

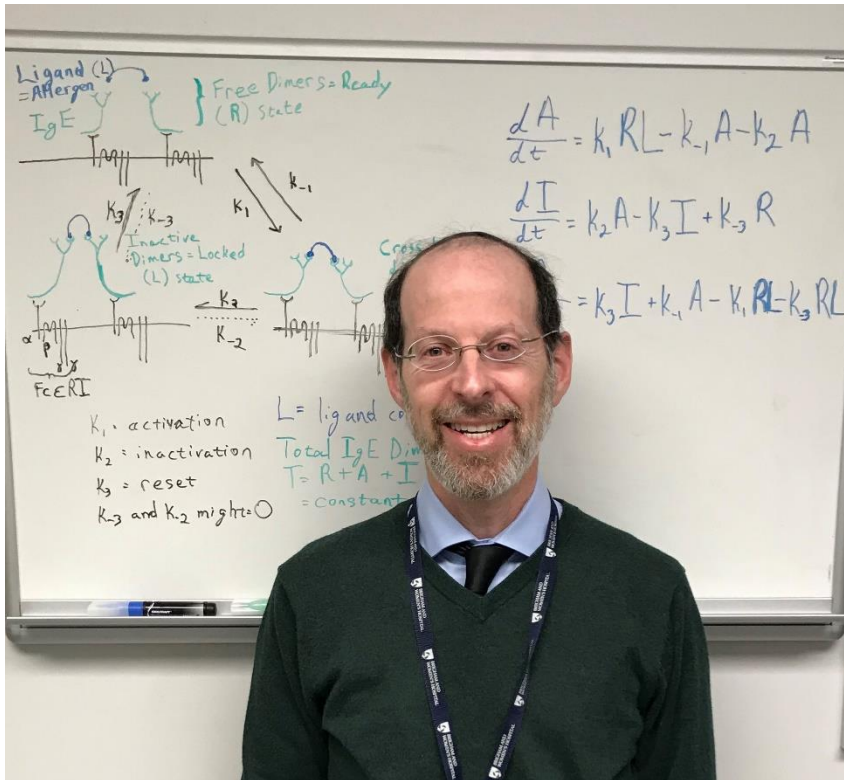
2024 Allergy and Immunology Overview and Update

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DISCLOSURES

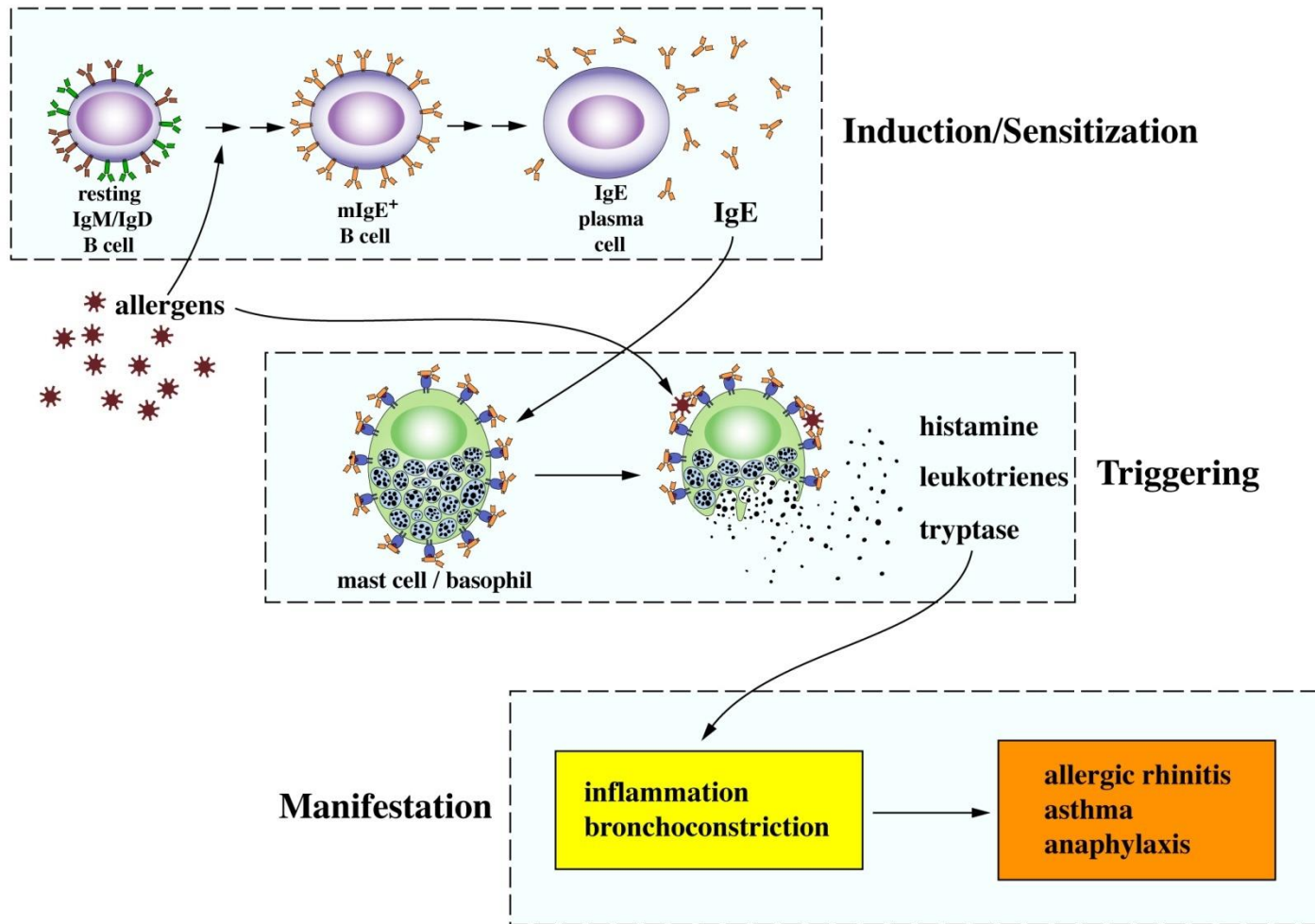
Discussion of an unapproved/ investigational
use of a commercial product/ device: None

Disclosed commercial relationship(s): None

Allergy/Immunology

- *Mast Cell + IgE Paradigm*
- Asthma
- Urticaria and Angioedema
- Anaphylaxis
- Drug Hypersensitivity
- Food Allergy
- Mastocytosis and Mast Cell Activation Syndromes
- Primary Immunodeficiency

The Mast Cell + IgE Paradigm



Asthma

- *A syndrome* with multiple endotypes
 - Th2 high (+ Eosinophils)
 - Eosinophilic (e.g., allergic)
 - Mixed granulocytic (Eos and PMNs)
 - Th2 low (few or no Eos)
 - Neutrophilic (high PMNs)
 - Pauci-immune (few or no PMNs)

Inflammatory subtypes in asthma: Assessment and identification using induced sputum

JODIE L. SIMPSON,^{1,3} RODNEY SCOTT,² MICHAEL J. BOYLE^{1,4} AND PETER G. GIBSON^{1,3}

¹*School of Medical Practice and Population Health, ²Medical Genetics, School of Biomedical Science, Hunter Medical Research Institute, The University of Newcastle, Callaghan, ³Department of Respiratory and Sleep Medicine, ⁴Immunology and Infectious Diseases, Hunter Medical Research Institute, John Hunter Hospital, New Lambton, New South Wales, Australia*

