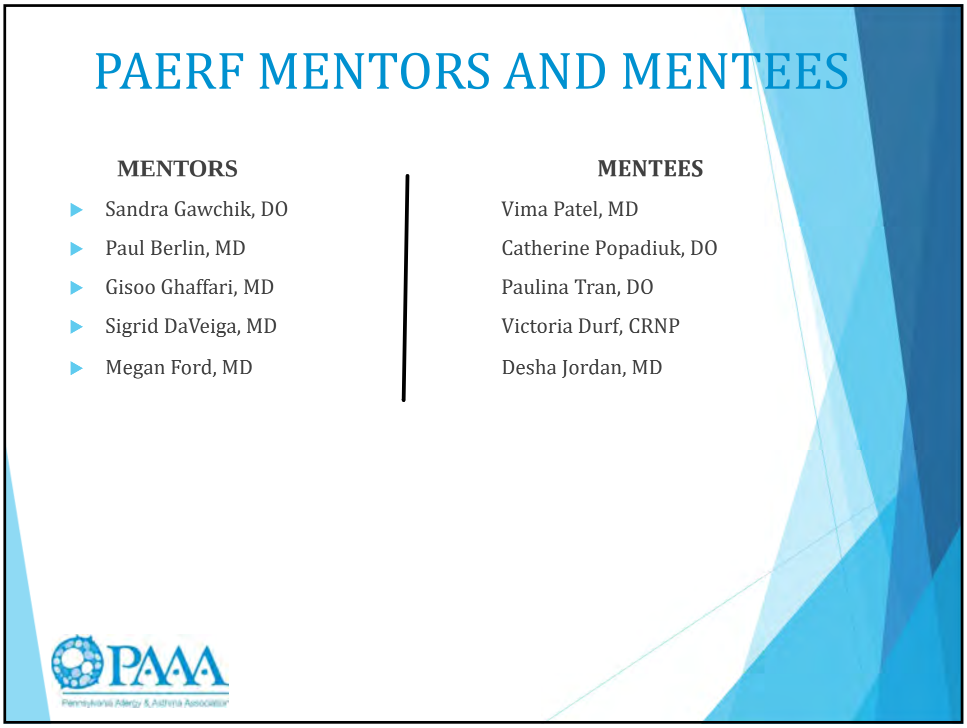
PAERF ABSTRACT PRESENTERS AND DIGITAL POSTERS

Top Clinical (tied) – Presenting Live:
Lauren Kaminsky (Penn State)
Vima Patel (University of Pennsylvania Hospital)

Top Case Report – Presenting Live:
Anthony Lacava (University of Pennsylvania Hospital)

Digital Posters:
Iwona Dziewa (Penn State College of Medicine)
Paul Faybusovich (Penn State Health College of Medicine)
Stanislaw Gabryszewski (Children's Hospital of Philadelphia)
Catherine Popadiuk (Penn State Milton S Hershey Medical Center)
Amandeep Sandhu (Children's Hospital of Philadelphia)
Di Sun (Children's Hospital of Philadelphia)
Sebastian Sylvestre (Penn State Hershey Medical Center)
Paulina Tran (Children's Hospital Of Philadelphia)

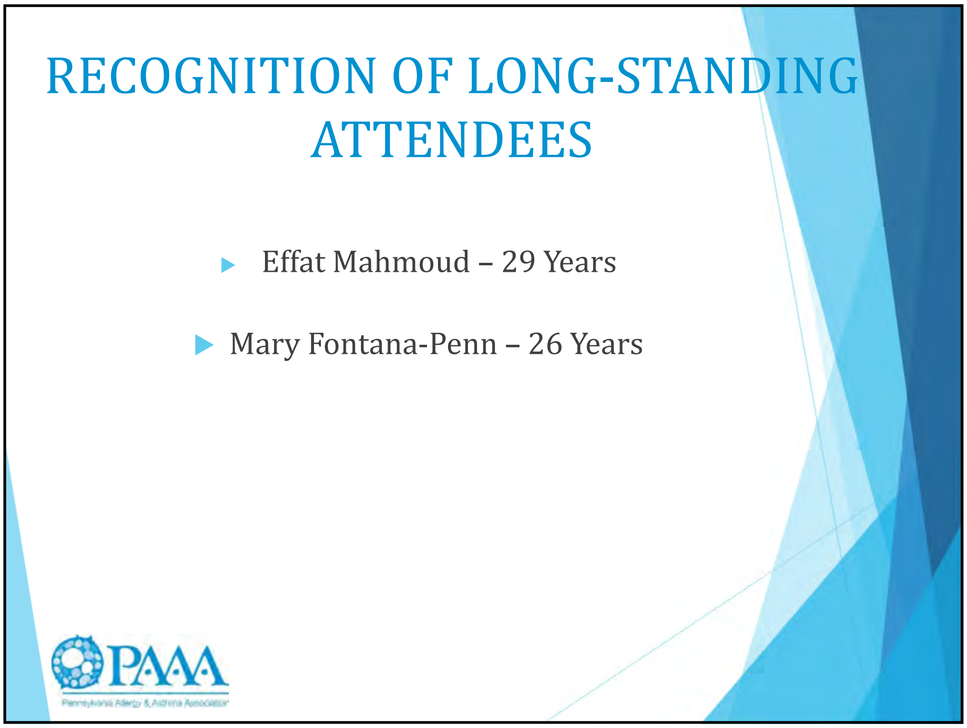
PAAA
Pennsylvania Allergy & Asthma Association



PAERF MENTORS AND MENTEES

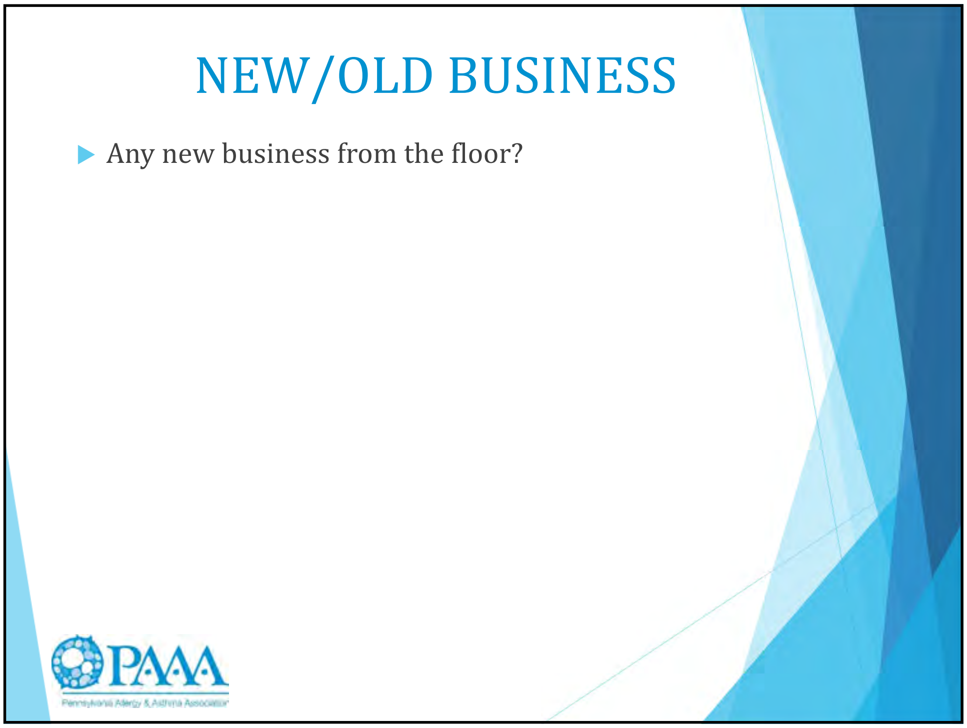
MENTORS	MENTEES
▶ Sandra Gawchik, DO	Vima Patel, MD
▶ Paul Berlin, MD	Catherine Popadiuk, DO
▶ Gisoo Ghaffari, MD	Paulina Tran, DO
▶ Sigrid DaVeiga, MD	Victoria Durf, CRNP
▶ Megan Ford, MD	Desha Jordan, MD

PAAA
Pennsylvania Allergy & Asthma Association



RECOGNITION OF LONG-STANDING ATTENDEES

- Effat Mahmoud – 29 Years
- Mary Fontana-Penn – 26 Years



NEW/OLD BUSINESS

- Any new business from the floor?

Incoming President's Remarks
Sigrid DaVeiga, MD

PAAA

Pennsylvania Allergy & Asthma Association

Mayer A. Green, MD Allergy Foundation Lecture:

The Brave New Biologic World of Asthma

Sally Wenzel, MD

Saturday, June 26, 2021
10:15 a.m. - 11:00 a.m.

The Brave New Biologic World of Asthma

Sally Wenzel, MD
Professor of Medicine
UPMC Chair in Translational Airway Biology

The University of Pittsburgh
Asthma Institute
@UPMC and the University of Pittsburgh School of Medicine

Declaration of Conflicts

- Multicenter clinical trial support:
    - AstraZeneca, Novartis, Sanofi, Knopp
- Consulting: AstraZeneca, Sanofi, GSK, Novartis, Knopp

Case #1

- 45 yo male with systemic corticosteroid (CS) dependent asthma for 10 yrs
  - Currently on 10-12.5 mg prednisolone daily + high dose combination therapy and additional ICS (~2000 mcg fluticasone equivalent)
  - Still exacerbates 2-3x per year, ACT 17
- No asthma or respiratory symptoms until mid 20s
- No seasonal symptoms but long history of “allergies”
  - No history of eczema, hives and no family history of asthma
  - No pets
  - Polyp surgery 5 yrs ago

Physiology and labs

- FEV1 64% predicted with FEV1/FVC 0.68
- 22% improvement in FEV1 post bronchodilator
- DLCO: 75% predicted
- FeNO 24 ppb
- IgE: 115 IU/μl Specific IgE testing negative
- Blood eos always <100/μl
- BAL with 1% eosinophils

Does this patient qualify for a Type-2 biologic targeted therapy?

- What would you do/add?
  - Azithromycin
  - Omalizumab?
  - Increase oral CSs?
  - LAMA
  - Taper OCS

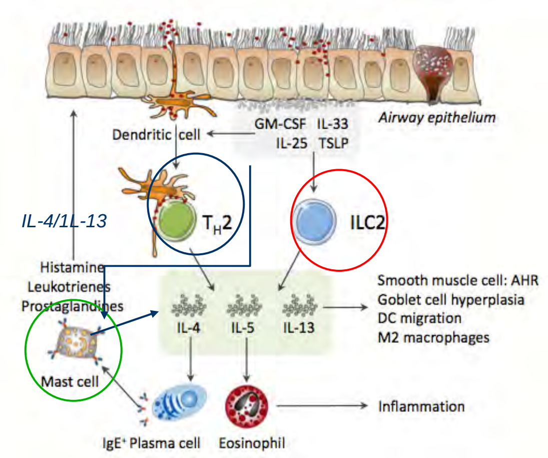
OCS tapered

- Patient asked to drop to 7.5 mg, call when symptoms worsened
- 2 weeks later, salbutamol use increased from 4 puffs per day to 8, with increased nocturnal awakening
- Asked to get complete blood count and differential
  - Blood eosinophils now 500/μl, FeNO 35 ppb
- Patient started on benralizumab
  - prednisone dose now 5 mg/day and total ICS dose 800 mcg

“Efficacy” of monoclonal therapies

- Added benefit “on top” of combination therapies
  - Must “at least” improve exacerbations and/or systemic CS use
  - Should improve symptoms/FEV1 *in addition* to exacerbations/CS use
  - Helpful if improves comorbidities
- Predictive and Response biomarkers available
- Ideally disease modifying
- Must be at least “acceptably” safe

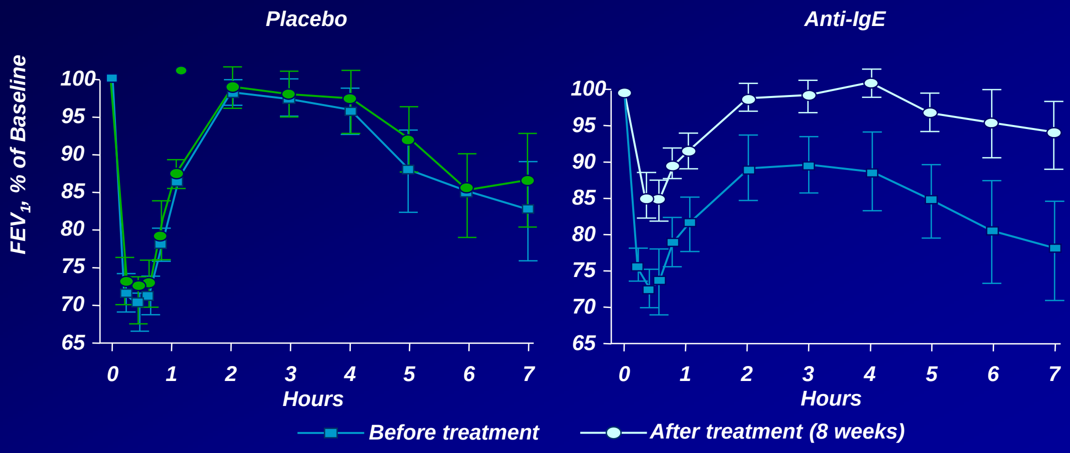
Th2/T2 Molecular Phenotypes



Hendricks, Allergy 2014

- Type-2 likely encompasses several molecular phenotypes
- Each involves participation of “Th2” /Type-2 cytokines, IL-4, 5 and -13 in poorly understood *and variable* mix
- Mechanistic pathways include traditional Th2, ILC2 and non-lymphoid sources of T2 cytokines

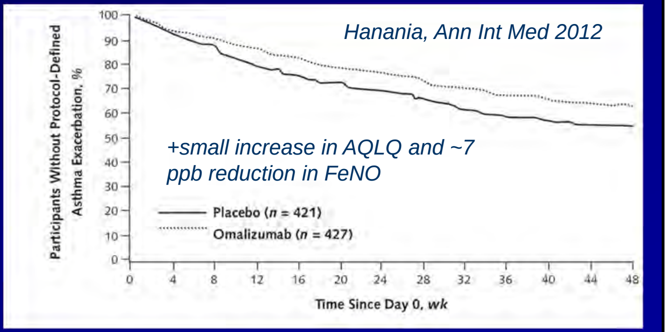
“Allergic Asthma”: 24 yrs of experience with biologics in asthma



Fahy JV, et al. Am J Respir Crit Care Med. 1997;155:1828-1834.

Developed in 2000s as add-on to ICS, but severe asthma definition now high dose combination

- Over 800 patients with severe asthma (high dose ICS+2nd controller)
- Primarily females, obese, FEV1~65% pred, 17% on OCS
- Average of 2 exacerbations in previous year
- FeNO ~29, IgE 175-180 IU/ml
  - IgE not predictive of response

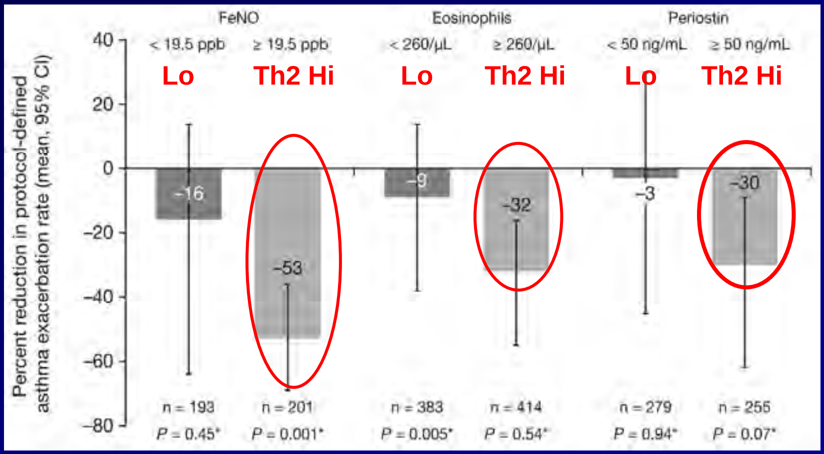


Hanania, Ann Int Med 2012

+small increase in AQLQ and ~7 ppb reduction in FeNO

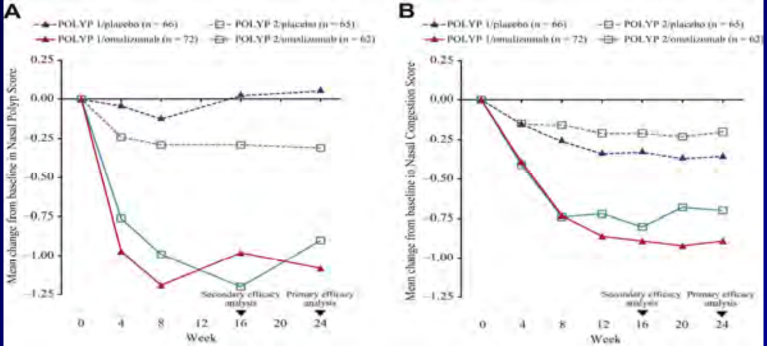
Rate of exacerbations in next year
Placebo 0.88/yr
Omalizumab 0.66/yr
25% reduction p=0.006

Better predictive biomarkers: blood eos and FeNO?



Hanania, AJRCCM May 2013

Omalizumab: nasal polyps

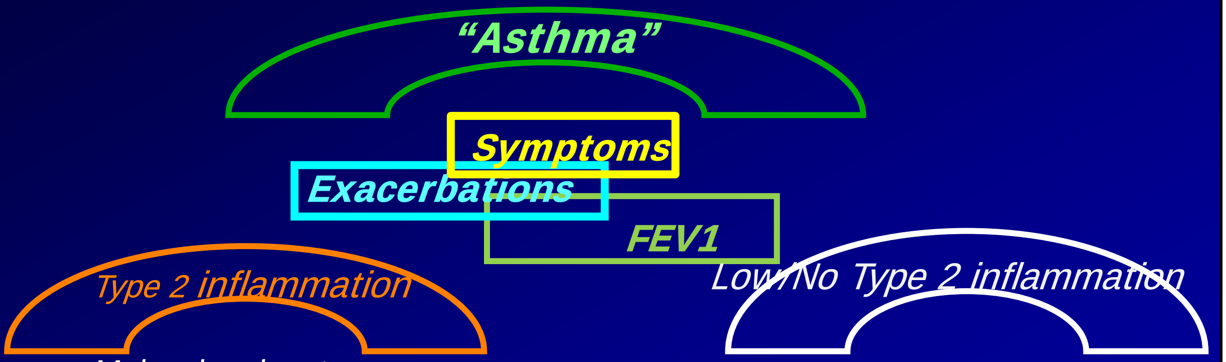


- Common co-morbidity with asthma, esp late onset/less allergic asthma
- Two 24 week studies *Gaevert P, et al J Allergy Clin Immunol 2020*
  - ~50% with mild-moderate asthma
- Improvements in most outcomes

Summary: 22 years of omalizumab

- Efficacy over combination therapies
  - ~25-30% reduction in exacerbations, less with increasing severity *Hanania Ann Int Med 2012*
  - Minimal effects on AQLQ, FEV1---none on symptoms
- Improves some comorbidities like nasal polyps *Gavaert JACI 2020*
- Biomarkers evolving
  - Original biomarkers (Total and specific IgE) unhelpful in evaluating responders or response
  - Some indication T2 biomarkers may be predictive biomarkers
- No evidence for disease modification
- Safety: anaphylaxis, injection site reactions

In 2021, the "asthma umbrella" has 2 smaller T2 "molecular parasols"



"Asthma"

Symptoms

Exacerbations

FEV1

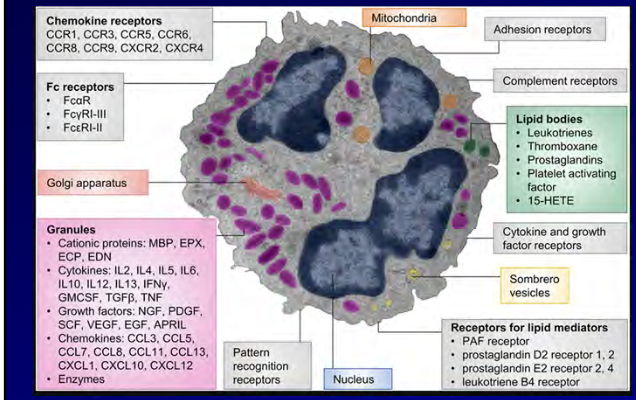
Type 2 inflammation

Low/No Type 2 inflammation

Molecular signatures,
reproducible biomarkers
Eosinophils ≥300/μl
FeNO ≥25 ppb

Repeated lack of T2 biomarkers

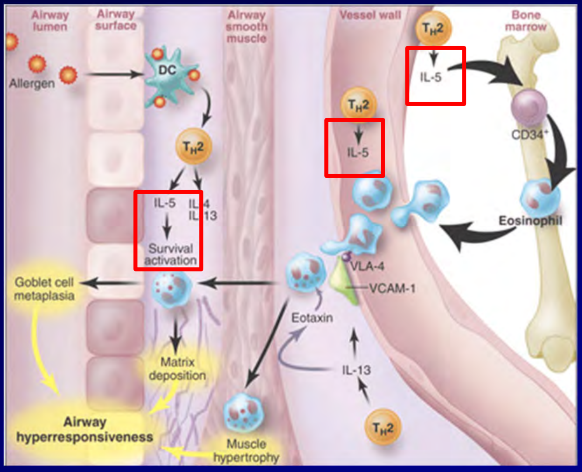
Eosinophil targeted therapies: Eosinophils do the right thing(s)

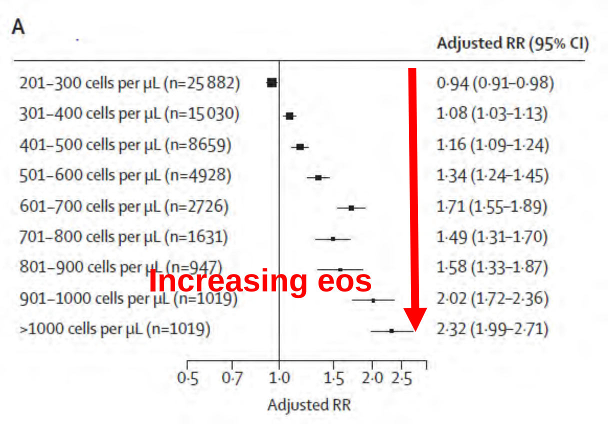


- Eosinophils are a storehouse of “nasties”
- Granules contain multiple cationic proteins, peroxidase, growth factors/chemokines
- Generate leukotrienes and other lipid mediators
- Receptors for both innate and adaptive immune processes

Diny, N et al Frontiers in Immunol 2017

IL-5: one of most potent pro-eosinophilic molecules

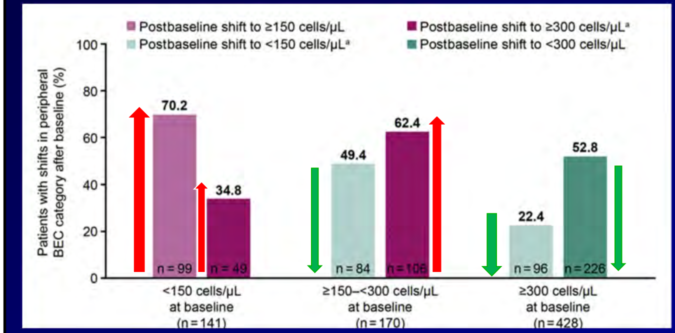




Price DB, Lancet Resp Med 2015

Wills-Karp M, Science 2004

Blood eosinophil stability over time in severe asthma

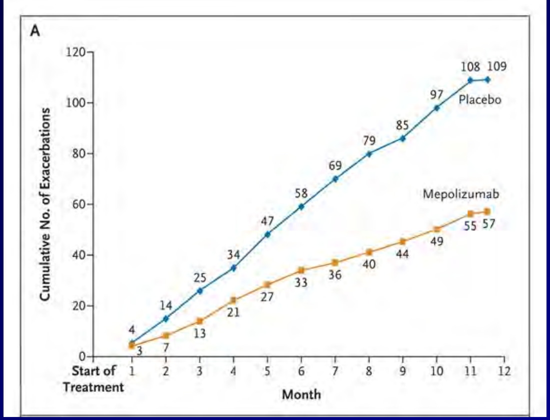


Lugogo N, et al Annals of Allergy, Asthma, Immunology 2020

- 300/μl considered threshold for “hi” eosinophils
- Of patients entering Anti-IL5R trial on placebo, 35% with low eos at entry reached 300/μl (“Hi eos”) at some point in trial
- Only 22% of those with >300/μl dropped below 150
- Patients with high eos more likely to stay that way

Anti-IL-5 approach confirms role of Eos and Type-2 cytokines

Haldar P et al. N Engl J Med 2009;360:973-984



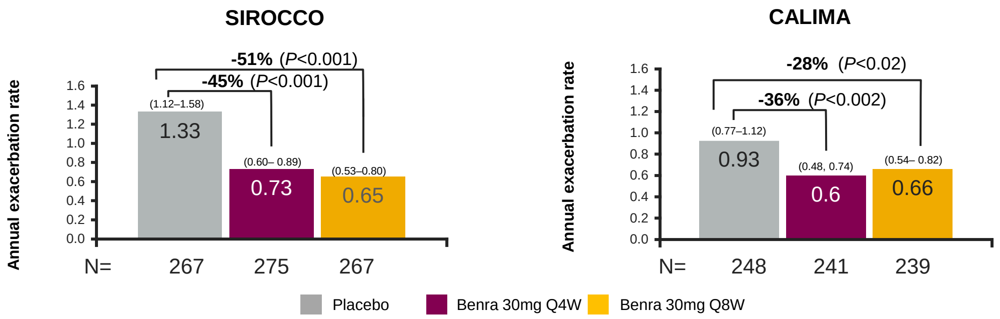
- Non-eosinophil targeted studies:
  - No efficacy
- Targeted Anti-IL-5 approach to “eosinophilic asthma” led to 40% reduction in asthma exacerbations
  - Majority *late onset eosinophilic* with sinusitis and nasal polyps
  - Did not work in allergen challenge model *Leckie et al Lancet 2000*
- 40-50% reductions in exacerbations
  - Some impact on FEV1/ACQ as well

The NEW ENGLAND JOURNAL of MEDICINE

Three marketed anti-IL-5 agents

- Two target the cytokine IL-5
  - Mepolizumab
  - Reslizumab (only one targeted by weight and IV admin)
- One targets the receptor, IL-5R in association with cytolytic event when antibody binds
  - Benralizumab
- Data to support reproducible clinical differences are very small
- Mepo and Benralizumab both home administration

Anti-IL-5R: Exacerbation rates decrease in pts with eos ≥300 cells/μL on high-dose ICS



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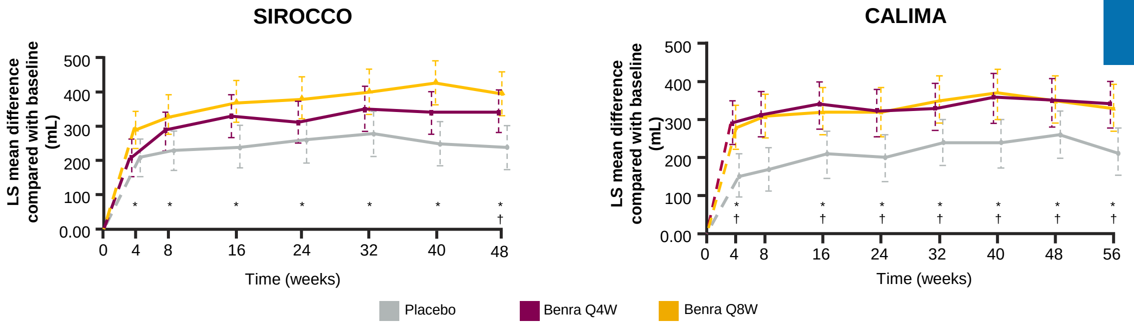
Bleecker ER et al. Lancet. 2016;388:2115-2127; FitzGerald JM et al. Lancet. 2016;388:2128-2141.

Small significant improvements in FEV_1

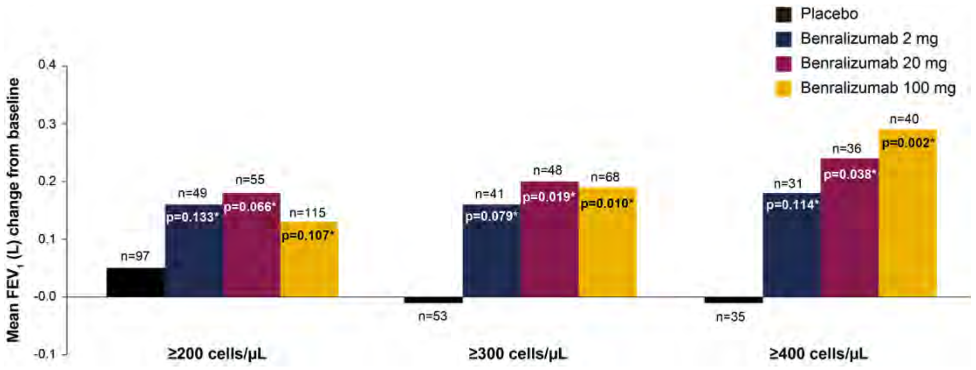


48 wks	Group LS MEANS	LS MEAN Difference (95% CI)
Q4W – placebo (mL)	345 vs 239	106 (16-196); *P*=0.022
Q8W – placebo (mL)	398 vs 239	159 (68-249); *P*=0.001

56 wks	Group LS MEANS	LS MEAN Difference (95% CI)
Q4W – Placebo (mL)	340 vs 215	125 (37, 213); *P*=0.005
Q8W – placebo (mL)	330 vs 215	116 (28, 204); *P*=0.010

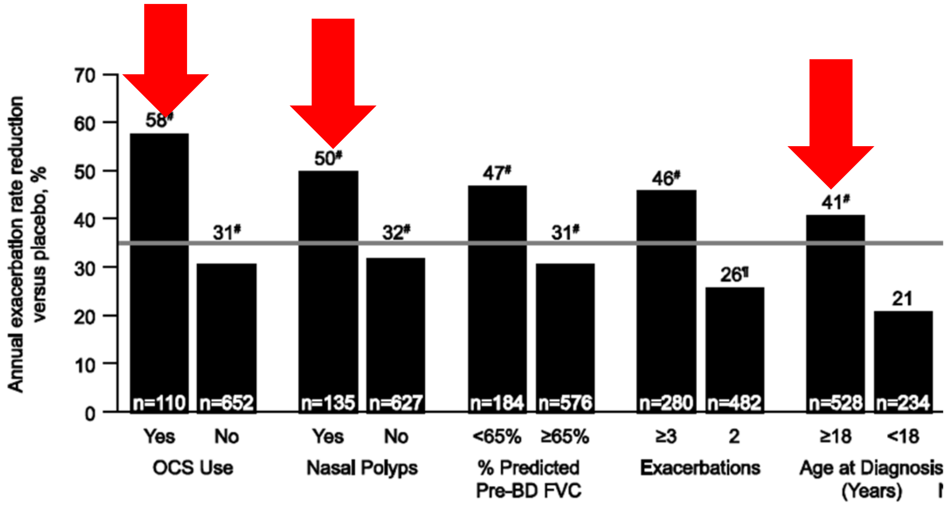
1. Bleecker ER et al. Lancet. 2016;388:2115-2127; 2. FitzGerald JM et al. Lancet. 2016;388:2128-2141.

Predictive biomarker: baseline eos improvement in FEV1 (and exacerbations)



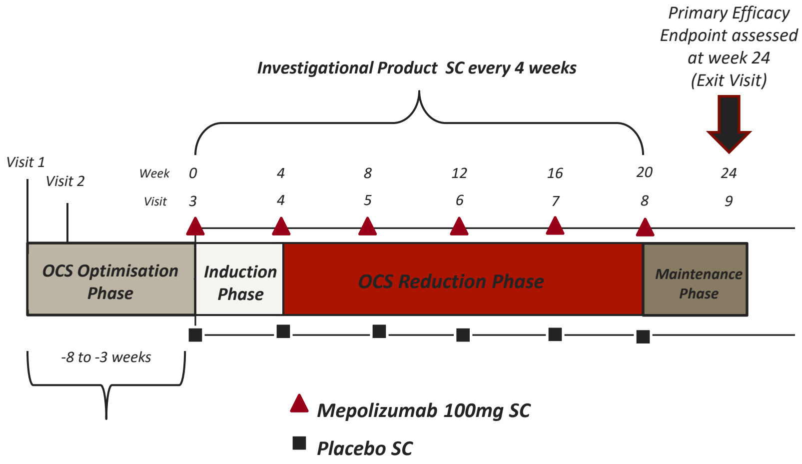
Eosinophil dose response also seen with mepolizumab and reslizumab,

Predictors of Response: Nasal polyps and age at onset



Bleecker E et al Eur Respir J 2018

CS sparing: Anti-IL-5/5Rs first molecules to consistently show reduction in OCS dose


Primary Efficacy Endpoint assessed at week 24 (Exit Visit)

Investigational Product SC every 4 weeks

Visit 1

Visit 2

Week	*0*	*4*	*8*	*12*	*16*	*20*	*24*
Visit	*3*	*4*	*5*	*6*	*7*	*8*	*9*

OCS Optimisation Phase

Induction Phase

OCS Reduction Phase

Maintenance Phase

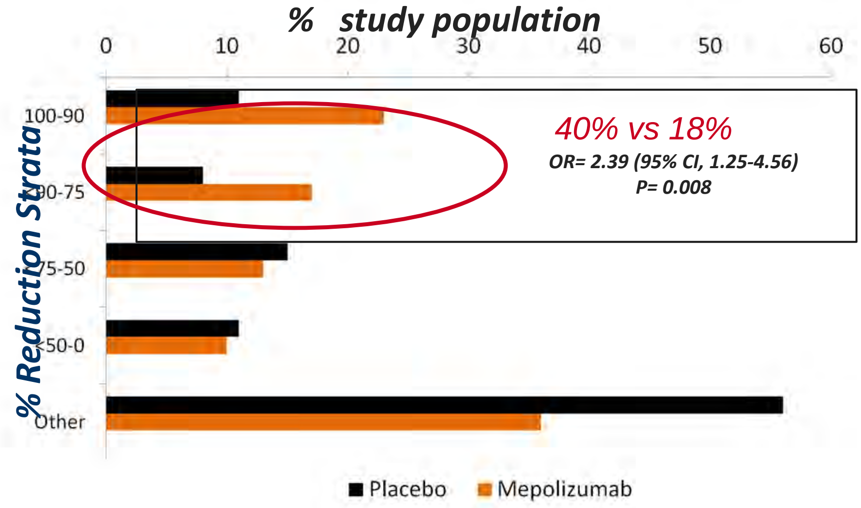
-8 to -3 weeks

▲ ***Mepolizumab 100mg SC***

■ ***Placebo SC***

Bel E, et al, N Engl J Med Sept 2014

40% of patients decreased OCS by ≥75% while decreasing exacerbations



40% vs 18%

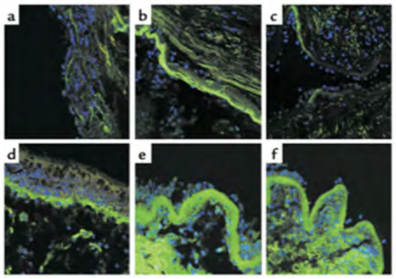
OR= 2.39 (95% CI, 1.25-4.56)

P= 0.008

Similar efficacy for Anti-IL5R Nair N Engl J Med 2017

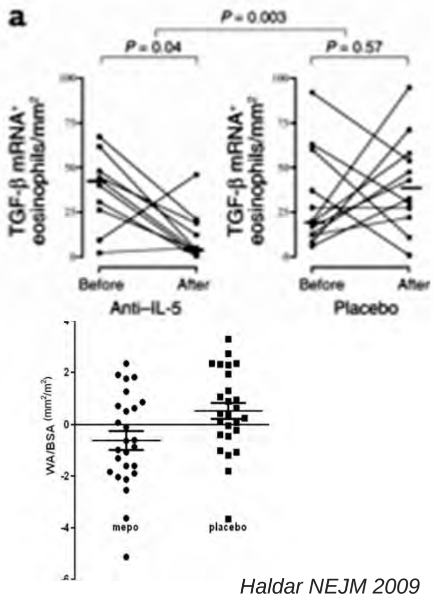
Disease Modification?

Tenascin
Normal *Asthma Pre* *Post*



Lumican

Flood-Page J Clin Invest 2003



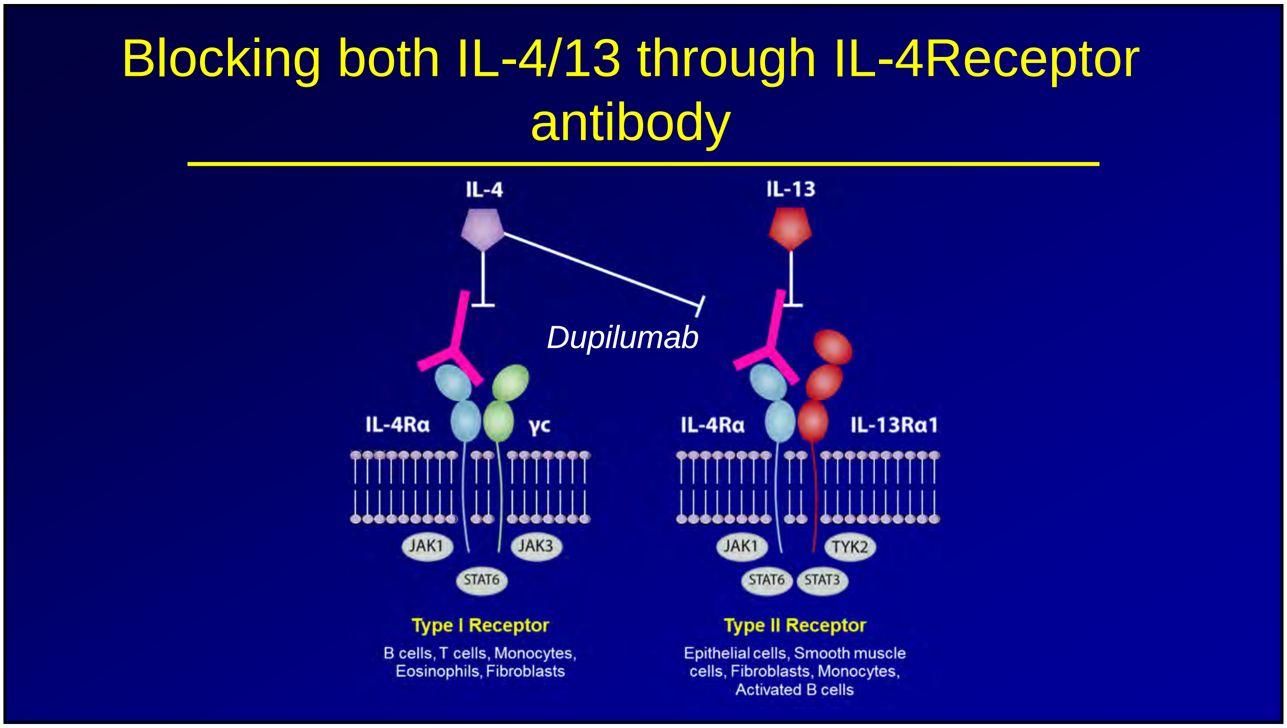
Haldar NEJM 2009

Safety

- Anti-IL-5/5Rs generally well tolerated
- Injection site reactions common but not severe
  - Reslizumab with black box warning for anaphylaxis
- Possible increased risk of shingles/zoster
- Anaphylaxis led to black box warning with reslizumab (also seen with benralizumab)
- Theoretical concerns regarding parasitic infections, cancer

Summary: Anti-IL-5s/IL-5R

- Efficacy over combination Rxs in patients *with elevated eosinophils*
  - Consistent 40-50% reduction in exacerbations
  - Modest effects on AQLQ, FEV1---none on sx
- *May* improve comorbidities like nasal polyps
  - Strongly steroid sparing
  - No effect in eosinophilic esophagitis or allergen challenge
- Predictive marker: Blood eosinophils
  - Best threshold unclear
  - No response biomarker
- Possible evidence for disease modification
  - Yet symptoms return within months of stopping Rx



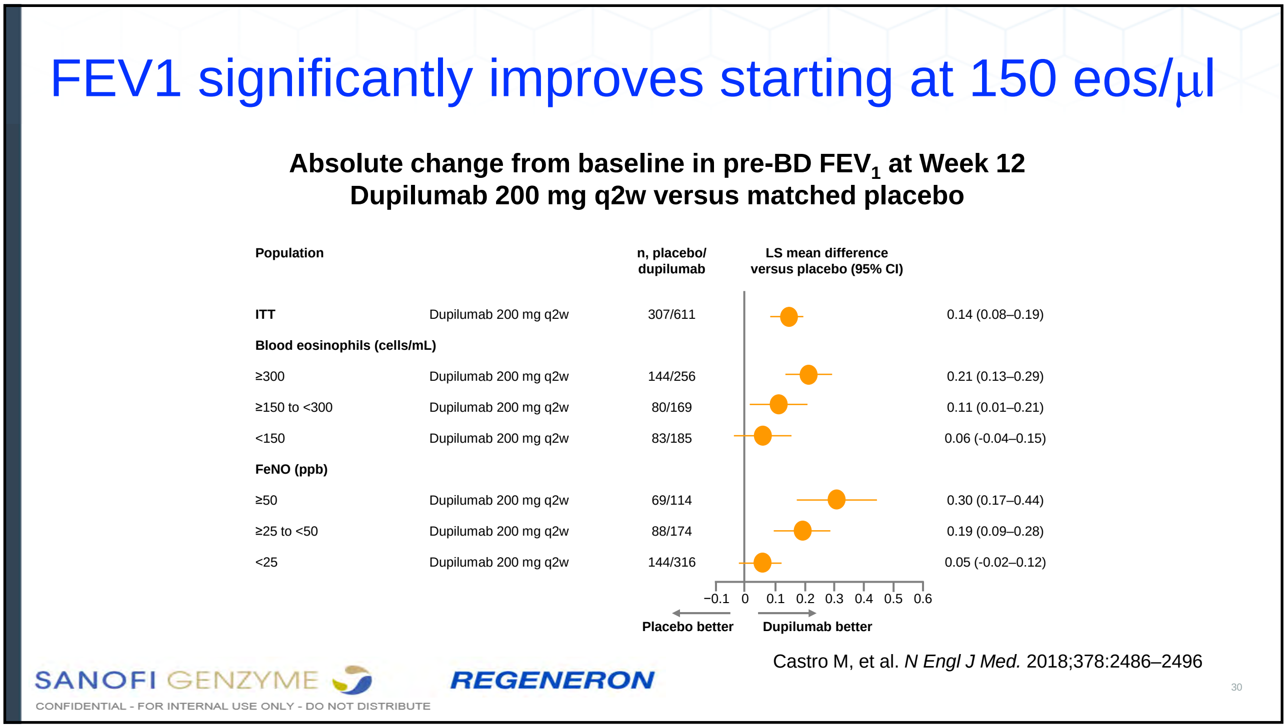
Blocking both IL-4/13 through IL-4Receptor antibody

Type I Receptor

B cells, T cells, Monocytes, Eosinophils, Fibroblasts

Type II Receptor

Epithelial cells, Smooth muscle cells, Fibroblasts, Monocytes, Activated B cells



FEV1 significantly improves starting at 150 eos/μl

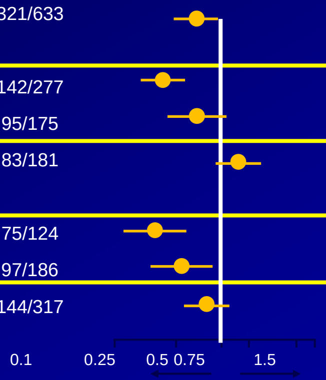
Absolute change from baseline in pre-BD FEV_1 at Week 12
Dupilumab 200 mg q2w versus matched placebo

Population		n, placebo/ dupilumab	LS mean difference versus placebo (95% CI)
ITT	Dupilumab 200 mg q2w	307/611	0.14 (0.08–0.19)
Blood eosinophils (cells/mL)			
≥300	Dupilumab 200 mg q2w	144/256	0.21 (0.13–0.29)
≥150 to <300	Dupilumab 200 mg q2w	80/169	0.11 (0.01–0.21)
<150	Dupilumab 200 mg q2w	83/185	0.06 (-0.04–0.15)
FeNO (ppb)			
≥50	Dupilumab 200 mg q2w	69/114	0.30 (0.17–0.44)
≥25 to <50	Dupilumab 200 mg q2w	88/174	0.19 (0.09–0.28)
<25	Dupilumab 200 mg q2w	144/316	0.05 (-0.02–0.12)

Castro M, et al. *N Engl J Med.* 2018;378:2486–2496

Exacerbations also improve with increasing background T2 biomarkers

Population		n, placebo/ dupilumab	Relative risk versus placebo (95% CI)
ITT	Dupilumab 300 mg q2w	321/633	0.54 (0.43–0.68)
Blood eosinophils (cells/mL)			
≥300	Dupilumab 300 mg q2w	142/277	0.33 (0.23–0.45)
≥150 to <300	Dupilumab 300 mg q2w	95/175	0.56 (0.35–0.89)
<150	Dupilumab 300 mg q2w	83/181	1.15 (0.75–1.77)
FeNO (ppb)			
≥50	Dupilumab 300 mg q2w	75/124	0.31 (0.19–0.49)
≥25 to <50	Dupilumab 300 mg q2w	97/186	0.44 (0.28–0.69)
<25	Dupilumab 300 mg q2w	144/317	0.79 (0.57–1.10)

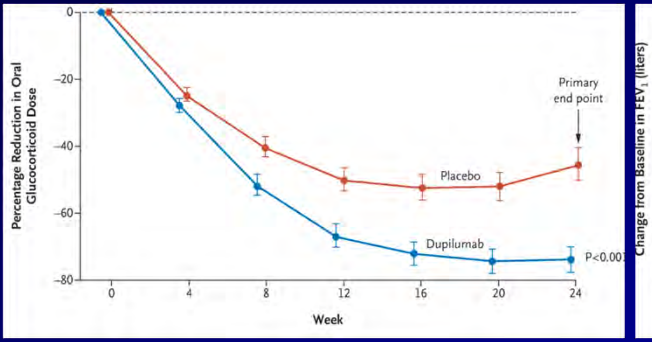


Dupilumab better **Placebo better**

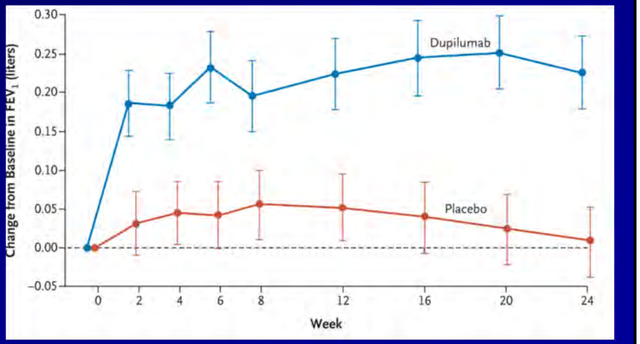
Castro M, et al. N Engl J Med. 2018;378:2486–2496

Similar to IL-5 approaches, dupilumab also efficacious in CS sparing trials

Change from Baseline in Daily OCS Dose Over Time.