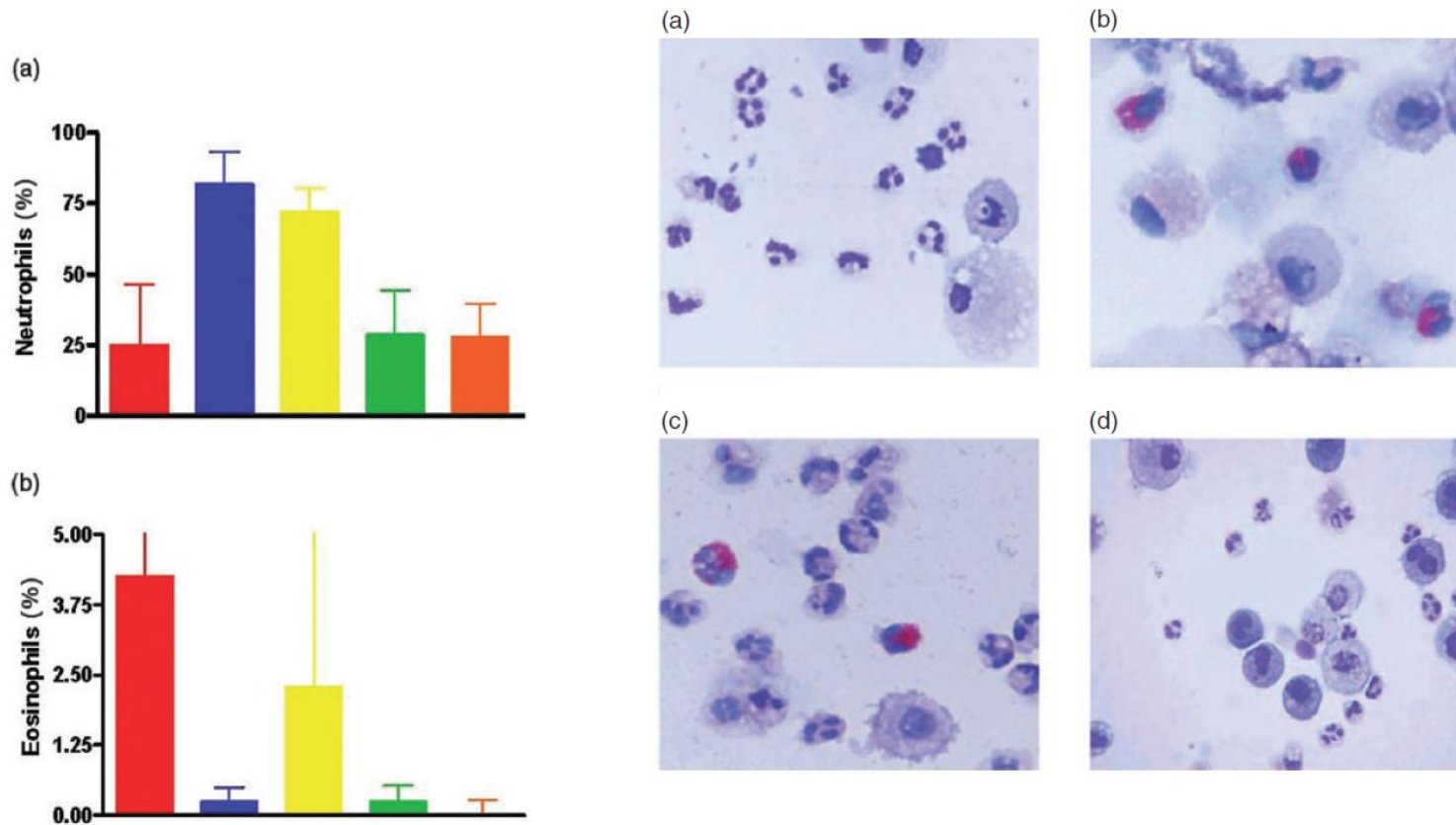
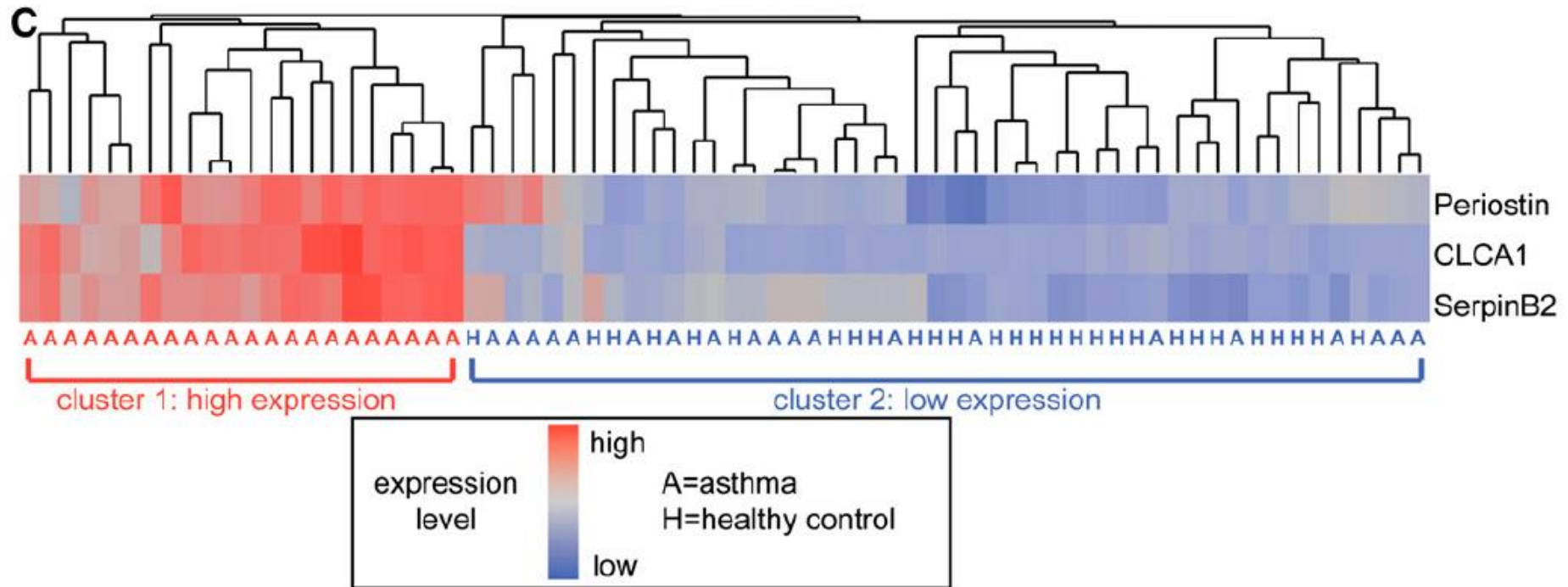


Figure 2 Sputum cytopins showing the four inflammatory subtypes of asthma: (a) neutrophilic asthma; (b) eosinophilic asthma; (c) mixed granulocytic asthma; (d) paucigranulocytic asthma.

Figure 1 (a) Induced sputum neutrophils and (b) eosinophils in asthma subgroups and healthy controls. Bars are median with error bars representing the interquartile range. (red) eosinophilic; (blue) neutrophilic; (yellow) mixed granulocytic; (green) paucigranulocytic; (orange) healthy.

T-helper Type 2-driven Inflammation Defines Major Subphenotypes of Asthma

Prescott G. Woodruff^{1,2}, Barmak Modrek³, David F. Choy⁴, Guiquan Jia⁴, Alexander R. Abbas³, Almut Ellwanger¹, Joseph R. Arron^{4*}, Laura L. Koth^{1,5}, and John V. Fahy^{1,2*}



Woodruff PG *et al.*
Am J Resp Crit Care Med
2009;180:388-395.

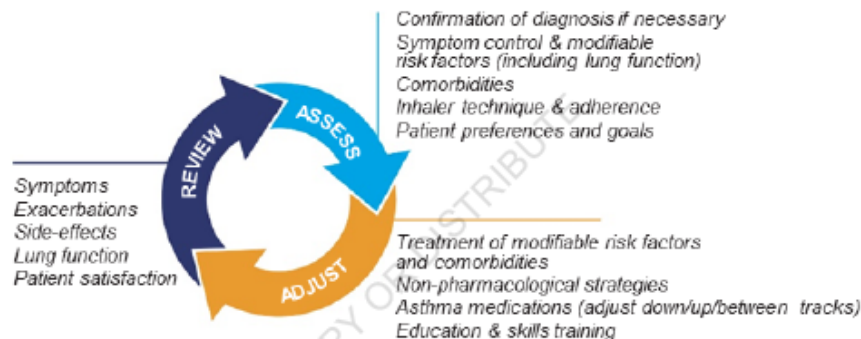
GINA 2021 Guidelines

Box 3-5A. Personalized management for adults and adolescents to control symptoms and minimize future risk

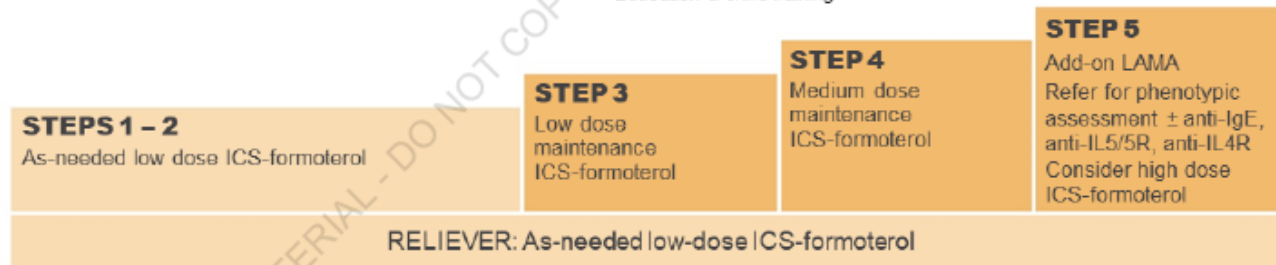
Adults & adolescents 12+ years

Personalized asthma management

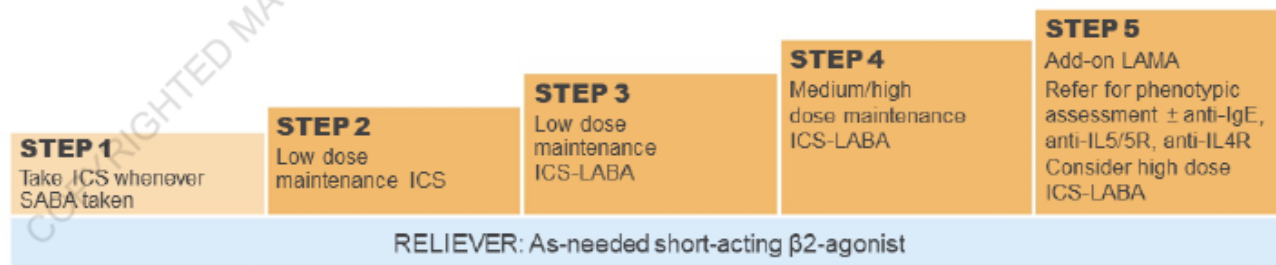
Assess, Adjust, Review
for individual patient needs



CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever



CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller



Other controller options for either track

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	Medium dose ICS, or add LTRA, or add HDM SLIT	Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS	Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects
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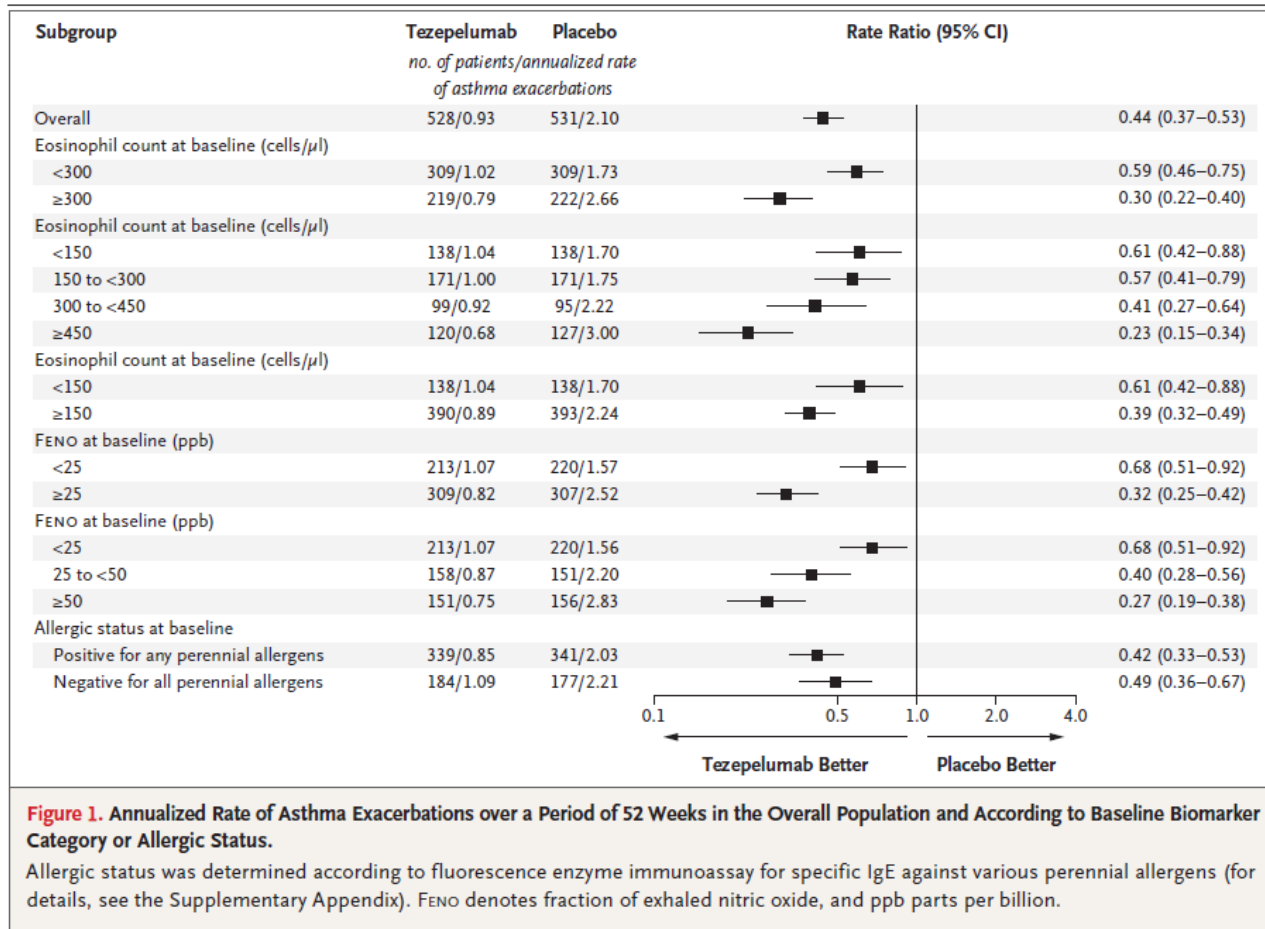
HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting β_2 -agonist; SLIT: sublingual immunotherapy. For recommendations about *initial* asthma treatment in adults and adolescents, see Box 3-4A (p.53) and 3-4B (p.54).

Asthma: Biologic Therapies

- Omalizumab = anti-IgE (for allergic)
- Mepolizumab, Reslizumab = anti-IL-5 (for eosinophilic asthma)
- Benralizumab = anti-IL-5R α chain (for eosinophilic asthma)
- Dupilumab = anti IL-4/13 receptor alpha chain (AD, asthma, CRSwNP, EoE)
- (Lebrikizumab = anti-IL-13 in patients with elevated serum periostin concentrations)
- Tezepelumab = anti Thymic Stromal Lymphopoietin (TSLP)

Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

Andrew Menzies-Gow, M.D., Jonathan Corren, M.D., Arnaud Bourdin, M.D.,
Geoffrey Chupp, M.D., Elliot Israel, M.D., Michael E. Wechsler, M.D.,
Christopher E. Brightling, F.Med.Sci., Janet M. Griffiths, Ph.D.,
Åsa Hellqvist, M.Sc., Karin Bowen, M.Sc., Primal Kaur, M.D.,
Gun Almqvist, M.Sc., Sandhia Ponnarambil, M.D., and Gene Colice, M.D.



Tezepelumab for severe, uncontrolled asthma

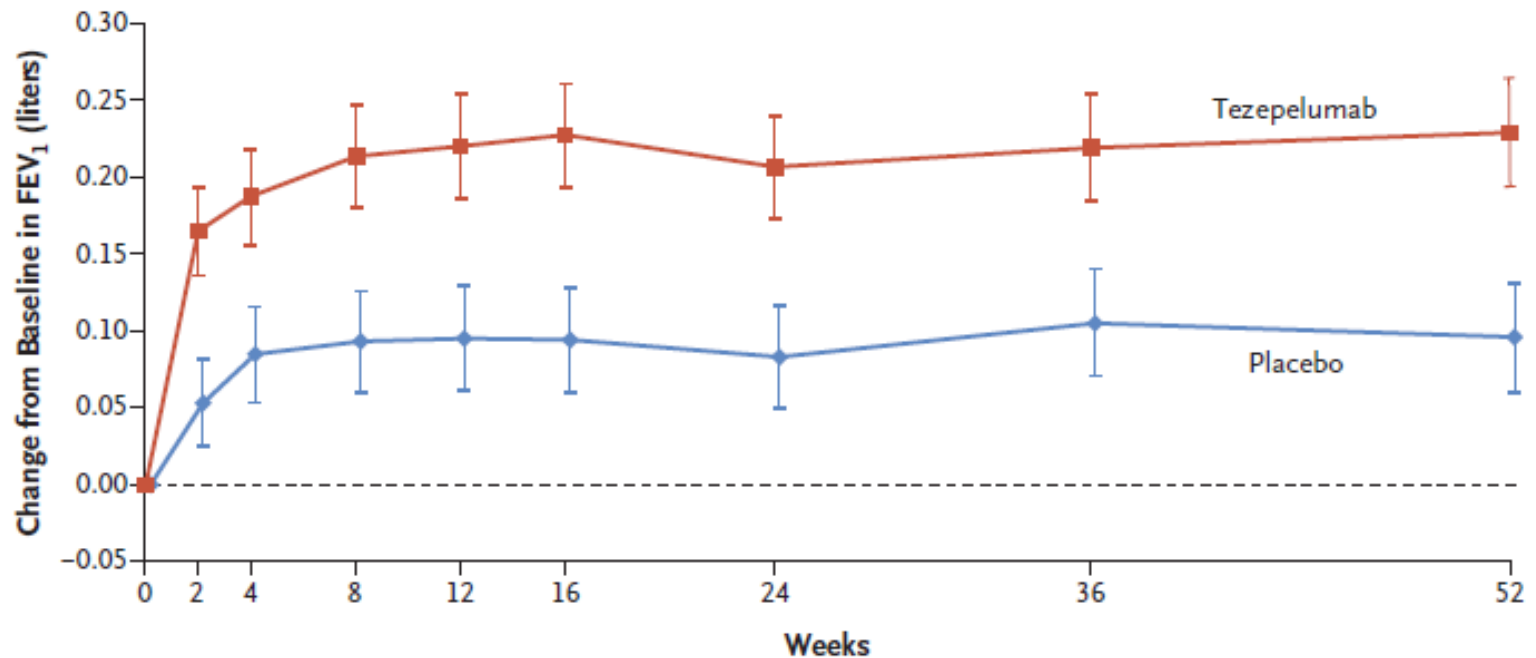


Figure 2. Change from Baseline to Week 52 in Prebronchodilator FEV₁.

I bars indicate 95% confidence intervals. FEV₁ denotes forced expiratory volume in 1 second.

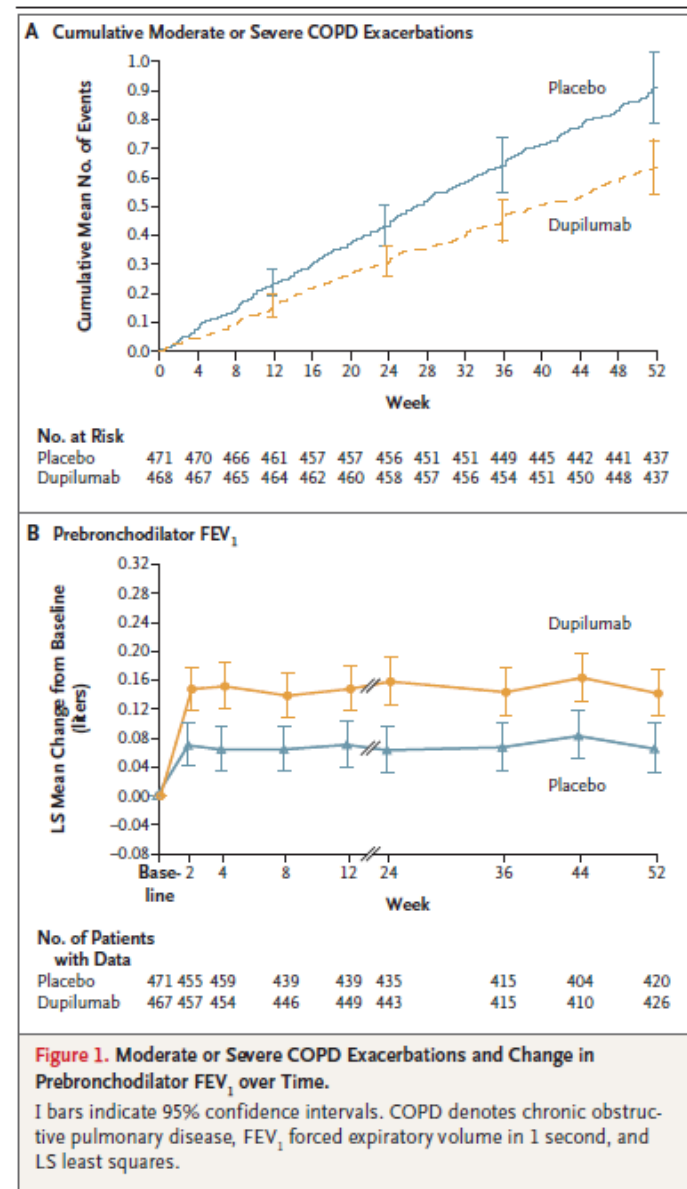
Dupilumab for COPD with type 2 Inflammation

ORIGINAL ARTICLE

Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

S.P. Bhatt, K.F. Rabe, N.A. Hanania, C.F. Vogelmeier, J. Cole, M. Bafadhel, S.A. Christenson, A. Papi, D. Singh, E. Laws, L.P. Mannent, N. Patel, H.W. Staudinger, G.D. Yancopoulos, E.R. Mortensen, B. Akinlade, J. Maloney, X. Lu, D. Bauer, A. Bansal, L.B. Robinson, and R.M. Abdulai, for the BOREAS Investigators*

- Patients with COPD and Eos > 300 cells/ μ L
- Bhatt SP et al. NEJM May 2023
- This appears more promising than benralizumab in COPD (see Criner GJ et al N Engl J Med 2019;381:1023-34.)