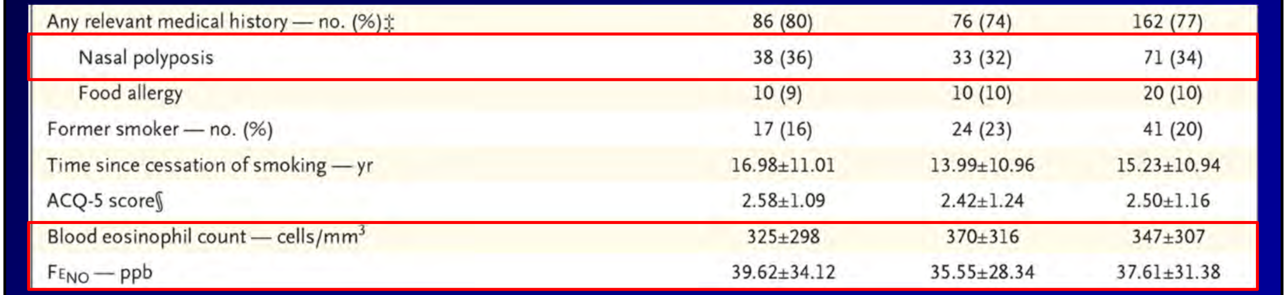


Change from baseline in FEV1 (liters)



Rabe K, N Engl J Med 2018

Similar to anti IL-5 studies, nasal polyps common co-morbidity

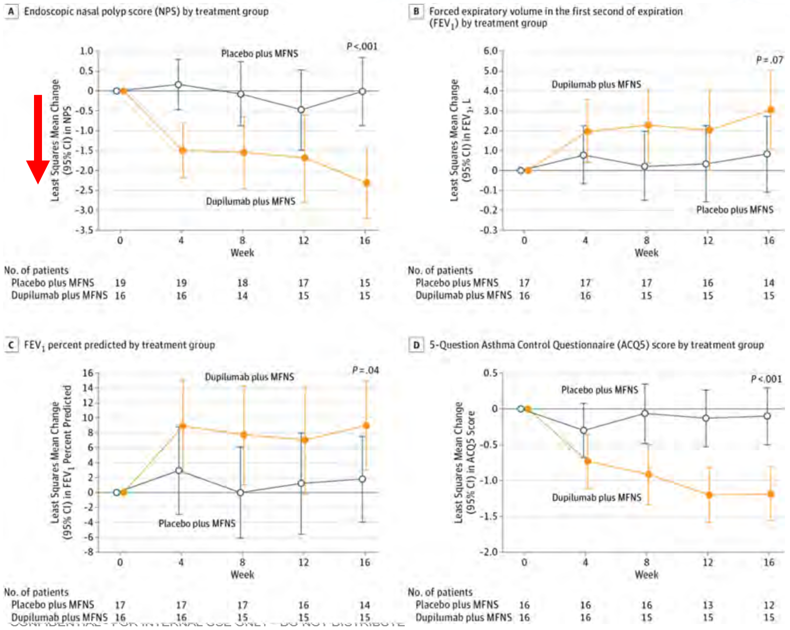


Any relevant medical history — no. (%)‡	86 (80)	76 (74)	162 (77)
Nasal polyposis	38 (36)	33 (32)	71 (34)
Food allergy	10 (9)	10 (10)	20 (10)
Former smoker — no. (%)	17 (16)	24 (23)	41 (20)
Time since cessation of smoking — yr	16.98±11.01	13.99±10.96	15.23±10.94
ACQ-5 score§	2.58±1.09	2.42±1.24	2.50±1.16
Blood eosinophil count — cells/mm^3	325±298	370±316	347±307
$F_{E_{NO}}$ — ppb	39.62±34.12	35.55±28.34	37.61±31.38

Type-2 biomarkers remain elevated despite systemic corticosteroids

Rabe K et al N Engl J Med 2018

Anti-IL-4Rα also improves nasal polyps (and asthma)

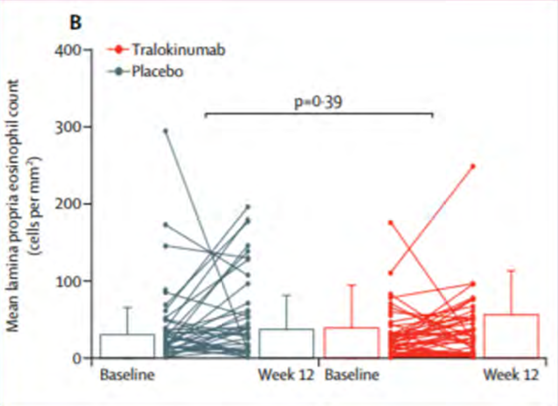


FDA approved for nasal polyps

Bachert C et al JAMA 2016
Bachert C Lancet 2019

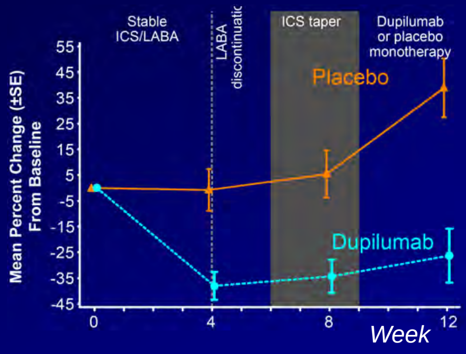
Tissue eosinophils do not decline with Anti-IL-13: questions eos as driver

- IL-4R activation increases eotaxin-family expression
  - Associated with lung eosinophilia
    - *Coleman et al Thorax 2013*
- Although decrease in *lung* eosinophils hypothesized to drive efficacy, despite increases in blood eosinophils, no data to support (including unpublished data with dupilumab)



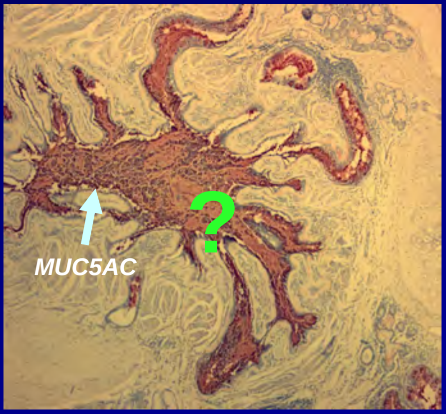
Russell et al Lancet Resp Med 2018

Anti-IL-4/13 efficacy through epithelial effects?



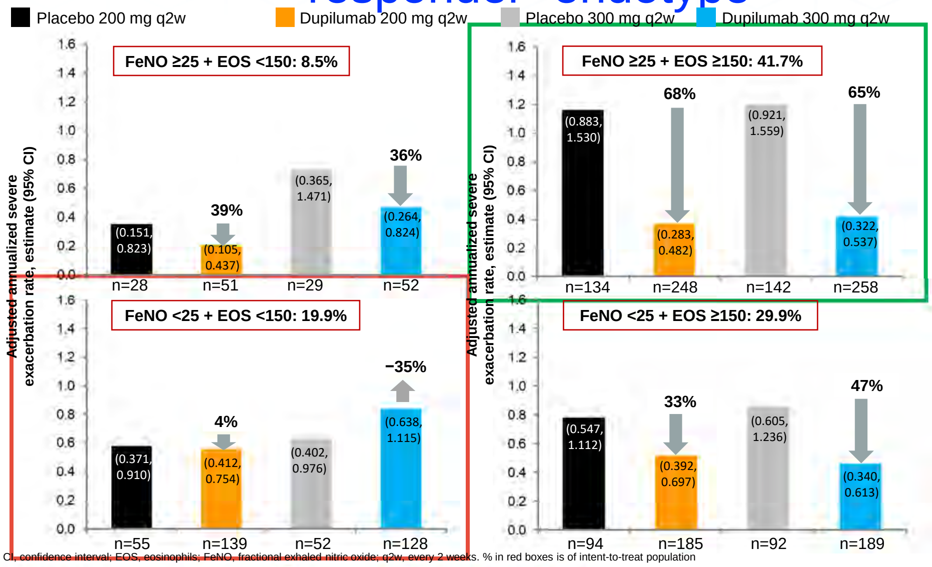
Correlation of FeNO with FEV$_1$
at Week 12: r = -0.408 P = 0.009

Wenzel N Eng lJ Med 2013



IL-13 strongly induces MUC5AC in vitro

FeNO + blood eos best define “T2/IL-4R responder” endotype



CI, confidence interval; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; q2w, every 2 weeks. % in red boxes is of intent-to-treat population

Highest exacerbation rates in those with elevations in both

SANOFI GENZYME REGENERON

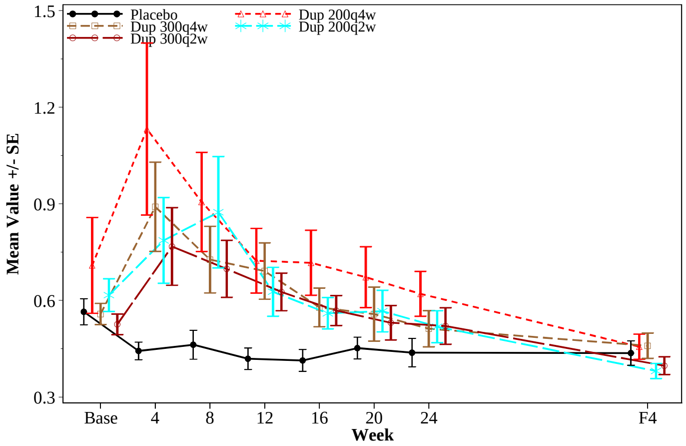
Castro M, et al. *N Engl J Med.* 2018;378:2486–2496

Safety

- Dupilumab generally well tolerated:
  - Injection site reactions common but not severe and no anaphylaxis to date
- Phase 3 trial excluded patients with eos >1500/μl as one patient developed EGPA like syndrome with more cases reported
- Theoretical risks include cancer, autoimmunity
  - Patients often report increasing muscle aches
  - Can see late marked increases in blood eos
  - Post marketing surveillance extremely important

Safety: Anti-IL4Rα increases blood eosinophils in subset

Wenzel, SE et al
Lancet 2016

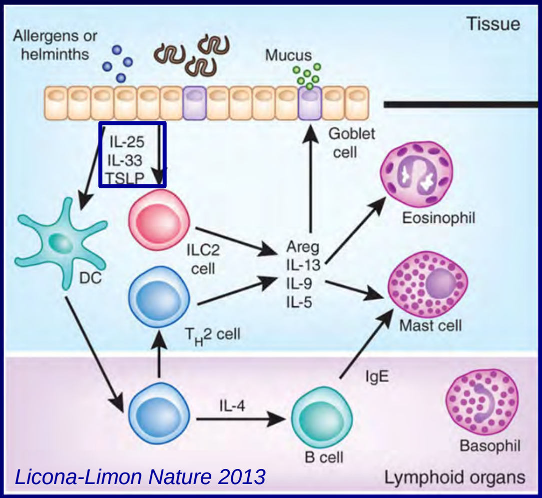


Impact on tissue eosinophils unknown
How to identify "benign" from pathologic (EGPA-like) increase unknown

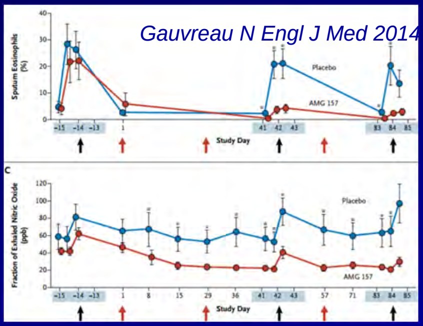
Summary: Anti-IL4R

- Efficacy on top of combination therapies
  - Consistent 60-70% reduction in exacerbations
- Improves comorbidities like nasal polyps and atopic dermatitis (FDA approved), possibly eosinophilic esophagitis
  - CS sparing effects *Rabe K, et al N Engl J Med 2018*
- Predictive biomarkers include both FeNO and blood eosinophils
  - "Index" may be better than either alone
  - Treatment decreases FeNO but NOT blood eosinophils
  - FeNO is also response biomarker for FEV1
- Disease modification: unknown
- Safety: Injection site reactions, possible EGPA and theoretical effects on cancer and autoimmunity

Tip of the iceberg: Targeting epithelial innate factors



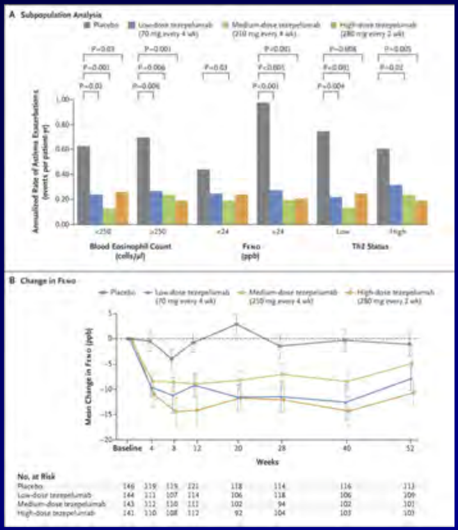
Licona-Limon Nature 2013



Gauvreau N Engl J Med 2014

- Anti-TSLP: Improved both early and late responses and decreased asthma exacerbations (NEJM 2017)
  - Decreased sputum (and blood) eosinophils
  - Decreased epithelial sourced FeNO
  - Broadest effector cell impact of any biologic to date

Anti-TSLP and moderate-severe asthma



Corren J et al. N Engl J Med 2017;377:936-946

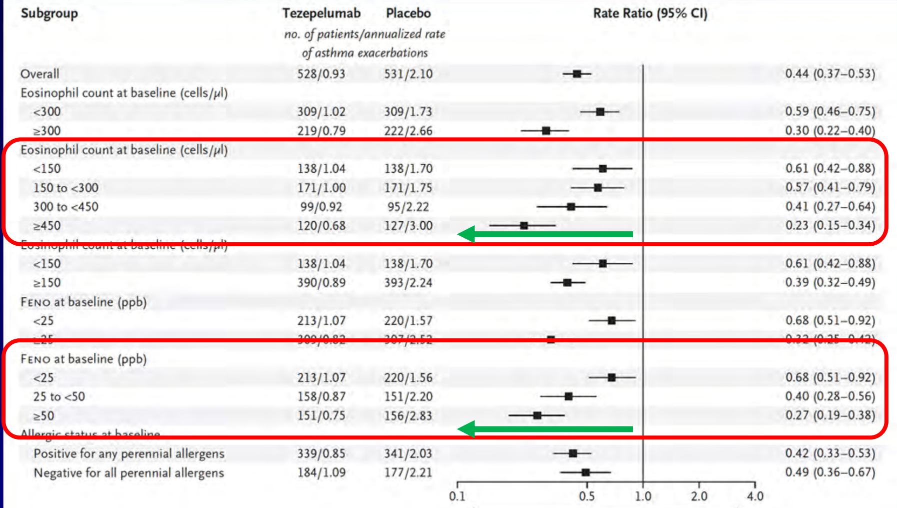
- 52 week 3 dose ranging study vs placebo in moderate to severe asthma
- Anti-TSLP (tezepelumuab) decreased exacerbations, symptoms and improved FEV1 while improving all T2 biomarkers
  - Regardless of FeNO or blood eos
  - In patients whose only asthma defining “biomarker” is bronchodilator reversibility
- Unclear relation to T2-Hi asthma as biomarker defined

The NEW ENGLAND JOURNAL of MEDICINE

Phase 3: Decreased exacerbations with low T2 biomarkers, best responses in T2-Hi

Blood eos

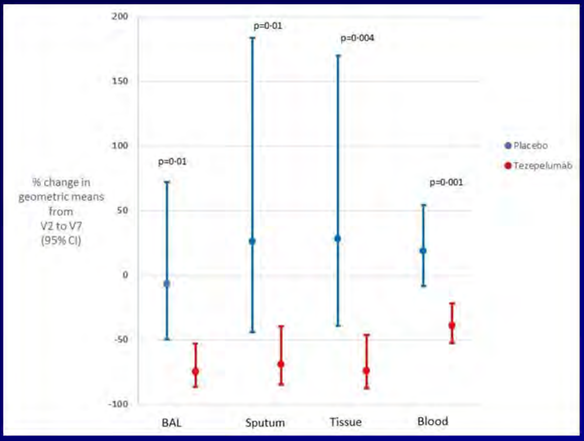
FeNO



Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/µl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/µl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
150 to <300	171/1.00	171/1.75	0.57 (0.41–0.79)
300 to <450	99/0.92	95/2.22	0.41 (0.27–0.64)
≥450	120/0.68	127/3.00	0.23 (0.15–0.34)
Eosinophil count at baseline (cells/µl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
≥150	390/0.89	393/2.24	0.39 (0.32–0.49)
FENO at baseline (ppb)			
<25	213/1.07	220/1.57	0.68 (0.51–0.92)
≥25	309/0.82	307/2.52	0.33 (0.25–0.42)
FENO at baseline (ppb)			
<25	213/1.07	220/1.56	0.68 (0.51–0.92)
25 to <50	158/0.87	151/2.20	0.40 (0.28–0.56)
≥50	151/0.75	156/2.83	0.27 (0.19–0.38)
Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
Negative for all perennial allergens	184/1.09	177/2.21	0.49 (0.36–0.67)

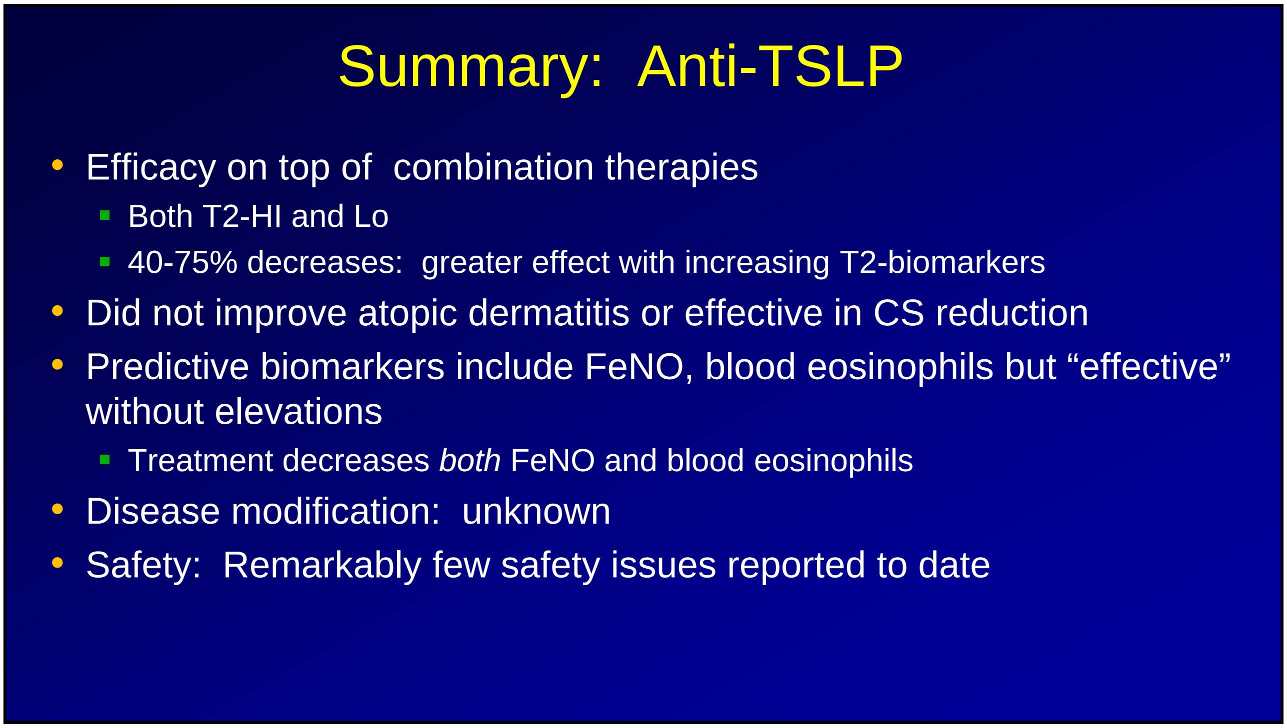
Menzies-Gow A et al N Engl J Med 2021

So how does anti-TSLP work?



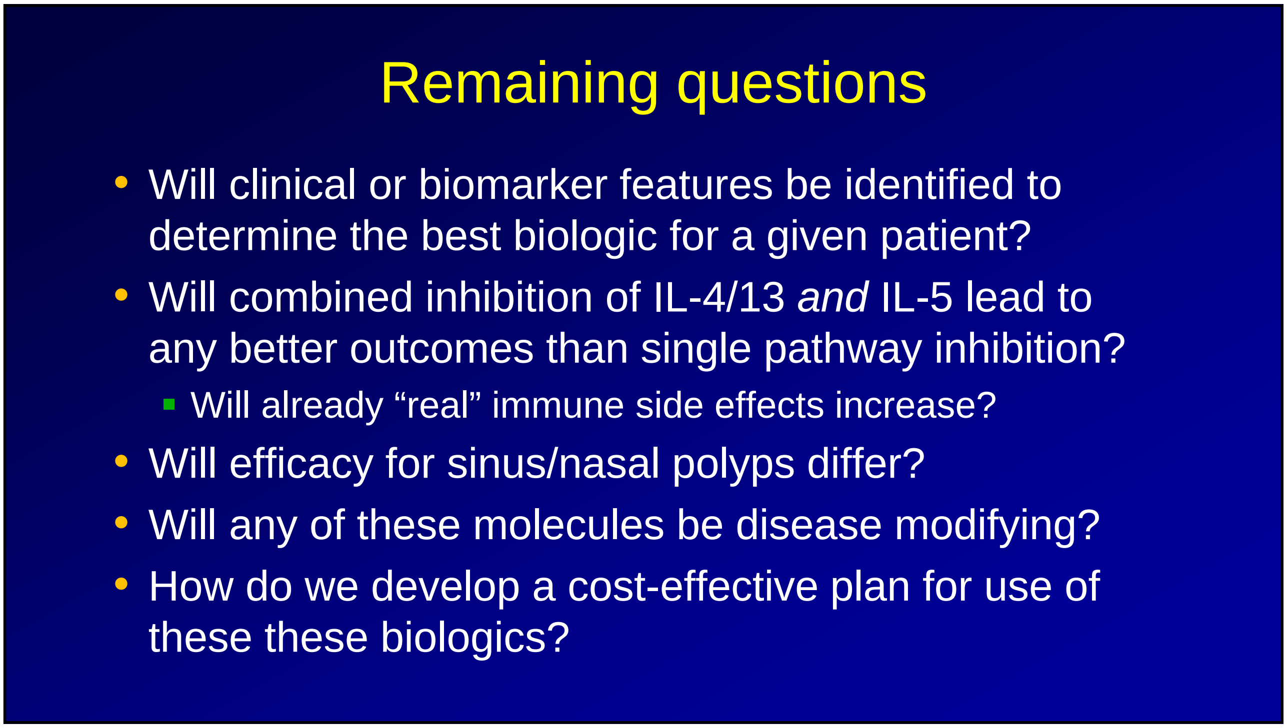
Sverrild A et al. Eur Resp J 2021

- No one knows
- First biopsy studies (x2) to show reduction in airway tissue eosinophils
  - But works in those without eosinophils as well ?
  - No effect on other cell types
- Also reduced mannitol-related airway hyper-responsiveness



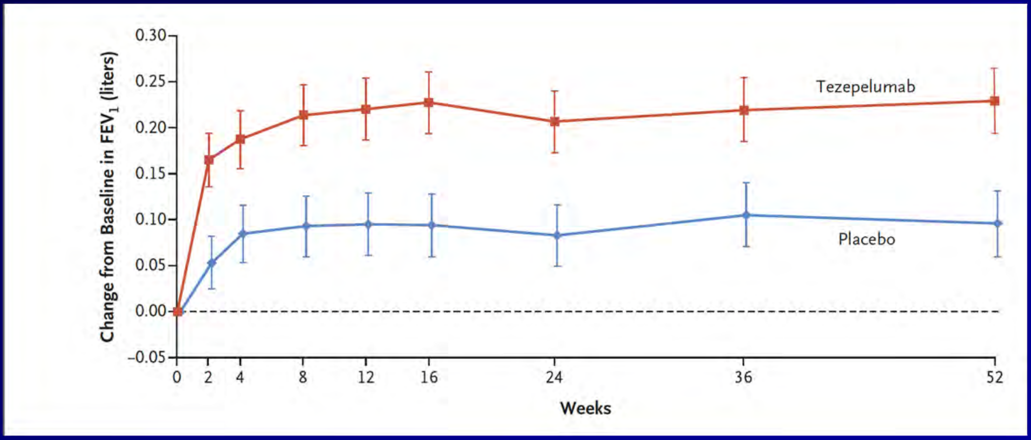
Summary: Anti-TSLP

- Efficacy on top of combination therapies
  - Both T2-HI and Lo
  - 40-75% decreases: greater effect with increasing T2-biomarkers
- Did not improve atopic dermatitis or effective in CS reduction
- Predictive biomarkers include FeNO, blood eosinophils but “effective” without elevations
  - Treatment decreases *both* FeNO and blood eosinophils
- Disease modification: unknown
- Safety: Remarkably few safety issues reported to date



Remaining questions

- Will clinical or biomarker features be identified to determine the best biologic for a given patient?
- Will combined inhibition of IL-4/13 *and* IL-5 lead to any better outcomes than single pathway inhibition?
  - Will already “real” immune side effects increase?
- Will efficacy for sinus/nasal polyps differ?
- Will any of these molecules be disease modifying?
- How do we develop a cost-effective plan for use of these these biologics?


0.30
0.25
0.20
0.15
0.10
0.05
0.00
−0.05
Change from Baseline in FEV$_1$ (liters)
Tezepelumab
Placebo
0
2
4
8
12
16
24
36
52
Weeks

47

PAAA

Pennsylvania Allergy & Asthma Association

Biomarkers for Systemic Anaphylaxis

Lawrence Schwartz, MD, PhD

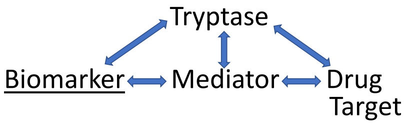
Saturday, June 26, 2021
11:00 a.m. - 11:45 a.m.

PENNSYLVANIA ALLERGY & ASTHMA ASSOCIATION
ANNUAL MEETING • JUNE 25 - 27, 2021

PAAA 2021 Annual Meeting

Biomarkers for Systemic Anaphylaxis

Lawrence B Schwartz, MD, PhD
Virginia Commonwealth University



Tryptase

Biomarker ⟷ Mediator ⟷ Drug Target

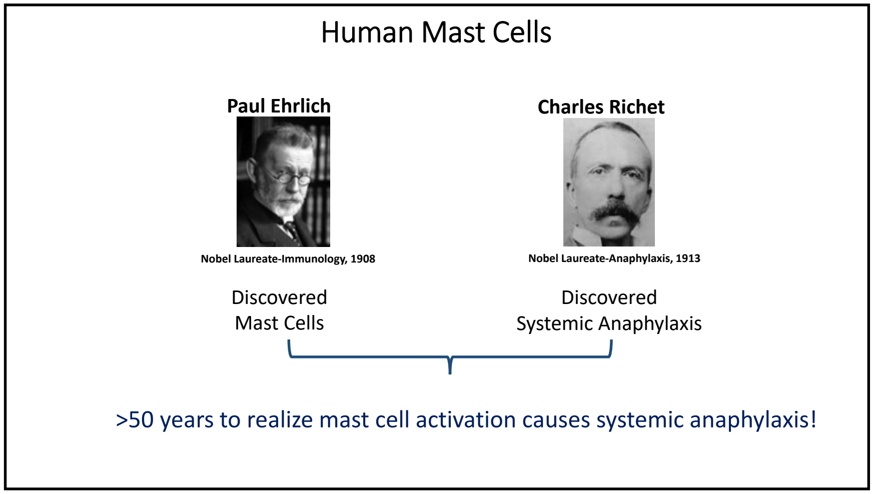
Disclosure Slide: Lawrence B. Schwartz, MD, PhD

Employment
- VCU/VCUHS

Research Grants
- NIH
- Novartis, GSK, Merck, Dyax-Shire-Takeda, CSL Behring, Deciphera, Blueprint

Consulting
- Genentech, Deciphera, Dyax-Shire-Takeda, CSL Behring, Deciphera, Blueprint, Allakos, Astra-Zeneca, GLG, Celldex

Other Financial Interests
- VCU Royalties/Licensing Fees:
  ThermoFisher-Phadia (tryptase test);
  Millipore, Santa Cruz, BioLegend, Hycult Biotech (mAbs);
  Genentech (tryptase inhibitor)
- Up-To-Date Card (royalties)
- Cecil's Textbook of Medicine Anaphylaxis chapter (royalties)
- NIH Study Section (honoraria)



Human Mast Cells

Paul Ehrlich

Nobel Laureate-Immunology, 1908

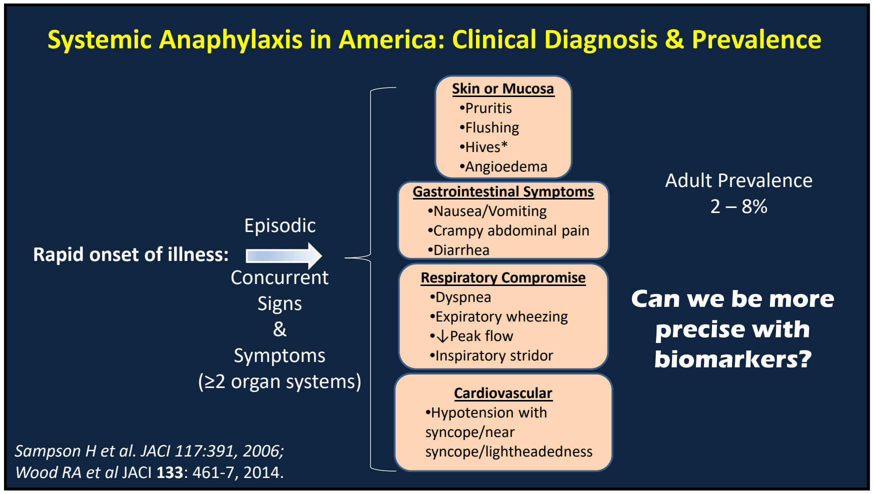
Discovered
Mast Cells

Charles Richet

Nobel Laureate-Anaphylaxis, 1913

Discovered
Systemic Anaphylaxis

>50 years to realize mast cell activation causes systemic anaphylaxis!



Systemic Anaphylaxis in America: Clinical Diagnosis & Prevalence

Rapid onset of illness: Episodic → Concurrent Signs & Symptoms (≥2 organ systems)

Skin or Mucosa
- Pruritis
- Flushing
- Hives*
- Angioedema

Gastrointestinal Symptoms
- Nausea/Vomiting
- Crampy abdominal pain
- Diarrhea

Respiratory Compromise
- Dyspnea
- Expiratory wheezing
- ↓Peak flow
- Inspiratory stridor

Cardiovascular
- Hypotension with syncope/near syncope/lightheadedness

Adult Prevalence
2 – 8%

Can we be more precise with biomarkers?

Sampson H et al. JACI 117:391, 2006;
Wood RA et al JACI **133**: 461-7, 2014.

Differential Diagnosis of Allergen:IgE:FcεRI-mediated Systemic Anaphylaxis

Pulmonary/Cardiogenic disorders

Vasovagal

Flushing disorders (benign, carcinoid syndrome, neuroendocrine tumors)

Panic attacks, Vocal cord dysfunction

Hereditary/Acquired Angioedema (bradykinin)

Complement activation (C3a, C5a)

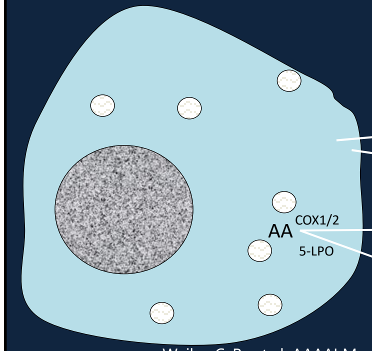
Scombroidosis (ingested histamine)

Other shock syndromes (septic, toxins, …)

Underlying 1° MCAS: mastocytosis/hereditary α-tryptasemia/idiopathic

Can we be more precise with biomarkers?

Commercially-Available Biomarkers Secreted in Response to Mast Cell Activation



Mature Tryptase

Histamine - - - - → N-Methylhistamine

AA $\xrightarrow{\text{COX1/2}}$ PGD2 - - - - → (±2,3-dinor-)11β-PGF2α

AA $\xrightarrow{\text{5-LPO}}$ LTC4 - - - - → LTE4

Weiler, C. R., et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management. J Allergy Clin Immunol 144(4): 883-896, 2019.

Commercial Biomarkers for Mast Cell Activation: *Cell Sources*

PREFORMED

NEWLY-GENERATED

Tryptase	Histamine → (N-methylhistamine)	PGD_2→11β-$PGF_{2\alpha}$	LTC_4→LTE_4
	Stored/Secreted (HDC)	H-PGDS	**LTC Synthase**
Mast cells >Basophils	**Mast cells** ≈Basophils	**Mast cells**	**Mast cells** Basophils

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Commercial Biomarkers for Mast Cell Activation: *Cell Sources*

PREFORMED

NEWLY-GENERATED

Tryptase Histamine → (N-methylhistamine) PGD_2→11β-$PGF_{2\alpha}$ LTC_4→LTE_4

Cell source

Time course for secretion and removal/metabolism

Acute vs Baseline

Migration from tissue into blood

Plasma vs serum vs urine

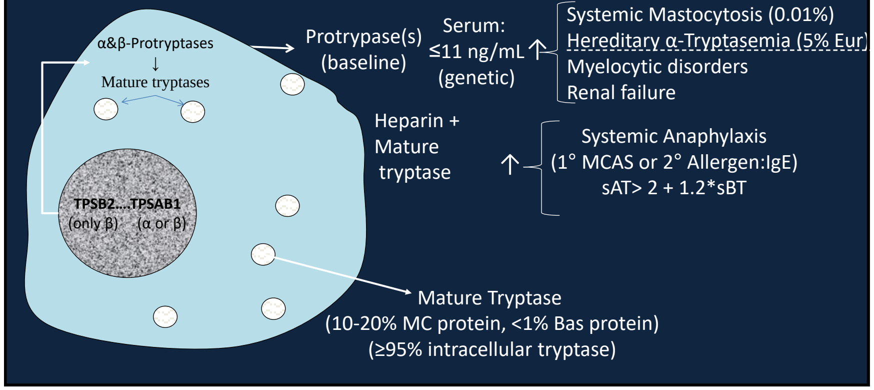
Pharmacologic interference

Sensitivity/Specificity/predictive value

Typical Laboratory Work-up of MCA Patient at VCU

1. Acute (1-2(4)h after onset) & baseline (before or >24h after MCA) serum tryptase levels
2. 24-hour or spot urinary 9α,11β-PGF_2, LTE_4 and N-methylhistamine/creatinine (?acute vs baseline).
3. ±D816V c-Kit: high-sensitivity, allele-specific PCR of gDNA from peripheral blood.
4. ± TPSAB1 CNV genetic test for hereditary α-Tryptasemia (GeneByGene, $169).
5. ± Further work-up for systemic mastocytosis or hereditary alpha-tryptasemia as clinically appropriate.
6. ± Hymenoptera venom IgE panel

α/β-Tryptase Secretion:
Unstimulated and Stimulated Mast Cells



α&β-Protryptases

↓

Mature tryptases

TPSB2....TPSAB1

(only β) (α or β)

Protrypase(s)
(baseline)

Serum:
≤11 ng/mL ↑
(genetic)

Systemic Mastocytosis (0.01%)
Hereditary α-Tryptasemia (5% Eur)
Myelocytic disorders
Renal failure

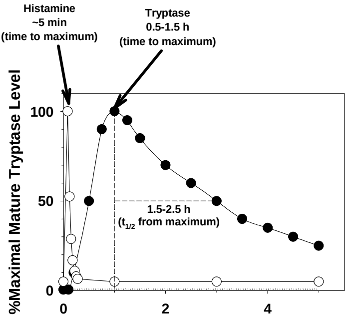
Heparin +
Mature
tryptase

↑

Systemic Anaphylaxis
(1° MCAS or 2° Allergen:IgE)
sAT> 2 + 1.2*sBT

Mature Tryptase
(10-20% MC protein, <1% Bas protein)
(≥95% intracellular tryptase)

Mature Tryptase & Histamine Levels in Plasma During Insect Sting-Induced Systemic Anaphylaxis~Clinical Severity



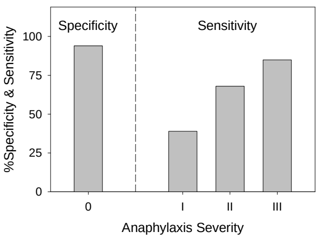
Peak Tryptase ~ hypotension~clinical severity
≠angioedema, respiratory, or GI involvement.

Peak tryptase:
Parenteral > Oral (food) triggers.

Peanut oral challenge-triggered anaphylaxis:
highest sAT ~ 2h (57%), 1h (7%)

J Clin Invest 83:1551, 1989

So what is cute over baseline nificant?



Overall Non-Mastocytosis PV
53% NPV
98% PPV

*Valent et al. Int Arch Allergy Immunol **157**:215-25, 2012: European Competency Network on Mastocytosis (ECNM)*

Emergency Department SA in children

De Schryver et al. J Allergy Clin Imm 137:1138-42, 2016
(<u>81% food</u> (TN>PN>milk)>?>venom>drug>other)

≥2 organ systems (CV, Respiratory, GI, skin/mucosa)
&/or
↓BP with likely allergen exposure

Compared [sAT>1.2xsBT +2] <u>vs</u> [sAT>11.4]

Sensitivity:
Algorithm > 11.4 cut-off
Severe (86%) > Mild-Moderate SA.

Perioperative SA

Baretto RL et al. Allergy 72:2031-4, 2017

Sensitivity	78%
Specificity	91%
PPV	98%
NPV	44%

---

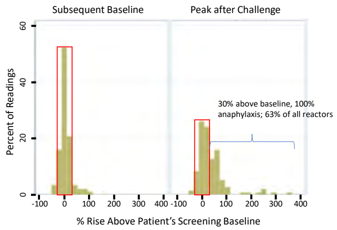
4 of 14 patients with severe anaphylaxis had acute tryptase >11.4 ng/mL and was severe

Patient	Baseline Tryptase	Acute Tryptase	1.2*sBT + 2
1	4.5	12.2	7.4
2	6	17	9.2
3	4	13	6.8
4	3	12	5.6

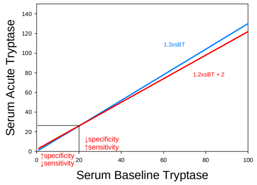
Acute collected 1 & 2 h after reaction onset;

>11.2: 4 of 14 anaphylaxis, 0 of 146 non-SA signs/symptoms; 0 of 45 non-reactors;

Peak tryptase 2 h >1 h post challenge.



Comparison of 30% above baseline
to 2 + 20% above baseline



The Tryptase Algorithm for Systemic Anaphylaxis

acute > [2 + (1.2 x baseline)]

1. High specificity
2. Sensitivity ~ clinical severity (↓BP) & collection timing

   Acute samples obtained 30 min - 4 hour after clinical onset, 1-2 hours best; sensitivity diminishes over time

   Some triggers, like foods, raise serum tryptase levels less than other triggers, like insect stings
3. sAT collection tips:

   Prescription or future order

   Order BMP; then call lab to add tryptase

   Retrieve plasma/serum drawn in ED

Why is the tryptase elevation lower for food vs insect sting triggered anaphylaxis of comparable severities?