Asthma and Aspirin Sensitivity

AERD = Aspirin Exacerbated Respiratory Disease (Samter's triad/tetrad):

- Asthma (often steroid dependent)
- Nasal polyposis (loss of smell)
- Aspirin and NSAIDS intolerance (decreased FEV1 > 12% upon exposure)
- Chronic rhino-sinusitis

Pathobiology: NOT IgE mediated, rather insufficient concentrations of PGE₂

- LT overproduction because PGE₂ inhibition of 5-LO pathway (and thus LT production) is insufficient; COX-1 inhibition further decreases PGE₂ generation. LT's such as LTC₄ produced by mast cells and eos;
- In some patients, eos overexpress LTC₄ synthase
- Platelets aggregate with eos, pmns, monos;

Management:

- **Leukotriene blockade (5-LO, LTR antagonists)**
- Surgery (polyps, sinuses)
- Aspirin desensitization
- Anti-IL-4/13 receptor alpha-chain (Dupilumab)

Allergic Bronchopulmonary Aspergillosis

Criteria:

Asthma

Pulmonary infiltrates/central bronchiectasis

Elevated total serum **IgE** >1000 ng/ml (note units!)

Peripheral **eosinophilia**

Positive skin test and RAST (IgE) to **Aspergillus**

Precipitins against Aspergillus

Treatment: Oral steroids, consider anti-fungals (itraconazole, voriconazole), and biologics = omalizumab, mepolizumab, benralizumab, and dupilumab

Associations: cystic fibrosis and HLA DR2

Urticaria and Angioedema

- Urticaria

Acute < 6 weeks , Chronic > 6 weeks

- Urticaria :

pruritic geographic macular lesions with central clearing of short duration (<24h) and variable size

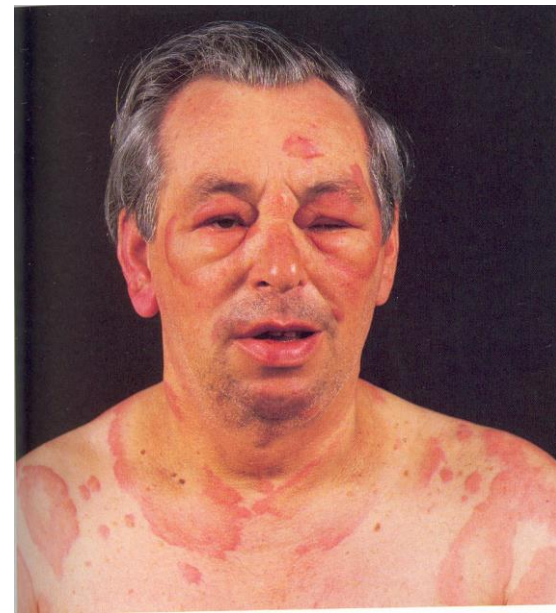
- Angioedema :

swelling \pm pain, associated with urticaria in 40-50% of cases

Acute Urticaria

A cause is found in 20% of cases:

- **Drugs:** aspirin and NSAIDS, Abx
- **Foods:** egg, milk, peanut and nuts, fish, shellfish, sesame
- **Infections** (viral/bacterial: HBV and HCV)
- **Contact Allergies** (animal dander and saliva; pollen from trees, grass, weeds)



Chronic Urticaria

(a cause is found in < 10% of cases)

Physical Urticarias

- Symptomatic Dermatographia
- Pressure (delayed)
- Exercise Induced
- Cold, solar, aquagenic, vibratory

Autoimmune :

IgG Anti-IgE Receptor (35-40%) or Anti-IgE (5-10%)
Autologous serum skin test positive or CU index

Hashimoto's Thyroiditis

elevated anti-peroxidase (TPO) and anti-microsomal antibodies, Graves disease

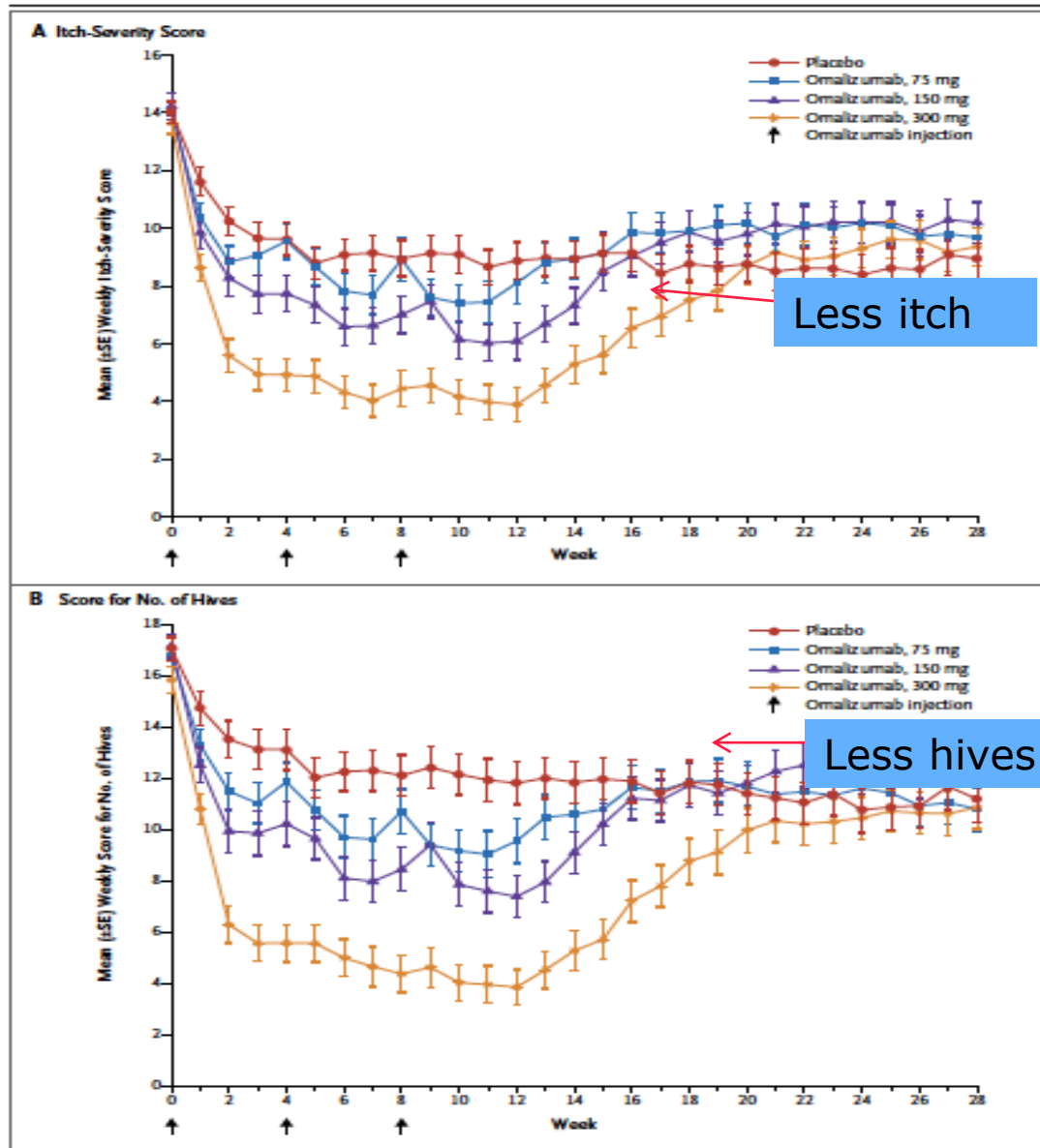
Connective tissue disorders, Malignancy

SLE, leukocytoclastic vasculitis, multiple myeloma, plasmocytoma, cryoglobulinemias

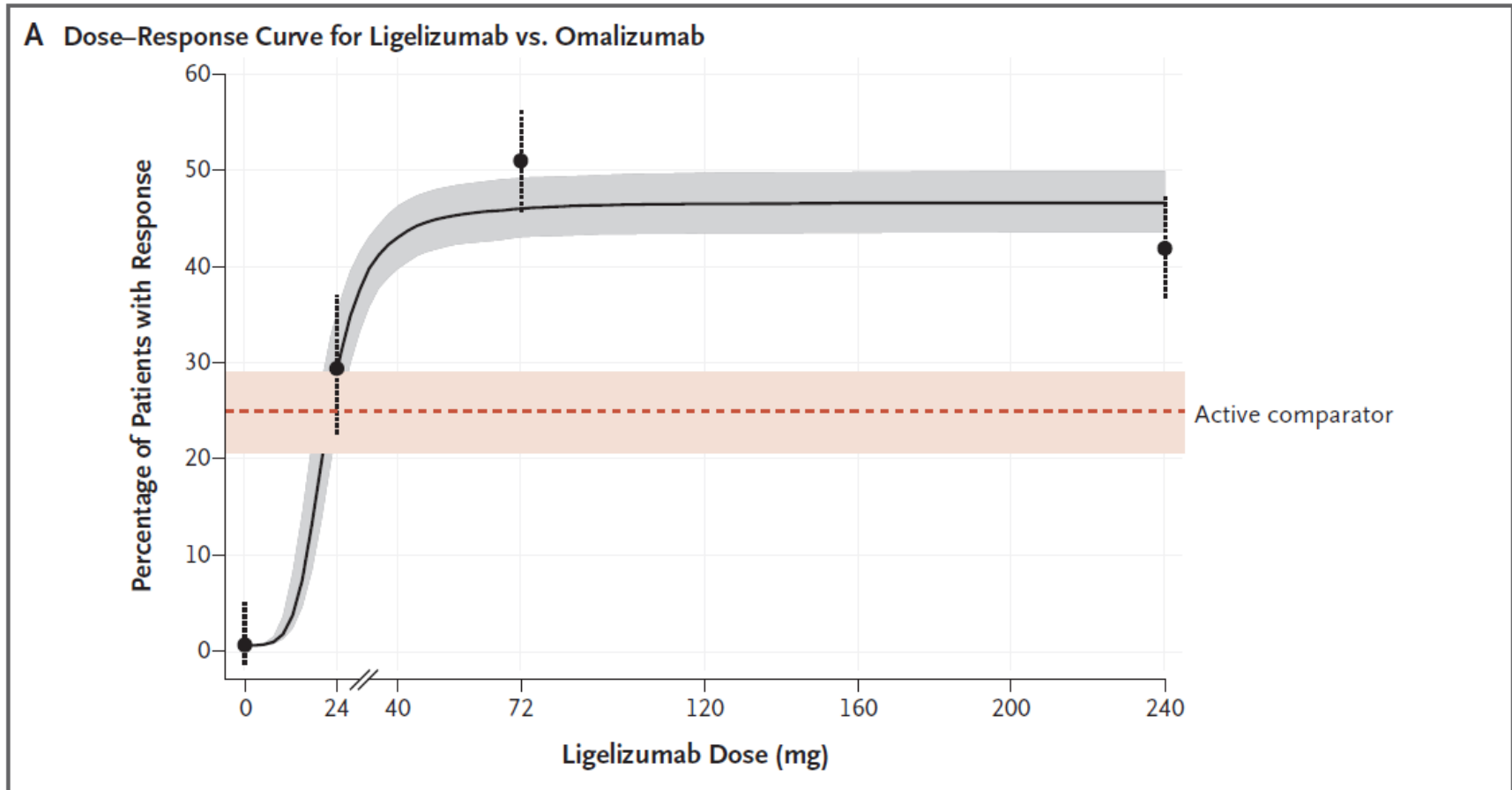
Urticaria: Treatment

- **H1 antagonists** nonsedating→sedating
 - **H2 antagonists** famotidine, cimetidine
 - [**Doxepin** (combined H₁ and H₂ antagonist)]
 - **Leukotriene antagonists** Montelukast
 - **Corticosteroids** (alternate day $\leq 20\text{mg}$)
 - **Others:** Colchicine, Dapsone, Hydroxychloroquine, Sulfasalazine, Cyclosporine, Plasmapheresis, IVIG, Levothyroxine
- Omalizumab Anti-IgE** (Chronic idiopathic urticaria/Cold-induced urticaria; **Omalizumab** Boyce 2007 JACI, Kaplan 2009, Maurer 2013 NEJM), and **Ligelizumab** (on the way) (Maurer 2019 NEJM)