The answer is not known, but could involve:

- Site of mast cell activation: mucosal vs vascular

  Tryptase levels in mucosal MCs are lower than in the skin or perivascular sites.

  Tryptase may diffuse into the circulation more efficiently from vascular than mucosal si
- Basophil activation may be more prominent?
- Activation of other cell types, such as monocytes/macrophages may occur?
- Secretion of PAF or other newly-generated mediators > degranulation?

Case 1

56 y/o stung by an insect, underlying HBP (HCTZ, lisinopril), c/o dizziness, dyspnea and chest pain. ER: hypotensive
Insect venoms, drugs, foods, radiocontrast dyes, latex: most common allergen triggers of SA.

Acute:
- EKG: Inferior MI
- Troponin: elevated
- Tryptase =15 ng/ml

Baseline (1 month later):
- Tryptase =4 (15 > 2+1.2x4=6.8)
- venom IgE skin test: positive

Systemic anaphylaxis to venom, which precipitated the MI.
Begin venom immunotherapy (↓risk of SA after future stings >95%)

Case 2

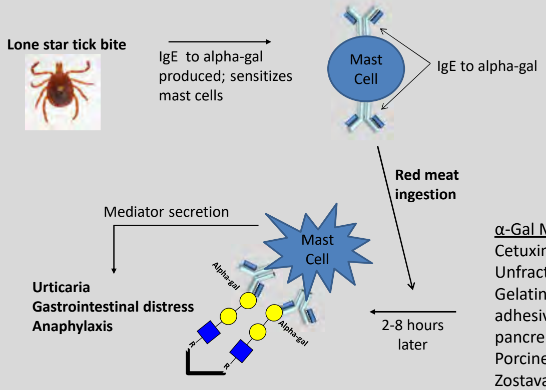
50 y/o awoke at 3 AM after asleep at 11 PM, covered with pruritic hives who passed out while walking to the bathroom. Spouse called EMT, BP(P) 80/-(125); IV fluids and epinephrine; to ED where BP & P normalized. Enjoys hiking, prior tick bites and earlier that evening enjoyed a steak dinner.

Acute tryptase = 13

1 month later…
- Baseline tryptase = 5
- IgE ImmunoCAP positive to beef and alpha-Gal (Gal α1,3 Gal)

~Delayed anaphylaxis (3-7 hours) to alpha-Gal after eating red meats.

Delayed Anaphylaxis to Red Meats



Lone star tick bite

IgE to alpha-gal produced; sensitizes mast cells

IgE to alpha-gal

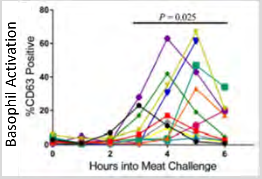
Red meat ingestion

2-8 hours later

Mediator secretion

Urticaria
Gastrointestinal distress
Anaphylaxis

Time after Meat Ingestion



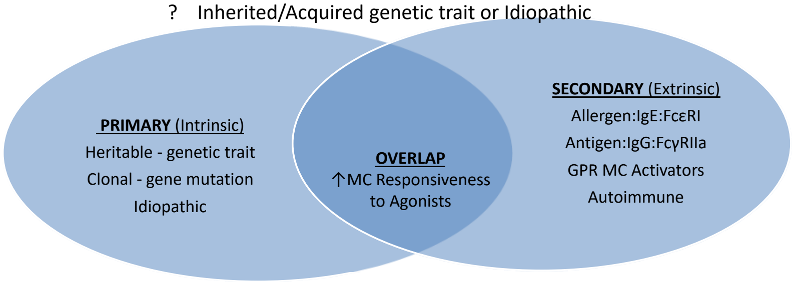
Commins et al. JACI 134:108-15, 2014

<u>α-Gal Medications</u> (immediate reactions)
Cetuximab
Unfractionated heparin
Gelatin (wound dressing, plasma expander, adhesives, absorbent pads, vaginal capsules, pancrelipase)
Porcine heart valve
Zostavax, Yellow Fever, MMR, rabies vaccines

Diagnosing Mast Cell Activation Syndrome

1. Clinical presentation of episodic <u>systemic</u> anaphylaxis events
2. Elevated acute MC biomarker(s)
3. Response to anti-MC mediator/activation therapies

? Inherited/Acquired genetic trait or Idiopathic



PRIMARY (Intrinsic)
Heritable - genetic trait
Clonal - gene mutation
Idiopathic

OVERLAP
↑MC Responsiveness to Agonists

SECONDARY (Extrinsic)
Allergen:IgE:FcεRI
Antigen:IgG:FcγRIIa
GPR MC Activators
Autoimmune

Weiler, C. R., et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management. J Allergy Clin Immunol 144(4): 883-896, 2019.

MCAS is NOT an Epidemic, more likely an Epiphenomenon

1. **Symptom Creep**: Fatigue, Fibromyalgia-like Pain, Dermographism, Tired Appearance, Chronically Ill Appearance, Edema, GERD, HBP, Drug Reactions, Abdominal Pain

2. **Unvalidated tests**
   chromogranin A: not produced by mast cells (*Hanjra P et al. JACI Pract 6:687-9, 2018), elevated with blockers of gastric acid production*

   Heparin: plasma pre<post venous occlusion min; no convincing evidence this stimulates MC activation or discriminates MCAS from either mastocytosis or healthy controls

Weiler, C. R., et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management. J Allergy Clin Immunol **144**(4): 883-896, 2019.

Case 3

25 y/o WF frequent ↓BP, ↑P, lightheaded spells; POTS dx; EDS (joint hyperextensibility) dx; ±(flushing or GI or dyspnea); negative FH of POTS or EDS.

Baseline: Tryptase = 4 ng/ml
Acute (<3 h after onset): Tryptase = 4 & 5 ng/ml (<6.5)
Baseline 24 h urine 11β-PGF$_{2\alpha}$, N-methylhistamine, LTE$_4$ = each wnl

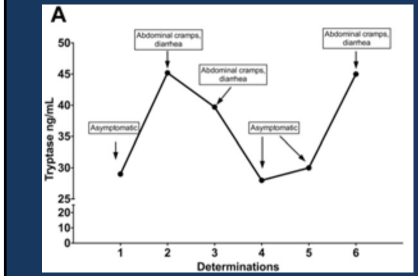
Acute tryptase < 6.8 (2 + 1.2x4); baseline <7 (current lower limit for α-tryptasemia)

Autonomic dysfunction, not MCA, ~ hypotensive/tachycardic episodes. Lack of a rise in sAT & other MCA biomarkers rule out hypotension due to anaphylaxis for that episode.

Case 4

Adult F: recurrent episodes diarrhea & abdominal cramps. Similar symptoms in 3|6 sibs. GI studies & bx wnl.

Acute tryptase levels 40-45, baseline levels 25-30, c/w mast cell activation.



Sabato et al. JACI 134:1448 (2014),
J Clin Immunol 38:457 (2018)

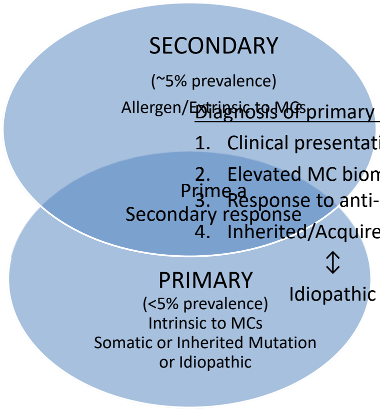
↑sBT and autosomal dominant inheritance.

MCAS; Hereditary Alpha-Tryptasemia
~ ↑*TPSAB1* ααααα(F)/α(M)

Concluding Comments

1. Tryptase appears to be the most specific marker for MCA, while metabolites of histamine, PGD2 or LTC4 may be more sensitive under certain scenarios, and can identify pharmaceutical targets of clinical benefit regardless whether mast cells are their source.
2. The acute tryptase levels must be compared to the baseline level to be informative, and the sensitivity varies with clinical severity, time of collection and type of trigger.
3. Mast cell activation syndrome when spontaneous episodes of anaphylaxis occur with discrete episodes of concurrent symptoms in at least two organ systems (skin, GI, pulmonary, cardiovascular), elevated biomarkers for mast cell activation, and response to pharmaceutical inhibition of mast cell mediators and/or mast cells are observed, and is more commonly seen with activating Kit mutations and possibly with various inherited genetic traits, including hereditary alpha-tryptasemia. Mast cell activation in a single organ system, such as skin with chronic urticaria or lungs with asthma, is not defined as a mast cell activation syndrome.

2° vs 1° Mast Cell Activation



SECONDARY

(~5% prevalence)

Allergen/Extrinsic to MCs

Prime a
Secondary response

PRIMARY
(<5% prevalence)
Intrinsic to MCs
Somatic or Inherited Mutation
or Idiopathic

<u>Diagnosis of primary Mast Cell Activation Syndrome</u>

1. Clinical presentation of <u>systemic</u> anaphylaxis
2. Elevated MC biomarker(s)
3. Response to anti-mediator/MC therapies
4. Inherited/Acquired genetic mutation

↕

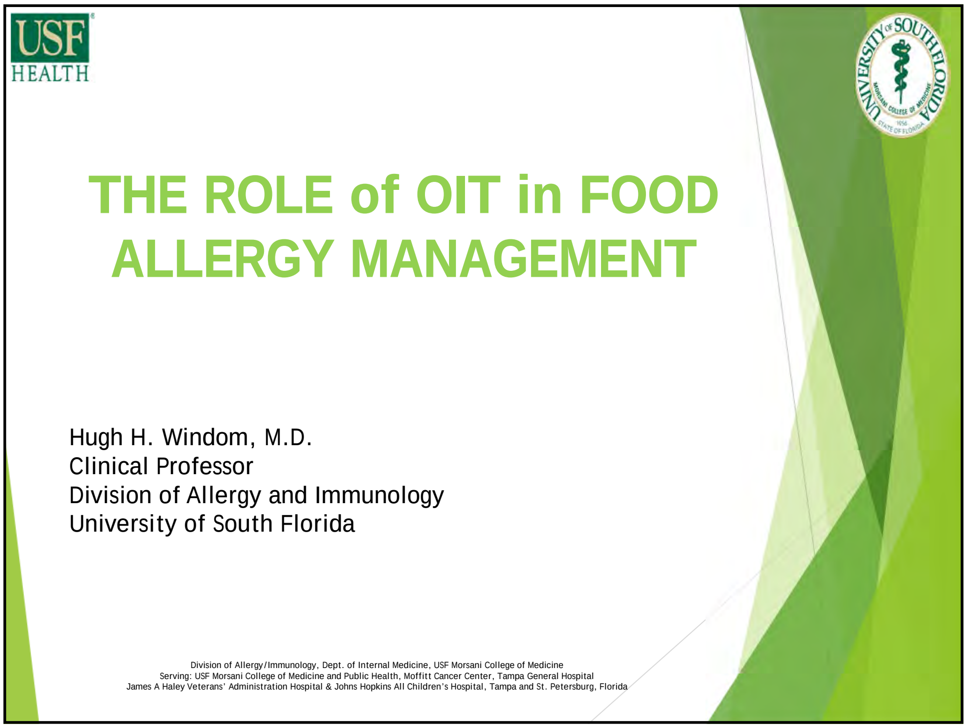
Idiopathic

Pennsylvania Allergy & Asthma Association

The Role of OIT in Food Allergy Management

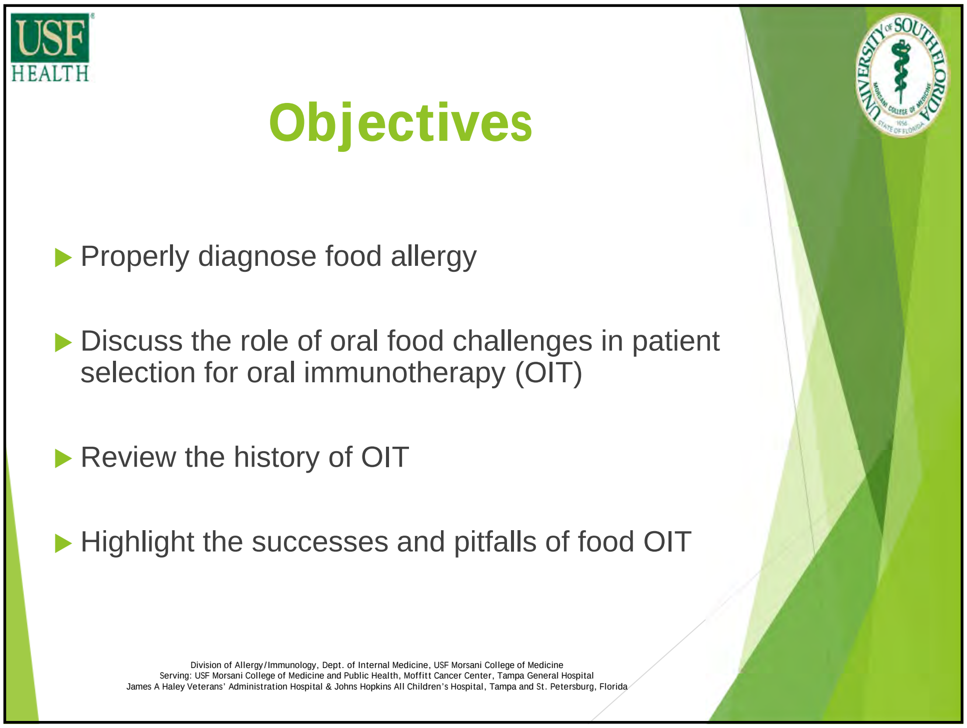
Hugh H. Windom, MD

Saturday, June 26, 2021
12:15 p.m. - 1:00 p.m.



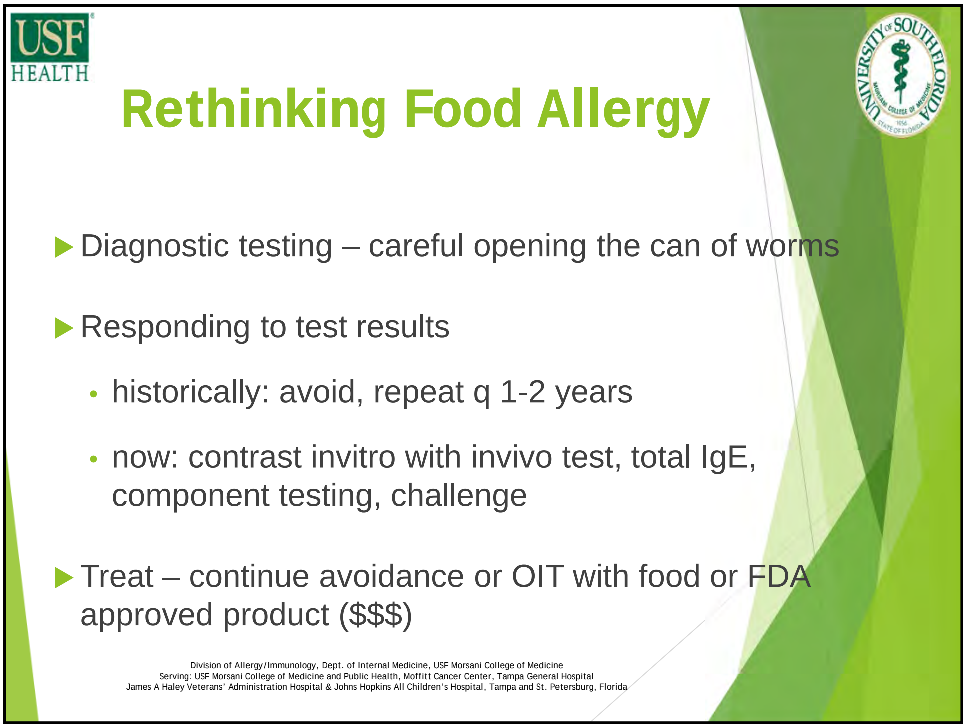
THE ROLE of OIT in FOOD ALLERGY MANAGEMENT

Hugh H. Windom, M.D.
Clinical Professor
Division of Allergy and Immunology
University of South Florida



Objectives

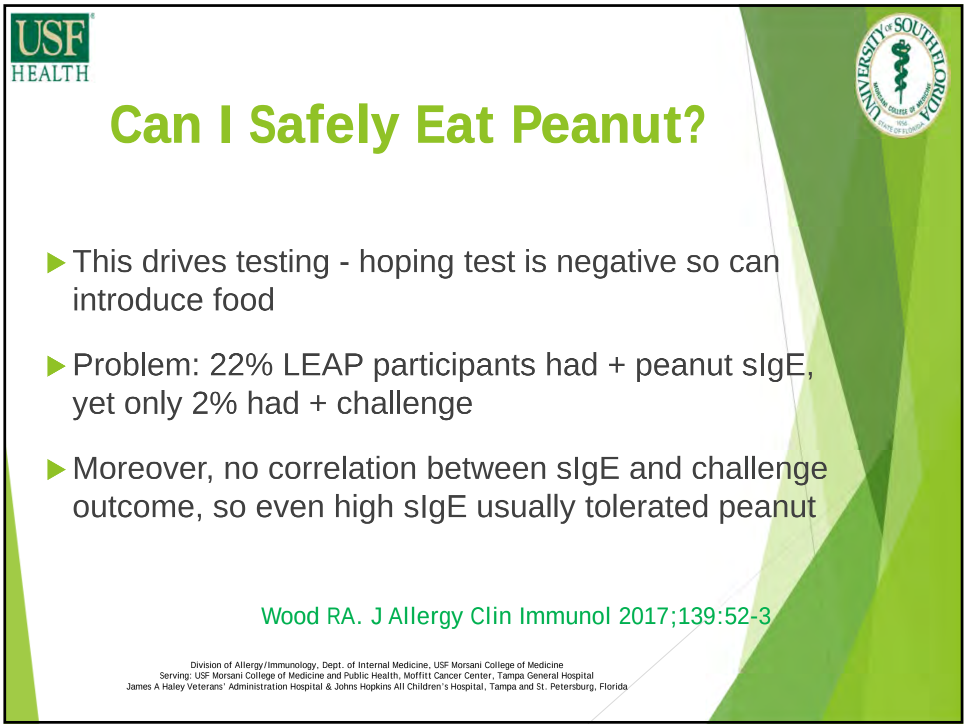
- Properly diagnose food allergy
- Discuss the role of oral food challenges in patient selection for oral immunotherapy (OIT)
- Review the history of OIT
- Highlight the successes and pitfalls of food OIT



Rethinking Food Allergy

- Diagnostic testing – careful opening the can of worms
- Responding to test results
  - historically: avoid, repeat q 1-2 years
  - now: contrast invitro with invivo test, total IgE, component testing, challenge
- Treat – continue avoidance or OIT with food or FDA approved product ($$$)

Division of Allergy/Immunology, Dept. of Internal Medicine, USF Morsani College of Medicine
Serving: USF Morsani College of Medicine and Public Health, Moffitt Cancer Center, Tampa General Hospital
James A Haley Veterans' Administration Hospital & Johns Hopkins All Children's Hospital, Tampa and St. Petersburg, Florida

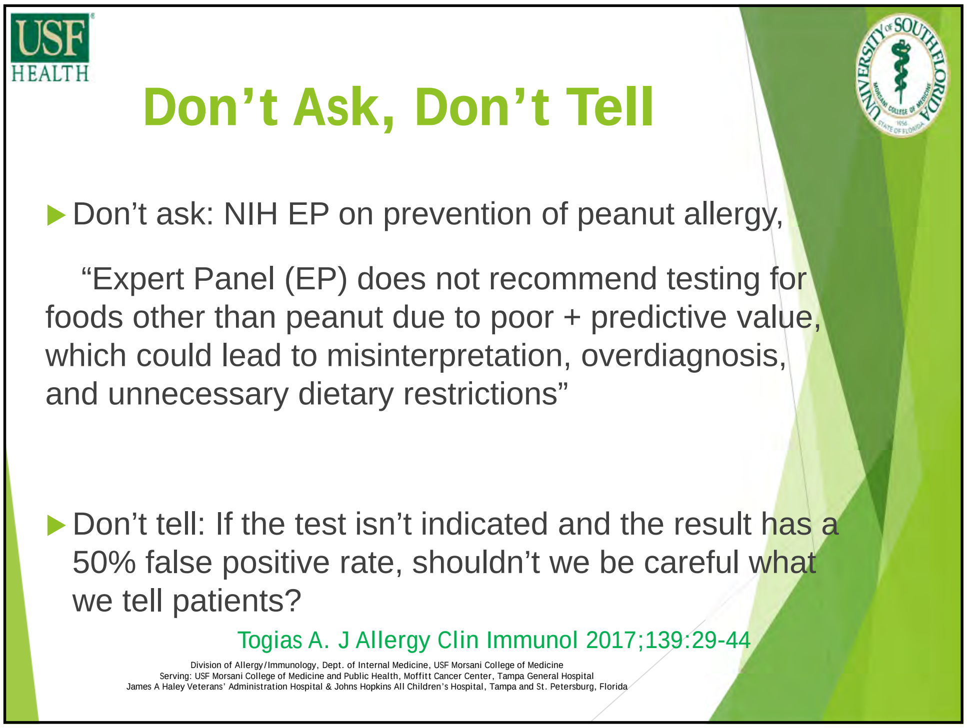


Can I Safely Eat Peanut?

- This drives testing - hoping test is negative so can introduce food
- Problem: 22% LEAP participants had + peanut sIgE, yet only 2% had + challenge
- Moreover, no correlation between sIgE and challenge outcome, so even high sIgE usually tolerated peanut

Wood RA. J Allergy Clin Immunol 2017;139:52-3

Division of Allergy/Immunology, Dept. of Internal Medicine, USF Morsani College of Medicine
Serving: USF Morsani College of Medicine and Public Health, Moffitt Cancer Center, Tampa General Hospital
James A Haley Veterans' Administration Hospital & Johns Hopkins All Children's Hospital, Tampa and St. Petersburg, Florida



USF HEALTH

Don’t Ask, Don’t Tell

- Don’t ask: NIH EP on prevention of peanut allergy,

“Expert Panel (EP) does not recommend testing for foods other than peanut due to poor + predictive value, which could lead to misinterpretation, overdiagnosis, and unnecessary dietary restrictions”

- Don’t tell: If the test isn’t indicated and the result has a 50% false positive rate, shouldn’t we be careful what we tell patients?

Togias A. J Allergy Clin Immunol 2017;139:29-44

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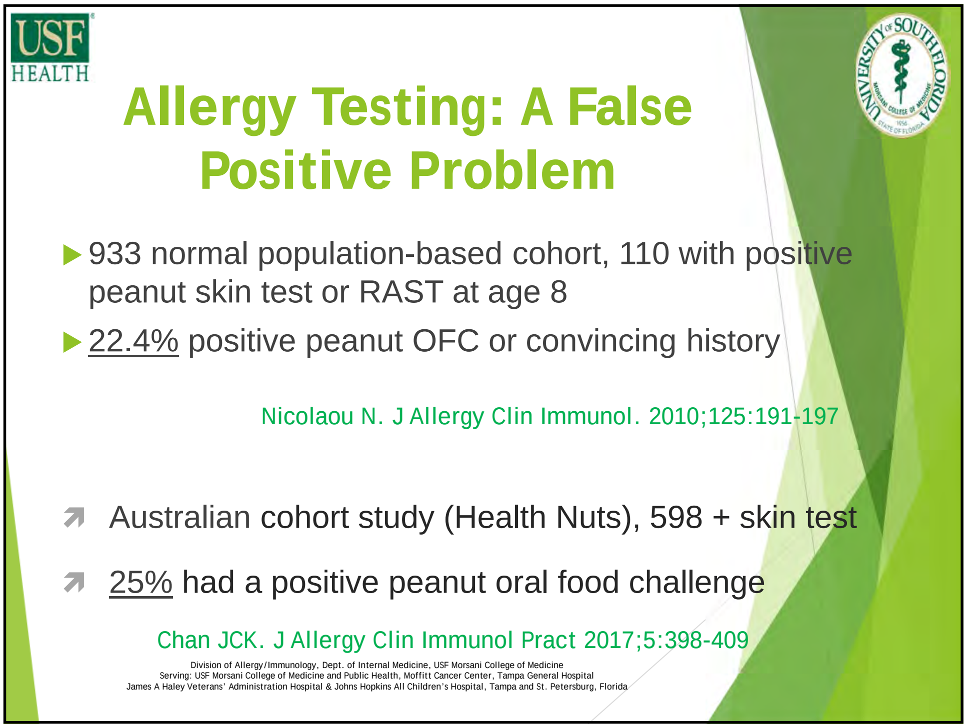

USF HEALTH

Allergy Testing: A False Positive Problem

- 933 normal population-based cohort, 110 with positive peanut skin test or RAST at age 8
- 22.4% positive peanut OFC or convincing history

Nicolaou N. J Allergy Clin Immunol. 2010;125:191-197

- Australian cohort study (Health Nuts), 598 + skin test
- 25% had a positive peanut oral food challenge

Chan JCK. J Allergy Clin Immunol Pract 2017;5:398-409

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Food Allergy: A Man-Made Disease

- Decades of telling atopic families to withhold highly allergenic foods early in life (LEAP study 2015)
- Over-diagnosis of food allergy leading to withholding of foods early in life
- Passivity of allergists in managing food allergy allowing unchecked hysteria in home and school

DuToit G. N Engl J Med 2015;372:803-13

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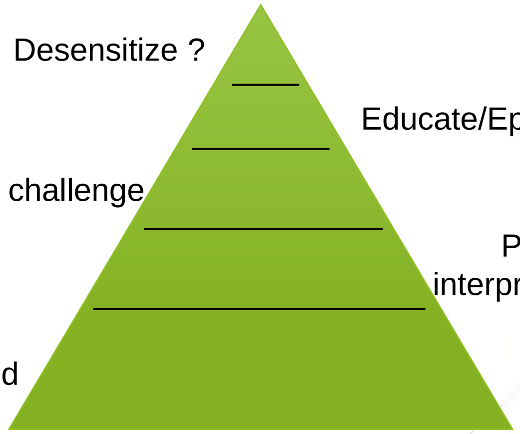
Breakdown of 'Food Allergy'



Desensitize ?

Educate/Epi

Oral food challenge

Properly interpreted testing

Suspected

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Be Confident When Negative

- 5,300 Aussie infant peanut study
- No infant with a negative skin test (n=226) or unmeasurable sIgE (n=162) had a + OFC
- These infants can introduce peanut at home, with exception of a strong history of reacting to peanut

Koplin JJ. J Allergy Clin Immunol 2016; 138:1131-41

Will I Die From Food Allergy?

Annual incidence of fatal anaphylaxis in food allergic people

- ER attendance due to injury…………..……… 1 in 10
- Death from any cause…………………..……..1 in 100
- Death due to accident……………......……1 in 5000
- Death due to murder…………………..……1 in 100,000
- Death due to food anaphylaxis...1 in 0.5-1,000,000
- Death due to lightning……………..……1 in 8,000,000

Turner PJ. J Allergy Clin Immunol Pract 2017;5:1169-78

Oral Food Challenge (OFC)

- Introduced into clinical practice 1976 (May CD. J Allergy Clin Immunol 1976;58:500-15)
- Serial increasing ‘doses’ of food
- Useful when
  - suspicion of sensitivity is low
  - desire to eat food is high
  - family anxiety is high
- Allergy tests are not an absolute indication or contraindication
- 2-3% anaphylaxis rate, one death 2016

OFC – Dosing Interval

- Q 20-30 minute is standard dosing interval
- German study of 67 peanut OFC’s q 2 hour dosing, median sIgE 74 and araH2 45
- 63 pts. reacted, 3 at the 1st dose of 3 mg peanut protein
- Median time to 1st objective symptom – 55 minutes

Blumchen K. J Allergy Clin Immunol 2014;134:390-8

Predictors of + OFC

- 572 food OFC's in children from 2009-13
- Allergen specific IgE / total IgE ('Ratio') correlated with outcome of OFC: higher Ratio more likely + OFC
- Ratio outperformed sIgE in predicting + OFC
- Finding c/w observation that atopics with high total IgE have background noise raising sIgE

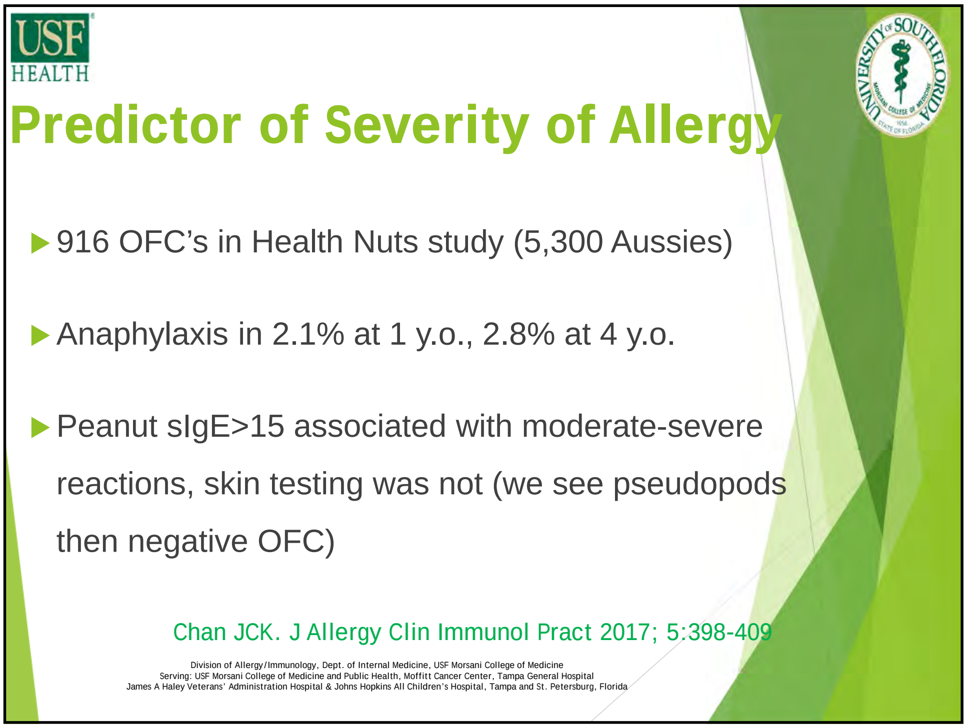
Gupta RS. J Allergy Clin Immunol Pract 2014; 2:300-5

Age as Predictor of Sensitivity

- Cumulative dose of peanut in 3 age groups:

Age group (yrs)	Peanut (median, mg)	n
< 5	790 (716-864)	29
5 – 10	310 (160-460)	61
> 10	70 (40-100)	36

van der Zee. J Allergy Clin Immunol 2011; 128:1031-6



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Predictor of Severity of Allergy

- 916 OFC's in Health Nuts study (5,300 Aussies)
- Anaphylaxis in 2.1% at 1 y.o., 2.8% at 4 y.o.
- Peanut sIgE>15 associated with moderate-severe reactions, skin testing was not (we see pseudopods then negative OFC)

Chan JCK. J Allergy Clin Immunol Pract 2017; 5:398-409

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Treating Food Allergy is not New

- 500 AD - the ancient Babylonian Talmud has instructions for treating egg sensitivity with egg white
- 1905 - Finkelstein successfully desensitizes nurslings with "milk idiosyncrasy" by gradually administering increasing drops of milk
- 1990's – subcutaneous therapy, National Jewish event
- 2004 – clinical OIT in US offices
- 2014 – FAST formed, >300 US/Canadian allergy providers sharing OIT experiences (www.foodOIT.org)
- 2021 meeting attendees have treated >8,000 patients

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OIT All Over the World

- Outcome of oral immunotherapy for persistent cow's milk allergy from 11 years of experience in Finland
  - Kaupila TK. Pediatr Allergy Immunol 2019:1-7
- Successful oral desensitization in children with cow's milk anaphylaxis: Clinical and laboratory evaluation up to nine-years follow-up
  - Alves-Correia M. Allergol Immunopathol 2019;47:133-40
- Oral Immunotherapy for Hazelnut Allergy: A single-center retrospective study on 100 patients
  - Moraly T. J Allergy Clin Immunol Pract 2020;8:704-9

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A Precursor to OIT

- 75% of milk allergic kids tolerate high heat milk products, casein heat stable, whey is not
- 88 milk allergic kids followed with interval OFC's
- Heated milk tolerant kids 28x more likely to become tolerant to unheated milk over 5 years
- Eating heated milk accelerates milk tolerance
- Casein IgG$_4$ increased over 5 yrs in heated milk tolerant kids

Kim JS. J Allergy Clin Immunol 2011; 128:125-31

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Baked Egg, Same Story

- Australian Health Nuts cohort, n = 5,270
- 186 with positive egg OFC were challenged with baked egg food
- Only 15% reacted positively to baked egg
- Eating heated egg foods accelerates egg tolerance

Chan JCK. J Allergy Clin Immunol Pract 2017; 5:398-409

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Milk/Egg Allergy Management

	Under 6 years old	**6 and older**
Low level suspicion	OFC whole food	OFC whole food
Moderate level suspicion	Muffin challenge*	OFC whole food
Strong history and tests	Muffin challenge**	Oral immunotherapy

* milk casein <1, can introduce muffins at home (96% negative muffin OFC)
**~~milk casein >20~~ recent baked reaction, go directly to OIT

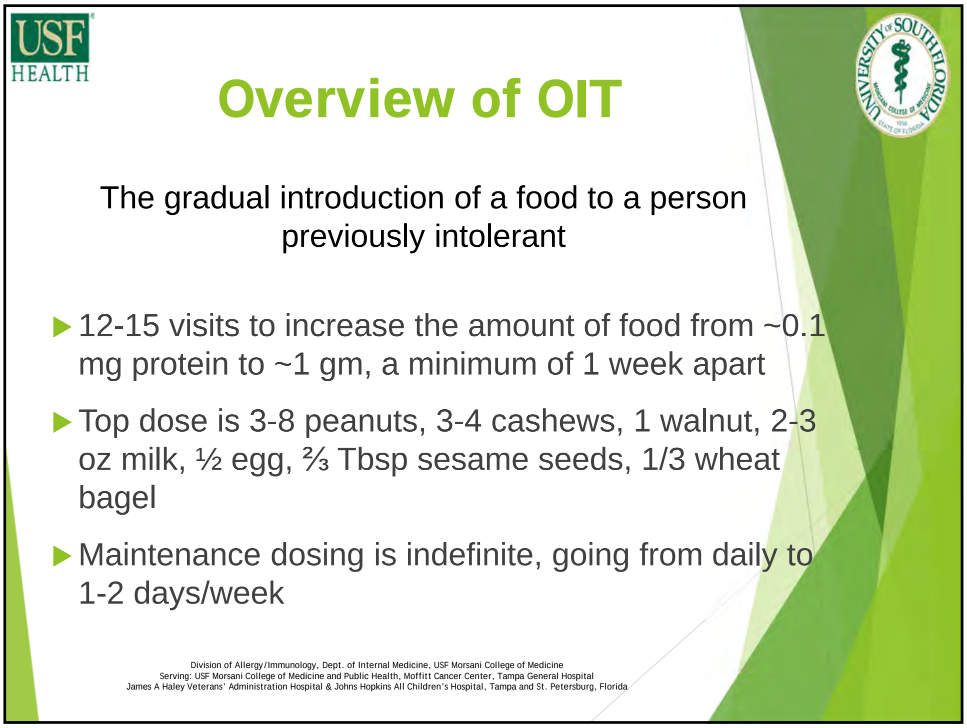
Introduction of Baked Milk

- 41 patients, 3 -18 yo, milk sIgE > 5 LU/L, + history
- 11 of 41 (27%) passed baked milk (BM) challenge
- 18 of 30 (60%) + OFC treated with epi
- No predictors of BM tolerance, median casein IgE in these patients was 22.7 KU/L

Dantzer JA. J Allergy Clin Immunol 2020;146:1434-37

Why Consider OIT

- Only current therapy is avoidance and carry epinephrine
- Accidents happen: 40% of food allergic 6 yo's had a reaction in prior 12 months (Wang Y. JACI Pract 2020;8:3515-24)
- Avoidance diets are burdensome
- Anxiety over accidental exposure
- OIT shown effective in hundreds of studies and tens of thousands of clinical patient experiences worldwide



Overview of OIT

The gradual introduction of a food to a person previously intolerant

- 12-15 visits to increase the amount of food from ~0.1 mg protein to ~1 gm, a minimum of 1 week apart
- Top dose is 3-8 peanuts, 3-4 cashews, 1 walnut, 2-3 oz milk, ½ egg, ⅔ Tbsp sesame seeds, 1/3 wheat bagel
- Maintenance dosing is indefinite, going from daily to 1-2 days/week

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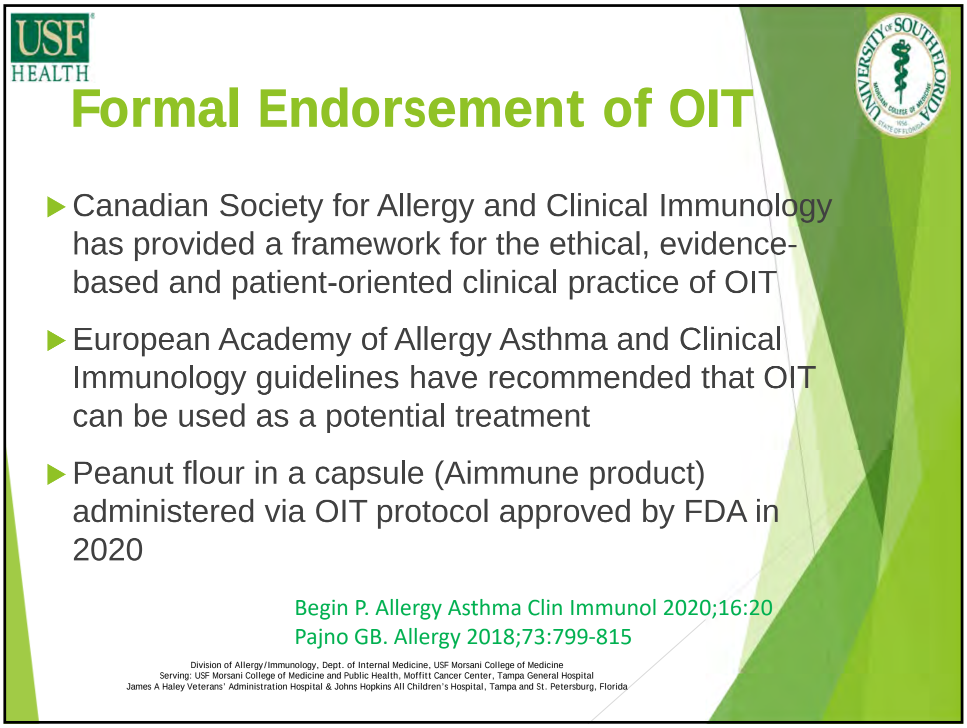

Formal Endorsement of OIT

- Canadian Society for Allergy and Clinical Immunology has provided a framework for the ethical, evidence-based and patient-oriented clinical practice of OIT
- European Academy of Allergy Asthma and Clinical Immunology guidelines have recommended that OIT can be used as a potential treatment
- Peanut flour in a capsule (Aimmune product) administered via OIT protocol approved by FDA in 2020

Begin P. Allergy Asthma Clin Immunol 2020;16:20
Pajno GB. Allergy 2018;73:799-815

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When is the Ideal Time for Peanut OIT

- A life-long allergy for 80% of patients
- Peanut specific IgE increases over 1st 5 years of life[1]
- Since a lower baseline sIgE is associated with greater likelihood of developing tolerance with OIT…

should we routinely be starting OIT early in life?