Omalizumab in CIU: 150 mg to 300 mg every 4 weeks

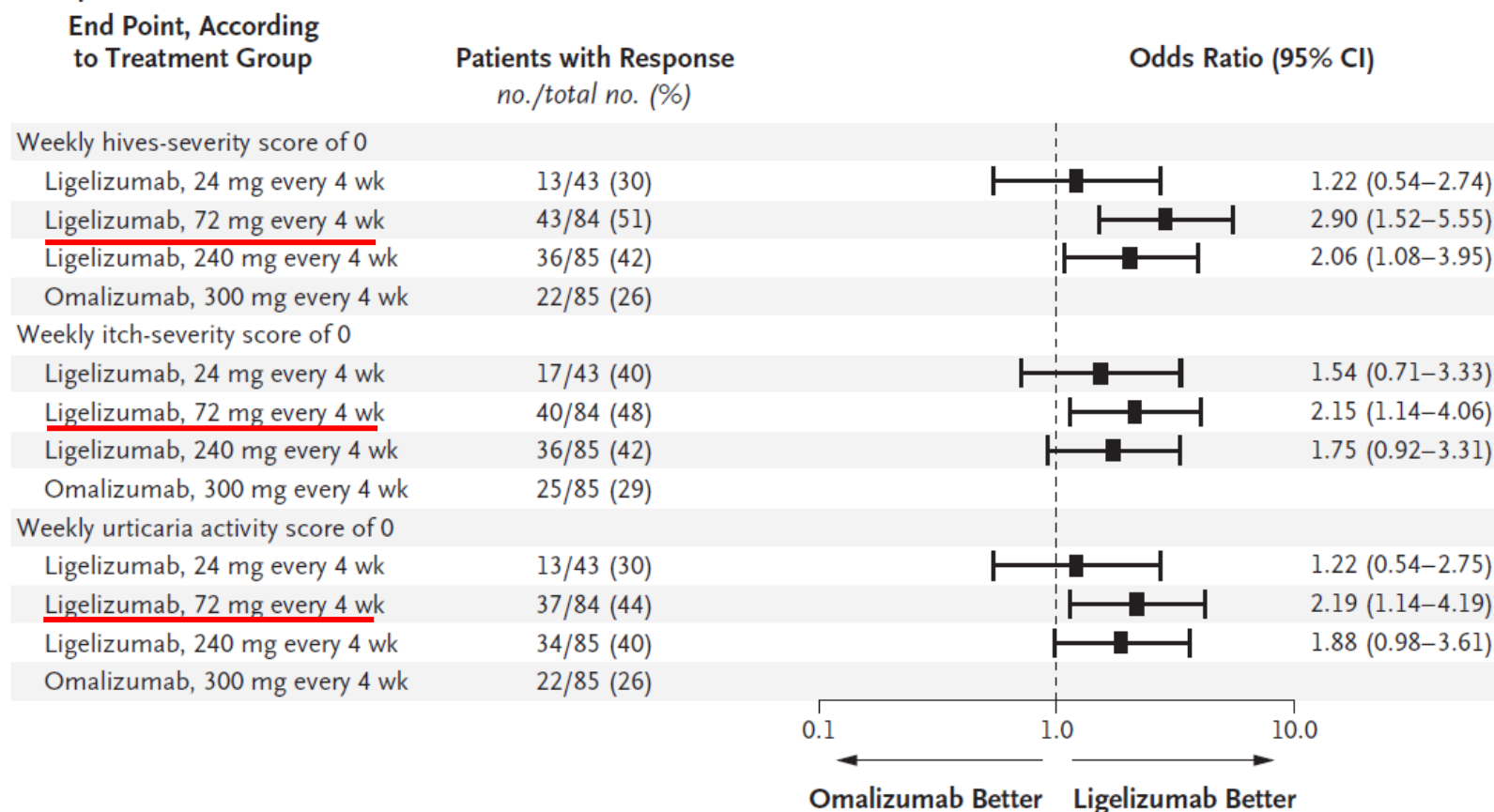


Ligelizumab vs Omalizumab for CU

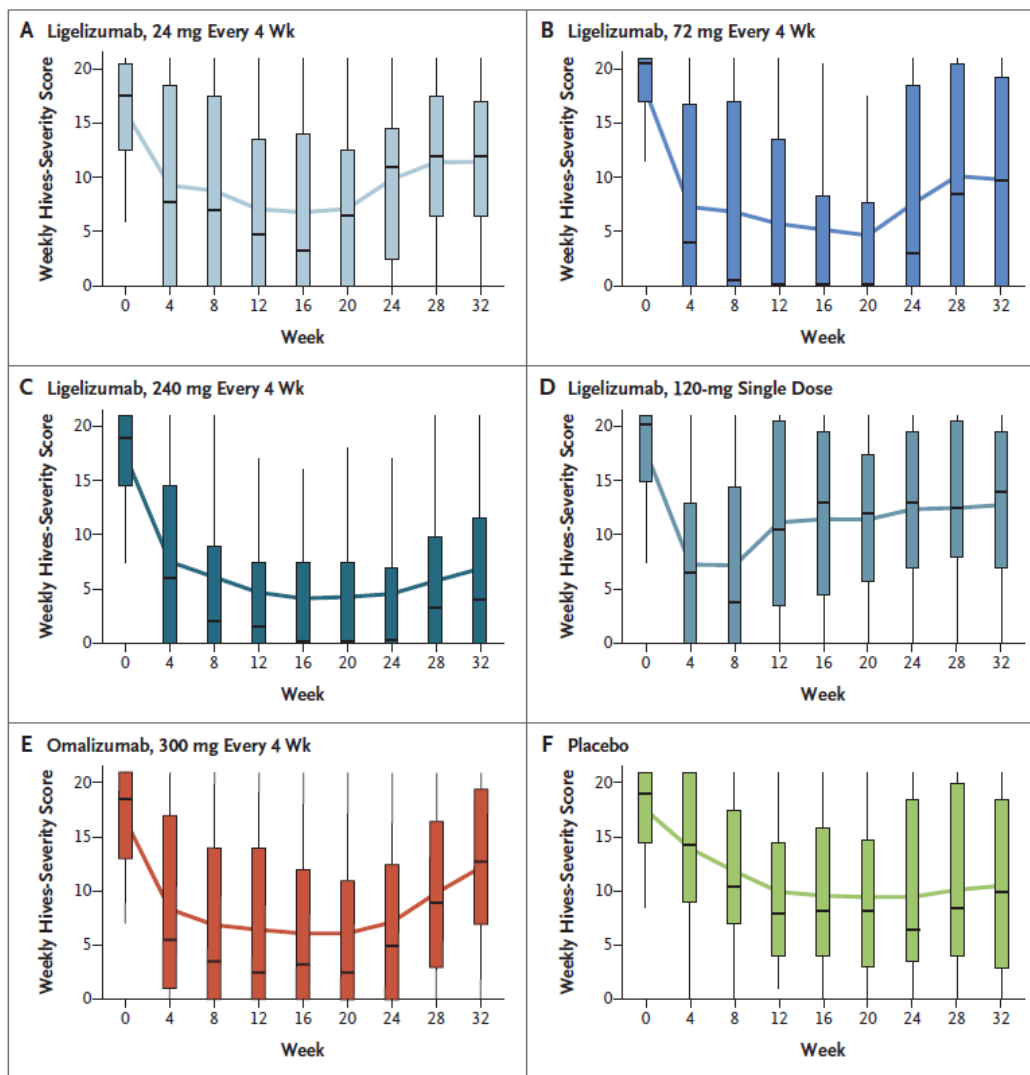


Ligelizumab vs Omalizumab for CU

B Response at Week 12



Ligelizumab vs Omalizumab for CU



On the way:
Lirentelimab
anti SIGLEC-8
for CU.
J Allergy
Clin Immunol
2022;
149:1683-90.

Angioedema (non mast cell mediated)

Hereditary

- C1inh deficiency : **Type I**
decreased level due to point/frame shift mutations of the SERPIN gene
- C1inh dysfunction: **Type II**
normal serum concentration but non-functional protein
C1Inh/C1Q Normal

Type III:

Factor XII and other mutations

Females, familial, menstrual periods (estrogen/progesterone)

Acquired

- Inhibitor(s) of C1inh : auto-Abs
B cell lymphomas
Excessive consumption (malignancies, connective tissue diseases SLE, HIV)

Hereditary and Acquired Angioedema

- **Symptoms:**

- episodic swelling of the head, face, neck, extremities and GI (abdominal pain, nausea and vomiting responsive to fluids and narcotics)

- **Diagnosis:**

	C4	C1INH	C1q	C2
Hereditary	↓	nl/↓	nl	+/-
Acquired	↓	nl/↓	↓	+/-

Therapy: Mast Cell Independent Angioedema

- Consider referral to an allergist immunologist with expertise in Hereditary Angioedema (HAE).
- Attenuated androgens (Stanozolol, Danazol) for prophylaxis
- Purified C1INH (plasma derived = Cinryze, Berinert, Haegarda; recombinant = Ruconest) for prophylaxis or acute attacks
- Icatibant = Bradykinin B2 receptor antagonist for acute attacks
- Ecallantide = Kallikrein inhibitor for acute attacks
- Lanadelumab-flyo = mAb Kallikrein inhibitor for prophylaxis
- Donidalorsen = antisense oligonucleotide inhibits kallikrein production by inducing degradation of kallikrein mRNA and prevented attacks (NEJM 2022;386:1026-33)

Anaphylaxis Definition and Clinical Manifestations

1. Acute onset of an illness (min to hrs) with involvement of the skin and/or mucosae (hives, pruritus, flushing) **and at least one of the following**
 1. Respiratory compromise (dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia)
 2. Reduced BP or symptoms (syncope)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (min to hrs)
 1. Skin and/or mucosae
 2. Respiratory compromise
 3. Reduced BP
 4. GI symptoms (colic, diarrhea)
3. Reduced BP after exposure to a known allergen for that patient (min to hrs)

Table I from Sampson et al
JACI 2006 117:391-397.

Frequency of Manifestations

- Cutaneous 90%
 - Urticaria and Angioedema 85-90%
 - Flushing 45-55%
 - Pruritus 2-5%
- Respiratory 40-60%
 - Dyspnea and Wheeze 45-50%
 - Laryngeal Angioedema 50-60%
 - Rhinitis 25-20%
- Dizziness, syncope, hypotension 30-35%
- Abdominal (n, v, colic, diarrhea) 25-30%
- Misc (HA 5-8%, SSCP 4-6%, Sz 1-2%)

Anaphylaxis: Triggers and Diagnosis

Foods: Peanuts, Tree Nuts, Seafood, Eggs, Milk, Sesame

Allergen Extracts, Vaccines, antisera

Hymenoptera Venom: Bees, Wasps, Yellow Jackets, Hornets, Fire Ants

Hormones (Progesterone Autoimmune Dermatitis), **Enzymes**

Monoclonal Abs :anti-TNF α , anti-CD20

Chemotherapy: platins, taxanes

Beta lactams, ASA and other **NSAIDS** (COX1>COX2), **vancomycin** (red person syndrome), **Radio Contrast Media**, **opiates** (direct mast cell activators)

Anesthetics: Curare Derivatives

Dialysis membranes

Acute :

Tryptase : total >11ng/ml, mature > 1 ng/ml

N-Methyl Histamine in 24 hour urine collection

Prostaglandin D2 metabolites (PG 11- β -F2- α) in 24 hour urine

Retrospective :

Antigen-Specific IgE

Specific IgE in serum (in vitro)

Skin Testing (in vivo)

Basophil activation FACS:
CD69/CD203

Management of Anaphylaxis

Epinephrine IM (not SC!) 0.3-0.5cc

recumbent position, quadriceps

Observation for a minimum of 6 Hours

Obtain a serum Tryptase

Oxygen

Anti-histamines H1 and H2,

Delayed, protracted anaphylaxis may occur 6 to 24 hours; late phase or secondary reaction requires repeat Epi in 16-36% of patients.

Steroids: single dose (IV or oral) do they decrease the risk of a late phase reaction? ([Not so much = JACI In Pract. 2017, 5\(5\), pg 1194-1205](#))

If β Blockade: Glucagon 5 - 15 $\mu\text{g}/\text{min}$ IV (*after* trying epi)

ACE inhibitors are implicated in severe/refractory

Education

Allergy evaluation

Auto injectable epinephrine

Drug Hypersensitivity

Common Drugs:

PCN and related Abx: IgE-mediated

- Cross reactivity with cephalosporins (10 % first generation, 1-2% 3rd -4th generation)

aztreonam is non- cross-reactive (except ceftazidime)

ASA and NSAID's: COX-1/COX-2 blockade, universal cross-reactivity

ACE-I (Kininase II): Bradykinin Mediated angioedema

Sulfonamides: no cross-reactivity with non-antibiotic medications such as furosemide (NEJM 2007)

Diagnosis:

- Skin test (E.g., PCN)
- Challenge (E.g., ASA, NSAIDs)

Management

Avoidance, MediAlert Bracelets

Desensitization (to Antibiotics, Aspirin, Chemotherapeutics, Monoclonal Antibodies)

Drug Allergy Practice Parameter 2022

- History is the essential dataset
 - morbilliform drug eruption (MDE)
 - urticaria-angioedema, anaphylaxis (classic mast cell, IgE or MRGPRX2 or other(?))
 - Severe Cutaneous Adverse Reaction (SCAR)
 - Atypical (e.g., headache, nausea, vomiting, diarrhea)
- Patient anxiety is non-negligible and is sometimes taken into account in the workup (e.g., whether to skin test before challenge)
- In general
 - Attempt to delabel
 - de-emphasis on skin test and preference for drug challenge

β -lactam antibiotics

- 10% of the population reports penicillin allergy
- But >95% of them tolerate penicillin when challenged
- The penicillin allergy label leads to use of less effective, more toxic, and more expensive antibiotics.

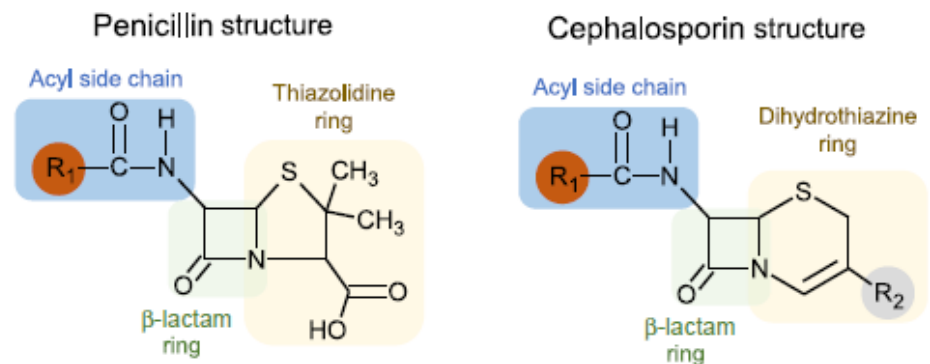


FIGURE 1. Structures of penicillin and cephalosporin showing the shared β -lactam ring (*green*) as well as the R₁-group side chains (*red*), which are another potential source of cross-reactivity between penicillins and cephalosporins. The R₂-group side chain is also shown in the cephalosporin structure (*gray*).

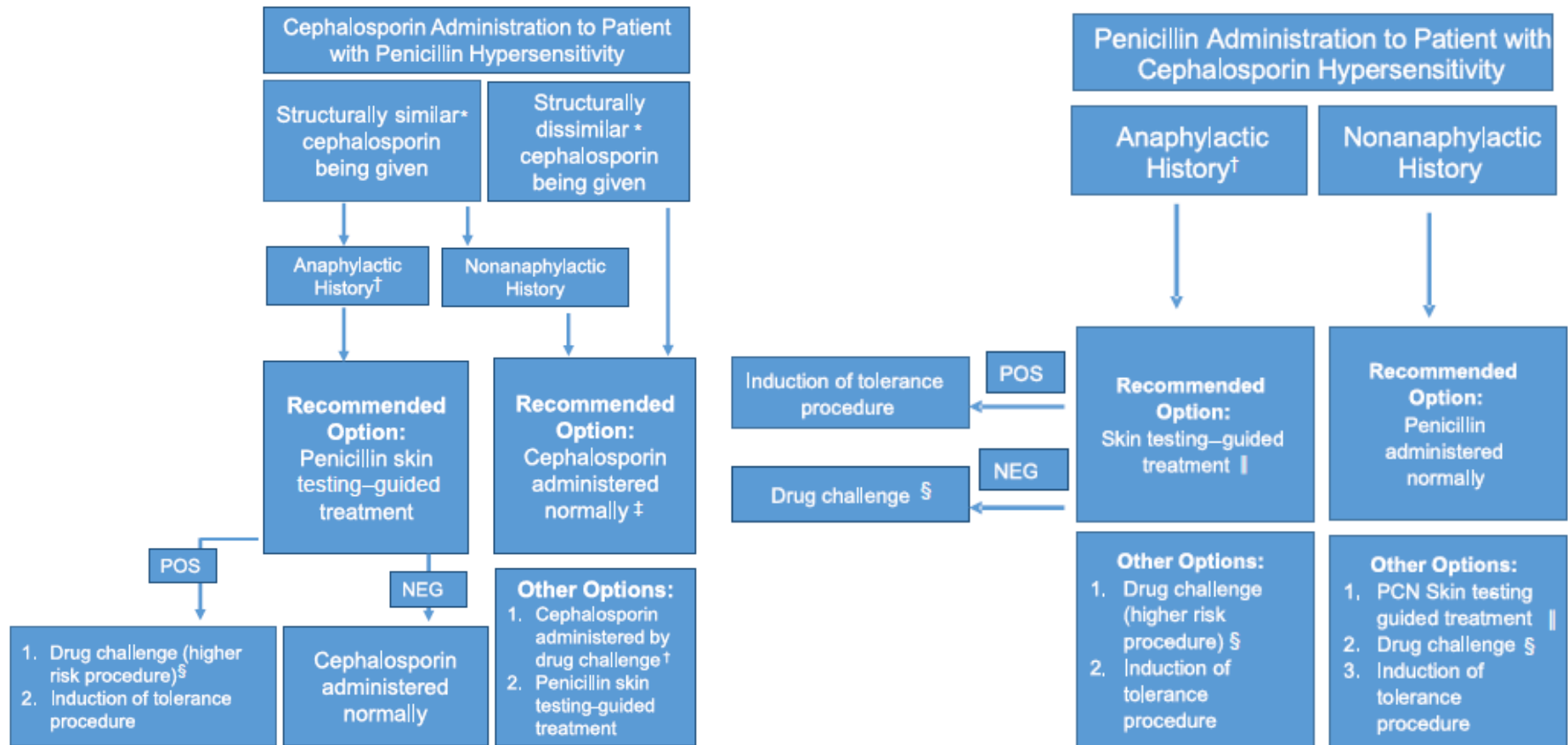
β -lactam antibiotics

	Cefazolin (first)	Cefaclor (second)	Cefadroxil (first)	Cefepime (fourth)	Cefotaxime (third)	Cefoxitin(second)	Cefprozil (second)	Ceftazidime (third)	Ceftriaxone (third)	Cephalexin (first)	Amoxicillin	Ampicillin	Aztreonam
Cefazolin (first)	-												
Cefaclor (second)		-								X		X	
Cefadroxil (first)			-				X			X	X		
Cefepime (fourth)				-	X				X				
Cefotaxime (third)				X	-				X				
Cefoxitin(second)						-							
Cefprozil (second)			X				-				X		
Ceftazidime (third)								-					X
Ceftriaxone (third)				X	X				-				
Cephalexin (first)		X	X							-		X	
Amoxicillin			X				X				-		
Ampicillin		X								X		-	
Aztreonam								X					-

FIGURE 2. Matrix of β -lactam antibiotics with identical R1-group side chains (red).

- Cross reactivity between penicillin and cephalosporins due to sensitivity to the shared β -lactam ring only in 2% of patients.
- Shared R1-group side chain is the more common mechanism, but cross reactivity is still lower than we previously thought
- Likewise, cross reactivity between carbapenems and other β -lactams is lower than we previously thought.
- Aztreonam does not cross react with any known β -lactam except ceftazidime.

β -lactam antibiotic HSR algorithms



Non- β -lactam antibiotics

- Sulfonamides
 - Challenge is now preferred in most situations over induction of tolerance or desensitization, \pm HIV if the reaction was MDE or urticaria > 5 years ago
 - But beware of SCARs, for which sulfonamides are among the most frequent culprit drugs!
- Fluoroquinolones
 - Cause benign delayed onset MDE in 2-3% of patients...
 - But only 5% of them react when rechallenged
- Macrolides
 - 1% of patients develop a benign delayed cutaneous reaction.
 - True IgE mediated reactions and anaphylaxis are very rare

Drug HSR: Onset and Kinetics

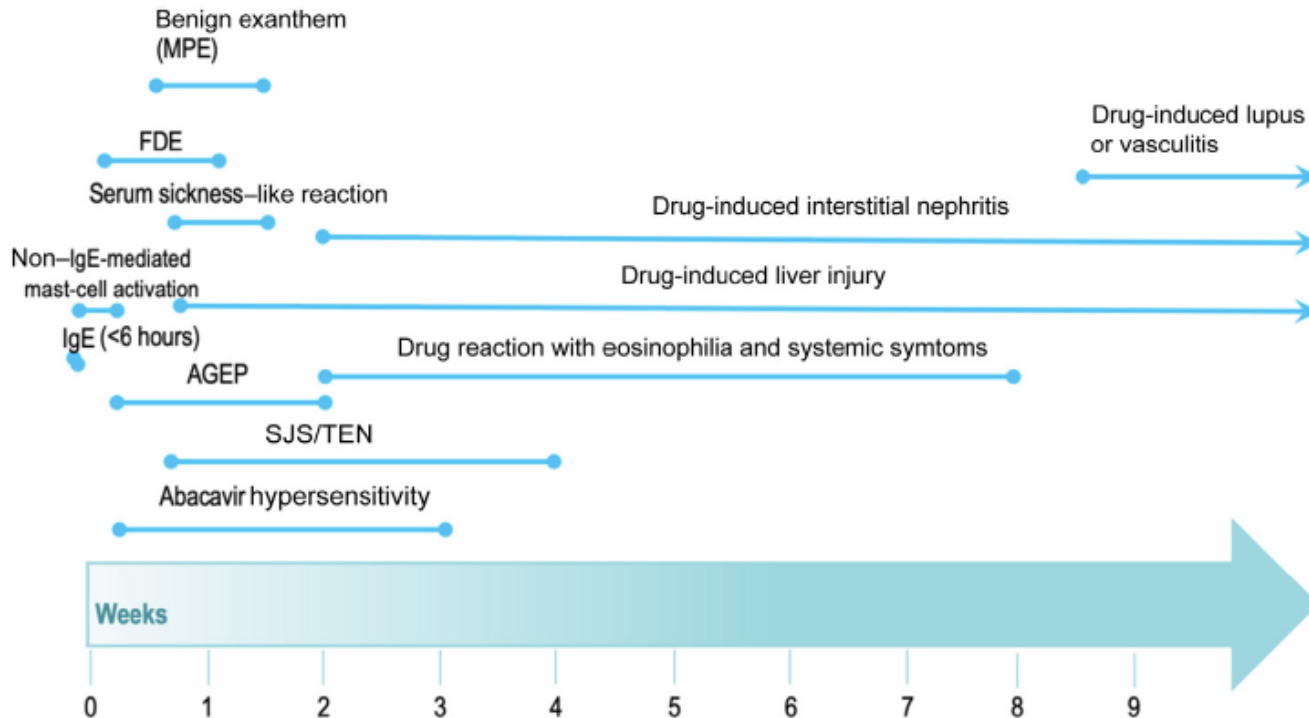


FIGURE 4. Timeline of drug HSRs. The latency period is the time from first ingestion of a drug to the time a drug reaction occurs. For IgE- and non-IgE-mediated immediate reactions, these occur within hours (<6 hours) of ingestion, whereas all delayed reactions occur after 6 hours of ingestion. The latency period is an extremely valuable clue along with other clinical features to determine the clinical phenotype of the reaction, with some reactions (eg, AGEP) occurring very quickly in association with antibiotics, whereas other reactions (eg, DRESS) have a minimum latency period of 2 to 3 weeks. A timeline outlining all drugs taken within 2 months of the first symptoms of a reaction and the evolution of the symptoms alongside the timing of initiation of specific drugs is a valuable tool to aid in drug causality for a given phenotype of reaction.

Drug HSR: Challenge Protocols

TABLE IV. Open drug challenge* protocols for nonsevere delayed reactions[†]

Challenge Procedure	Dose [‡]	Observation
1-step	1 tab or full <i>PO</i> dose [§]	60 min to 2 h
2-step	Step 1: 1/10th <i>PO/IV/IM/SC</i> dose Step 2: Full <i>PO/IV/IM/SC</i> dose	30 min 60 min to 2 h
Other*	Multiple-day challenge or graded reintroduction	Outpatient procedure
Criteria for positive reaction	Fever, urticaria, facial swelling, exanthem, hypoxia, hypotension, mouth urogenital or eye soreness, fixed or blistering eruption, target or atypical target lesions	
Criteria for possible reaction [¶]	Isolated joint pain, appetite change, persistent pruritus without rash	
Doubtful reaction [¶]	Dizziness, tachycardia, subjective lip/tongue swelling, subjective throat tightness, lump in throat, dyspnea, transient pruritus without rash, headache	

IM, Intramuscular; *IV*, intravenous; *PO*, *per os* [by mouth]; *SC*, subcutaneous.

*Sometimes called desensitization or induction of drug tolerance, but the mechanism is unknown at this time and probably functions more like a challenge reaction like when beyond a critical dose, a reaction can recur.