[1]Neuman-Sunshine DL. Am Allergy Asthma Immunol 2012;108:326-31

Early Age Peanut OIT

- N = 37, 9-36 month olds with + OFC to peanut
- 1:1 randomization to OIT reaching 300 vs 3,000 mg peanut protein (PP)
- OIT stopped at 36 months or as early as 12 months if sIgE<15, SPT<8 mm and no reactions to dosing
- DBOFC to 5 gm PP when stopped and 4 wks later

Vickery BP. J Allergy Clin Immunol 2017;139:173-81

USF HEALTH

Early Age Peanut OIT

- 5/37 dropped, 2 non-adherence, 3 adverse events (2 GI, 1 went on to EGD having 30 eos's)
- Remainder treated for 12-36 months, all high dose group passed exit OFC, 17/19 low dose passed
- All but one passing exit OFC passed 4-week OFC (sustained unresponsiveness - SU)
- The 8/37 failing to reach SU had higher sIgE and sIgE/IgE
- Epi given once, at home

Vickery BP. J Allergy Clin Immunol 2017;139:173-81

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Preschool Age Peanut OIT

- Canadian study of 270 kids, 9 – 71 months old
- Positive peanut history or food challenge, 6% never-eaten had median sIgE 19
- 243 reached 300 mg peanut protein – 90%
- Epinephrine used in 4.1%

Soller L. J Allergy Clin Immunol Pract 2019;7:2759-67

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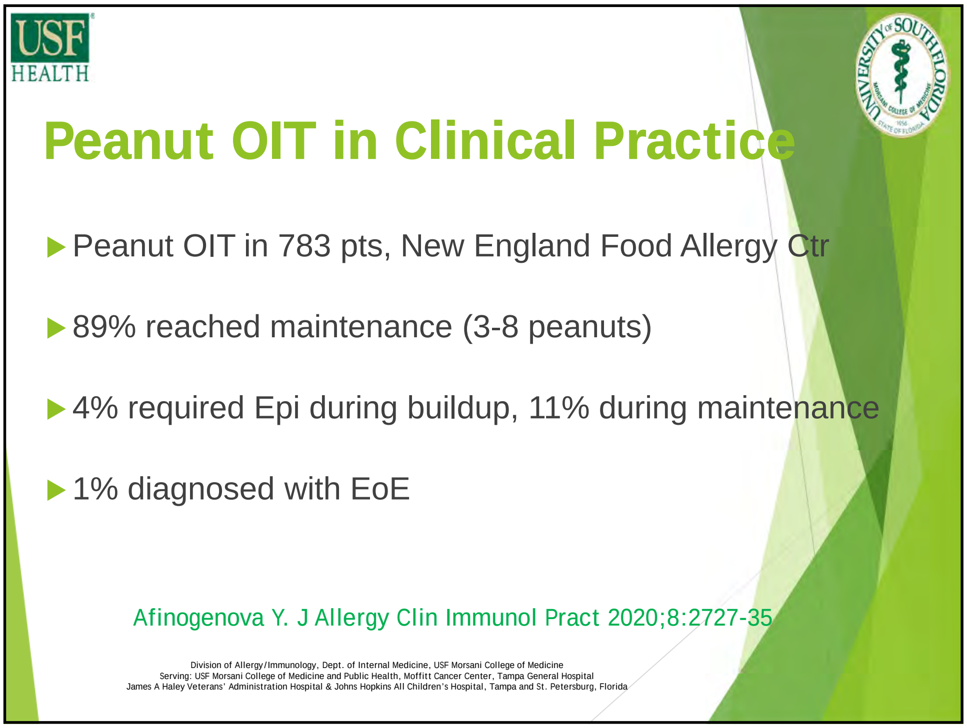

Peanut OIT in Clinical Practice

- Peanut OIT in 783 pts, New England Food Allergy Ctr
- 89% reached maintenance (3-8 peanuts)
- 4% required Epi during buildup, 11% during maintenance
- 1% diagnosed with EoE

Afinogenova Y. J Allergy Clin Immunol Pract 2020;8:2727-35

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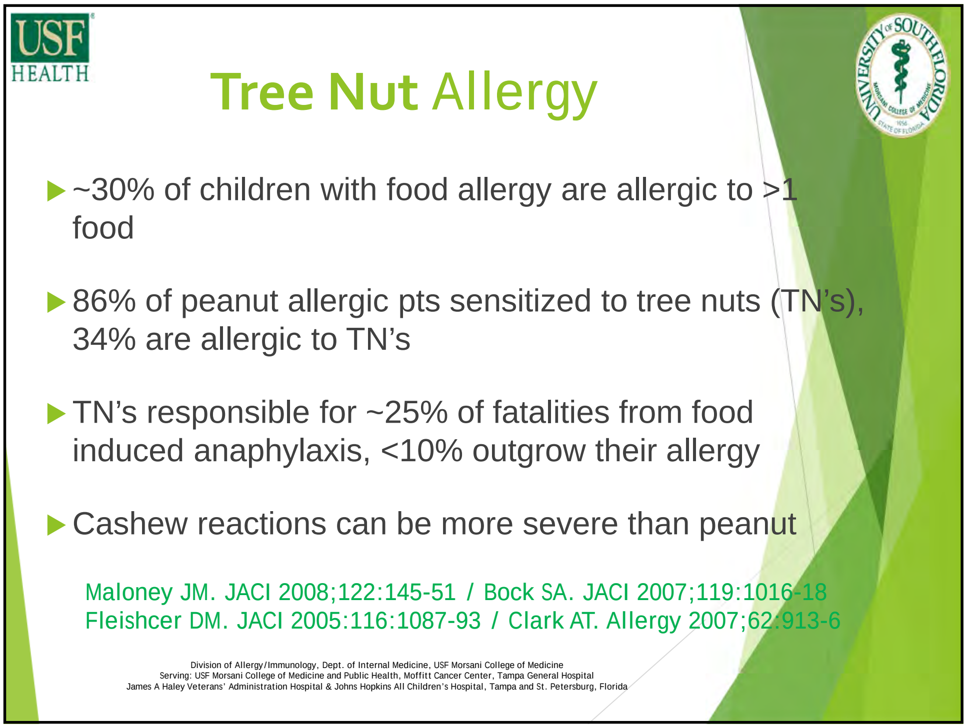

Tree Nut Allergy

- ~30% of children with food allergy are allergic to >1 food
- 86% of peanut allergic pts sensitized to tree nuts (TN's), 34% are allergic to TN's
- TN's responsible for ~25% of fatalities from food induced anaphylaxis, <10% outgrow their allergy
- Cashew reactions can be more severe than peanut

Maloney JM. JACI 2008;122:145-51 / Bock SA. JACI 2007;119:1016-18
Fleishcer DM. JACI 2005:116:1087-93 / Clark AT. Allergy 2007;62:913-6

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Walnut and Cashew Are Dominant Nuts

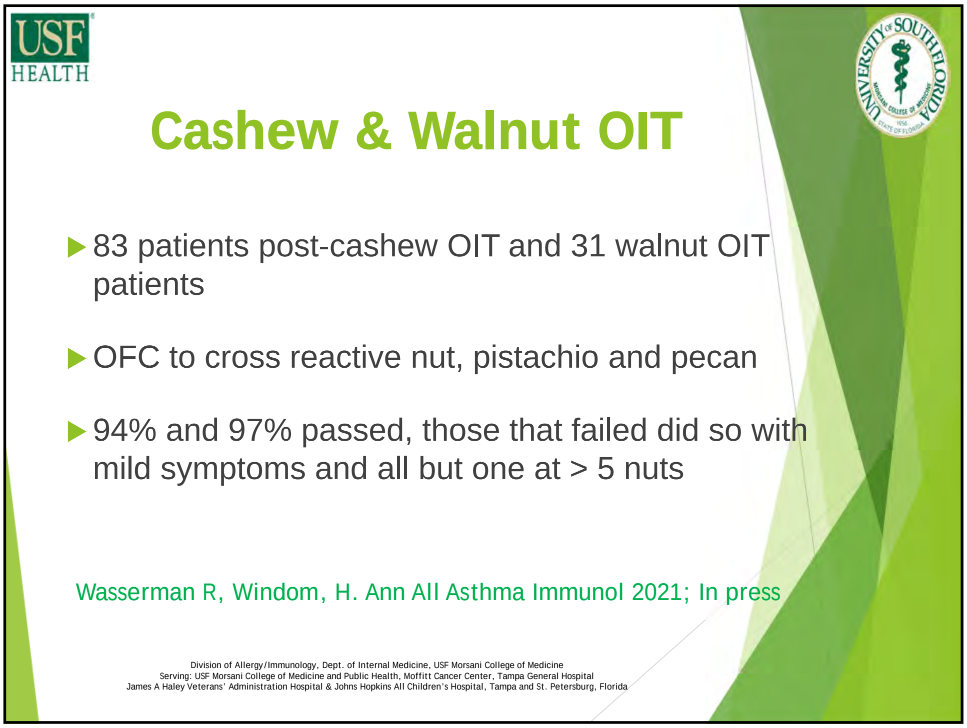
- 60 food allergic children at Stanford did multi-OFC's
- All pistachio allergic patients (42) reacted to cashew, whereas 4 of 46 cashew allergic patients tolerated pistachio
- All pecan allergic patients (29) reacted to walnut, whereas 3 of 32 walnut allergic patients tolerated pecan
- Epi used in 5 of 311 OFC's (1.6%)

Andorf S. J Allergy Clin Immunol Pract 2017;5:1325-34

Walnut OIT: Nut Cracker

- Cross reactivity in their prior study: 100% of pecan and 79% hazelnut pts. were also allergic to walnut
- 55 walnut pts. 4-20 y.o., OIT to 4 gm protein (~6 nuts)
- 89% reached maintenance, 15% took Epi
- 82% were pecan +OFC, all passed OFC after OIT
- 93% of the 15 pts. co-allergic to hazelnut either passed hazelnut OFC or tolerated >2 nuts
- 26% of 19 pts. co-allergic to cashew improved

Elizur A. Lancet Child Adolesc Health 2019; 3:312-21



Cashew & Walnut OIT

- 83 patients post-cashew OIT and 31 walnut OIT patients
- OFC to cross reactive nut, pistachio and pecan
- 94% and 97% passed, those that failed did so with mild symptoms and all but one at > 5 nuts

Wasserman R, Windom, H. Ann All Asthma Immunol 2021; In press

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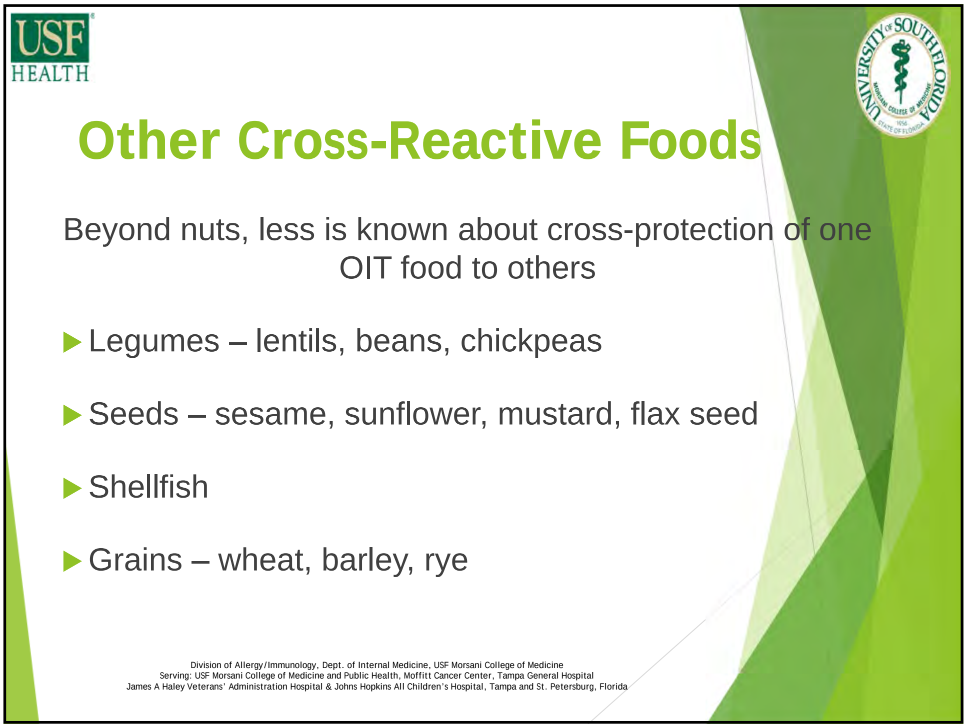

Other Cross-Reactive Foods

Beyond nuts, less is known about cross-protection of one OIT food to others

- Legumes – lentils, beans, chickpeas
- Seeds – sesame, sunflower, mustard, flax seed
- Shellfish
- Grains – wheat, barley, rye

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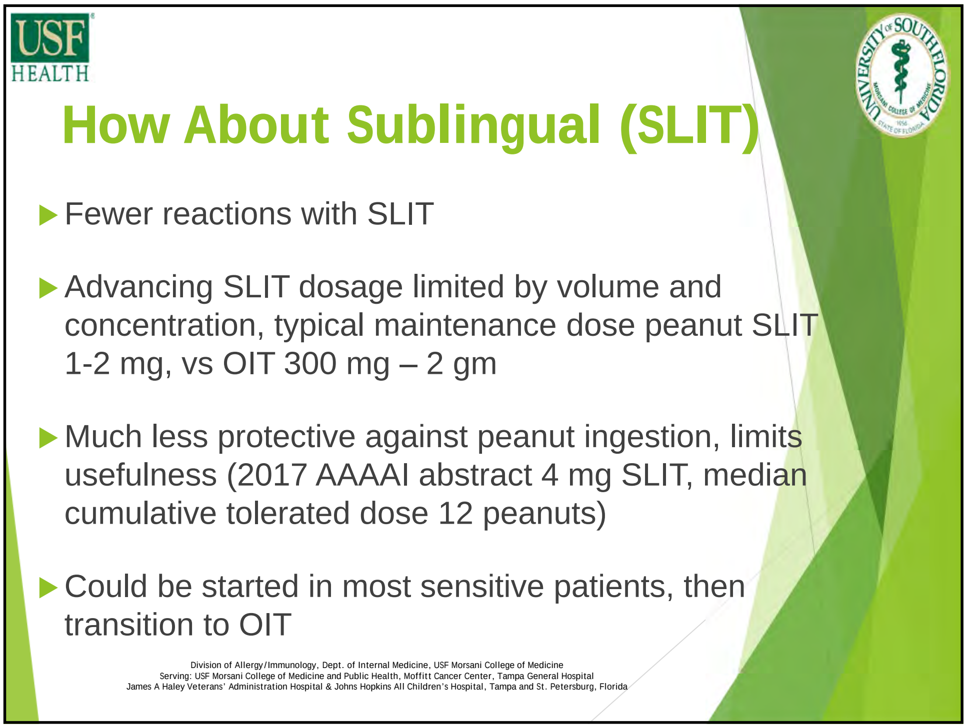

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How About Sublingual (SLIT)

- Fewer reactions with SLIT
- Advancing SLIT dosage limited by volume and concentration, typical maintenance dose peanut SLIT 1-2 mg, vs OIT 300 mg – 2 gm
- Much less protective against peanut ingestion, limits usefulness (2017 AAAAI abstract 4 mg SLIT, median cumulative tolerated dose 12 peanuts)
- Could be started in most sensitive patients, then transition to OIT

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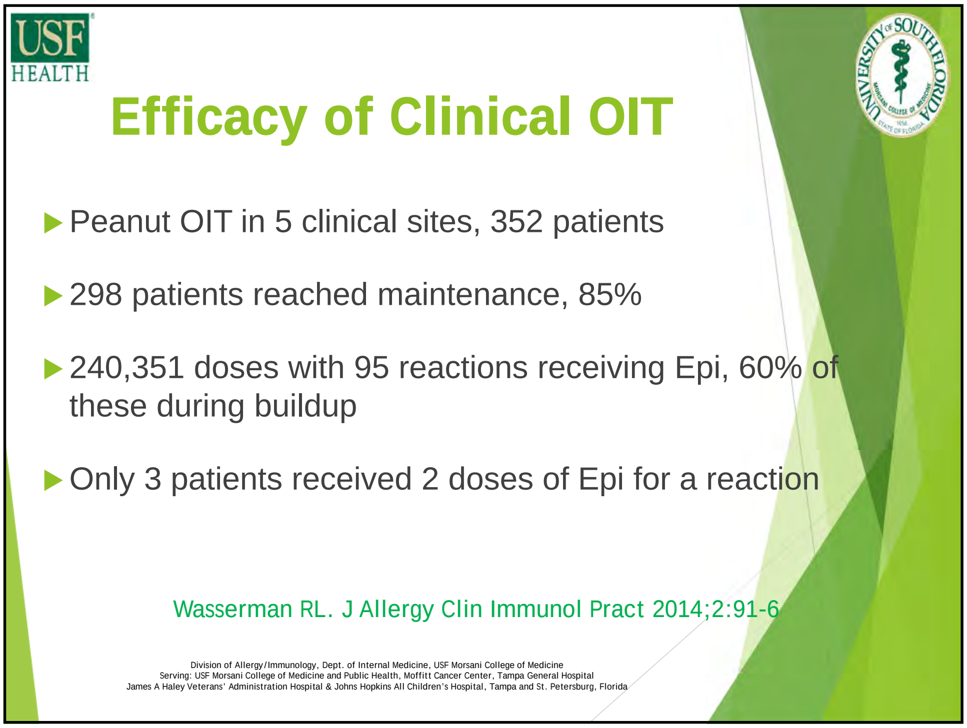

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Efficacy of Clinical OIT

- Peanut OIT in 5 clinical sites, 352 patients
- 298 patients reached maintenance, 85%
- 240,351 doses with 95 reactions receiving Epi, 60% of these during buildup
- Only 3 patients received 2 doses of Epi for a reaction

Wasserman RL. J Allergy Clin Immunol Pract 2014;2:91-6

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Safety of Clinical OIT

- Peanut OIT in 783 patients at NE USA site
- 89% reached maintenance
- 4% patients used Epi during buildup; 11% during maintnenance – no hospitalizations, no fatalities
- 1% diagnosed with eosinophilic esophagitis

Afinogenova Y. J Allergy Clin Immunol Pract 2020;8:2727-35

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Epinephrine Use with OIT

- More Epi use post-OIT than pre-OIT

  - rarely severe anaphylaxis

  - predictable timing, not random and when unprepared

  - taught to use Epi early, they go to ER <50% of time

- Does this discourage patients?

  - our 152 peanut OIT patients 26 used Epi, 92% reached target dosing vs. 83% non-Epi users

Chu DK. www.thelancet.com, April 25, 2019
Windom H. Ann Allergy Asthma Immunol, 2019;123:S53

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Epinephrine Use: OIT vs. Allergy shots

Site	# patients	Age	Epi use Yr 1
OIT in TX	67	4-18	8%
SCIT in NY	459	5-70	8%

J Allergy Clin Immunol 2019;143: AB275. Ab#836
Allergy Asthma Proc 2019;40:338-42

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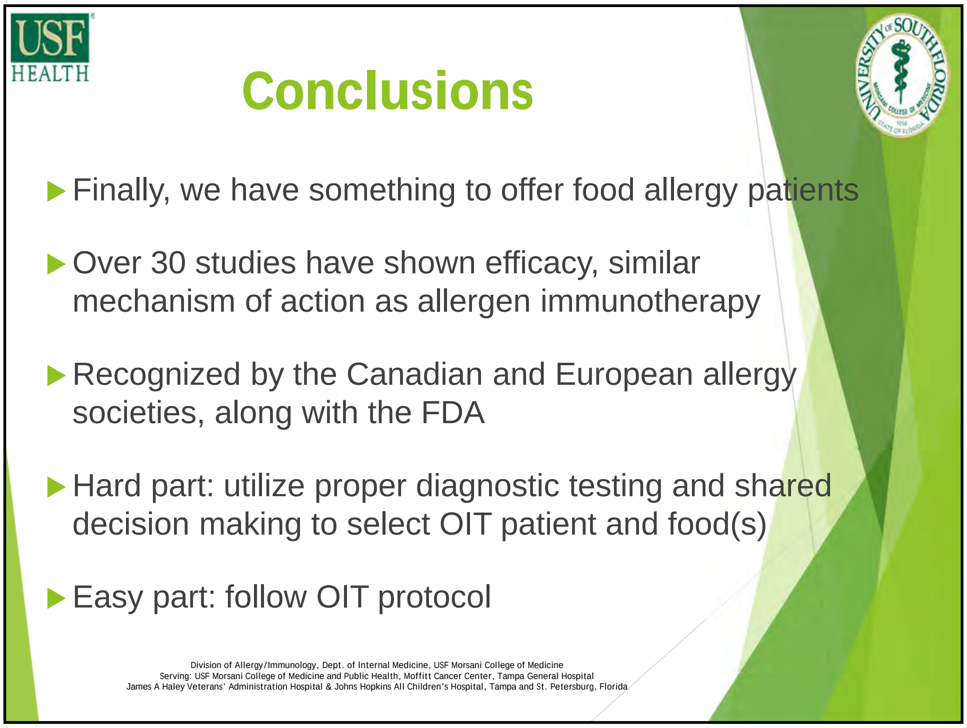
Commercial Capsule, Patch…

- *Aimmune* (now Nestle) peanut flour in capsule (top dose 300 mg protein), trade name Palforzia
- *DBV* has a single dose patch - ~50% reach target goal of 10x baseline OFC threshold
- Biologics under investigation



Conclusions

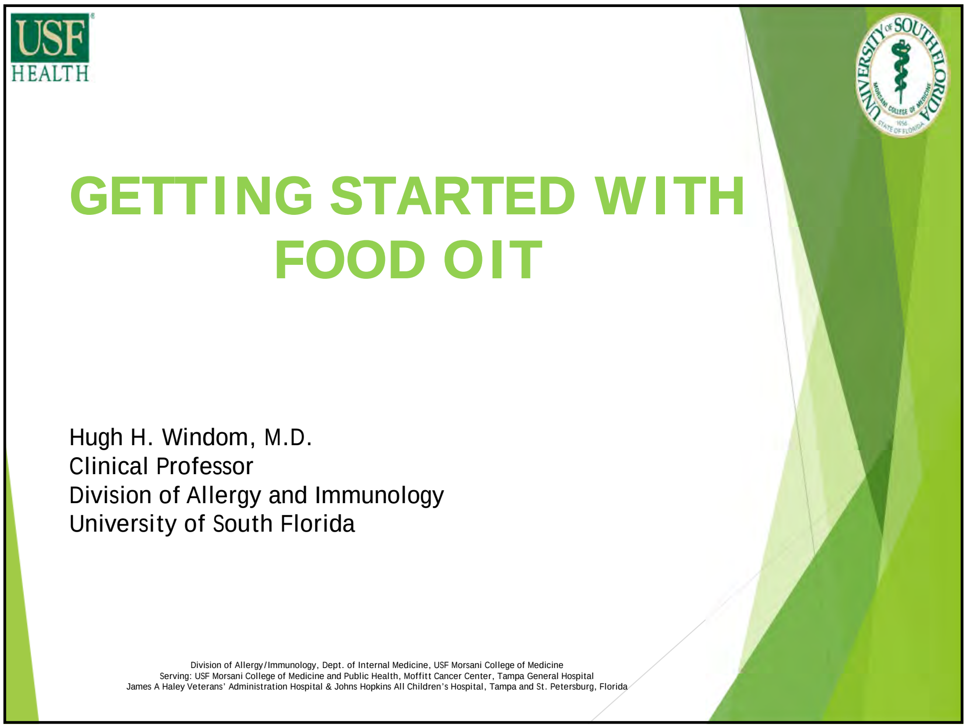
- Finally, we have something to offer food allergy patients
- Over 30 studies have shown efficacy, similar mechanism of action as allergen immunotherapy
- Recognized by the Canadian and European allergy societies, along with the FDA
- Hard part: utilize proper diagnostic testing and shared decision making to select OIT patient and food(s)
- Easy part: follow OIT protocol

Pennsylvania Allergy & Asthma Association

Getting Started with Food OIT

Hugh H. Windom, MD

Saturday, June 26, 2021
1:00 p.m. - 2:00 p.m.



GETTING STARTED WITH FOOD OIT

Hugh H. Windom, M.D.
Clinical Professor
Division of Allergy and Immunology
University of South Florida

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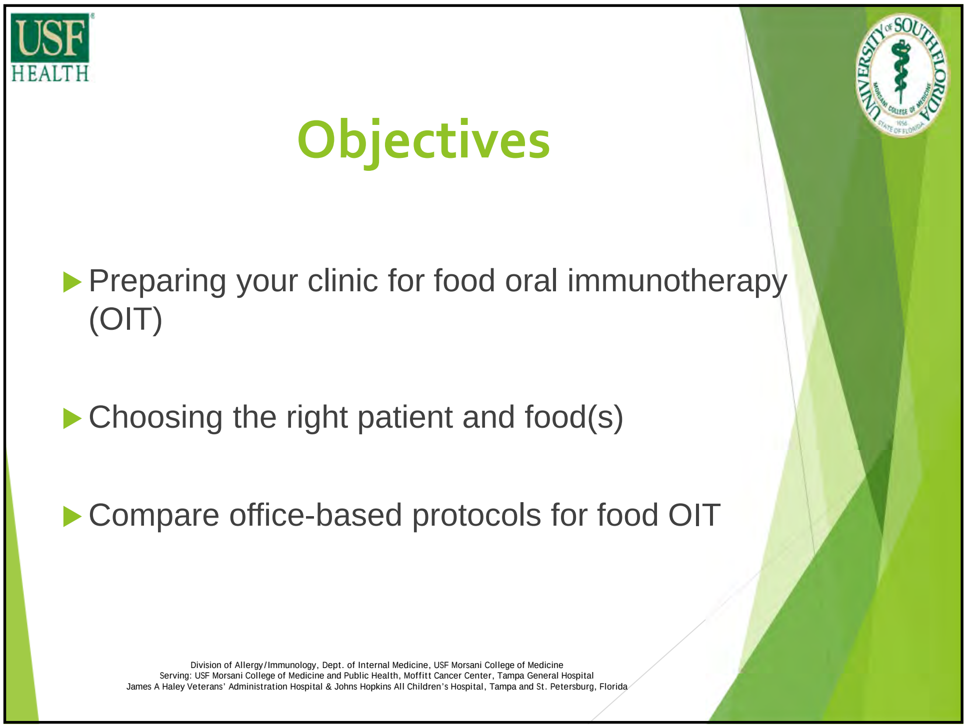

Objectives

- Preparing your clinic for food oral immunotherapy (OIT)
- Choosing the right patient and food(s)
- Compare office-based protocols for food OIT

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Modern Food OIT, How it Began

- 6 patients with severe peanut anaphylaxis
- Gradual build-up of oral doses, following day one challenge
- “Biteproof” state dependent of persistent exposure could be achieved

Mansfield, L. Ann Allergy Asthma Immunol 2006; 97: 266-7

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Food Allergy Support Team (FAST)

- >400 A/I providers in US and Canada, online community
- 4th annual meeting held June 2021
- Registry funded by Mylan, 3 clinics reporting their patient experiences, over 1,500 cases
- www.fastOIT.org

Wasserman RL. Ann Allergy Asthma Immunol 2018;121:272-5

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Preparing your Office

- Adequate space to prepare food and administer dose
- Staff education, assign an OIT lead person
- OFC experience – measuring doses, anaphylaxis readiness
- Committed physicians and/or extenders
- Establish workflow that provides adequate time for visits and phone calls

Wasserman R. J Allergy Clin Immunol Pract 2021; 9:1826-38

Patient Selection

- Diagnoses by testing and history or OFC
- Motivated patient and family
- Education and counseling to enable shared decision making
- Goal setting – bite proof vs. free eating
- Financial commitment
- OIT is not for everyone

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Patient Preparation

- Review FAQ’s
- Discuss and sign consent form
- Both parents need to be on board, particularly if in separate houses
- Timing of starting – stabilize comorbid atopy, less crazy time of year (e.g. after soccer season)

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Ideal Age for OIT

- Earlier the better, from efficacy and tolerability view
- Long lived allergy foods (peanut/tree nuts) definitely early
- Short lived allergy foods (egg/milk) attempt ’ladder’, if fail or historic reaction and testing ‘scary’, start ASAP
- Is there a too-old age?, no, but diminishing returns and interest after high school

USF HEALTH

OFC before OIT?

- Systemic reaction within 2 years, + tests – No
- Distant hx. systemic reaction, low sIgE < 2 – Yes
- Distant hx. systemic reaction, high sIgE > 15 – No
- Distant hx. systemic reaction, sIgE 2-15 – Maybe
- No prior food consumption – Yes (unless sIgE>15, ara H2 elevated, and IgE <1000)

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Commonly Treated Foods

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Food Sources

- Peanut – peanut flour light roast 12% diluted in distilled water, flour capsules from local pharmacy, or roasted peanuts (www.byrdmill.com)
- Egg – use egg white powder diluted in distilled water (6 gm = 1 egg) or egg white liquid (3 tbsp = 1 egg)
- Milk – use milk (any fat content) diluted in distilled water, can flavor with chocolate/strawberry syrup

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Food Sources

- Tree nuts – flour/meal diluted in water, then nut fraction (www.nuts.com)
- Sesame – flour diluted in water, seeds (~20% protein), or Tahini (check protein content on label)
- Wheat – vital wheat gluten (70% protein) or Dave's Awesome bagel (wheat, rye, barley)

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Alternative Peanut Sources

- Peanut - ~25% protein (PP), peanuts weigh 800-1,500mg, if use 1 gm average, then ~250 mg of PP
- Peanut flour – 12% and 28% fat, the former 50% PP, the latter 41% PP
- Peanut butter – 1 tsp ~ 1.3 gm PP or 5 peanuts (a little more if jar says 8 gm=2T, little less if 7gm=2T)
- M&M's - ~150 mg PP, ~60% of 'normal' 1 gm peanut

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Food	Day 1	Updose & Maintenance
Peanut	flour, diluted	peanuts, Bamba, PB, M&M's, Reese's
Milk	diluted whole milk	milk, other dairy products
Egg	egg white liquid / powder	egg white liquid, eggs
Cashew	flour or cashew milk	cashews, cashew milk
Walnut	meal or walnut milk	walnuts, walnut milk
Hazelnut	flour/meal	hazelnuts
Sesame	flour diluted	sesame seeds, Tahini
Wheat	vital wheat gluten (VWG), bagel	VWG, multi-grain bagel

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OIT Office Supplies

- 4 & 8 oz plastic or glass bottles www.sks-bottle.com
- 1, 3, 5, and 10 cc disposable syringes
- Anaphylaxis med cart
- Scale for patients: portable milligram scale, Amazon $20-$30
- Scale for office: 50 gm capacity, 1 mg readability, ~ $350

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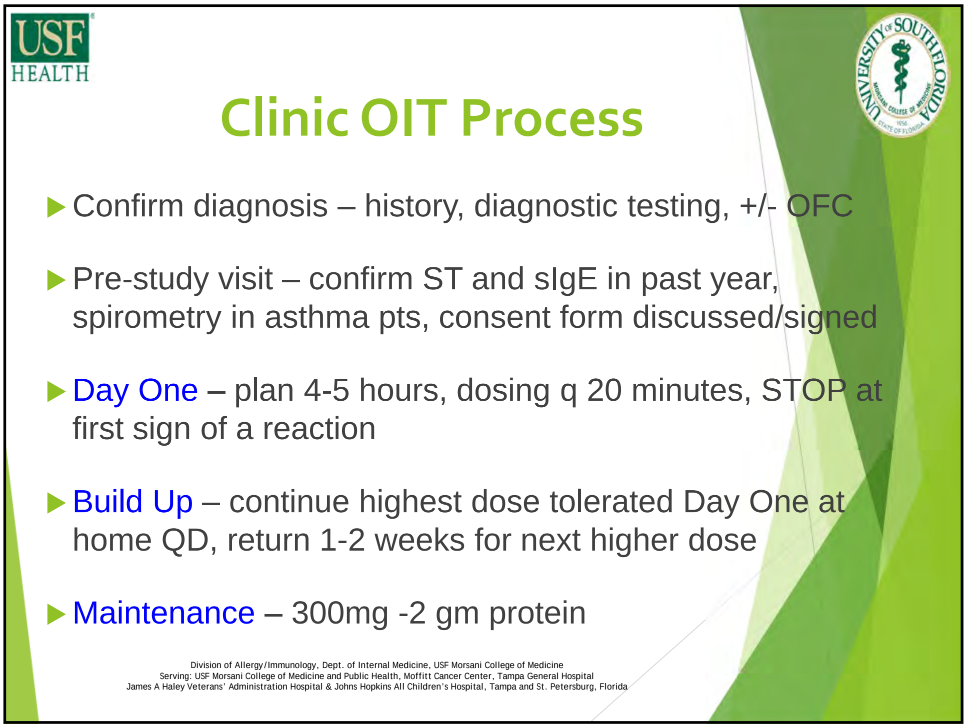
Standard Research Protocol

- Day One dose escalation, 4-5 doses, some require pre-entry OFC
- Build Up phase with QD daily dosing at home, then 2 hour visit every 1-2 weeks for dose increase
- Maintenance phase of ongoing daily dosing
- Stop, rechallenge for sustained unresponsiveness



Clinic OIT Process

- Confirm diagnosis – history, diagnostic testing, +/- OFC
- Pre-study visit – confirm ST and sIgE in past year, spirometry in asthma pts, consent form discussed/signed
- Day One – plan 4-5 hours, dosing q 20 minutes, STOP at first sign of a reaction
- Build Up – continue highest dose tolerated Day One at home QD, return 1-2 weeks for next higher dose
- Maintenance – 300mg -2 gm protein

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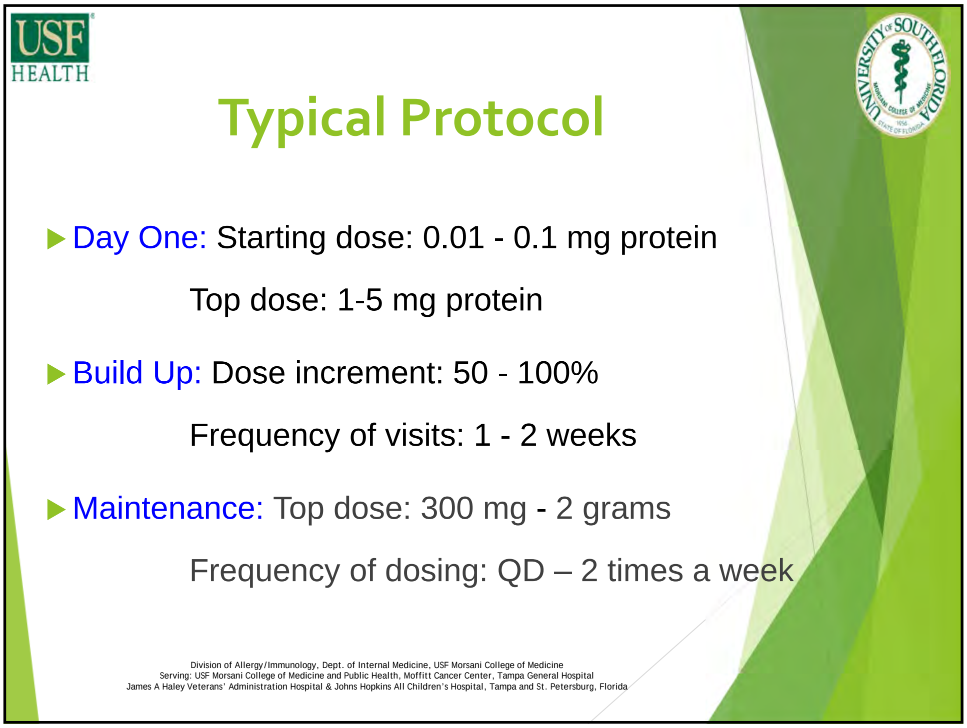

Typical Protocol

- Day One: Starting dose: 0.01 - 0.1 mg protein

  Top dose: 1-5 mg protein
- Build Up: Dose increment: 50 - 100%

  Frequency of visits: 1 - 2 weeks
- Maintenance: Top dose: 300 mg - 2 grams

  Frequency of dosing: QD – 2 times a week

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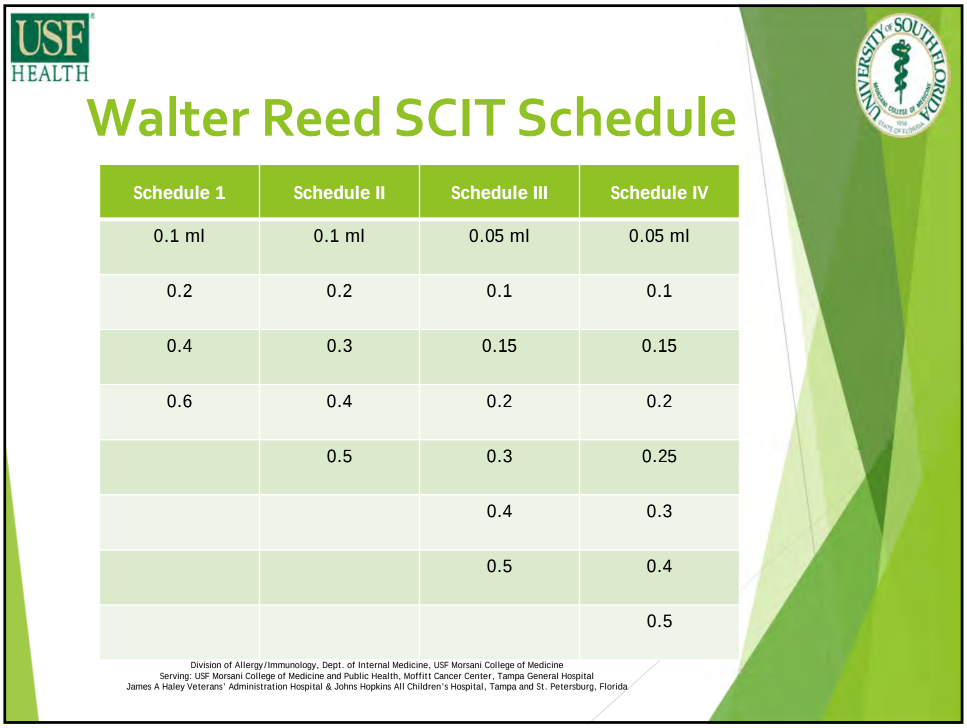

Walter Reed SCIT Schedule

Schedule 1	Schedule II	Schedule III	Schedule IV
0.1 ml	0.1 ml	0.05 ml	0.05 ml
0.2	0.2	0.1	0.1
0.4	0.3	0.15	0.15
0.6	0.4	0.2	0.2
	0.5	0.3	0.25
		0.4	0.3
		0.5	0.4
			0.5

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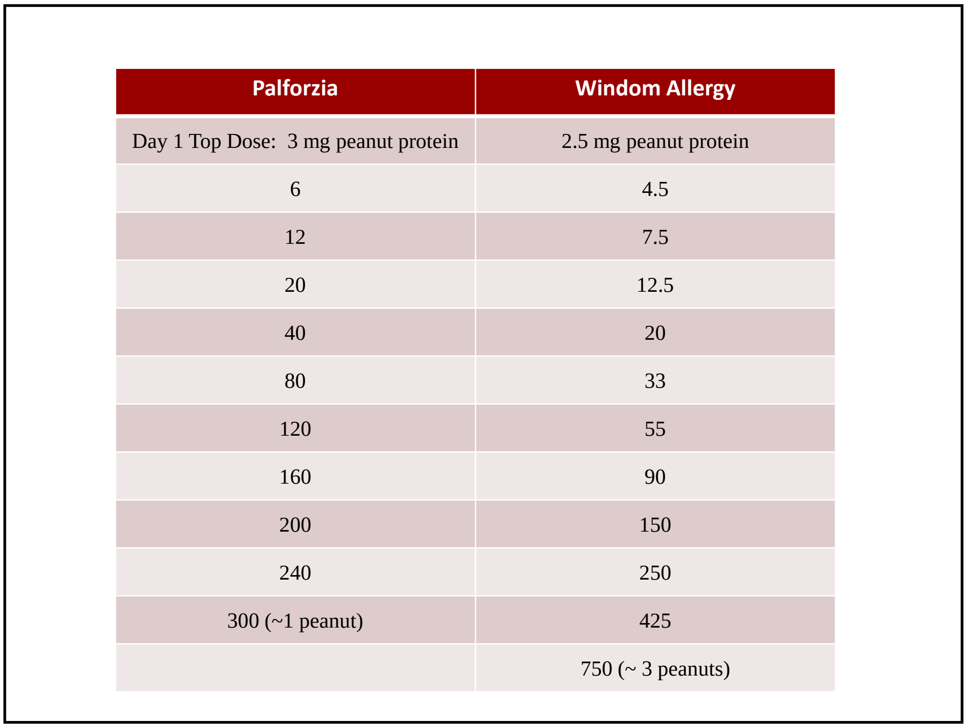

Palforzia	Windom Allergy
Day 1 Top Dose: 3 mg peanut protein	2.5 mg peanut protein
6	4.5
12	7.5
20	12.5
40	20
80	33
120	55
160	90
200	150
240	250
300 (~1 peanut)	425
	750 (~ 3 peanuts)

Palforzia	Windom Allergy
3 mg peanut protein	2.5 mg peanut protein
6 (100%)	4.5 (80%)
12 (100%)	7.5 (67%)
20 (67%)	12.5 (67%)
40 (100%)	20 (60%)
80 (100%)	33 (65%)
120 (50%)	55 (61%)
160 (33%)	90 (64%)
200 (25%)	150 (67%)
240 (20%)	250 (67%)
300 (25%)	425 (70%)
	750 (76%)

An Accelerated Protocol

(or OFC roll-over into OIT)

- Day One is an oral food challenge (OFC)
- 1st buildup dose is 1-2 doses back from provocative dose
- 9/11 patients were successfully updosed to 8 peanuts
- Very similar to Day One dosing by Mansfield since 2005

Bird JA. J Allergy Clin Immunol Pract 2015; 3:433-5

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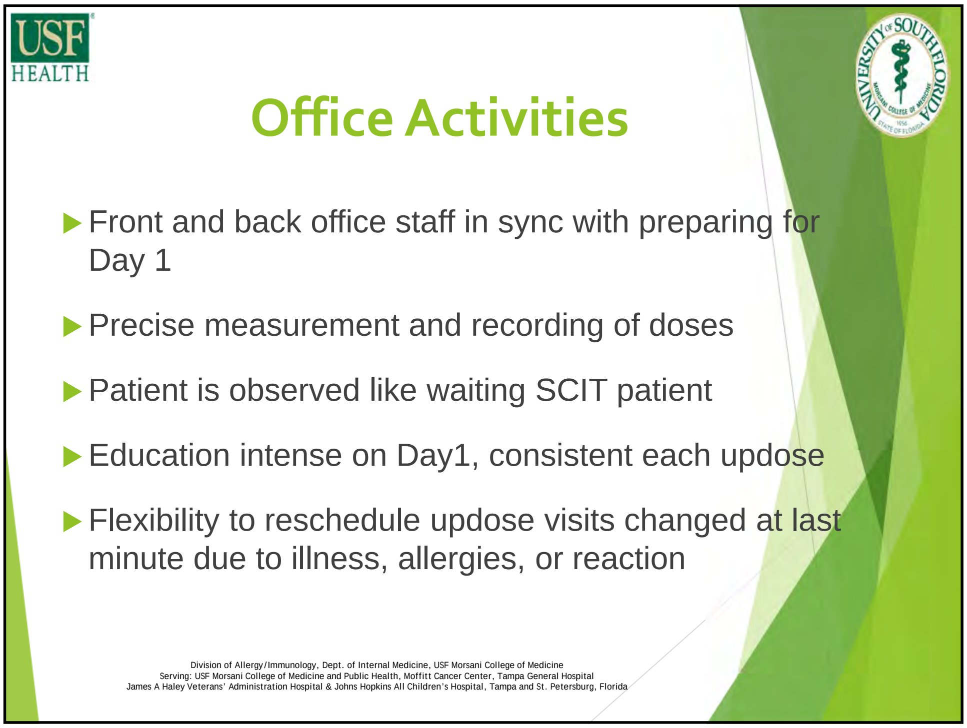


Office Activities

- Front and back office staff in sync with preparing for Day 1
- Precise measurement and recording of doses
- Patient is observed like waiting SCIT patient
- Education intense on Day1, consistent each updose
- Flexibility to reschedule updose visits changed at last minute due to illness, allergies, or reaction

Home Activities

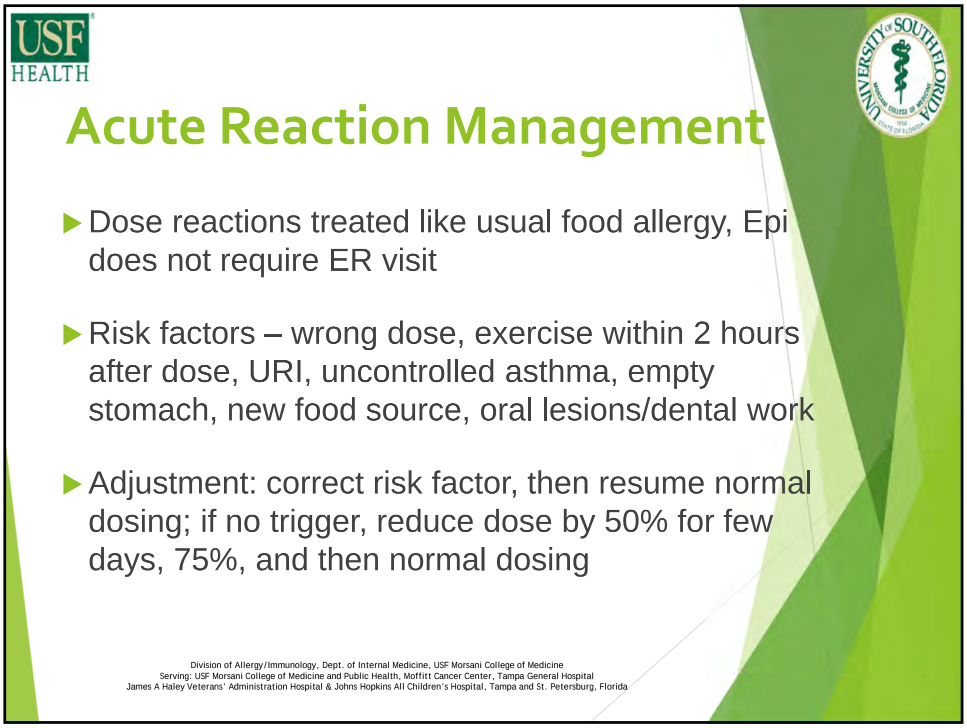
- Safety Rules handout taken home from each visit
- Daily dosing important, but not essential
- Time of dosing flexible, unless historic problem
- No exercise for 2 hours after dosing or ½ hour before
- Trigger factors can be exercise, infection, flaring atopy, menses, empty stomach, new food source

Dosing Goals

- A conversation with patient/family pre-OIT is critical
- Bite-proof vs free eating
- We focus on safety, aiming for 0.5 – 1 gm protein
- Staple foods different, most want to eat normally
- Egg and milk so common in diet, scheduled dosing becomes less important

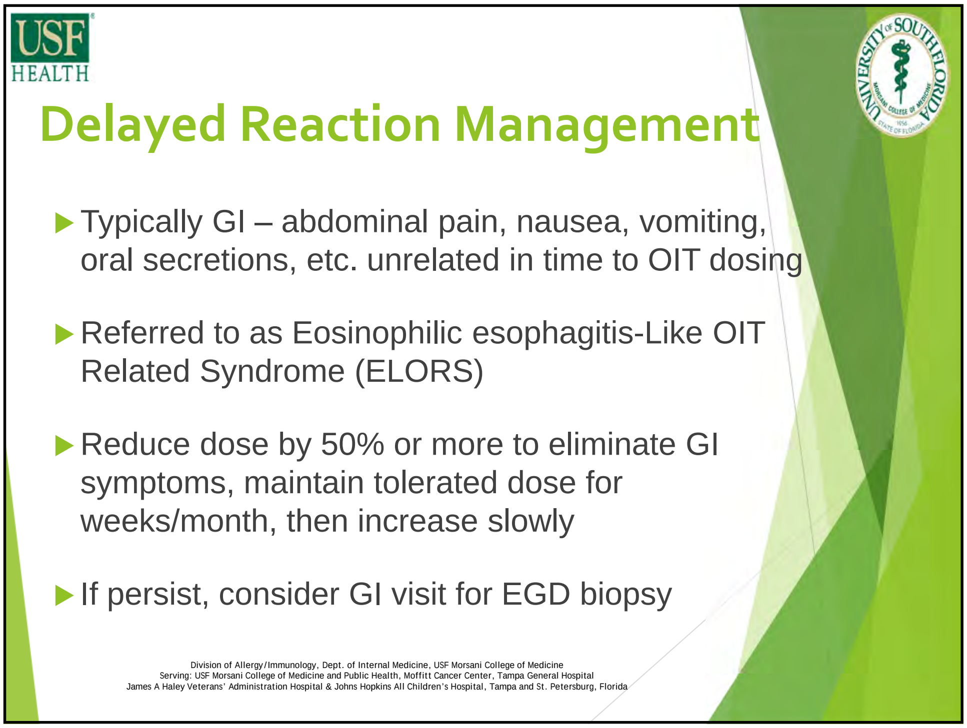
Keys to Successful OIT

- Motivated family, right age patient (younger the better, except maybe egg/milk)
- 1:1 nursing Day One, build up visits are like a Xolair or allergy shot visit
- Doctor sees patient every visit
- Constantly remind patient of reaction risk factors
- It is not a race



Acute Reaction Management

- Dose reactions treated like usual food allergy, Epi does not require ER visit
- Risk factors – wrong dose, exercise within 2 hours after dose, URI, uncontrolled asthma, empty stomach, new food source, oral lesions/dental work
- Adjustment: correct risk factor, then resume normal dosing; if no trigger, reduce dose by 50% for few days, 75%, and then normal dosing



Delayed Reaction Management

- Typically GI – abdominal pain, nausea, vomiting, oral secretions, etc. unrelated in time to OIT dosing
- Referred to as Eosinophilic esophagitis-Like OIT Related Syndrome (ELORS)
- Reduce dose by 50% or more to eliminate GI symptoms, maintain tolerated dose for weeks/month, then increase slowly
- If persist, consider GI visit for EGD biopsy

Recurring Reactions

- If early in course, sometime better to stop, cool off, and then resume with ‘low and slow’ dosing
- If later in course, make big 10-fold drop in dose
- If doing multi-foods, drop a food, pick it up later
- If still struggling, consider SLIT, biologic, or resume avoidance

Long Term Management

- After reaching maintenance (M), return 2-3 months for high dose challenge; if pass reduce dosing to 6 days/week
- See them annually for invitro +/- invivo testing, repeat high dose challenge, reduce dosing 5 days/week
- Next year same, go to 3-4 days
- Next year same, go to 1-2 days
- But, lots of flexibility based on test results, reactions

OIT: Why Some Fail

- 427 pts. starting food OIT, 83% reached maintenance
- Failures: 37% GI symptoms, 27% allergic reactions, 19% loss to f/u, 16% other reasons
- Young age and low sIgE correlate with success in peanut and egg, not milk
- 25 (7%) stopped after maintenance: 10 taste aversion, 6 allergic rxns., 4 unrelated medical problems, 2 GI symptoms, 3 other

Hague AR. J Allergy Clin Immunol 2017;139:AB134

Multi-Food OIT

- ~30% of our 500+ patients did multi-food OIT
- Saves time and money to combine foods vs sequential single food OIT
- Typically no more than 3 foods, may choose not to combine sIgE>100 foods, esp. milk and in older pts
- Same protocol, just cut Day 1 doses by 1/extra food
- Can always drop a food(s) if trouble building up

Multi-Food vs Peanut OIT

- 2014-18, 77 multi-food OIT compared to 162 peanut OIT
- Mean of 2.3 foods used
- 74% of multi-food (MF) pts reached maintenance vs. 85% peanut, over median 231 days vs. 248 days
- Reasons for d/c: non-compliance, anxiety, and delayed GI issues
- Epi used in 1st year in 8% MF vs. 14% peanut patients

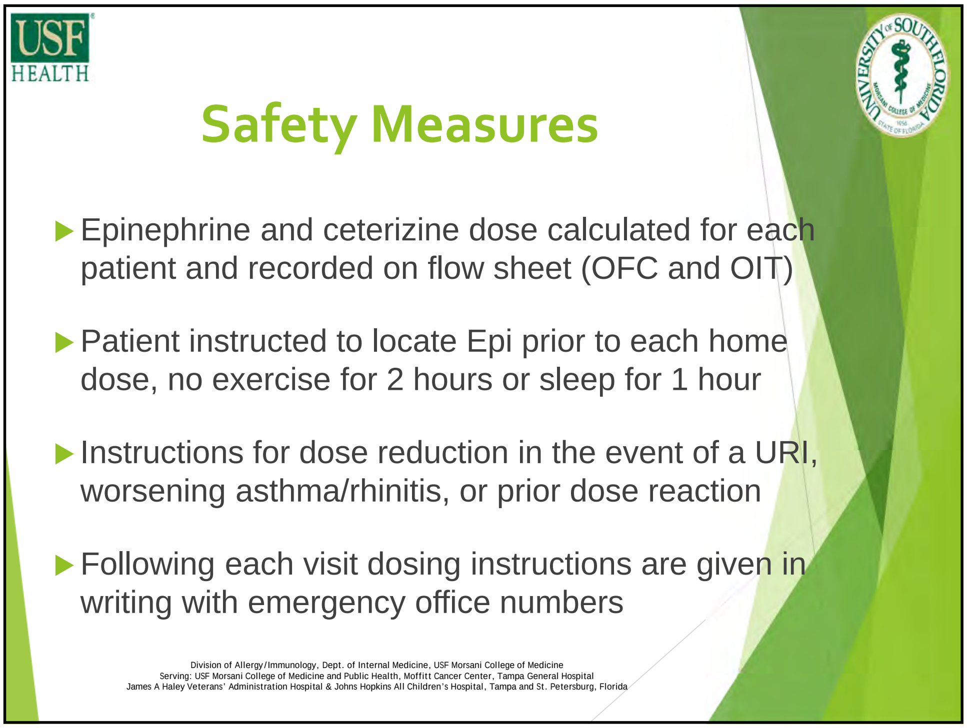
Gasich L. J Allergy Clin Immunol 2020;1454:AB133

Multi-Tree Nut OIT

- Cashew and/or walnut are usually adequate
- Most common grouping is peanut/cashew/walnut

Scenario 1: never eaten walnut with sIgE 6, total IgE 300 and skin test 6/20

Scenario 2: same walnut story, but strong hx and testing to peanut (IgE 60) and cashew (IgE 3)



Safety Measures

- Epinephrine and ceterizine dose calculated for each patient and recorded on flow sheet (OFC and OIT)
- Patient instructed to locate Epi prior to each home dose, no exercise for 2 hours or sleep for 1 hour
- Instructions for dose reduction in the event of a URI, worsening asthma/rhinitis, or prior dose reaction
- Following each visit dosing instructions are given in writing with emergency office numbers

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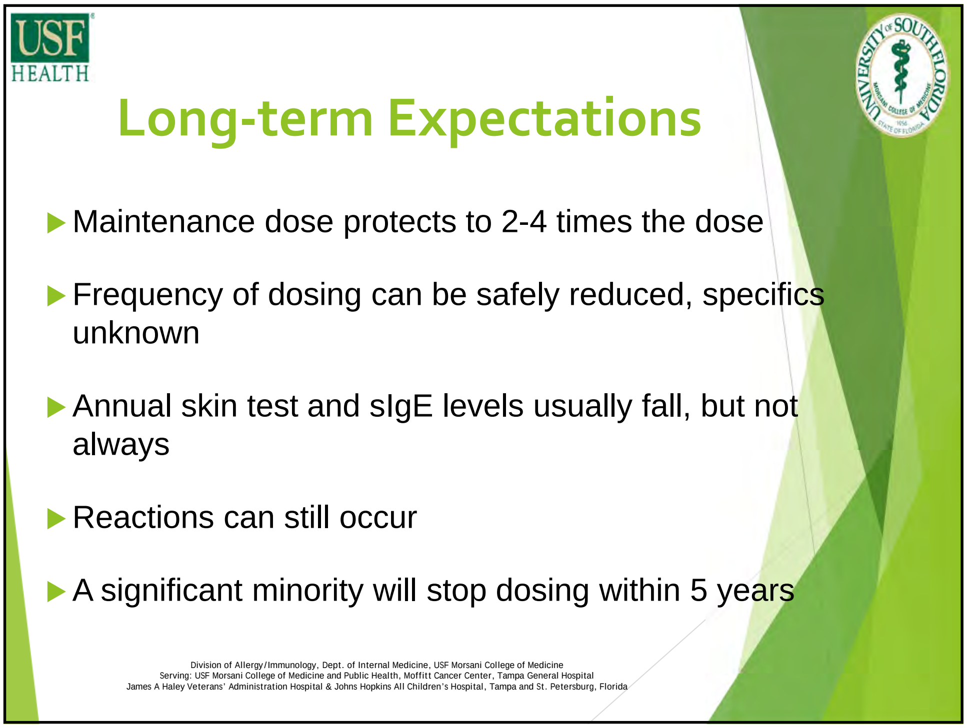

Long-term Expectations

- Maintenance dose protects to 2-4 times the dose
- Frequency of dosing can be safely reduced, specifics unknown
- Annual skin test and sIgE levels usually fall, but not always
- Reactions can still occur
- A significant minority will stop dosing within 5 years

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Physician Experience with OIT

- OIT is one of the most fun and rewarding things I have done.
- OIT has been THE most rewarding thing I've done in my Allergy practice in 40 years.
- I have never had more committed and appreciative patients.

Conclusions

- Office space and staff preparation, OFC experience, patient selection, education, and adherence to dosing schedules
- Using real food to allow safe eating of food, is currently our best treatment option
- Not for every patient, not for every office

Pennsylvania Allergy & Asthma Association

PRESENTATIONS FOR SUNDAY, JUNE 27, 2021

Abstract Presentations

1. Clinical Outcomes of Patients with Idiopathic Anaphylaxis Receiving Omalizumab
   Lauren Kaminsky, MD, PhD | Penn State Health
2. Safety and Outcomes of Penicillin Allergy Evaluation in Pregnant Women
   Vima Patel, MD | Hospital of the University of Pennsylvania
3. Sulfite Hypersensitivity: A Case of Asthma Triggered by Sulfites
   Anthony LaCava, MD | Hospital of the University of Pennsylvania

Overview on the Management of EoE
Evan Dellon, MD, MPH

Deficiencies of the Innate Immune System
Jordan Orange, MD, PhD

Controversies in EoE
Evan Dellon, MD, MPH

NK Cell Function and Deficiences
Jordan Orange, MD, PhD

Pennsylvania Allergy & Asthma Association

Clinical Outcomes of Patients with Idiopathic Anaphylaxis Recieving Omalizumab

Lauren Kaminsky, MD, PhD

Sunday, June 27, 2021
7:45 a.m. - 7:55 a.m.

Clinical outcomes of patients with idiopathic anaphylaxis receiving omalizumab: A retrospective case series and literature review

Lauren Kaminsky, MD, PhD
June 27, 2021

PGY-4, Fellow-in-Training
Penn State Health Milton S. Hershey Medical Center

Disclosures

- None

Background

- Idiopathic anaphylaxis (IA) involves episodes of anaphylaxis without a specific trigger
- Management includes antihistamines and mast cell stabilizers, but some patients continue to have episodes of anaphylaxis
- Omalizumab, an anti-IgE monoclonal antibody, is not approved by the FDA for treatment of IA but has been used in patients with IA under concurrent diagnoses of asthma or chronic idiopathic urticaria

Background

- Use of omalizumab in the treatment of patients with IA is not well-studied and is underreported
- Omalizumab has been shown to be beneficial for IA and clonal mast cell disorders such as mastocytosis
- We compiled reported outcomes on omalizumab use in the treatment of IA in patients without underlying mast cell clonality
  - Case series of experience at 2 academic centers
  - Systematic literature review

Methods- Case series

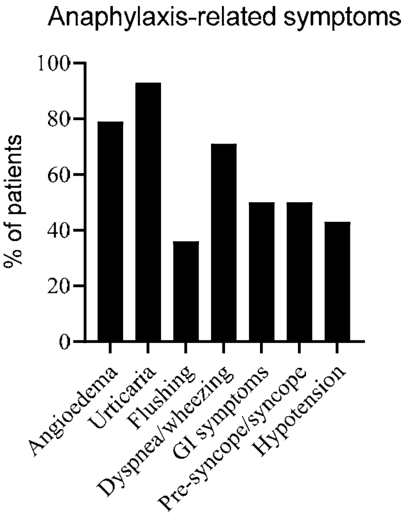
- Inclusion criteria:
  - Included patients with physician diagnosis of IA and anaphylactic manifestations of at least 2 organ systems simultaneously
- Exclusion criteria:
  - Documented evidence of clonal mast cell disorder (positive bone marrow biopsy, *KIT* mutant mast cells)
  - REMA score ≥2 and no further evaluation for clonal mast cell disorder
- Formal review by the IRB was not required for this study

Methods- Systematic literature review

- Search of PubMed updated March 2021 using terms: “Idiopathic anaphylaxis” or “Mast cell activation syndrome” or “MCAS” AND “Omalizumab” or “Xolair” or “anti-immunoglobulin E” with filter to include human studies with full text available
- Prospective, retrospective, and case studies involving use of omalizumab for treating IA without evidence of clonal mast cell disorders were included along with abstracts from ACAAI and AAAAI annual meetings over 5 years through 2020

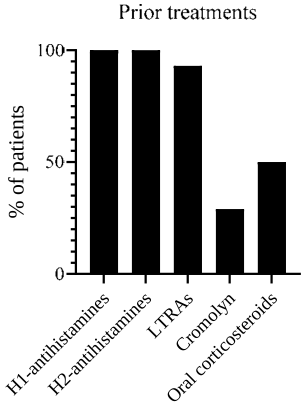
Results- Case series

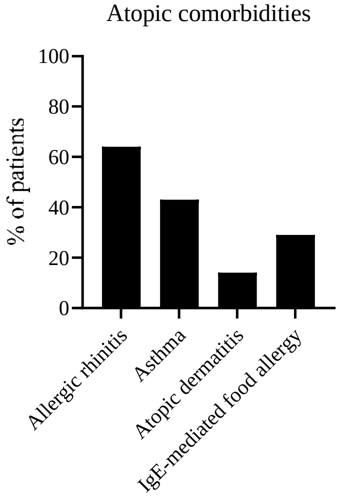
- 14 patients identified
- 13 of 14 patients met the WAO diagnostic criteria for anaphylaxis with 1 patient having skin symptoms + GI symptoms
- 13 females, 1 male
- Median age at omalizumab start of 36 years (range 15-51 years)
- Frequency of IA varied prior to omalizumab: 2 total lifetime episodes to multiple/month


Anaphylaxis-related symptoms

Results- Case series

- 11 of 14 patients had atopic comorbidities
- Prior treatments→

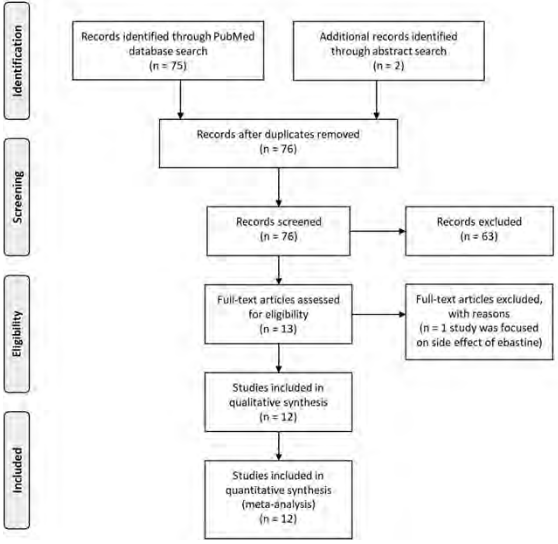

Prior treatments


Atopic comorbidities

Results- Systematic review

- 12 studies met inclusion criteria:
    - 9 case reports (N=9)
    - 1 abstract (N=1)
    - 1 prospective study (N=5)
    - 1 DBPC trial (N=6)
- Total of 21 patients identified
- Median age at omalizumab start: 42 years (range 11-54yrs) (N=15/21)
- Females (N=8, 50%), Males (N=8, 50%), sex identified for 16/21 (76%)
- IA episodes varied from multiple per year to multiple per month

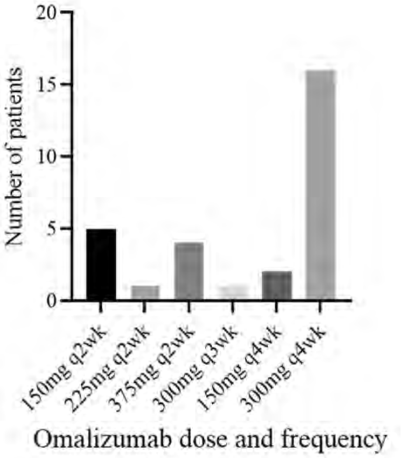
PRISMA diagram



Results- **Combined**

- Total 35 patients identified
- Median age 36yrs at omalizumab start (range 11-54yrs, N=29)
- 70% female (N=21/30), 30% male (N=9/30)
- Starting dose of 300mg q4wks most frequent (N=16) →
- Median duration of follow-up: 1yr (range 0.08-12yrs, N=29)

Known starting dose of omalizumab (N=29):



Results- Response to omalizumab

Case series:

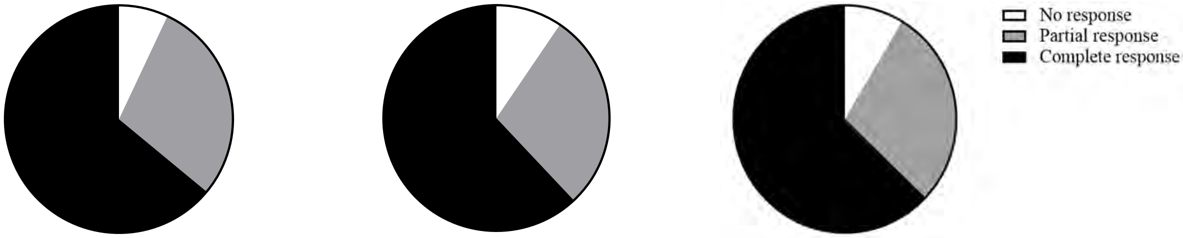
- Complete response (no anaphylaxis episodes) (N=9, 64%)
- Partial response (N=4, 29%)
- No response (N=1, 7%)

Systematic review:

- Complete response (N=13, 62%)
- Partial response (N=6, 28.5%)
- No response (N=2, 9.5%)

Combined (N=35):

- Complete response (N=22, 63%)
- Partial response (N=10, 28.5%)
- No response (N=3, 8.5%)



Omalizumab was effective in reducing frequency of IA in most patients who were already optimized on combination of antihistamines, LTRAs, cromolyn, and/or OCs

Results- Combined

- Adverse events with omalizumab:
  - <u>Case series</u>: cough, chest tightness, feeling hot
  - <u>Systematic review</u>: fatigue, edema of larynx, dyspnea, fever, headache, malaise, nausea, abdominal pain, bleeding, pruritus, local rash, sweating

Limitations

- Small size
- Use of case reports, abstract
- Absence of confirmation of the lack of mast cell clonality (BM biopsy, *KIT* mutation testing) although utilized REMA score
- Lack of placebo control

- Larger, placebo-controlled studies are needed to be able to make further management recommendations for use of omalizumab in IA

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- University of Washington/ Northwest Asthma and Allergy Center
    - Daniel H. Petroni, MD, PhD
    - Kestutis Aukstuolis, DO

Thank you to the PAAA for the opportunity to give this talk today!

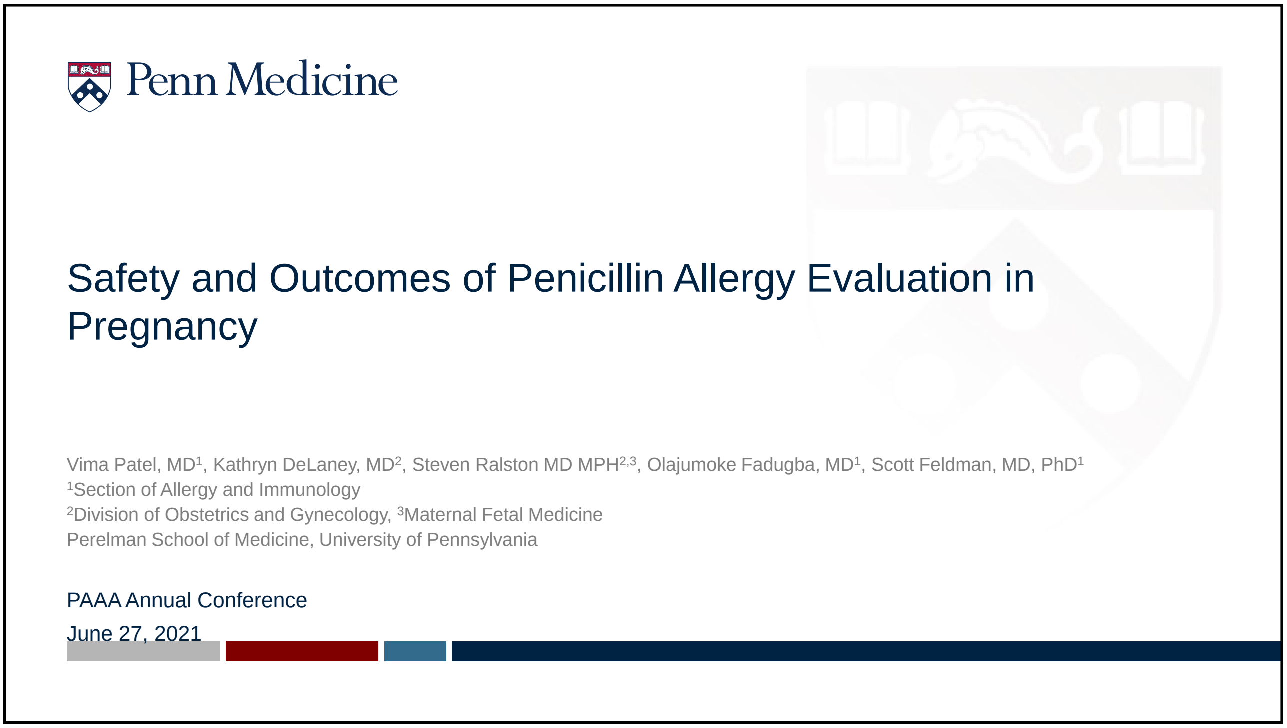
Questions?

Pennsylvania Allergy & Asthma Association

Safety and Outcomes of Penicillin Allergy Evaluation in Pregnant Women

Vima Patel, MD

Sunday, June 27, 2021
7:55 a.m. - 8:05 a.m.



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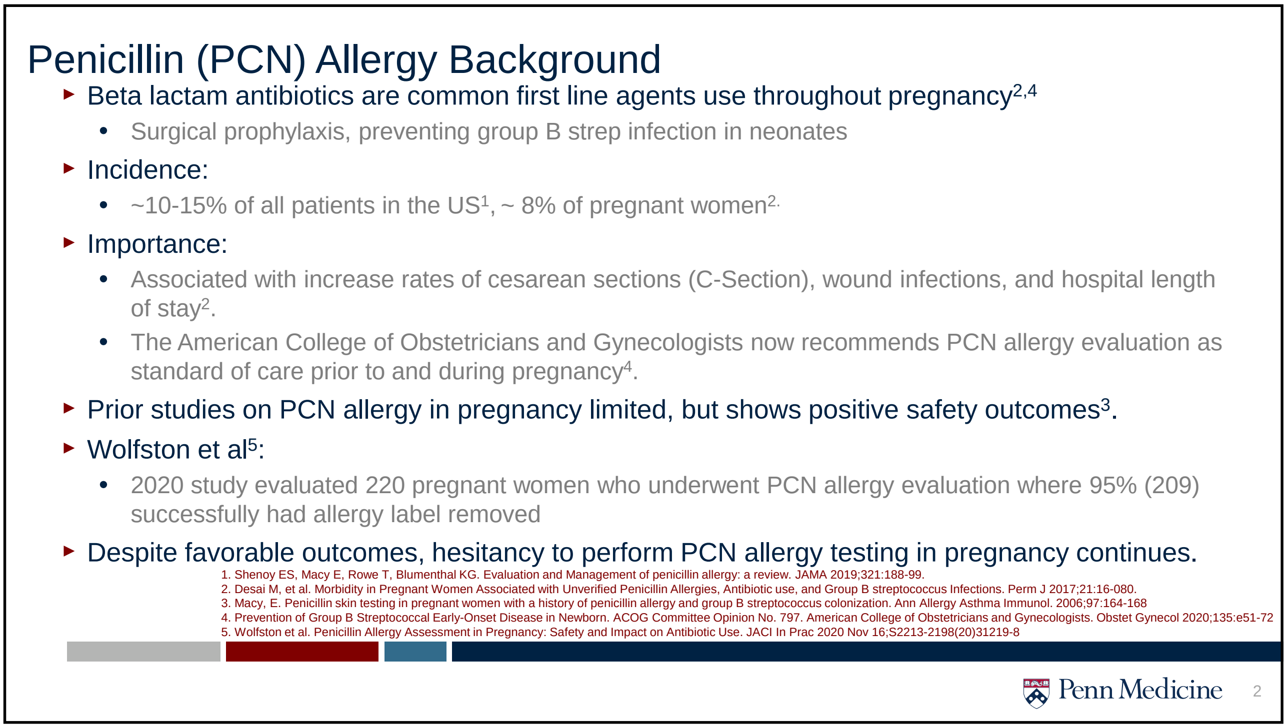
Safety and Outcomes of Penicillin Allergy Evaluation in Pregnancy

Vima Patel, MD[1], Kathryn DeLaney, MD[2], Steven Ralston MD MPH[2,3], Olajumoke Fadugba, MD[1], Scott Feldman, MD, PhD[1]
[1]Section of Allergy and Immunology
[2]Division of Obstetrics and Gynecology, [3]Maternal Fetal Medicine
Perelman School of Medicine, University of Pennsylvania

PAAA Annual Conference
June 27, 2021



Penicillin (PCN) Allergy Background

- Beta lactam antibiotics are common first line agents use throughout pregnancy[2,4]
  - Surgical prophylaxis, preventing group B strep infection in neonates
- Incidence:
  - ~10-15% of all patients in the US[1], ~ 8% of pregnant women[2.]
- Importance:
  - Associated with increase rates of cesarean sections (C-Section), wound infections, and hospital length of stay[2].
  - The American College of Obstetricians and Gynecologists now recommends PCN allergy evaluation as standard of care prior to and during pregnancy[4].
- Prior studies on PCN allergy in pregnancy limited, but shows positive safety outcomes[3].
- Wolfston et al[5]:
  - 2020 study evaluated 220 pregnant women who underwent PCN allergy evaluation where 95% (209) successfully had allergy label removed
- Despite favorable outcomes, hesitancy to perform PCN allergy testing in pregnancy continues.

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Objectives

- Primary Aim
  - Determine safety PCN allergy testing in pregnancy by assessing outcomes of outpatient evaluation
- Secondary Aims
  - Evaluate the safety penicillin evaluation in pregnancy and in pregnancy outcomes.

Methods

- Single academic center; retrospective review
- Pregnant women with PCN allergy label were referred by their obstetrics provider to an outpatient allergy clinic from 09/01/2019 to 12/31/2020 (15months)
- Referrals were triaged prior to visits and all patients underwent informed consent
- PCN allergy evaluation
  - Penicillin skin test (PST): prick and intradermal
  - If PST negative, oral PCN or Amoxicillin graded challenge
- Data reviewed included:
  - Index reactions
  - PST and challenge results
  - Gestational age (GA) at testing and delivery
  - Delivery outcomes and complications
  - Antepartum, intrapartum, and postpartum antibiotic use

Index Reactions of Penicillin Allergic Women Evaluated by Outpatient Allergy

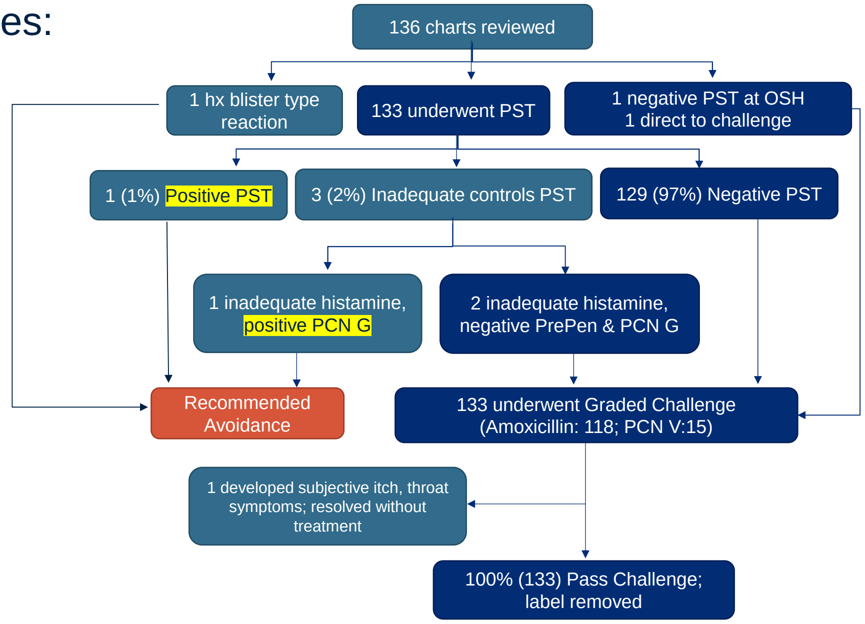
	All (n=136)
Index Drug	
Penicillin or Aminopenicillin	112 (82%)
Cephalosporin	4 (3%)
Unknown	19 (14%)
None*	1 (<1%)
Time (μ +/-SD)	22.1 +/-9.1
>10 years	115 (85%)
6-10 years	9 (6%)
<5 years	11 (8%)
Symptoms	
Unspecified Rash	60 (44%)
Hives	53 (39%)
Angioedema/Facial Swelling	5 (4%)
Shortness of Breath	6 (4%)
Throat Symptoms	2 (1%)
Prolonged GI symptoms	1 (<1%)
Dizziness	1 (<1%)
Unknown	11 (8%)
Non-IgE/Other**	18 (13%)

*1 patient without known reaction to PCN, label present due to family history PCN allergy

**Other symptoms included fever, joint pain, pruritis, blistering lesions, delayed GI symptoms, morbilliform rash, family history

Primary Outcomes:

Penicillin Allergy Evaluation



136 charts reviewed

1 hx blister type reaction

133 underwent PST

1 negative PST at OSH
1 direct to challenge

1 (1%) Positive PST

3 (2%) Inadequate controls PST

129 (97%) Negative PST

1 inadequate histamine, positive PCN G

2 inadequate histamine, negative PrePen & PCN G

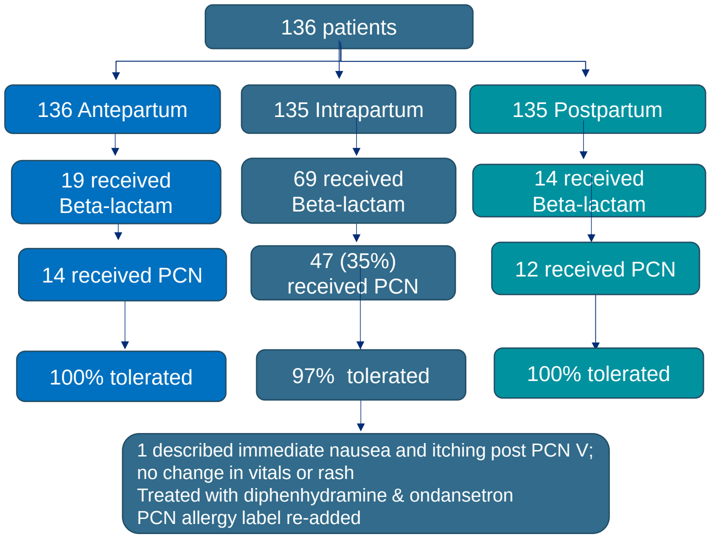
Recommended Avoidance

133 underwent Graded Challenge (Amoxicillin: 118; PCN V:15)

1 developed subjective itch, throat symptoms; resolved without treatment

100% (133) Pass Challenge; label removed

Antibiotic Use in Pregnancy After PCN Allergy Evaluation



136 patients

136 Antepartum

19 received Beta-lactam

14 received PCN

100% tolerated

135 Intrapartum

69 received Beta-lactam

47 (35%) received PCN

97% tolerated

1 described immediate nausea and itching post PCN V; no change in vitals or rash
Treated with diphenhydramine & ondansetron
PCN allergy label re-added

135 Postpartum

14 received Beta-lactam

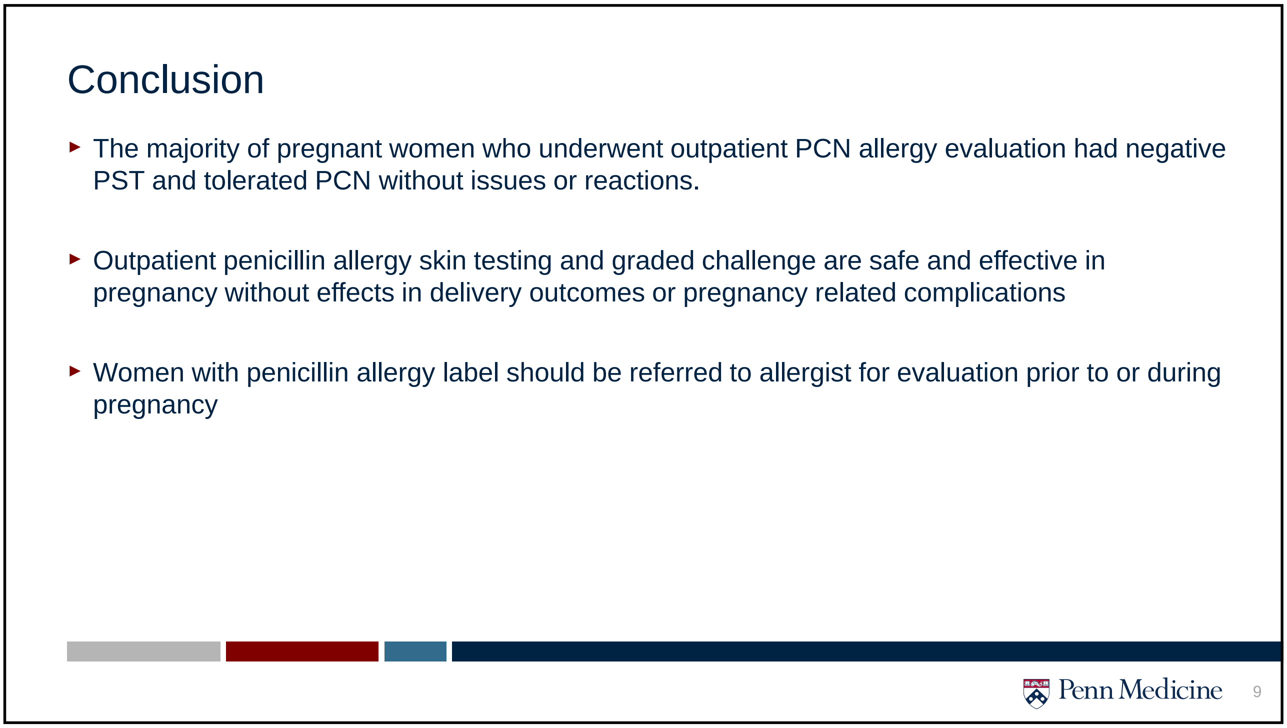
12 received PCN

100% tolerated

Secondary Aims:

Delivery and Pregnancy Outcomes

	All (n=1484)	Penicillin Allergy Eval (n=135)	No Penicillin Allergy Eval (n=1349)	chi^2 p-value
GA at delivery (weeks) (µ +/-SD)	38.5 (2.4)	38.8 (1.5)	38.5 (2.4)	
Type of birth				
Vaginal	452 (30%)	36 (27%)	416 (31%)	0.32
C-section	1032 (70%)	99 (73%)	933 (69%)	
Neonatal birthweights (gms) (µ +/- SD)	3185.5 (625.2)	3289.4(497.0)	3174.3(635.6)	
Complications				
Composite	273 (18%)	18 (13%)	255 (19%)	0.10
Preterm labor	186 (13%)	9 (7%)	177 (13%)	0.03
Gestational hypertension	60 (4%)	6 (4%)	54 (4%)	0.80
Preeclampsia/eclampsia	59 (4%)	5 (4%)	54 (4%)	0.87
Premature rupture of Membranes (PROM)	27 (2%)	5 (4%)	22 (2%)	0.09
Placental abruption	10 (<1%)	1 (<1%)	9 (<1%)	0.92



Conclusion

- The majority of pregnant women who underwent outpatient PCN allergy evaluation had negative PST and tolerated PCN without issues or reactions.
- Outpatient penicillin allergy skin testing and graded challenge are safe and effective in pregnancy without effects in delivery outcomes or pregnancy related complications
- Women with penicillin allergy label should be referred to allergist for evaluation prior to or during pregnancy

Pennsylvania Allergy & Asthma Association

Sulfite Hypersensitivity: A Case of Asthma Triggered by Sulfites

Anthony LaCava, MD

Sunday, June 27, 2021
8:05 a.m. - 8:15 a.m.

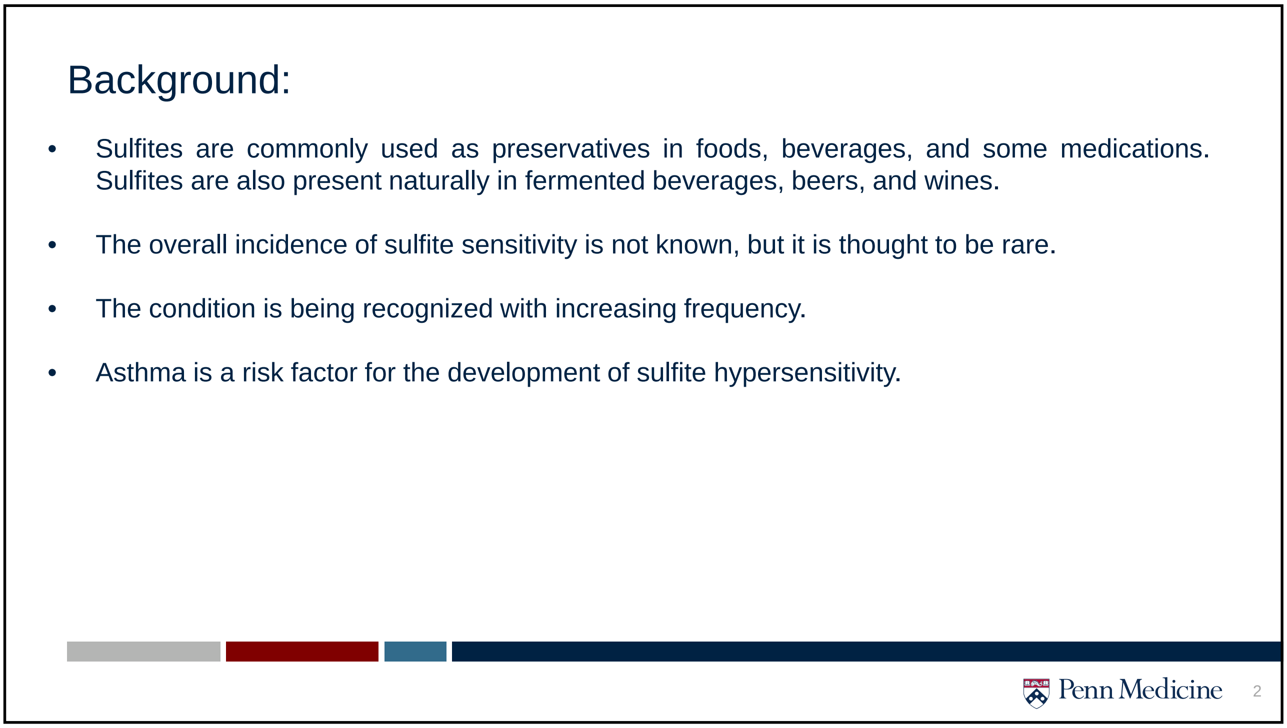
Penn Medicine

Section of Allergy and Immunology

Sulfite Hypersensitivity: A Case of Asthma Triggered by Sulfites

Anthony LaCava MD, Olajumoke Fadugba MD

June 27th, 2021

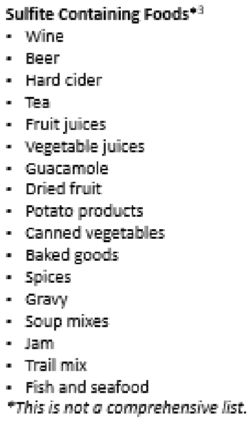


Background:

- Sulfites are commonly used as preservatives in foods, beverages, and some medications. Sulfites are also present naturally in fermented beverages, beers, and wines.
- The overall incidence of sulfite sensitivity is not known, but it is thought to be rare.
- The condition is being recognized with increasing frequency.
- Asthma is a risk factor for the development of sulfite hypersensitivity.

Sulfite Containing Foods and Medications:

- Sulfite Containing Foods:

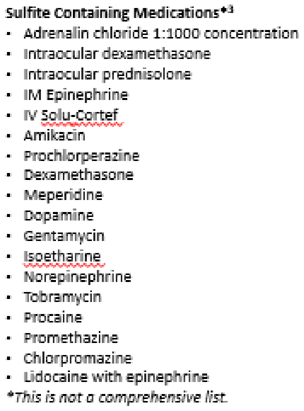


Sulfite Containing Foods*[3]

- Wine
- Beer
- Hard cider
- Tea
- Fruit juices
- Vegetable juices
- Guacamole
- Dried fruit
- Potato products
- Canned vegetables
- Baked goods
- Spices
- Gravy
- Soup mixes
- Jam
- Trail mix
- Fish and seafood

**This is not a comprehensive list.*

- Sulfite Containing Medications:



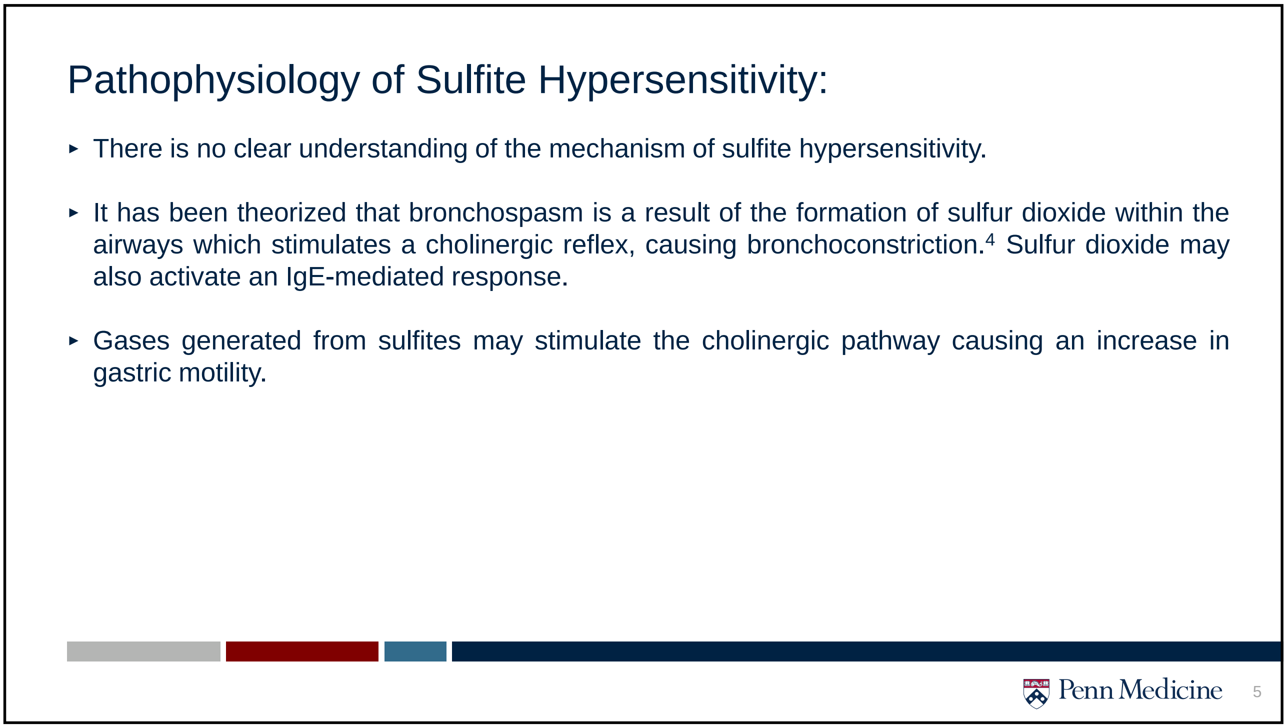
Sulfite Containing Medications*[3]

- Adrenalin chloride 1:1000 concentration
- Intraocular dexamethasone
- Intraocular prednisolone
- IM Epinephrine
- IV Solu-Cortef
- Amikacin
- Prochlorperazine
- Dexamethasone
- Meperidine
- Dopamine
- Gentamycin
- Isoetharine
- Norepinephrine
- Tobramycin
- Procaine
- Promethazine
- Chlorpromazine
- Lidocaine with epinephrine

**This is not a comprehensive list.*

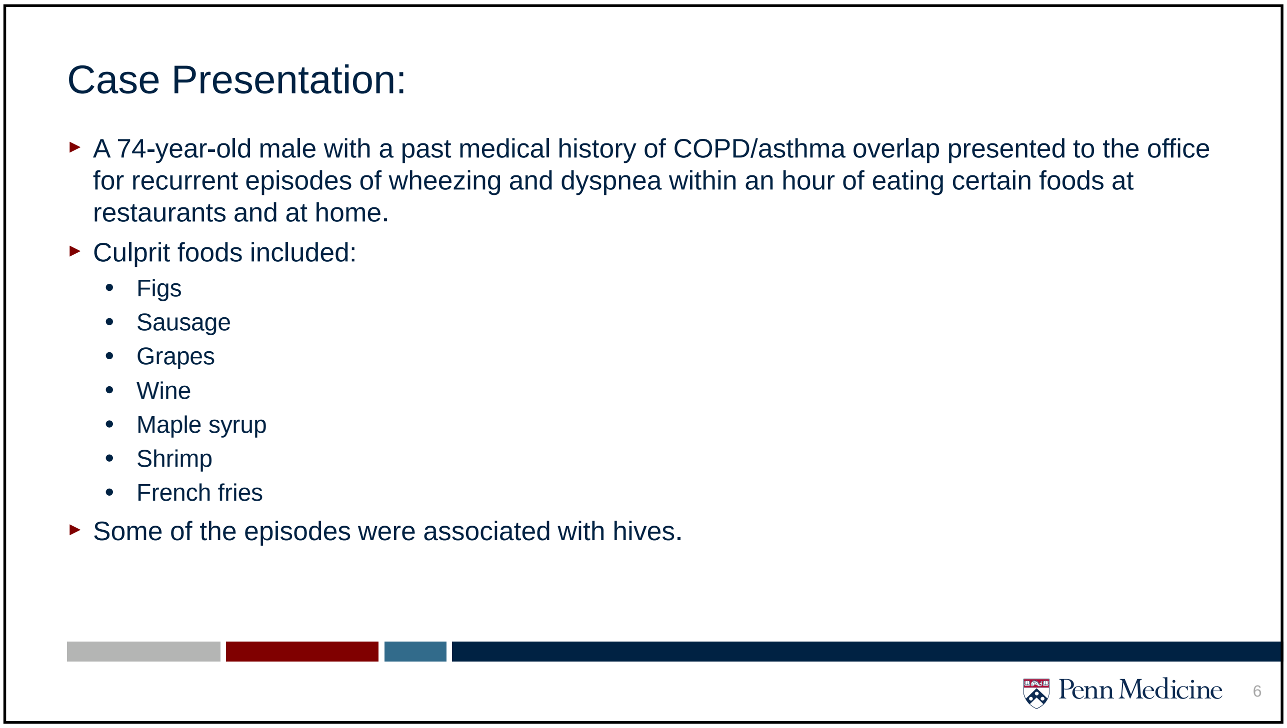
Clinical Manifestations:

- The most frequent clinical manifestation of sulfite hypersensitivity is acute exacerbation of asthma in predisposed individuals.
- It may also manifest with:
  - urticaria and/or angioedema
  - gastrointestinal disturbances (nausea, vomiting, diarrhea, abdominal pain)
  - anaphylaxis
- The pathophysiology of sulfite hypersensitivity is poorly understood.



Pathophysiology of Sulfite Hypersensitivity:

- There is no clear understanding of the mechanism of sulfite hypersensitivity.
- It has been theorized that bronchospasm is a result of the formation of sulfur dioxide within the airways which stimulates a cholinergic reflex, causing bronchoconstriction.[4] Sulfur dioxide may also activate an IgE-mediated response.
- Gases generated from sulfites may stimulate the cholinergic pathway causing an increase in gastric motility.



Case Presentation:

- A 74-year-old male with a past medical history of COPD/asthma overlap presented to the office for recurrent episodes of wheezing and dyspnea within an hour of eating certain foods at restaurants and at home.
- Culprit foods included:
  - Figs
  - Sausage
  - Grapes
  - Wine
  - Maple syrup
  - Shrimp
  - French fries
- Some of the episodes were associated with hives.

Case Presentation:

- Select episodes are described below:
  - He ate a salad from a salad bar and within one hour developed wheezing, shortness of breath and chest tightness, requiring administration of albuterol with relief.
  - He ate apple crumb pie that contained figs on top which triggered asthma symptoms.
  - He develops shortness of breath and wheezing within one hour of eating sausage.
  - He develops hives immediately after eating grapes, red wine, white wine.
  - He experiences shortness of breath and wheezing with maple syrup.
  - He experiences diffuse hives within minutes of consumption of shrimp, crab, lobster, clams, and oysters.

Case Presentation:

- Spirometry was obtained which revealed an FEV1/FVC of 67% and an FEV1 of 71% with a significant bronchodilator response.
- The patient was diagnosed with sulfite sensitivity and was placed on a sulfite-free diet. He was started on Fluticasone-Salmeterol 250-50 mcg one puff twice daily.
- Strict avoidance of sulfite-containing foods and drinks resulted in full control of respiratory symptoms.

Discussion:

- Our patient was able to gain full control of his respiratory symptoms with improved baseline control of his asthma/COPD and with strict avoidance of sulfite-containing foods and drinks.

- While food challenges may be used as confirmatory testing or to exclude sensitivity when pretest probability is low, our patient's history was sufficiently convincing for a sulfite sensitivity.

- As some of his reactions were consistent with possible anaphylaxis, he questioned the safety of using auto-injectable epinephrine, which contains sulfite.
  - However, the general consensus is that the benefit of using epinephrine in an episode of anaphylaxis outweighs the risk. The sulfite level in epinephrine is below the level at which known sulfite-sensitive individuals will react.

Conclusions:

- Sulfite hypersensitivity is rare, but it is increasingly recognized.

- The mechanism of sulfite hypersensitivity is poorly understood, but is thought to involve formation of sulfur dioxide which causes bronchoconstriction via a cholinergic reflex.

- Management consists of optimization and control of baseline asthma (if present), sulfite avoidance measures, bronchodilators for bronchospasm, and epinephrine for anaphylaxis (if indicated).

Thank You!

References:

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Pennsylvania Allergy & Asthma Association

Overview on the Management of EoE

Evan Dellon, MD

Sunday, June 27, 2021
8:15 a.m. - 9:00 a.m.

PAAA does not have permission to share slides

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Pennsylvania Allergy & Asthma Association

Deficiencies of the Innate Immune System

Jordan Orange, MD, PhD

Sunday, June 27, 2021
9:00 a.m. - 9:45 a.m.

Deficiencies of the Innate Immune System …and IEI context

Jordan Orange, MD PhD

Reuben S. Carpentier Professor

Columbia University

Disclosures

- Scientific Advisory Board membership
  - ADMA biologics, Gigagen
- Consultancies
  - CSL, Cytovia, Enzyvant, Editas, Grifols, Sigilon, Sobi, Takeda, Teva
- Editor/Author
  - Up to date

Primary Immunodeficiency / Inborn Errors of Immunity

Genetic inability of the immune system to provide an advantage over the environment

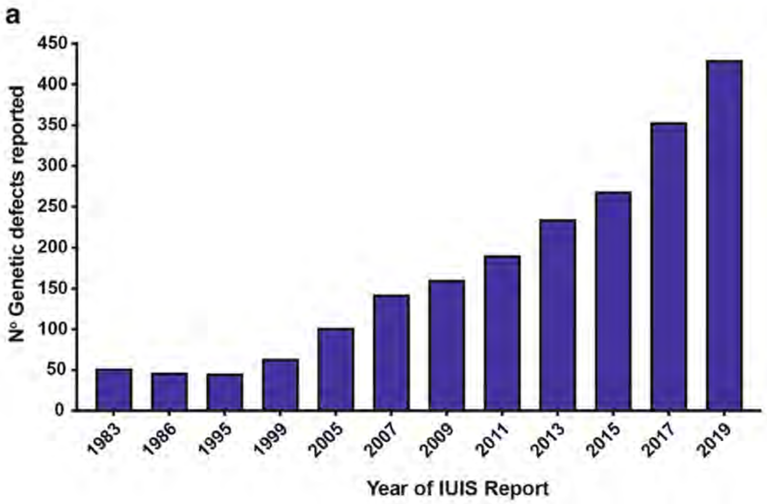
- 2020: >400 diseases
- Uniform newborn screening for SCID
- Banner successes in gene therapy and promise for genetic “surgery”
- Mechanisms informing novel therapies for cancer and autoimmunity (i.e. tofacitinib)
- Insightful and unexpected biology
- Opportunities for precision medicine

The IUIS classification

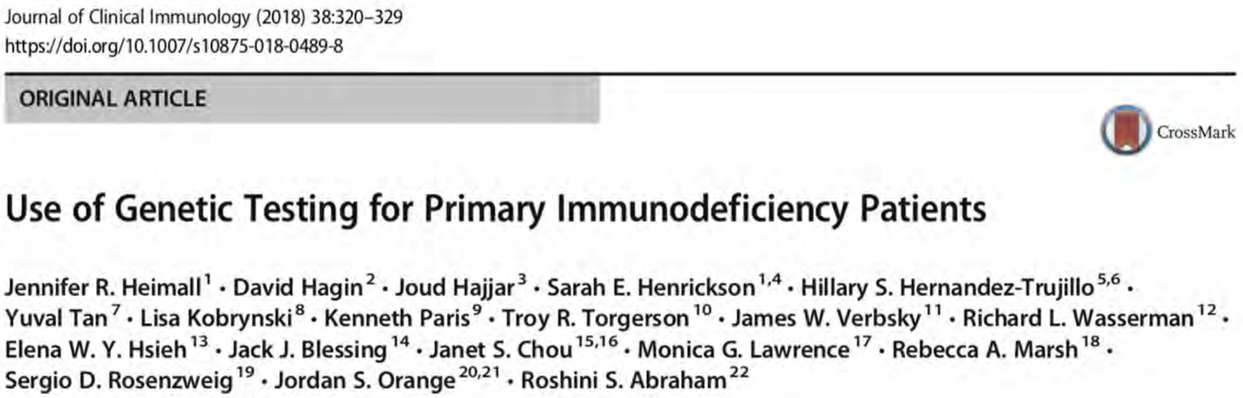
IUIS table #	PIDD classification	#Genes/PIs 2017	#Genes/PIs 2020
1	**Immunodeficiencies affecting cellular and humoral immunity**	49	58
2	**Combined immunodeficiencies with associated or syndromic features**	67	63
3	**Predominantly antibody deficiencies**	40	46
4	**Diseases of immune dysregulation**	40	45
5	**Congenital defects of phagocyte number, function or both**	39	41
6	**Defects in intrinsic and innate immunity**	52	64
7	**Autoinflammatory disorders**	36	42
8	**Complement deficiencies**	30	36
9	***Bone Marrow Failure Syndromes***		43
10	**Phenocopies of PID**	12	12

Total = 416 (64 new genes)

Growth of PIDs (IEIs) is exponential



Open access: https://link.springer.com/article/10.1007%2Fs10875-019-00737-x



Journal of Clinical Immunology (2018) 38:320–329
https://doi.org/10.1007/s10875-018-0489-8

ORIGINAL ARTICLE

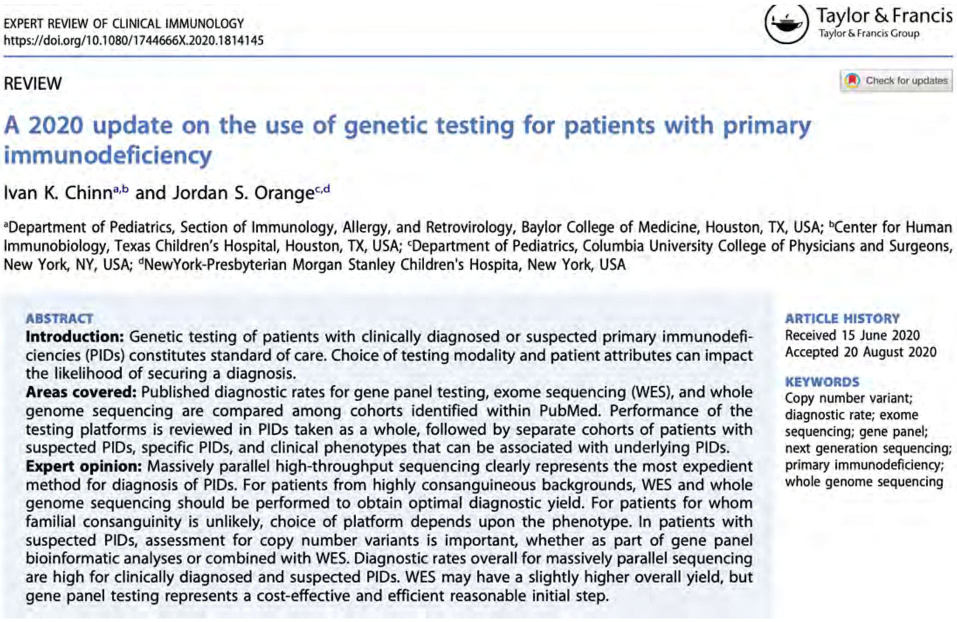
Use of Genetic Testing for Primary Immunodeficiency Patients

Jennifer R. Heimall[1] · David Hagin[2] · Joud Hajjar[3] · Sarah E. Henrickson[1,4] · Hillary S. Hernandez-Trujillo[5,6] · Yuval Tan[7] · Lisa Kobrynski[8] · Kenneth Paris[9] · Troy R. Torgerson[10] · James W. Verbsky[11] · Richard L. Wasserman[12] · Elena W. Y. Hsieh[13] · Jack J. Blessing[14] · Janet S. Chou[15,16] · Monica G. Lawrence[17] · Rebecca A. Marsh[18] · Sergio D. Rosenzweig[19] · Jordan S. Orange[20,21] · Roshini S. Abraham[22]

- Choice of test need by case-by-case
- Follow up genetic or functional tests may be needed
- Genetic testing is not prerequisite to initiate therapy

Types of genetic analyses available

- Sanger “direct” sequencing - individual genes
- “next gen” - massively parallel sequencing panels
- Whole exome sequencing
  - Varying coverage, varying analysis,
- Whole genome sequencing
- RNA seqencing
- Copy number variation (also important)
  - Karyotype, FISH, Chromosomal microarray (CMA, SNPchip)



EXPERT REVIEW OF CLINICAL IMMUNOLOGY
https://doi.org/10.1080/1744666X.2020.1814145

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REVIEW

Check for updates

A 2020 update on the use of genetic testing for patients with primary immunodeficiency

Ivan K. Chinn[a,b] and Jordan S. Orange[c,d]

[a]Department of Pediatrics, Section of Immunology, Allergy, and Retrovirology, Baylor College of Medicine, Houston, TX, USA; [b]Center for Human Immunobiology, Texas Children’s Hospital, Houston, TX, USA; [c]Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY, USA; [d]NewYork-Presbyterian Morgan Stanley Children's Hospita, New York, USA

ABSTRACT

Introduction: Genetic testing of patients with clinically diagnosed or suspected primary immunodeficiencies (PIDs) constitutes standard of care. Choice of testing modality and patient attributes can impact the likelihood of securing a diagnosis.

Areas covered: Published diagnostic rates for gene panel testing, exome sequencing (WES), and whole genome sequencing are compared among cohorts identified within PubMed. Performance of the testing platforms is reviewed in PIDs taken as a whole, followed by separate cohorts of patients with suspected PIDs, specific PIDs, and clinical phenotypes that can be associated with underlying PIDs.

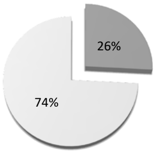
Expert opinion: Massively parallel high-throughput sequencing clearly represents the most expedient method for diagnosis of PIDs. For patients from highly consanguineous backgrounds, WES and whole genome sequencing should be performed to obtain optimal diagnostic yield. For patients for whom familial consanguinity is unlikely, choice of platform depends upon the phenotype. In patients with suspected PIDs, assessment for copy number variants is important, whether as part of gene panel bioinformatic analyses or combined with WES. Diagnostic rates overall for massively parallel sequencing are high for clinically diagnosed and suspected PIDs. WES may have a slightly higher overall yield, but gene panel testing represents a cost-effective and efficient reasonable initial step.

ARTICLE HISTORY
Received 15 June 2020
Accepted 20 August 2020

KEYWORDS
Copy number variant; diagnostic rate; exome sequencing; gene panel; next generation sequencing; primary immunodeficiency; whole genome sequencing

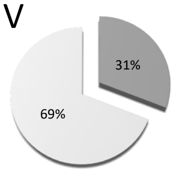
Diagnostic yield

NGS



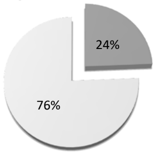
Total *n* = 1,196
(16 studies)

ES + CNV



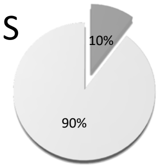
Total *n* = 542
(4 studies)

ES



Total *n* = 435
(8 studies)

WGS



Total *n* = 886
(1 study)

Ivan Chinn and Jordan Orange

Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders

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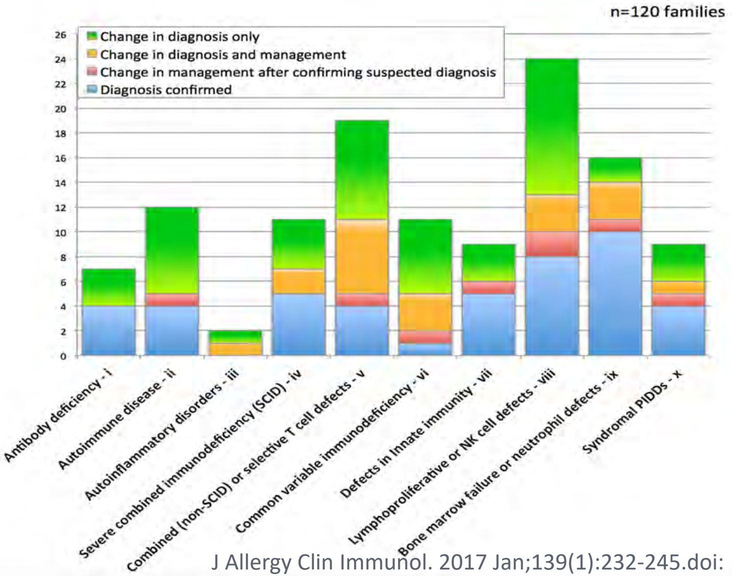
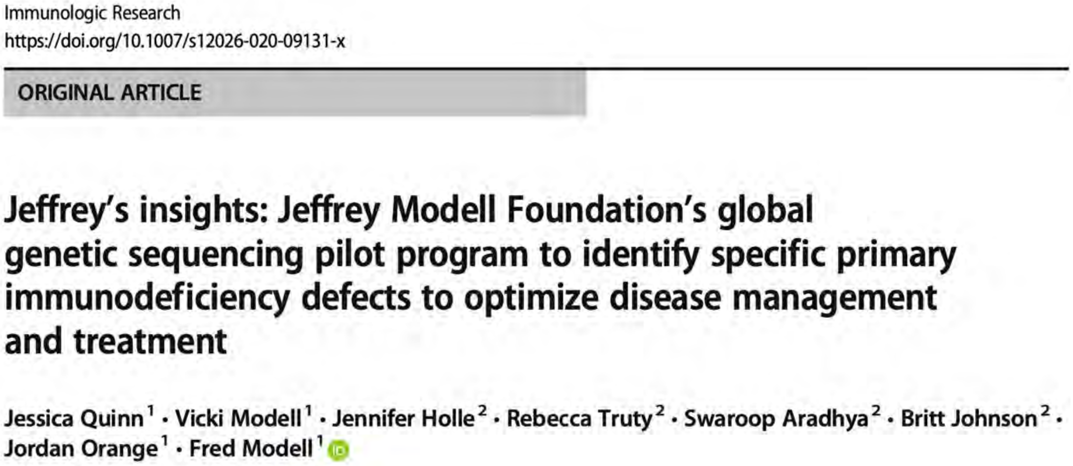
**Asbjørg Stray-Pedersen, MD, PhD,[a,b,c,d,e]* Hanne Sørmo Sorte, MS,[f,g]* Pubudu Samarakoon, MS,[f,g]
Tomasz Gambin, PhD,[a,h] Ivan K. Chinn, MD,[b,c,i] Zeynep H. Coban Akdemir, PhD,[a] Hans Christian Erichsen, MD, PhD,[e]
Lisa R. Forbes, MD,[b,c,i] Shen Gu, PhD,[a] Bo Yuan, PhD,[a,j] Shalini N. Jhangiani, MS,[a,j,k] Donna M. Muzny, MS,[a,j,k]
Olaug Kristin Rødningen, PhD,[f] Ying Sheng, PhD,[f] Sarah K. Nicholas, MD, PhD,[b,c,i] Lenora M. Noroski, MD, MPH,[c,i]
Filiz O. Seeborg, MD, MPH,[c,i] Carla M. Davis, MD,[c,i] Debra L. Canter, MS,[c,i] Emily M. Mace, PhD,[b,c] Timothy J. Vece, MD,[i]
Carl E. Allen, MD, PhD,[i,l,m] Harshal A. Abhyankar, MS,[i,l,m] Philip M. Boone, MD, PhD,[a,j] Christine R. Beck, PhD,[a,j]
Wojciech Wiszniewski, MD, PhD,[a,j] Børre Fevang, MD, PhD,[g,n] Pål Aukrust, MD, PhD,[g,n]
Geir E. Tjønnfjord, MD, PhD,[g,o] Tobias Gedde-Dahl, MD, PhD,[o] Henrik Hjorth-Hansen, MD, PhD,[p,q]
Ingunn Dybedal, MD, PhD,[o] Ingvild Nordøy, MD, PhD,[g,n] Silje F. Jørgensen, MD,[n] Tore G. Abrahamsen, MD, PhD,[e,g]
Torstein Øverland, MD,[e] Anne Grete Bechensteen, MD, PhD,[e] Vegard Skogen, MD, PhD,[r] Liv T. N. Osnes, MD, PhD,[s]
Mari Ann Kulseth, PhD,[f] Trine E. Prescott, MD,[f] Cecilie F. Rustad, MD,[f] Ketil R. Heimdal, MD, PhD,[f]
John W. Belmont, MD, PhD,[j] Nicholas L. Rider, DO,[b,c,i] Javier Chinen, MD, PhD,[c,i] Tram N. Cao, MS,[b,c,i] Eric A. Smith, BSc,[t]
Maria Soledad Caldirola, BSc,[u] Liliana Bezrodnik, MD,[u] Saul Oswaldo Lugo Reyes, MD,[v]
Francisco J. Espinosa Rosales, MD,[v] Nina Denisse Guerrero-Cursaru, BSc,[w] Luis Alberto Pedroza, PhD,[w]
Cecilia M. Poli, MD,[b,x] Jose L. Franco, MD, PhD,[y] Claudia M. Trujillo Vargas, PhD,[y] Juan Carlos Aldave Becerra, MD,[z]
Nicola Wright, MD,[aa] Thomas B. Issekutz, MD,[bb] Andrew C. Issekutz, MD,[bb] Jordan Abbott, MD,[cc]
Jason W. Caldwell, DO,[dd] Diana K. Bayer, DO,[ee] Alice Y. Chan, MD, PhD,[ff] Alessandro Aiuti, MD, PhD,[gg]
Caterina Cancrini, MD, PhD,[hh] Eva Holmberg, MD,[ii] Christina West, MD, PhD,[jj] Magnus Burstedt, MD, PhD,[ii]
Ender Karaca, MD,[a] Gözde Yesil, MD,[a,kk] Hasibe Artac, MD,[ll] Yavuz Bayram, MD,[a] Mehmed Musa Atik, BSc,[a]
Mohammad K. Eldomery, MD,[a] Mohammad S. Ehlayel, MD, PhD,[mm] Stephen Jolles, MD, PhD,[nn] Berit Flatø, MD, PhD,[oo]
Alison A. Bertuch, MD, PhD,[i,l] I. Celine Hanson, MD,[b,c,i] Victor W. Zhang, PhD,[j] Lee-Jun Wong, PhD,[j] Jianhong Hu, PhD,[j,k]
Magdalena Walkiewicz, PhD,[j] Yaping Yang, PhD,[j] Christine M. Eng, MD,[j] Eric Boerwinkle, PhD,[a,k,pp]
Richard A. Gibbs, PhD,[a,j,k] William T. Shearer, MD, PhD,[c,i] Robert Lyle, PhD,[f] Jordan S. Orange, MD, PhD,[b,c,i]‡ and
James R. Lupski, MD, PhD, DSc (Hon)[a,i,j,k]‡** *Houston, Tex; Oslo, Trondheim, and Tromsø, Norway; Warsaw, Poland; Buenos Aires, Argentina; Mexico City, Mexico; Quito, Ecuador; Santiago, Chile; Medellin, Colombia; Lima, Peru; Alberta, Calgary, and Halifax, Nova Scotia, Canada; Denver, Colo; Winston-Salem, NC; Iowa City, Iowa; San Francisco, Calif; Milan and Rome, Italy; Umeå, Sweden; Istanbul and Konya, Turkey; Doha and Ar-Rayyan, Qatar; and Cardiff, United Kingdom*

Getting an answer: Therapeutic Implications



J Allergy Clin Immunol. 2017 Jan;139(1):232-245.doi: 10.1016/j.jaci.2016.05.042.

Pretest probability at work



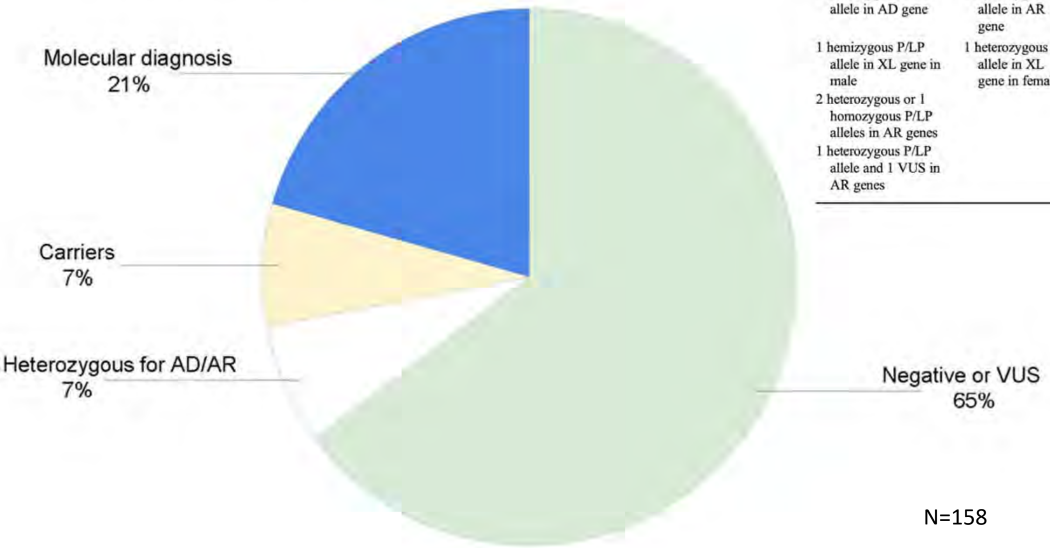
Immunologic Research
https://doi.org/10.1007/s12026-020-09131-x

ORIGINAL ARTICLE

Jeffrey's insights: Jeffrey Modell Foundation's global genetic sequencing pilot program to identify specific primary immunodeficiency defects to optimize disease management and treatment

Jessica Quinn[1] · Vicki Modell[1] · Jennifer Holle[2] · Rebecca Truty[2] · Swaroop Aradhya[2] · Britt Johnson[2] · Jordan Orange[1] · Fred Modell[1]

Pretest probability at work



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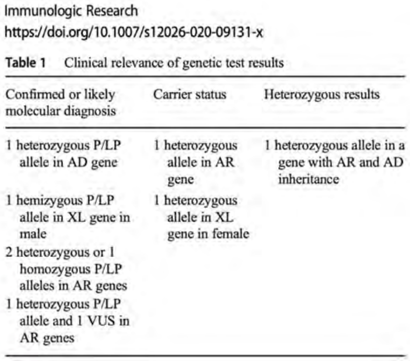


Immunologic Research
https://doi.org/10.1007/s12026-020-09131-x

Table 1 Clinical relevance of genetic test results

Confirmed or likely molecular diagnosis	Carrier status	Heterozygous results
1 heterozygous P/LP allele in AD gene	1 heterozygous allele in AR gene	1 heterozygous allele in a gene with AR and AD inheritance
1 hemizygous P/LP allele in XL gene in male	1 heterozygous allele in XL gene in female	
2 heterozygous or 1 homozygous P/LP alleles in AR genes		
1 heterozygous P/LP allele and 1 VUS in AR genes		

Innate Immunity - Definition

HARDWIRED immune defense against foreign or dangerous material

All function is encoded within the germline DNA

Danger

Foreign

Three paradigms in innate immunity

1. Recognition
2. Amplification
3. Response

Recognition

Distinguishing good from bad

- Pattern recognition
- Danger
  - Foreign (foreign and dangerous)
    - Non-self (yes – think pathogen)
    - But, not all non-self is dangerous (think food)
  - Alarm (think cancer)
  - Damage (think stress)
  - Innate vs adaptive (adaptive cells can use innate systems)
  - Lectins/collectins (MBL)
  - Antimicrobial peptides
- Dedicated Pattern Recognition Receptors (PRRs)

Amplification

Generation of a signal after recognition to enable a response

- Intracellular
  - Adaptors, kinases, GEFs
  - Result in Ca^{++} fluxes, motor functions
  - transcriptional activation.
- Extracellular
  - Chemokines
  - Anaphalotoxins C3a, C4a, C5a

Response

Function directed at eliminating or containing danger

- Inflammation
  - Effects on local physiology (vascular permeability, Î blood flow, endothelial activation)
- Innate effector mechanisms
  - Soluble proteins (antimicrobials, complement, apoptosis inducing)
  - Phagocytosis - reactive metabolites
  - Cytotoxicity
- Initiation of adaptive immunity
  - Cytokines (polarize T cells, increase adhesion)
  - Chemokines - Recruit adaptive immune cells
  - Costimulation - to adaptive immune cells
  - Antigen processing

Pattern Recognition

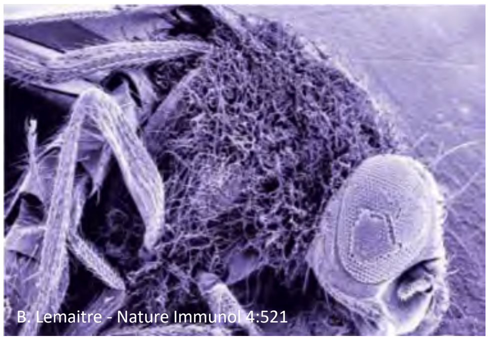
- A central theme in innate immunity
  - Inherent means to call immunity into action
- Pattern Recognition Receptors (PRRs)
  - Germline DNA-encoded means for immediate recognition of danger
  - Arguably appreciated decades
  - Defined as such after discovery of Toll-like receptor (TLR) system
- PAMP – pathogen-associated molecular pattern
- DAMP – Danger-associated molecular pattern

Pattern Recognition Receptors

- Five broad structurally defined families
  - Leucine rich repeat (LRR) containing
    - Toll-like receptors (TLRs), NOD-like receptors (NLRs)
  - RNA-sensing RIG-I-like receptors (RLRs)
    - Retinoic acid inducible gene I (RIG-I)
  - DExD/Hbox Helicases (DDX)
  - Pyrin and HIN domain-containing (PYHIN)
  - C-type lectin receptors (CLRs)
    - Dectin-1
- Sub-cellular location specific
  - Cell surface (TLRs, CLRs)
  - Endosomal (TLRs)
  - Cytoplasmic (RLRs, NLRs)

Toll-like receptors (TLRs)

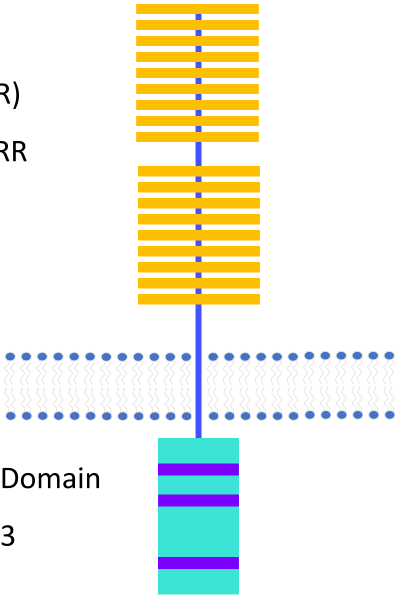
The beginning of PRR and the most established LRR-containing PRRs



B. Lemaitre - Nature Immunol 4:521

Nature Rev. Immunol. 2013 13:454

Toll-like receptors (TLRs) - Recognition



Leucine Rich Repeats (LRR)

19-25 tandem copies of LRR

XLXXLXLXX

Toll/IL-1receptor (TIR) Domain

Box1, Box2, Box3

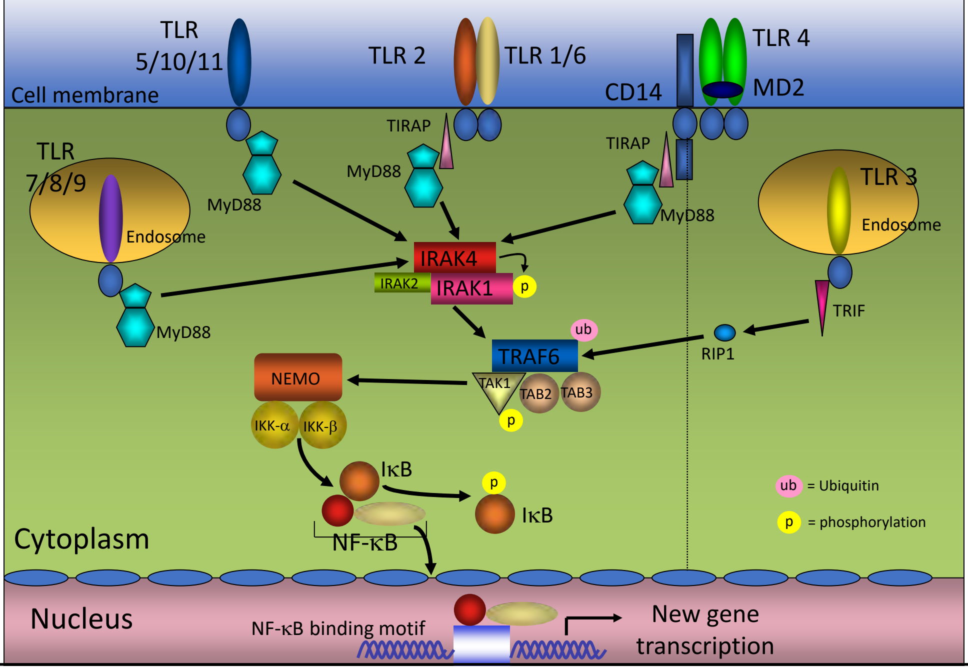
10 human TLRs (1-10), TLR11-13 are mice only!

TLRs and their exemplary ligands

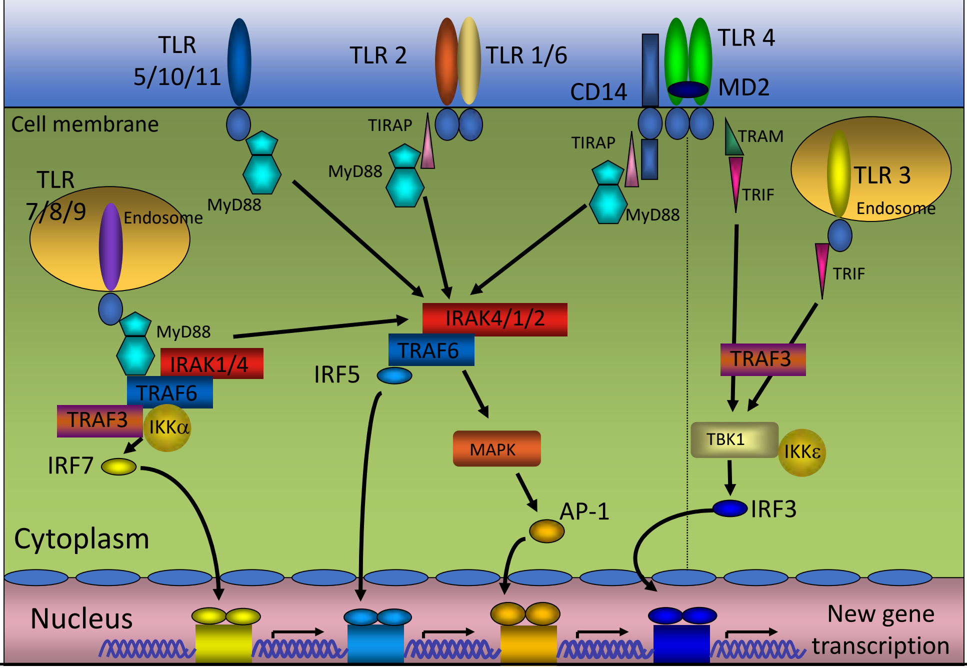
Recognize both PAMPs and DAMPs

TLR	Location	Ligand	Source
TLR1/2	surface	Lipoarabinomannan, Triacyl lipopetides	Mycobacteria Bacteria
TLR2±6	surface	Zymosan, Peptidoglycan HSP70	Fungi, Bacteria Host
TLR3	endosomal	ds RNA	Viruses
TLR4	surface	lipopolysaccharide RSV fusion protein HSP70	Gr- bacteria RSV Host
TLR5	surface	Flagellin	Flagelated bacteria
TLR6/2	surface	Diacyl lipopeptides	Mycoplasma
TLR7/8	endosomal	ss GU RNA, Short dsRNA Imidazoquinolones	Viruses Synthetic
TLR9	endosomal	Unmethylated CpG motifs	Bacteria, DNA viruses
TLR10	Unknown	Influenza triggered	Influenza virus

TLR signal generation to NF-κB after ligation



TLR induction of other transcription factors



Important targets of TLR-induced transcription factors Amplification - Response

- NF-κB - ggg ACT TTC C (ggg RNN YYC C, R=purine Y=pyrimidine)
  Pro inflammatory cytokines - TNF, IL-1, IL-6, IL-12,
  Adhesion molecules, Antimicrobial peptides,
  Chemokines, iNOS, Other transcription factors (IRFs)
  Apoptosis regulators, Complement components (some)
  Antigen processing machinery, Immunoglobulin genes
- Interferon regluatory factor (IRF)3 - IFNβ, chemokines
- IRF7 - IFNα, IFNβ , chemokines
- IRF5 - Pro inflammatory cytokines
- AP-1 - Pro inflammatory cytokines

NOD-like receptors NLRs

- **Nucleotide-binding oligomerization domain (NOD)**
- Cytoplasmic sensing
- Nucleotide binding domain and a LRR
  - Can include a CARD or Pyrin domain
- Over 20 different NLRs
  - Ligation leads to inflammasome induction
    - cell death (pyroptosis)
    - proinflammatory cytokine (IL-1β, IL-18)
    - Procaspase-1 secretion

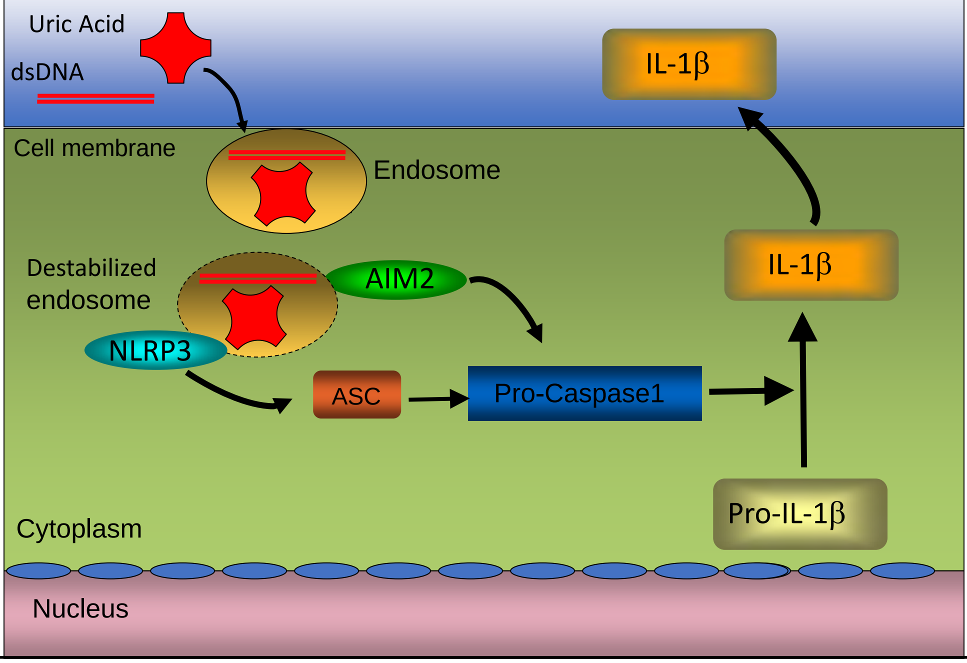
Major NLR PRR types

- NOD family
  - NOD2 binds peptidoglycan Muramyldipeptide
    - Mutated in Crohn’s disease (<30%)
- NALP family (AKA NLRP)
  - **Nacht domain leucine-rich repeat and PYD containing proteins (NALPs)**
  - NALP3 (cryopyrin, NLRP3)
    - Recognizes Alum (vaccine adjuvant)
    - Mutated in autoinflammatory diseases
    - Muckle-wells, CINCA, Familial cold autoinflammatory syndrome
  - NALP1 (NLRP1)
    - Recognizes bacterial muramyldipeptide

PYHIN - PRRs

- **PYrin and HIN domain-containing**
- AIM (absent in melanoma) family
  - non-NLR but functional overlap
  - AIM2 –First identified cytosolic DNA sensor
- IFI16 (Interferon-γ inducible protein 16)
  - Nuclear localization
  - Senses viral DNA
  - Signals through STING (Stimulator of InTerferon Genes protein) to produce type-I interferon

NLR inflammasome



Uric Acid

dsDNA

IL-1β

Cell membrane

Endosome

Destabilized endosome

AIM2

IL-1β

NLRP3

ASC

Pro-Caspase1

Pro-IL-1β

Cytoplasm

Nucleus

RLR PRRs

- **RNA-sensing RIG-I-like receptors**
- Cytoplasmic sensors
- Viral RNA sensors (dsRNA, <u>cytosolic DNA</u>)
- RIG1 (retinoic acid inducible gene I)
  - Discovered for TLR-independent sensing of viral RNA[1]
  - RNA helicase
  - TLR-independent induction of IFN by dsRNA
  - Recognizes in vitro transcribed dsRNA, influenza, paramyxovirus[2]
- MDA5 (Melanoma-differentiation associated gene 5)
  - RNA helicase that complexes with RIG1
  - Recognizes poly I:C, picornavirus[2]
  - Both unwind dsRNA to enable signaling through assembled complex via CARD domain[3]

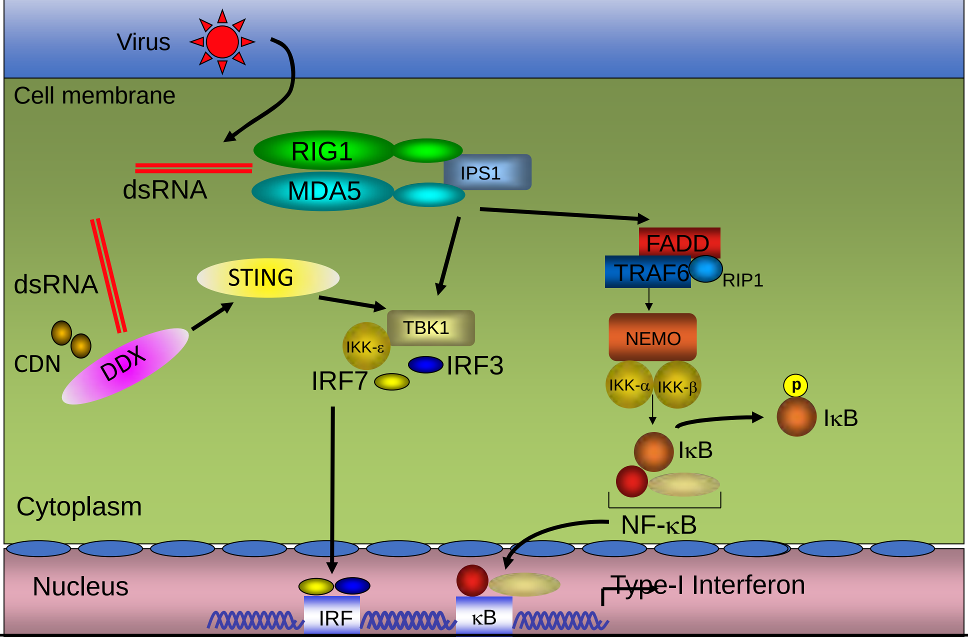
[1]Kato, et. al. Immunity 2005 23:19, [2]Kato, et. al. Nature 2006 441:101, [2]Ishii, et. al. Nat. Immunol. 2006 7:40,

DDX PRRs

- **DDX family (DExD/H box helicases)**
  - DDX3, DDX9, DDC36, DDX41, DDX60
- Cytoplasmic sensor
- Sense cytosolic DNA and cyclic dinucleotides (CDNs)
- Activate STING (Stimulator of InTerferon Genes protein)
- STING activation leads to type-I interferon production – STING can also bind CDNs
  - TMEM173 gene
  - Gain of function mutation results in SAVI syndrome (STING-associated vasculopathy with onset in infancy)[2]

[1]Zhang, et. al. Nat. Immunol 2011 12:959 [2]Liu, et. al, NEJM 2014 371:507

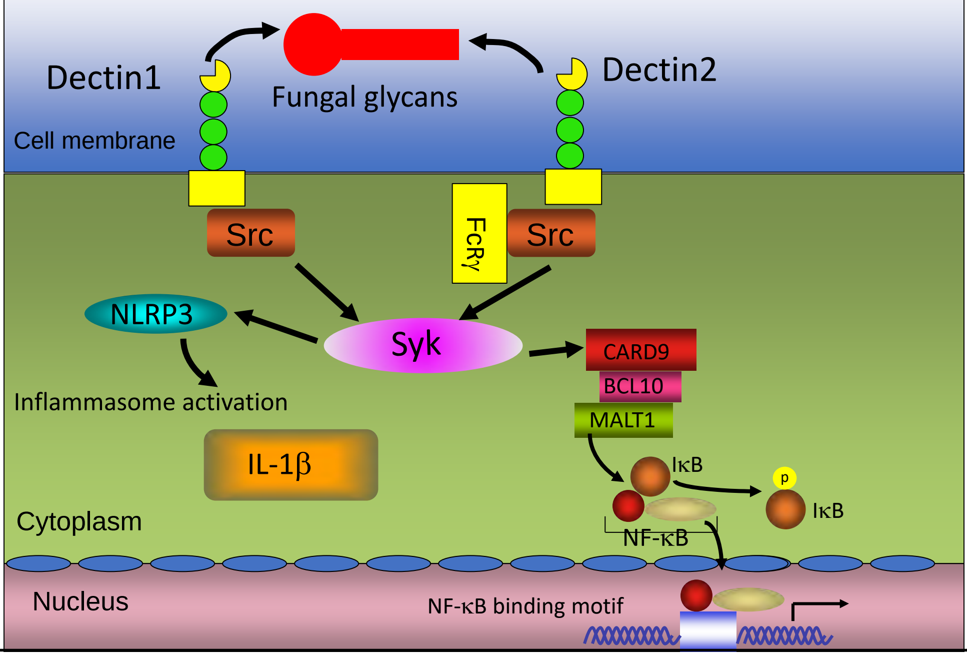
RLR and DDX cytoplasmic sensors



C-type lectin receptor (CLR) PRRs

- Cell surface sensors
- Dectin-1/2
  - recognizes fungal cell wall β-glucan (mold allergen uptake)
  - Induces – Syk/CARD9
  - Pathway promotes TH-17 response
- DC sign
  - Recognizes sugars containing mannose and fucose
  - Binds facilitates cell entry of allergens (Arah1/Der p1/2)
- Mannose Receptor
  - Sugars terminating mannose, fucose, or *N*-acetylglucosamine
  - Broad pathogen recognition - Includes candida
  - Facilitates allergen cell entry – Der p1/2, Ara h1

CLR fungal sensing



Innate immune defects and IEIs

- Any phase of innate immunity – recognition, amplification, response – can be defective.
  - Innate disorders can affect one or more phases
- Abnormal susceptibility or response to routine environmental exposures
  - Can lead to infection or inflammation
- Broad array of defects
  - pattern recognition
  - NK cells
  - Complement
  - Inflammasome
  - Phagocytes
- For the purposes of IUIS are table 5 and separately consider others even though they are part of ”innate immunity”


Happy Homemakers


cluster of E. coli on a food particle

US Agricultural research service

The IUIS classification – “innate immunity 228”

IUIS table #	PIDD classification	#Genes/PIs 2017	#Genes/PIs 2020
1	**Immunodeficiencies affecting cellular and humoral immunity**	49	58
2	**Combined immunodeficiencies with associated or syndromic features**	67	63
3	**Predominantly antibody deficiencies**	40	46
4	**Diseases of immune dysregulation**	40	45
5	**Congenital defects of phagocyte number, function or both**	39	41
6	**Defects in intrinsic and innate immunity**	52	64
7	**Autoinflammatory disorders**	36	42
8	**Complement deficiencies**	30	36
9	***Bone Marrow Failure Syndromes***		43
10	**Phenocopies of PID**	12	12

Total = 416 (64 new genes)

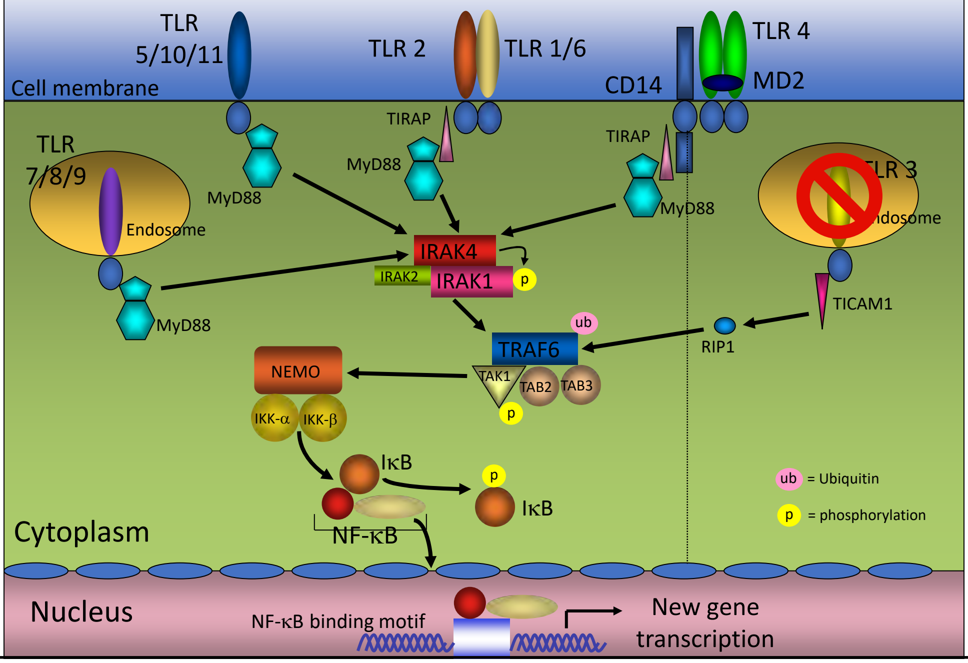
The IUIS defects in intrinsic and innate immunity 64 diseases 2020

- Mendelian susceptibility to mycobacterial disease
  - IL12RB1, IL12B, IL12RB2, IL23R, IFNGR1, IFNGR2, STAT1lof, CYBB, IRF8, SPPL2A, TYK2, ISG15, RORC, JAK1
- Epidermodysplasia verruciformis
  - TMC6, TMC8, CIB1, CXCR4
- Severe viral predisposition
  - STAT1lof, STAT2, IRF9, IRF7, IFNAR1, INFAR2, FCGR3A, MDA5, POLR3A/C/F
- Herpes simplex encephalitis
  - TLR3, UNC93B1, TRAF3, TICAM1, TBK1, RIF3, DBR1
- Invasive fungal disease
  - CARD9
- Mucocutaneous candidiasis
  - IL17RA/C/F, STAT1gof, TRAF3IP2
- TLR signaling deficiency with bacterial susceptibility
  - IRAK4, MYD88, IRAK1, TIRAP
- Non hematopoietic
  - RPSA, HMOX, NBAS, RANBP2, CLCN7, SNX10, OSTM1, PLEKHM1, TCIRG1, TNFSF11, NCTSN, PSEN, PSENEN
- Others
  - IRF4, IL18BP

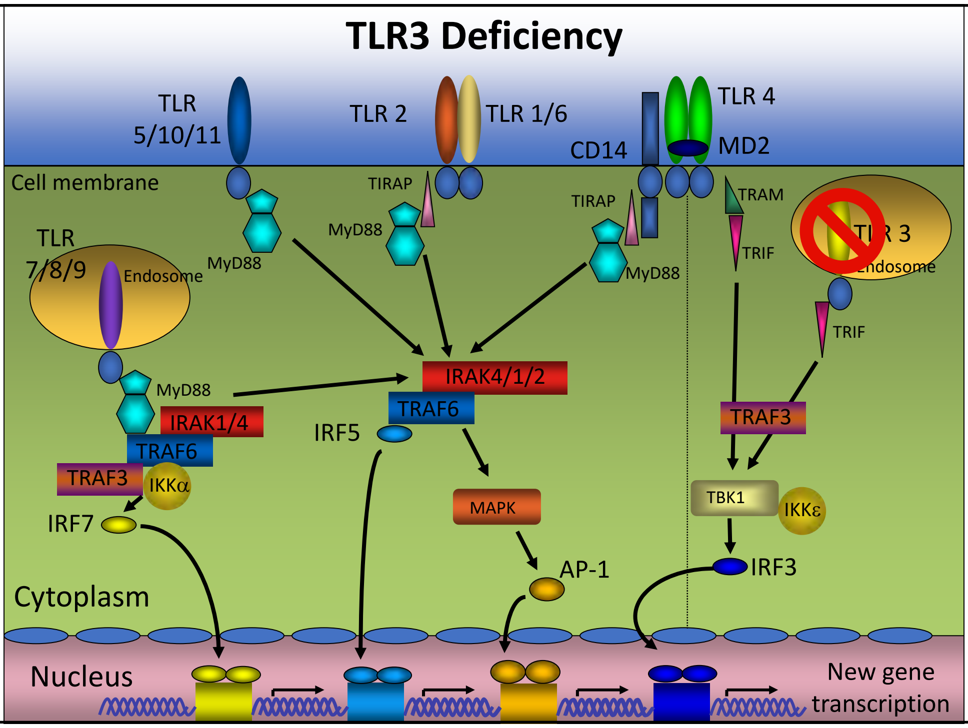
Innate defects – 3 examples

- TLR
- Fungal recognition
- Severe COVID-19

TLR3 Deficiency

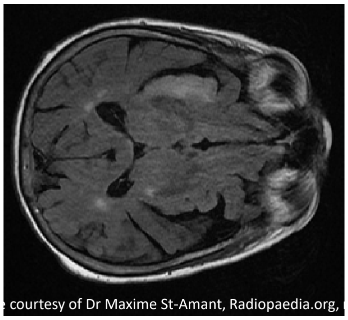


TLR3 Deficiency

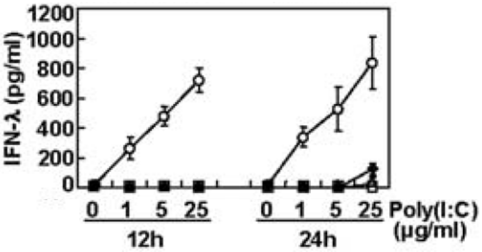


TLR3 deficiency

- HSV encephalitis (HSE)
- Influenza cerebritis
- **Autosomal dominant**
- Defective IFN-α, -β and -λ production
  - CNS role for IFN-λ



courtesy of Dr Maxime St-Amant, Radiopaedia.org,



14 SEPTEMBER 2007 VOL 317 SCIENCE

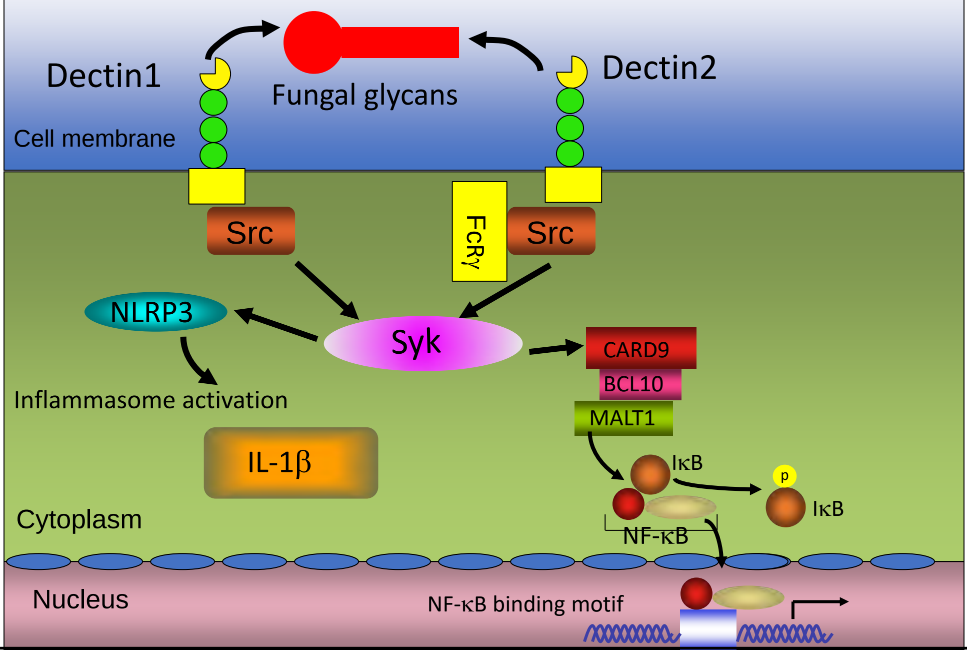
Chronic Mucocutaneous Candidiasis

- Chronic non-invasive Candidal infections
  - Oral thrush +/- esophageal involvement
  - Vulvovaginal Candidiasis
  - Candidal dermatitis
  - Candidal Onychomycosis
- Can present in childhood through adulthood

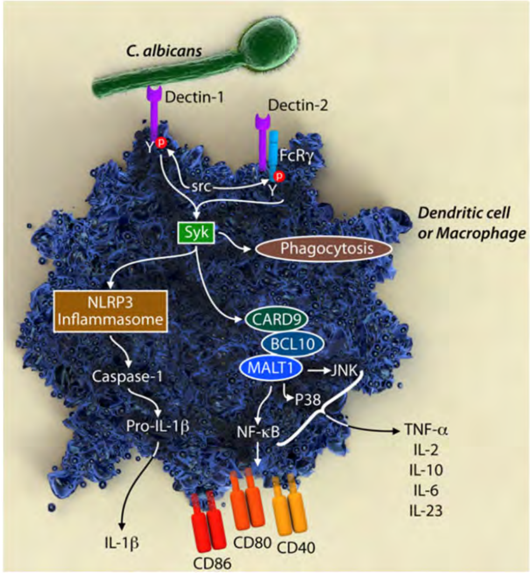
Chronic Mucocutaneous Candidiasis

Courtesy of Kate Sullivan MD, PhD

CLR fungal sensing



CMCC: breakdown in innate Candida immunity



J Allergy Clin Immunol. 2012 Feb;129(2):294-305

- Dectin-1 -> fungal β-glucan
- Induces – Syk/CARD9
  - Pathway prompotes TH-17 response
- Dectin-1 mutation (truncation)
  - Fails to bind β-glucan
  - Strictly mucocutateous
- CARD9 mutation (no expression)
  - Some invasive infection “deep dermatophytosis”
- IL-17F, IL-17RA (receptor), STAT1 GOF
  - Mostly TH-17 cell, but illustrate the point

What about COVID?
Yes… innate immunity IEI

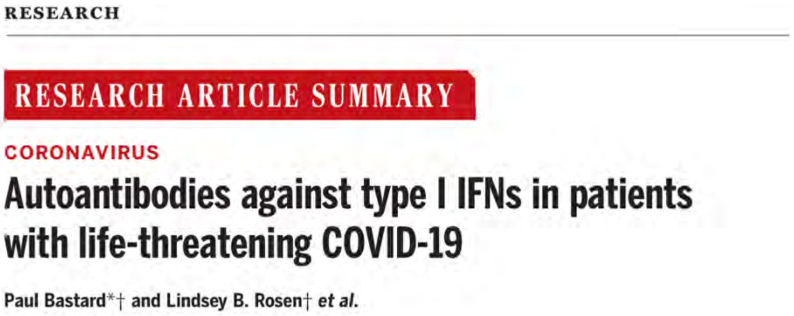
RESEARCH

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Qian Zhang *et al.*



RESEARCH

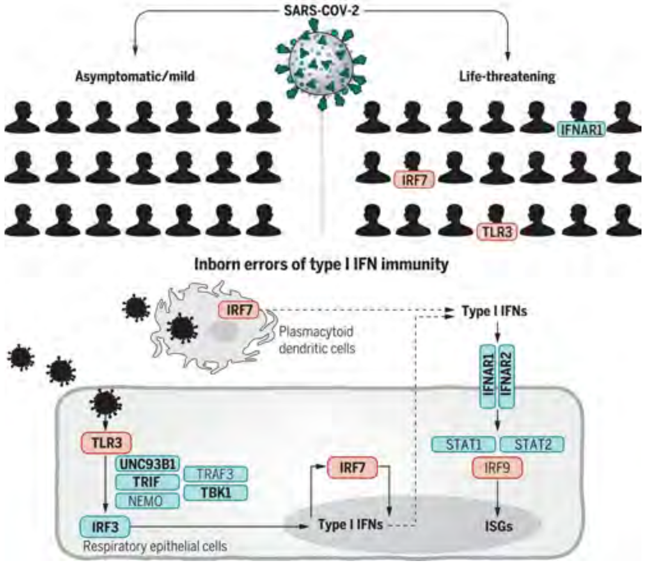
RESEARCH ARTICLE SUMMARY

CORONAVIRUS

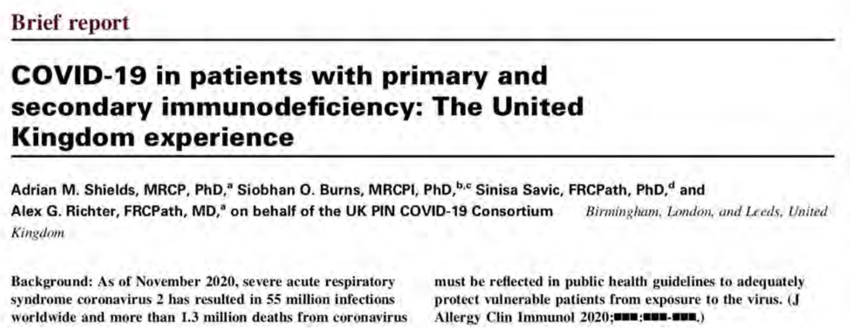
Autoantibodies against type I IFNs in patients with life-threatening COVID-19

Paul Bastard*† and Lindsey B. Rosen† *et al.*

Inborn errors of TLR3- and IRF7-dependent type I IFN production and amplification underlie life-threatening COVID-19 pneumonia.



Qian Zhang et al. Science 2020;370:eabd4570



Brief report

COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience

Adrian M. Shields, MRCP, PhD,[a] Siobhan O. Burns, MRCPI, PhD,[b,c] Sinisa Savic, FRCPath, PhD,[d] and Alex G. Richter, FRCPath, MD,[a] on behalf of the UK PIN COVID-19 Consortium *Birmingham, London, and Leeds, United Kingdom*

Background: As of November 2020, severe acute respiratory syndrome coronavirus 2 has resulted in 55 million infections worldwide and more than 1.3 million deaths from coronavirus

must be reflected in public health guidelines to adequately protect vulnerable patients from exposure to the virus. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

- PID n=67 (inpatient mortality = 37.5%), CVID mode
  - Case Fatality Ratio 31.6%
  - Infection-fatality ratio 20.0%
  - Univariate risks for hospitalization, Age, prophylactic abx, Diabetes, heart disease
  - Univariate risks for death, Age, lymphopenia, Diabetes, Renal disease
- SID n=33 (inpatient mortality = 44.0%)
  - Case Fatality Ratio 39.2%
  - Infection-fatality ratio 33.3%
  - Univariate risks for hospitalization, Age
  - Univariate risks for death, none!

Conclusions

- PID/IEI has entered a meaningful new genomic era and underscore the contributions of elements of host defense and immune function
- Pretest probability by an immunologist equates to roughly a 25% genetic diagnostic yield
- Innate immunity underlies initial defenses and immune control and mechanisms of Recognition/Amplification/Response underlie 4 IEI categories accounting for 223 diseases
- There are 64 IEI specifically defined as innate and inherent immunity
- COVID-19 uncovers particular innate PIDs having overall high CFR/IFR

Pennsylvania Allergy & Asthma Association

Controversies in EoE

Evan Dellon, MD

Sunday, June 27, 2021
10:00 a.m. - 10:45 a.m.

PAAA does not have permission to share slides

Pennsylvania Allergy & Asthma Association

NK Cell Function and Deficiences

Jordan Orange, MD, PhD

Sunday, June 27, 2021
10:45 a.m. - 11:30 a.m.

NK cell function and deficiencies

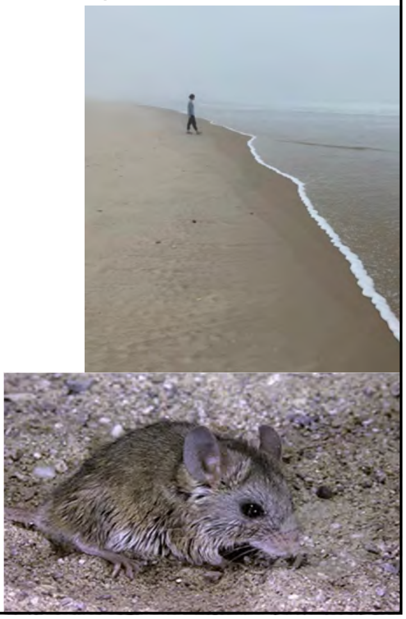
Jordan Orange, MD PhD
Reuben S. Carpentier Professor
Columbia University

Disclosures

- Scientific Advisory Board membership
  - ADMA biologics, Gigagen
- Consultancies
  - CSL, Cytovia, Enzyvant, Editas, Grifols, Sigilon, Sobi, Takeda, Teva
- Editor/Author
  - Up to date

Natural Killer cells in human immunity

- Important in anti-viral defense
  - Especially herpes viruses
- Important in tumor surveillance
- Some key divergent evolution
- Rare human deficiencies result in susceptibility to infections and malignancy



NK Cells

NK cells are lymphocytes important in immune regulation and host defense that are capable of being specifically activated or inhibited after the ligation of germline-encoded receptors.

Cytotoxicity

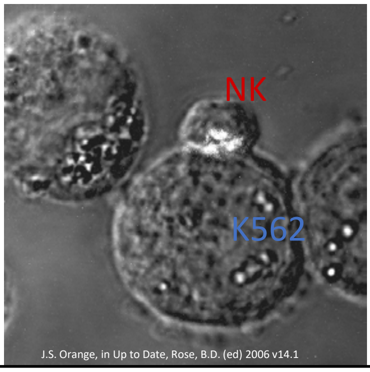
- Contact dependent danger recognition
- Antibody dependent

Cytokine Production

- inflammation
- promoting immunity

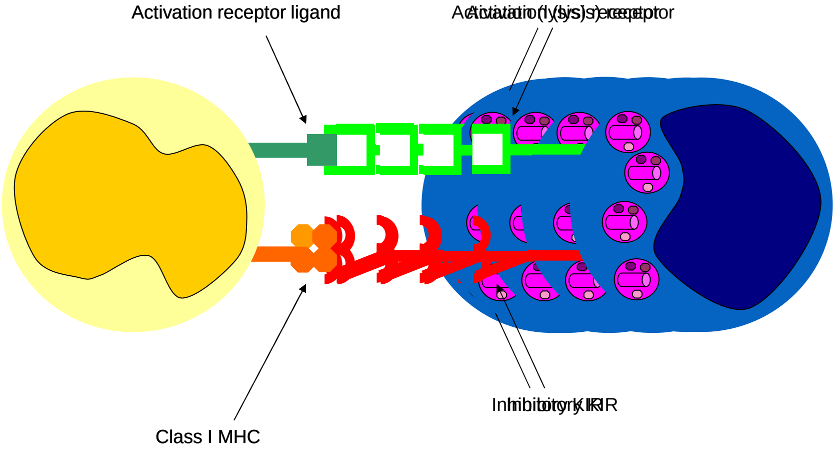
Costimulation

- contact dependent stimulation



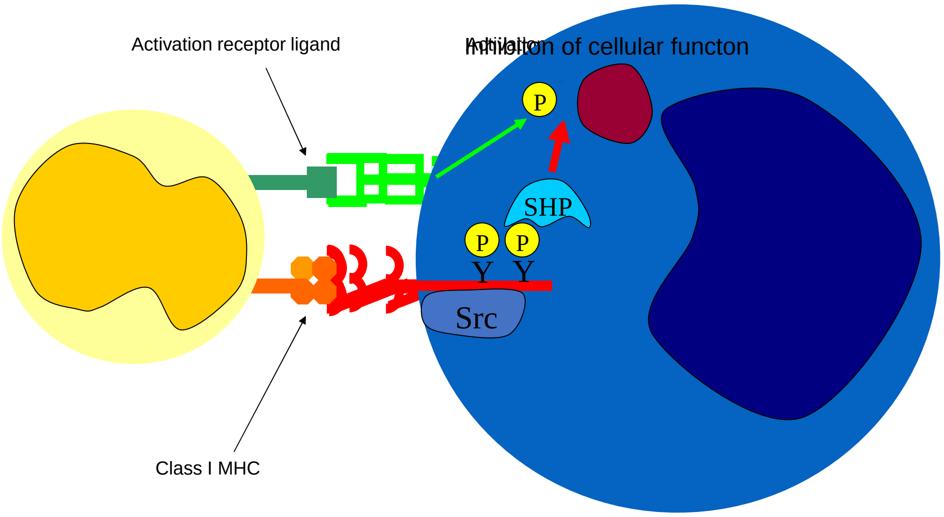
J.S. Orange, in Up to Date, Rose, B.D. (ed) 2006 v14.1

NK cell function - inhibition

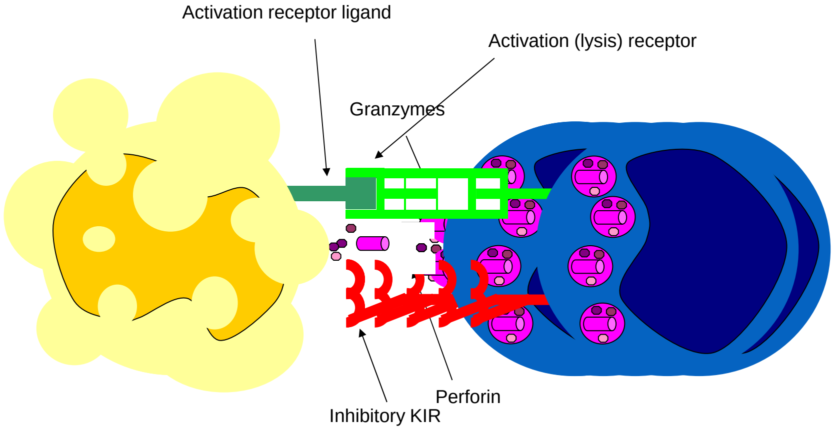


Orange and Ballas Clin. Immunol. 2006 118:1-10

KIR: Restraining NK cell function



NK cell activation - “missing self”



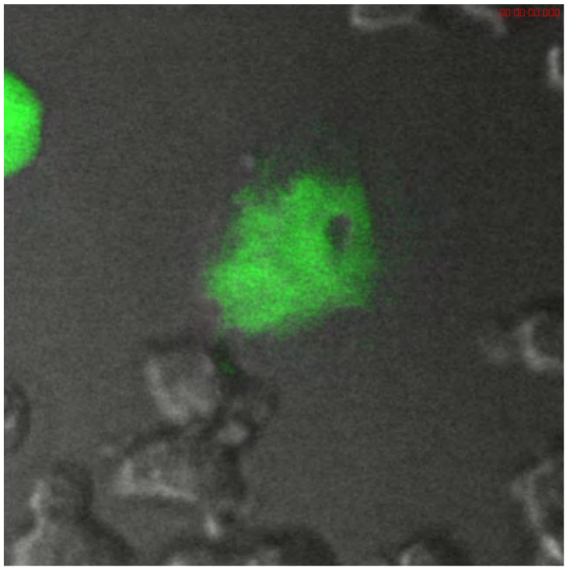
Orange and Ballas Clin. Immunol. 2006 118:1-10

Critical concepts in NK cell biology

- Linkages between KIR “haplotype” and disease
- Regulatory NK cells
  - Costimulation
  - High potency cytokine producing subsets
- Licensing
  - Need to see self MHC to be enabled
  - Relevance to HSCT – human data
- “Memory”
  - “adaptive” like features
  - Contact hypersensitivity, viral infections
  - Human data convincing (CMV, EBV, Hanta, ChikV, HIV)

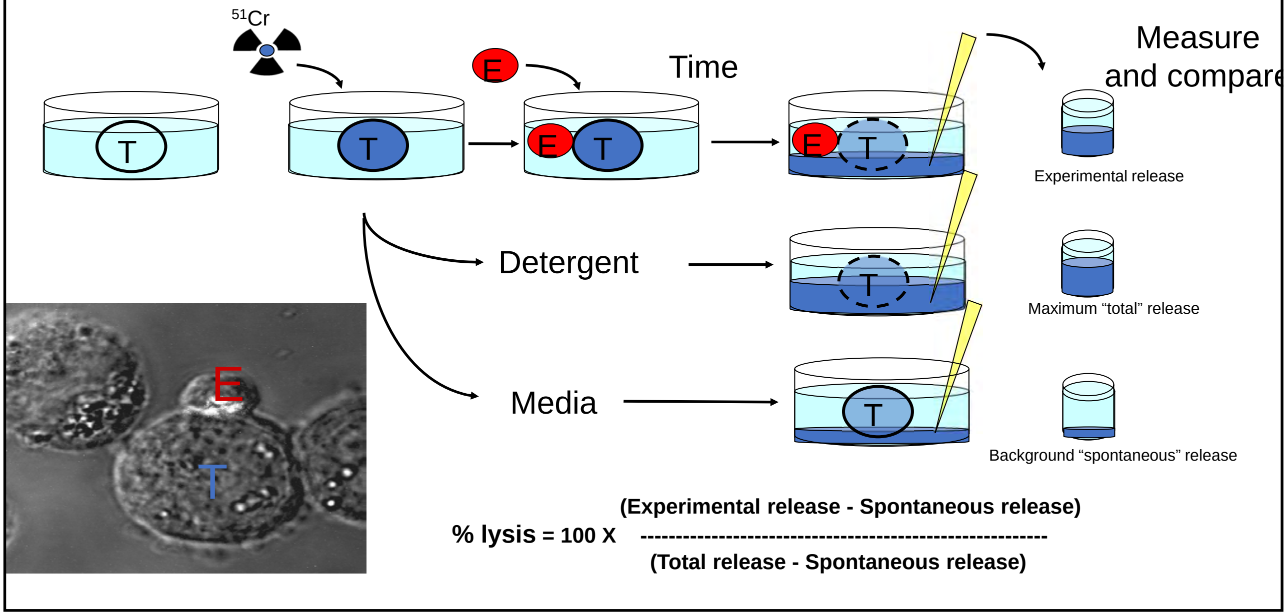
NK cell antiviral killing

Green = Vital dye
Red = death marker



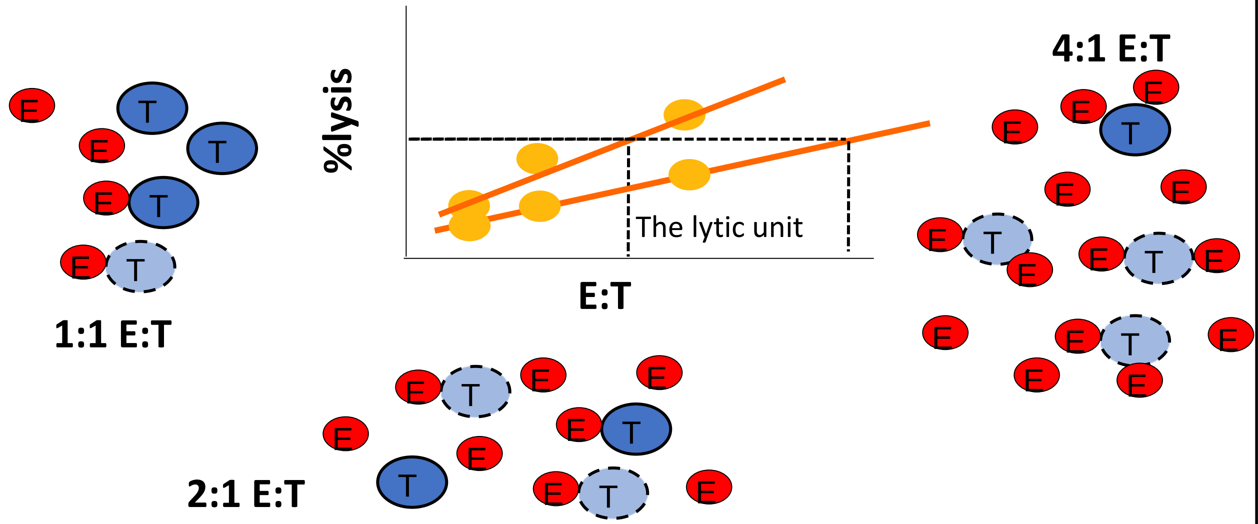
Stacey Yermakova-Smith (Orange Laboratory)

Measuring cytotoxicity



$$\% \text{ lysis} = 100 \text{ X } \frac{\text{(Experimental release - Spontaneous release)}}{\text{(Total release - Spontaneous release)}}$$

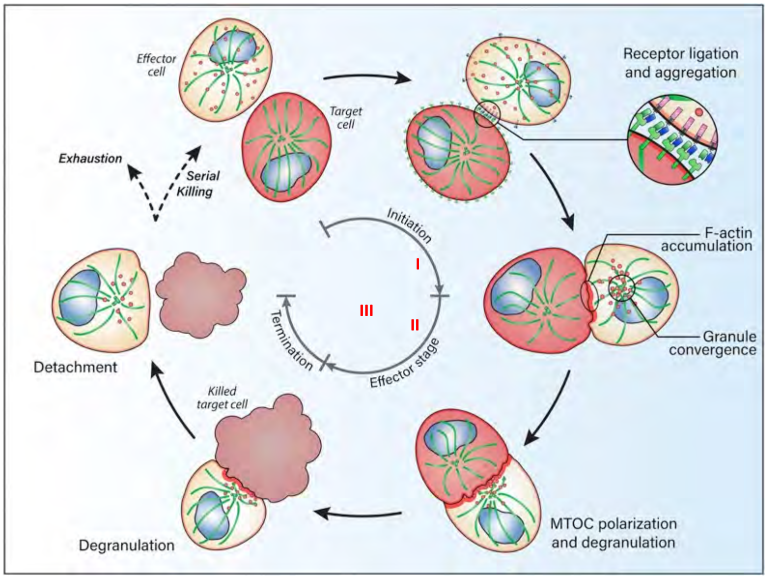
Anatomy of NK cell cytotoxicity assay



How do NK cells kill?

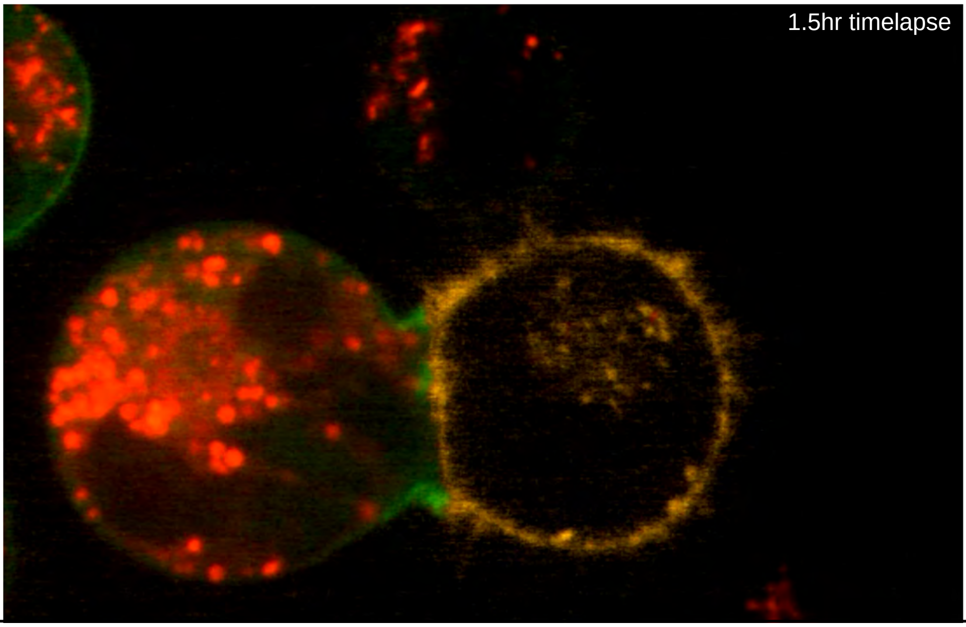
Three Stages:

- I. Initiation
  - I. Migration
  - II. Adhesion/Activation
- II. Effector
  - I. F-actin accumulation
  - II. Granule convergence
  - III. MTOC polarization
  - IV. Degranulation
- III. Termination
  - I. Detachment
  - II. Serial Killing

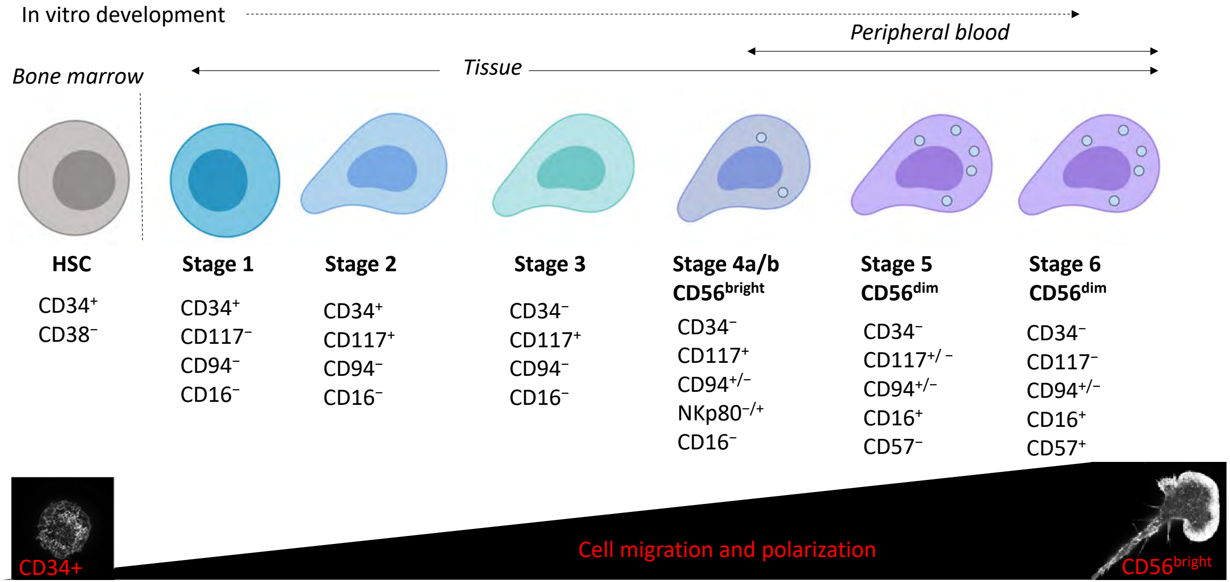


(Mukherjee et al., 2017)

NK cell cytotoxicity – the mechanics



Human NK cell development

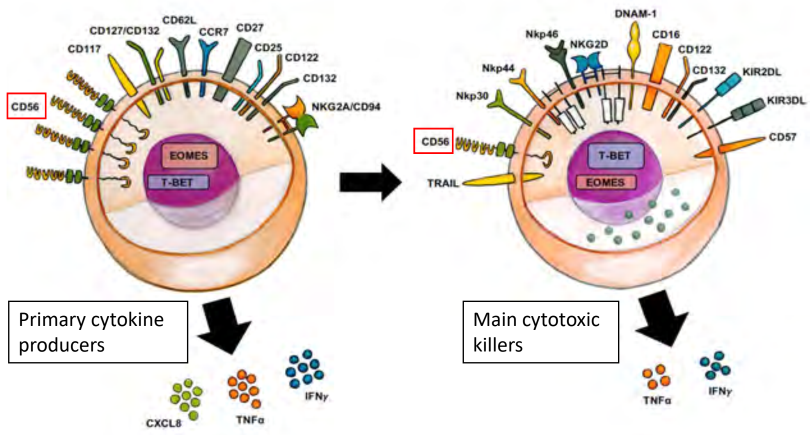


HSC	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4a/b CD56^{bright}**	**Stage 5 CD56^{dim}**	**Stage 6 CD56^{dim}**
CD34^{+}	CD34^{+}	CD34^{+}	CD34^{-}	CD34^{-}	CD34^{-}	CD34^{-}
CD38^{-}	CD117^{-}	CD117^{+}	CD117^{+}	CD117^{+}	CD117$^{+/-}$	CD117^{-}
	CD94^{-}	CD94^{-}	CD94^{-}	CD94$^{+/-}$	CD94$^{+/-}$	CD94$^{+/-}$
	CD16^{-}	CD16^{-}	CD16^{-}	NKp80$^{-/+}$	CD16^{+}	CD16^{+}
				CD16^{-}	CD57^{-}	CD57^{+}

Human natural killer cells

CD56^{bright} NK cell

CD56^{dim} NK cell

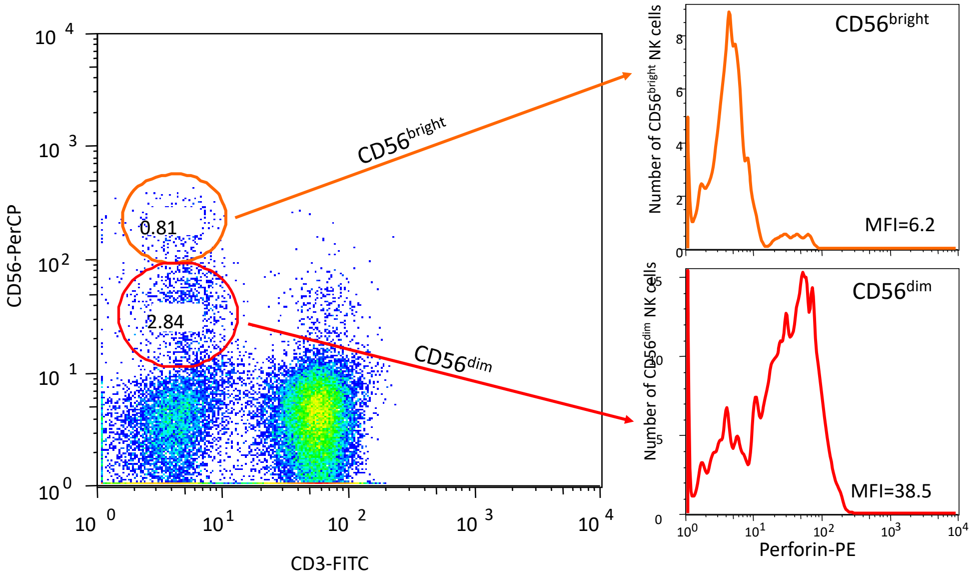


Primary cytokine producers

Main cytotoxic killers

Gunesch JT et al. Mol. Immunology 2018

NK cell functional subsets



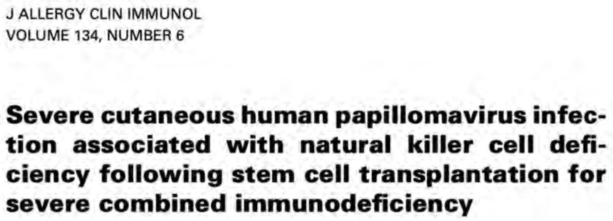
Orange and Ballas Clin. Immunol. 2006 118:1-10

>50 IEI that impair NK cells

- Four categories
    - all include major impairments other than NK cells
- Development/survival
    - IL2RG, JAK3, STAT1GOF, STAT5b, DKC1…
- Mechanics of cytotoxicity
    - PFP1, UNC13D, RAB27A, CORO1A, IGTB2…
- Signaling for cytotoxicity
    - SH2D1A, PLCG2, MAGT1…
- Other functions/unclear
    - TAP1, TAP2, IL21R…

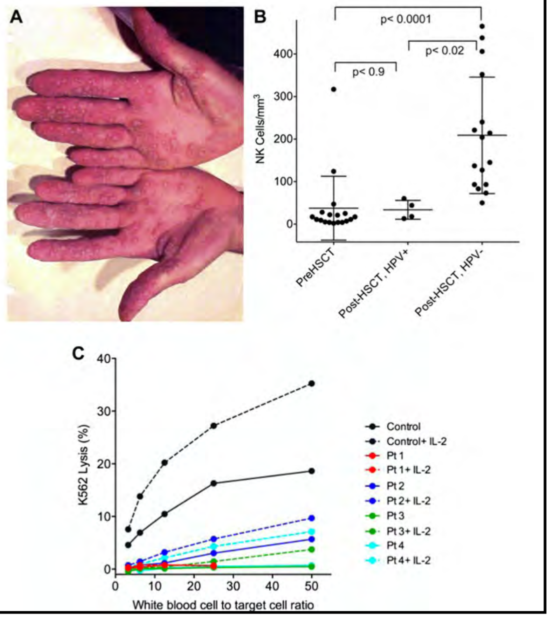
Critical lessons learned from NK-IEI

- NK in SCID… HPV post transplant

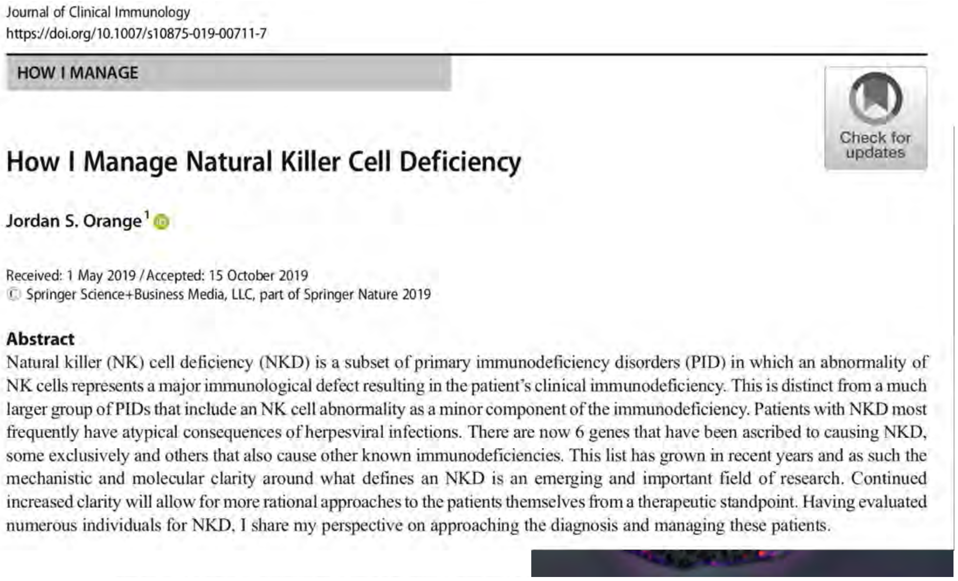


J ALLERGY CLIN IMMUNOL
VOLUME 134, NUMBER 6

Severe cutaneous human papillomavirus infection associated with natural killer cell deficiency following stem cell transplantation for severe combined immunodeficiency



"NKD"



Journal of Clinical Immunology
https://doi.org/10.1007/s10875-019-00711-7

HOW I MANAGE

How I Manage Natural Killer Cell Deficiency

Jordan S. Orange[1]

Received: 1 May 2019 / Accepted: 15 October 2019

Abstract

Natural killer (NK) cell deficiency (NKD) is a subset of primary immunodeficiency disorders (PID) in which an abnormality of NK cells represents a major immunological defect resulting in the patient's clinical immunodeficiency. This is distinct from a much larger group of PIDs that include an NK cell abnormality as a minor component of the immunodeficiency. Patients with NKD most frequently have atypical consequences of herpesviral infections. There are now 6 genes that have been ascribed to causing NKD, some exclusively and others that also cause other known immunodeficiencies. This list has grown in recent years and as such the mechanistic and molecular clarity around what defines an NKD is an emerging and important field of research. Continued increased clarity will allow for more rational approaches to the patients themselves from a therapeutic standpoint. Having evaluated numerous individuals for NKD, I share my perspective on approaching the diagnosis and managing these patients.

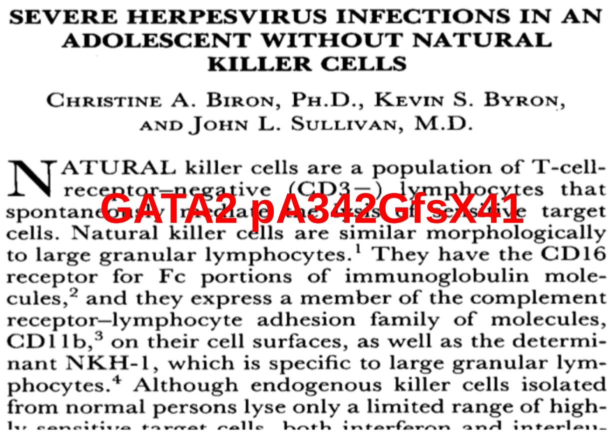
There are 2 types of NKD

Classical (developmental) NKD – cNKD (dNKD)

- Abnormal Development
- Can be low in number
- Can be missing subsets as a feature of development or survival
- "Half baked" NK cells
- 7 defined genetically

Functional NKD fNKD

- Normal development
- Abnormal function
- "broken" NK cells
- 1 defined genetically

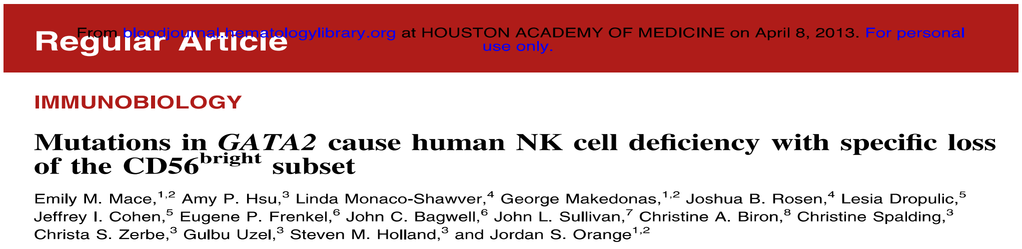


SEVERE HERPESVIRUS INFECTIONS IN AN ADOLESCENT WITHOUT NATURAL KILLER CELLS

CHRISTINE A. BIRON, PH.D., KEVIN S. BYRON, AND JOHN L. SULLIVAN, M.D.

NATURAL killer cells are a population of T-cell-receptor–negative (CD3−) lymphocytes that spontaneously mediate the lysis of sensitive target cells. Natural killer cells are similar morphologically to large granular lymphocytes.[1] They have the CD16 receptor for Fc portions of immunoglobulin molecules,[2] and they express a member of the complement receptor–lymphocyte adhesion family of molecules, CD11b,[3] on their cell surfaces, as well as the determinant NKH-1, which is specific to large granular lymphocytes.[4] Although endogenous killer cells isolated from normal persons lyse only a limited range of highly sensitive target cells, both interferon and interleu-

GATA2 pA342GfsX41



Regular Article

IMMUNOBIOLOGY

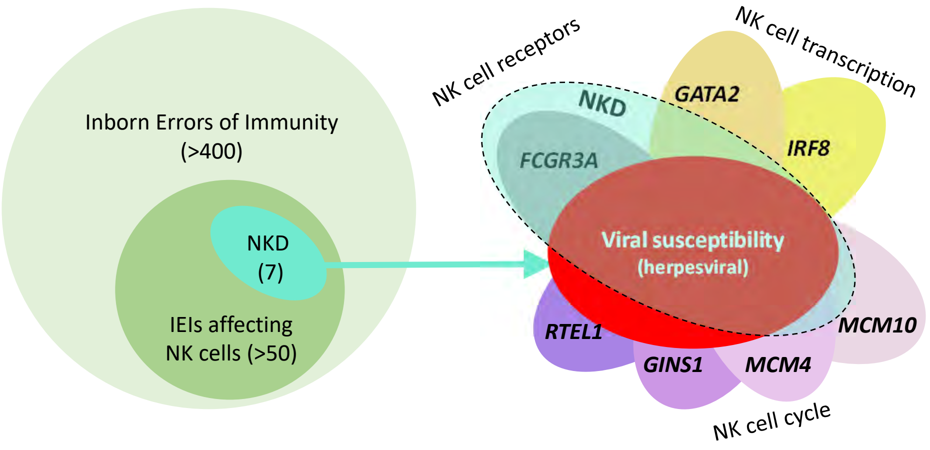
Mutations in *GATA2* cause human NK cell deficiency with specific loss of the CD56^{bright} subset

Emily M. Mace,[1,2] Amy P. Hsu,[3] Linda Monaco-Shawver,[4] George Makedonas,[1,2] Joshua B. Rosen,[4] Lesia Dropulic,[5] Jeffrey I. Cohen,[5] Eugene P. Frenkel,[6] John C. Bagwell,[6] John L. Sullivan,[7] Christine A. Biron,[8] Christine Spalding,[3] Christa S. Zerbe,[3] Gulbu Uzel,[3] Steven M. Holland,[3] and Jordan S. Orange[1,2]

Thresholds for “deficiency”

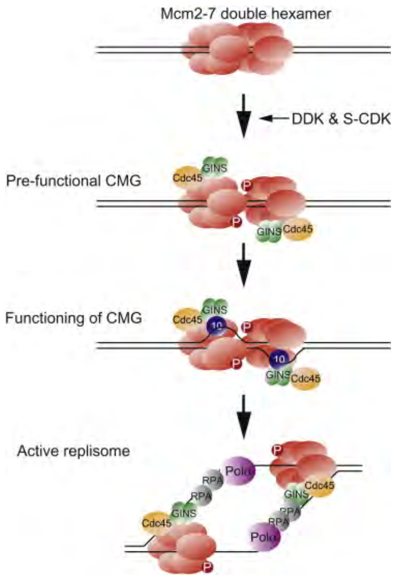
- ≤1% of total lymphocytes
- ≥20% bright

IEI that affect NK cells and NKD



Modified from: Mace and Orange, Immunol. Rev. 2019

GINS-MCM-CDC45 (CMG) complex



Watase G. et al Curr. Biol. 22(4) 2012

Establishing a Novel Cause of Patient Phenotype

Novel gene criteria:

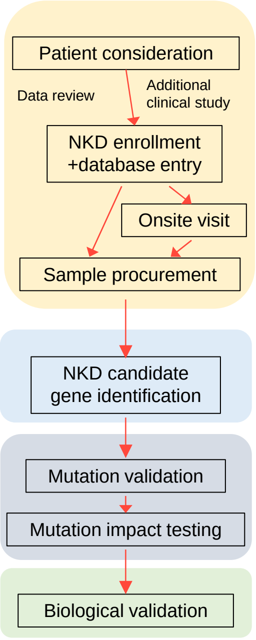
1. Variant does not occur in healthy individuals
2. Variant must impair, destroy, or alter the function of the protein.
3. Observed immune cell defect should be caused by the variant.

…Functional immunogenomics

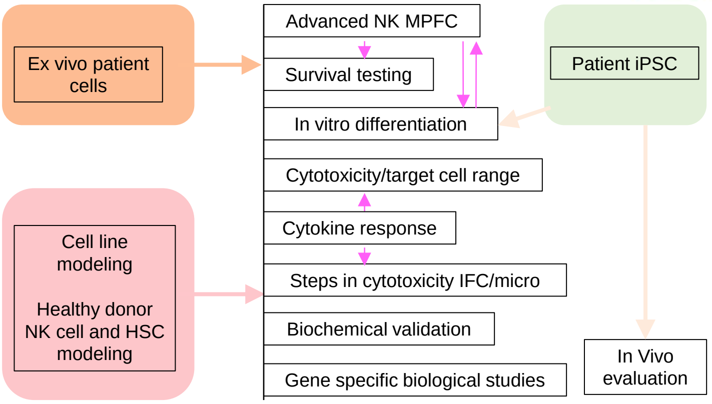
(Adapted from Casanova et al., 2014)

NEAR (NK Cell Evaluation And Research) Program at Columbia

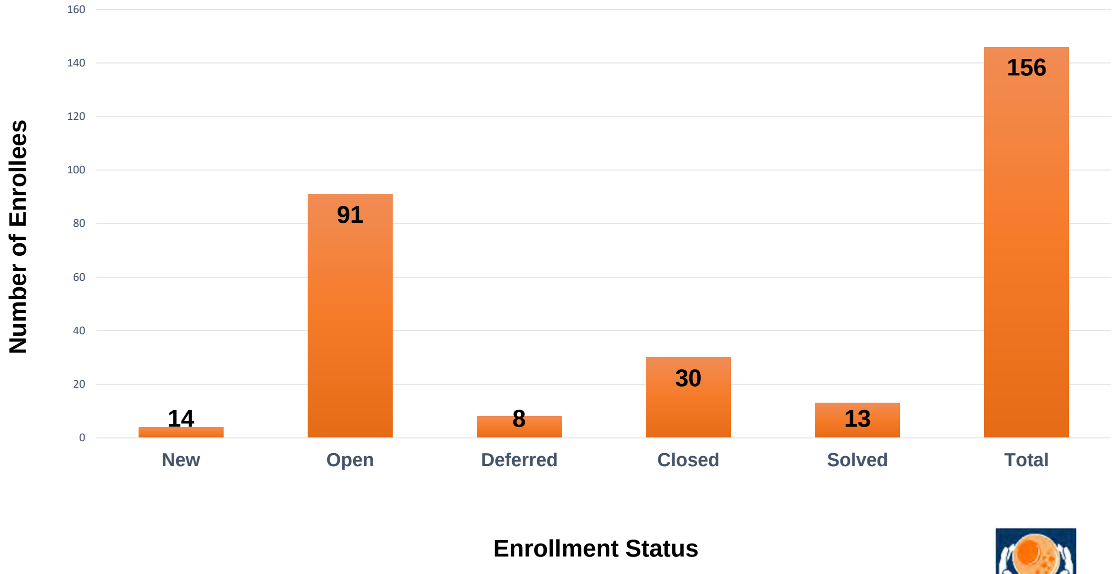
Pipeline



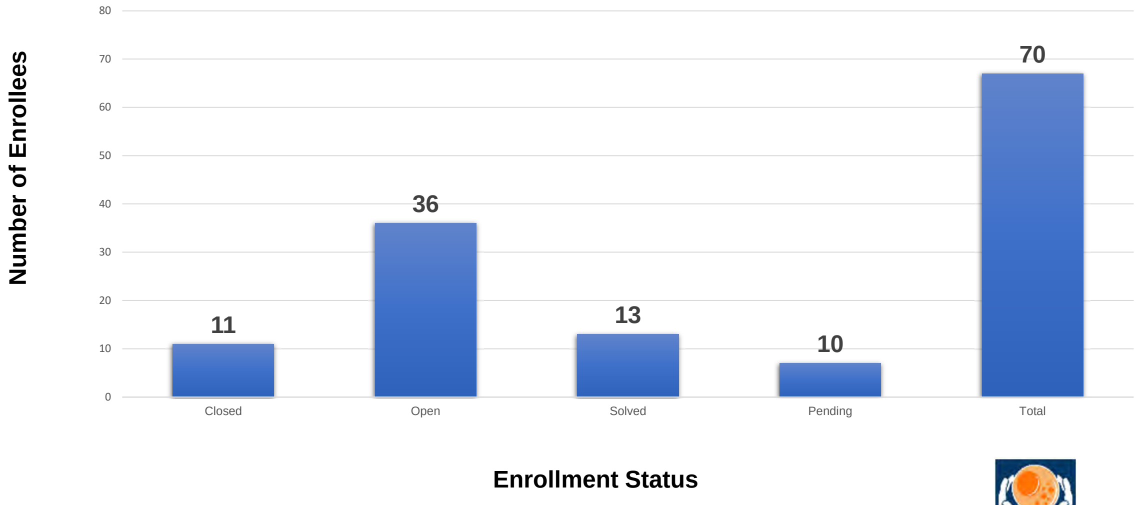
Biological Validation

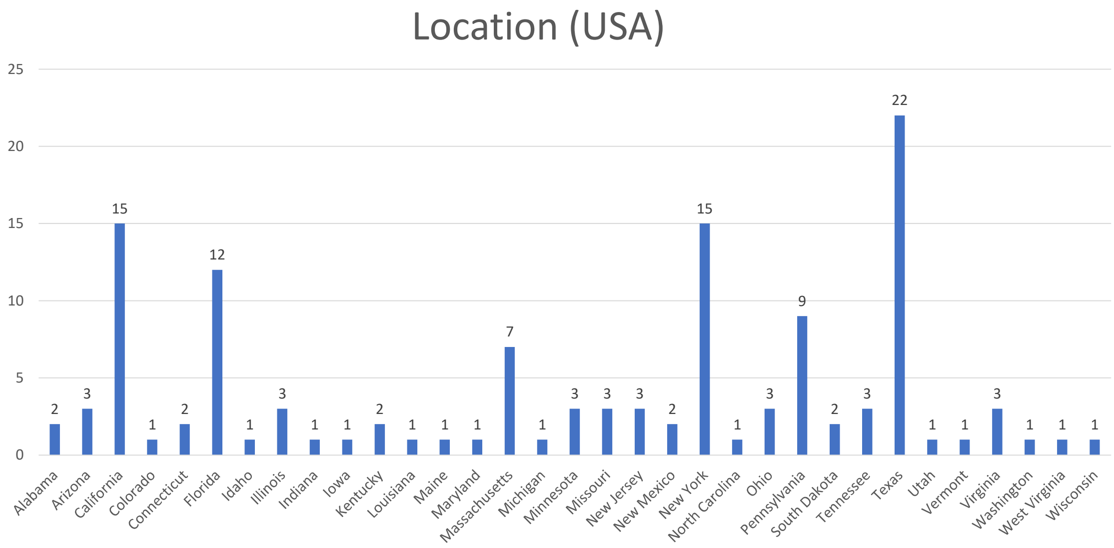


NEAR Patients



WES submissions for NEAR Patients




Location (USA)
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Arizona
California
Colorado
Connecticut
Florida
Idaho
Illinois
Indiana
Iowa
Kentucky
Louisiana
Maine
Maryland
Massachusetts
Michigan
Minnesota
Missouri
New Jersey
New Mexico
New York
North Carolina
Ohio
Pennsylvania
South Dakota
Tennessee
Texas
Utah
Vermont
Virginia
Washington
West Virginia
Wisconsin

29


ARCTIC OCEAN
Greenland
Svalbard (Nor.)
ARCTIC OCEAN
United States
Canada
Iceland
Norway
Sweden
Finland
Russia
United Kingdom
Den.
Neth.
Ireland
Estonia
Latvia
Belarus
Ger.
Pol.
Ukraine
Kazakhstan
Mongolia
Rom.
Georgia
Azer.
Uzb.
Turkm.
Kyrgyzstan
Tajikistan
United States
ATLANTIC
OCEAN
Portugal
Spain
France
Italy
Bulgaria
Greece
Turkey
Syria
Iraq
Iran
Afg.
Pakistan
Nepal
Bhutan
China
N. Korea
S. Korea
Japan
Tunisia
Lebanon
Israel
Jordan
Kuwait
Morocco
Algeria
Libya
Egypt
Saudi Arabia
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Burma
Laos
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Mauritania
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ATLANTIC
OCEAN
eSwatini
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Australia
New Caledonia
New Zealand
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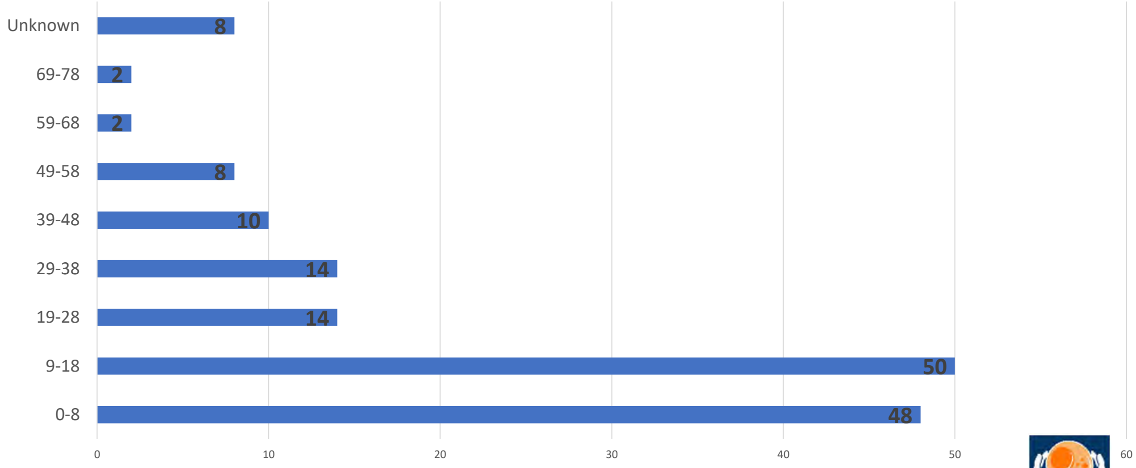
Age Range


Unknown
69-78
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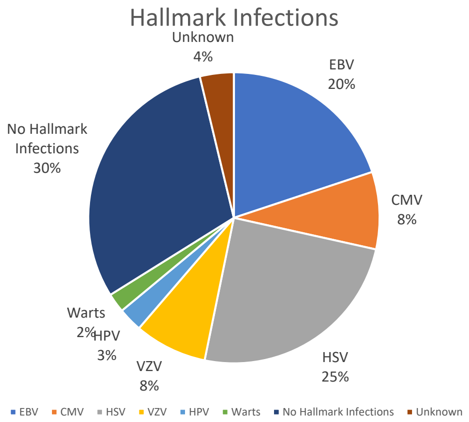
39-48
29-38
19-28
9-18
0-8
8
2
2
8
10
14
14
50
48
0
10
20
30
40
50
60

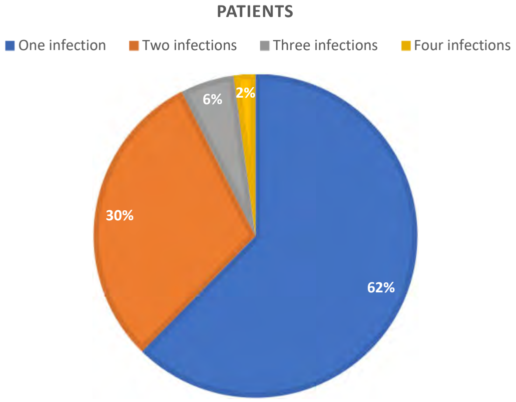
Hallmark Infections

Hallmark Infections	Reported Diagnosis
Epstein-Barr Virus	37
Cytomegalovirus	16
Herpes Simplex Virus	47
Varicella Zoster Virus	15
Human Papillomavirus	5
Warts	5
No Hallmark Infections	56
Unknown	7



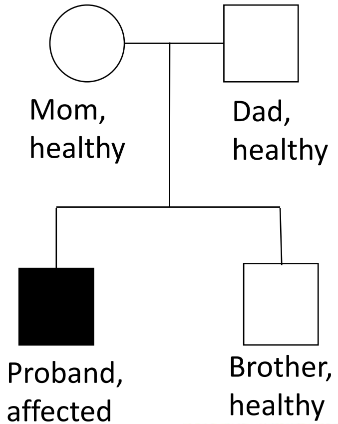
Hallmark Infections

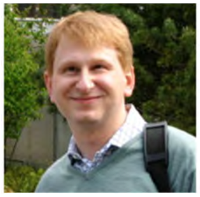
Infection Occurrence	Reported Cases
One infection	58
Two infections	28
Three infections	5
Four infections	2



NEAR referral - Clinical Presentation

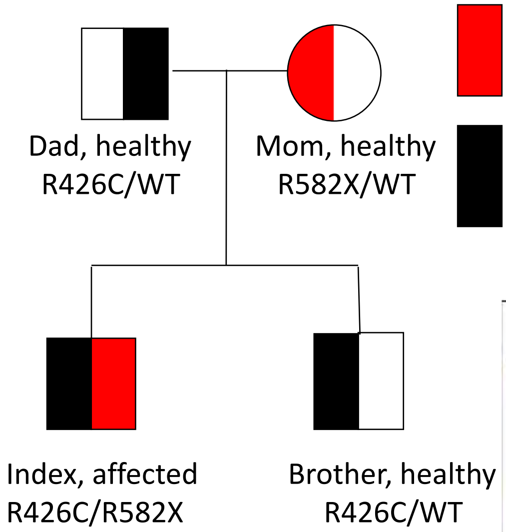
- Infant male
- non-consanguineous parents
- Fever and diarrhea
- Organomegaly
- Hypothyroidism
- Infections
    - (*S. aureus, K. pneumoniae*)
- Immune abnormality
    - Normal immunoglobulin
    - Low but normally distributed T cells
    - Very low NK cells (1)
- Progressive CMV, died following HSCT





Collaboration with Dr. Stephen Jolles, University Hospital of Wales

Compound heterozygous *MCM10* mutations

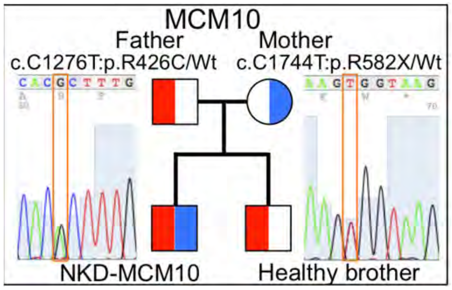


🟥 Exon 13
c.C1744T
R582X

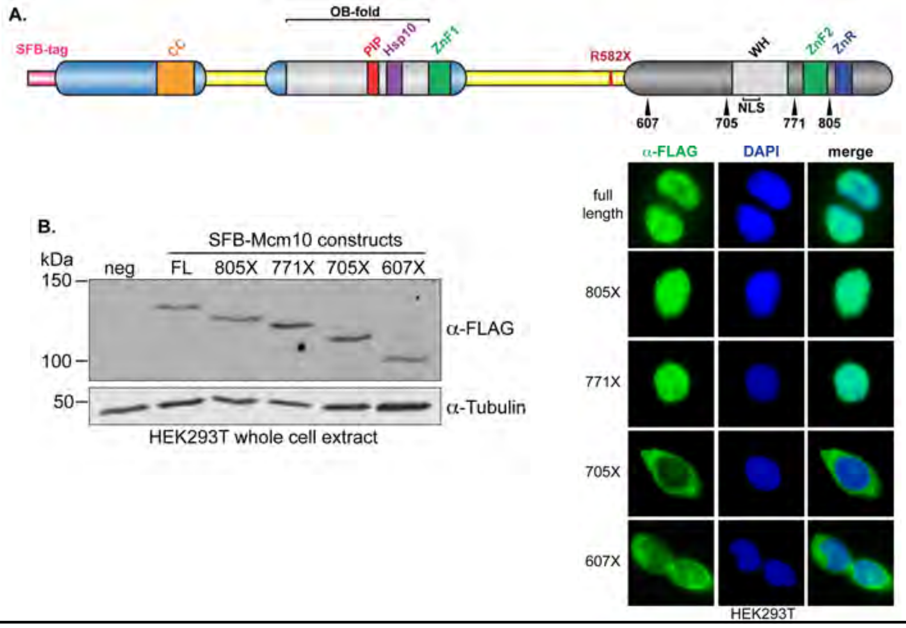
Premature stop codon
ExAC: not found
Mutation Taster: **disease causing** (1.0)

⬛ Exon 10
c.C1276T
R426C

ExAC: 4.12 X 10^{-5} (heterozygous)
Mutation Taster: **disease causing** (0.99)
PolyPhen: **damaging** (1.0)

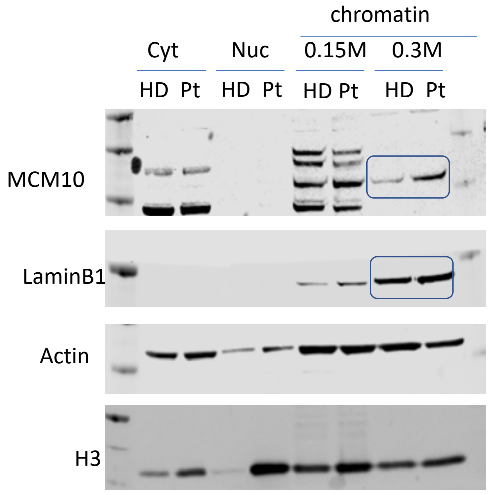


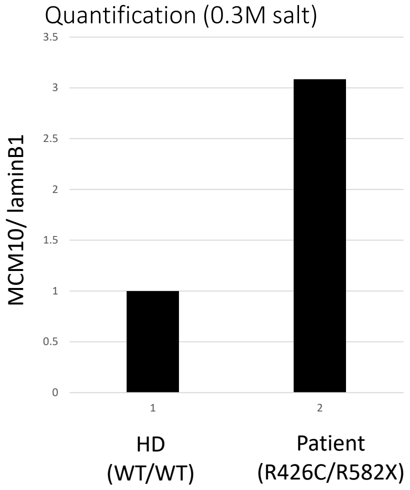
Impaired nuclear translocation (premature stop)



Impact of the patient's MCM10 missense variant: Retention by chromatin

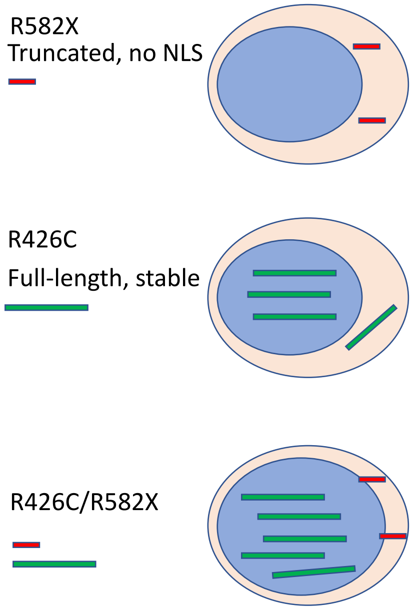
Salt gradient chromatin extraction





Matilde Conte, PhD

Mutation impact MCM10



R582X
Truncated, no NLS

Decreased protein in and out of nucleus

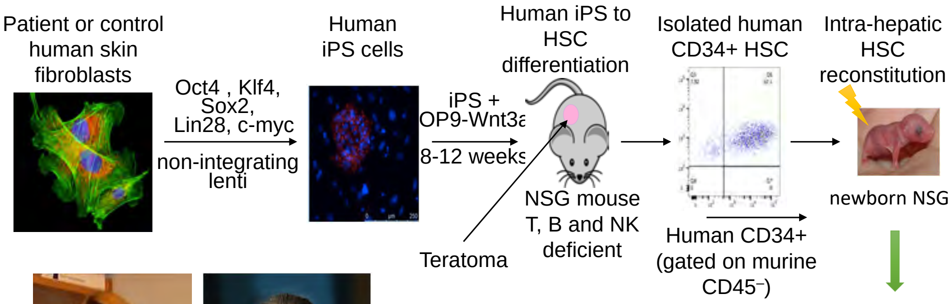
R426C
Full-length, stable

Impaired function with increased nuclear localization

R426C/R582X

Decreased protein with impaired function
Decreased firing leads to DNA retention
Nuclear size increased

Patient-Derived induced Pluripotent Stem Cell Xenografts



Patient or control human skin fibroblasts

Oct4 , Klf4, Sox2, Lin28, c-myc

non-integrating lenti

Human iPS cells

iPS + OP9-Wnt3a

8-12 weeks

Human iPS to HSC differentiation

NSG mouse T, B and NK deficient

Teratoma

Isolated human CD34+ HSC

Human CD34+ (gated on murine CD45⁻)

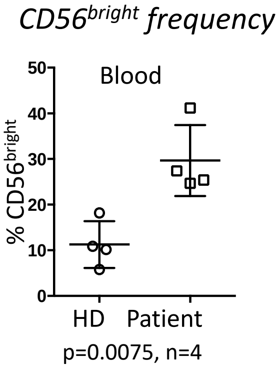
Intra-hepatic HSC reconstitution

newborn NSG

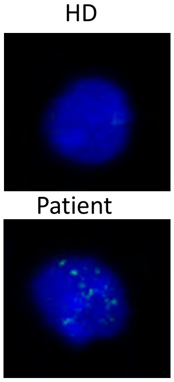
Analysis of human hematopoiesis and human NK development day 28 post HSC reconstitution:
- Phenotyping
- Functional assays

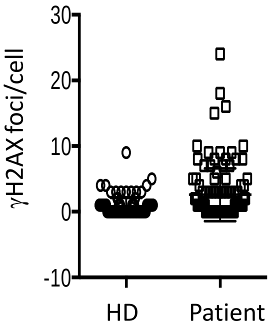
Drs. Silke Paust and Malgorzata Borowiak, Scrips Inst/Baylor College of Medicine

NK cell reconstitution in humanized mice from iPSC



p=0.0075, n=4





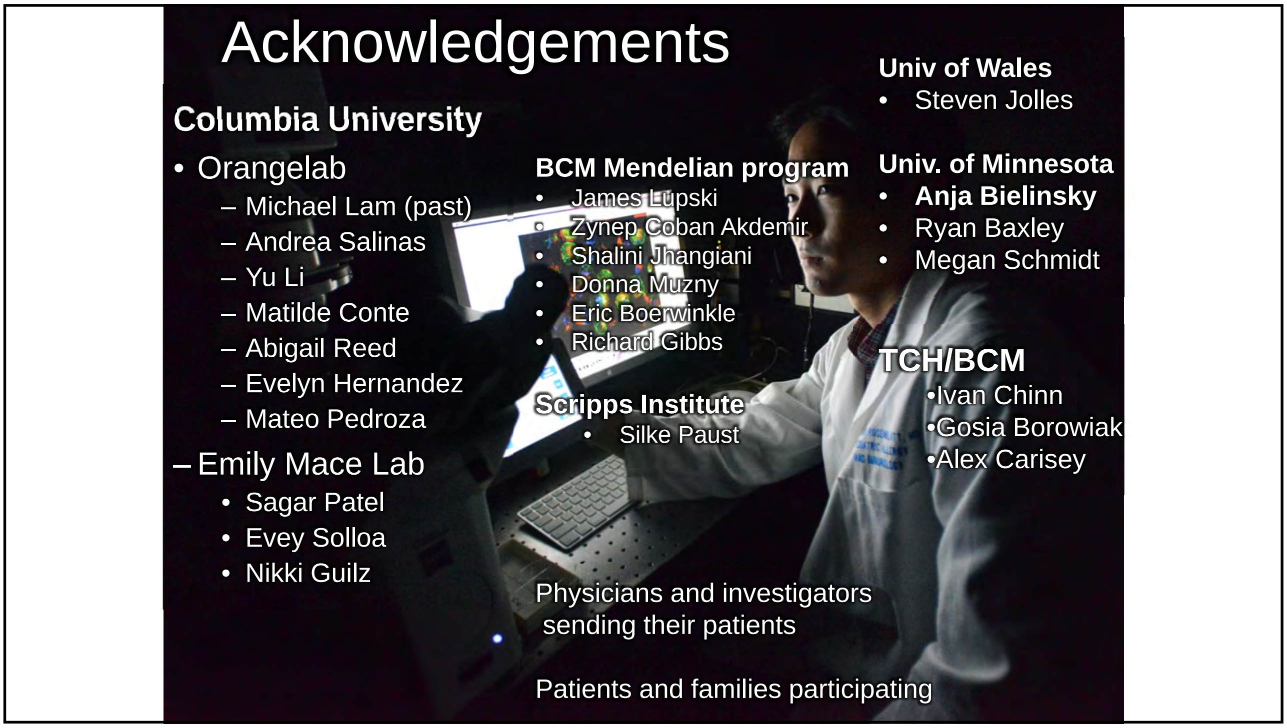
p<0.0001, n=88-108

Recapitulation of the patient NK cell phenotype and induction of DNA damage repair

Drs. Silke Paust and Malgorzata Borowiak, Baylor College of Medicine

Conclusions

- NK cell biology represents an evolving field in immunology
  - Requirements for IL-15 in development but some redundancy in humans
- PID/IEI has entered a meaningful new genomic era
  - IEI provide valuable insights into NK cell biology
- NK cell deficiency is an emerging IEI characterized by susceptibility to herpesviruses
  - Signal around the MCM complex and transcriptional factors
  - Defining critical signals of NK cell value to human host defense
  - Defining potential thresholds for concern (premature)



Acknowledgements

Columbia University

- Orangelab
  - Michael Lam (past)
  - Andrea Salinas
  - Yu Li
  - Matilde Conte
  - Abigail Reed
  - Evelyn Hernandez
  - Mateo Pedroza
- Emily Mace Lab
  - Sagar Patel
  - Evey Solloa
  - Nikki Guilz

BCM Mendelian program

- James Lupski
- Zynep Coban Akdemir
- Shalini Jhangiani
- Donna Muzny
- Eric Boerwinkle
- Richard Gibbs

Scripps Institute

- Silke Paust

Univ of Wales

- Steven Jolles

Univ. of Minnesota

- **Anja Bielinsky**
- Ryan Baxley
- Megan Schmidt

TCH/BCM

- Ivan Chinn
- Gosia Borowiak
- Alex Carisey

Physicians and investigators sending their patients

Patients and families participating