[†]Contraindicated for SCARs or any situation in which documented organ failure has occurred.

[‡]Comparably dosed oral solution may be used (1/10th or full dose).

[§]For very low-risk patients without significant comorbidities or reactions that have occurred more distantly (>5 y), single full-dose challenge may be used.

^{||}For mild exanthems, full-dose challenge may be used.

[¶]Consider placebo-controlled challenges or placebo treatment lead-in for possible or doubtful reactions to confirm or refute delayed HSR.

Rapid Drug Desensitization

Medication:	<i>Tocilizumab</i>
Target Dose (mg)	570.0
Standard bag volume (ml)	250
Final infusion rate (ml/hr)	80
Final concentration (mg/ml)	2.280
Standard infusion time (min)	187.5

Solution	Volume (mL)	Conc. (mg/mL)	Total mg/bag	Total vol used (mL)
Solution 1	250	0.023	5.700	9.25
Solution 2	250	0.228	57.000	18.75
Solution 3	250	2.262	565.514	250.00

Step	Solution	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0114	0.0114
2	1	5.0	15	1.25	0.0285	0.0399
3	1	10.0	15	2.50	0.0570	0.0969
4	1	20.0	15	5.00	0.1140	0.2109
5	2	5.0	15	1.25	0.2850	0.4959
6	2	10.0	15	2.50	0.5700	1.0659
7	2	20.0	15	5.00	1.1400	2.2059
8	2	40.0	15	10.00	2.2800	4.4859
9	3	10.0	15	2.50	5.6551	10.1410
10	3	20.0	15	5.00	11.3103	21.4513
11	3	40.0	15	10.00	22.6206	44.0719
12	3	80.0	174.375	232.50	525.9281	570.0000

Total time:	339.375 min = 5.66 hours
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Non-IgE Hypersensitivity Drug Reactions: SCARs

- SCAR = Severe Cutaneous Adverse (drug) Reaction
- **DRESS** syndrome: eosinophilia, rash, systemic symptoms such as fever, LFN, LFT elevations
anti-convulsants: cross-reactivity is high (HLA-B* 1502)
phenytoin, phenobarbital, carbamazepine
role of HHV6 or HHV-7 (or both) reactivation
- Erythema Multiforme (**EM**) → Steven's Johnson Syndrome (**SJS**) → Toxic Epidermal Necrolysis (**TEN**)
sulfonamides, beta-lactams
Abacavir: fever, rash, systemic involvement (HLA-B*5701)
Quinolones: universal cross-reactivity
- Acute Generalized Exanthematous Pustulosis (**AGEP**)

Figure S1: Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). Early stage of SJS or TEN maculopapular rash (A).



Flaccid blisters and large epidermal sheets easily detached at pressure points or minimal friction trauma, revealing large areas of exposed, red sometimes oozing dermis (C).



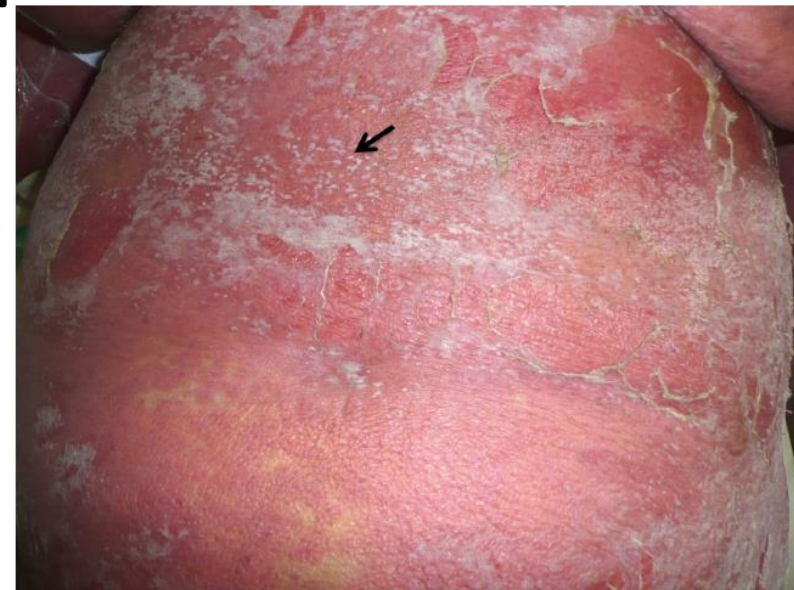
Figure S5: Acute generalized exanthematous pustulosis (AGEP). Non-follicular pustules (arrow) arising on oedematous erythema of the trunk (A).

EM → SJS → TEN

T cell mediated
Can NOT challenge or desensitize to these

Duong TA et al. Lancet 2017;
390(10106):1996-2011

AGEP:



Food Allergy: Statistics

- In adults most allergic food reactions are caused by peanut, tree nuts, fish, and shellfish; other common culprit foods include milk, egg, wheat, soy, and sesame.
- Responsible annually in US for approximately:
 - 30,000 anaphylactic reactions
 - 2,000 hospitalizations
 - 150-200 deaths

Severity of Food Reactions



- Severity of allergic reactions to foods is multifactorial and variable
- Severity CANNOT be predicted by:
 - Degree of severity of past reactions
 - Level of sIgE or size of SPT wheal
- Most common cofactor for severe rxns: **Asthma**
- Other factors affecting severity include:
 - Amount ingested
 - Food form (cooked, raw, processed)
 - Co-ingestion of other foods/empty stomach
 - Concomitant intake of alcohol (increases absorption)

Food Allergy: Diagnosis

- Food skin tests detect food-specific mast cell reactivity, presumed to be IgE dependent
- Positive food skin test indicates a *possibility* the patient has symptomatic reactivity to a specific food
 - 50% positive predictive accuracy
 - Positive FST are only suggestive of the presence of clinical food allergy; food specific serum IgE only indicates immune sensitization, not proof of clinically meaningful reaction.
 - Neither the size of a skin prick test wheal nor a serum food specific IgE level predicts the severity of a clinical reaction
 - Skin tests/sIgE results MUST be interpreted in the context of the clinical history of an individual patient (pretest probability)
 - IgE food antigen component testing may help with risk assessment.
- Negative food skin test essentially confirms the absence of IgE-mediated food reaction
 - >95% negative predictive accuracy

Example: Peanut Component Tests

TABLE 1 Common Components of the Peanut

Component	Protein Type	Clinical Significance
Ara h 1	Seed-storage protein	Major peanut allergen
 Ara h 2	Seed-storage protein	Major peanut allergen; component most predictive of clinical peanut allergy
Ara h 3	Seed-storage protein	Major peanut allergen
Ara h 4	Isoform of Ara h 3	Potential major peanut allergen
Ara h 6	Seed-storage protein	Major peanut allergen
 Ara h 8	Birch pollen homolog	Labile protein; not usually associated with severe reactions; associated with pollen sensitization
Ara h 9	Lipid-transfer protein	Stable protein; associated with more-severe symptoms in Mediterranean region; associated with peach allergy

Adapted from Sicherer SH, Sampson HA. Food allergy: a review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol*. 2018;141(1):46.

Food Allergy: Management

- Once the diagnosis of food allergy has been established the only proven therapy is STRICT elimination of the offending allergen
- Educate patients/families to avoid accidental ingestion (ALWAYS READ LABELS)
- Document prescription for and training in the proper use and indication of Epipen (Jr)
- Support and Education: Food Allergy and Anaphylaxis Network (www.foodallergy.org)

Food Allergy Treatment: Desensitization

- Mostly Oral Immunotherapy (OIT), but some Sublingual Immunotherapy (SLIT) and Epicutaneous Immunotherapy (EPIT) trials
- Patients are mostly children and teens
- Foods: peanut, milk, egg, wheat, walnut, hazelnut, and multiple
- Appears less successful with increasing age, severity of sensitization, or clinical reaction
- Must be continued indefinitely to maintain desensitized state (\neq tolerance)
- Increased risk of anaphylaxis and other allergic reactions during buildup and maintenance
- Increased incidence of eosinophilic esophagitis with longer term ingestion
- Omalizumab (anti-IgE) helpful in decreasing reactions.

Omalizumab for the Treatment of Multiple Food Allergies: OUTMATCH

Table 2. Successful Consumption of Prespecified Threshold Dose at Week 16.*

End Point and Food Challenge	No. of Participants	Omalizumab	Placebo	Difference (95% CI)	P Value
		<i>no./total no. (%)</i>		<i>percentage points</i>	
Primary end point†					
Peanut	177	79/118 (67)	4/59 (7)	60 (47 to 70)	<0.001
Key secondary end points‡					
Cashew	99	28/68 (41)	1/31 (3)	38 (19 to 52)	<0.001
Egg	71	34/51 (67)	0/20 (0)	67 (46 to 79)	<0.001
Milk	62	27/41 (66)	2/21 (10)	56 (30 to 74)	<0.001
Other secondary end points‡					
Walnut	78	30/47 (64)	4/31 (13)	51 (27 to 68)	—
Hazelnut	24	11/17 (65)	1/7 (14)	50 (–2 to 78)	—
Wheat	20	9/12 (75)	1/8 (13)	63 (13 to 88)	—

* The food challenges at the end of the first stage of the trial were started at week 16 and were conducted during separate visits spanning up to a 4-week period. The 95% confidence intervals (CIs) are exact unconditional confidence intervals. $P < 0.001$ (unadjusted two-sided P value from Fisher's exact test) for the primary end point and the key secondary end points.

† The primary end point was consumption of a single dose of at least 600 mg of peanut protein, without dose-limiting symptoms. This end point was tested at the $P < 0.0001$ level of significance at the interim analysis, which included 165 children and adolescents.

‡ The secondary end points were consumption of a single dose of at least 1000 mg of food protein without dose-limiting symptoms. Key secondary end points, which were tested only if the primary end point was significant at $P < 0.0001$ at the interim analysis, were tested at the $P < 0.005$ level of significance. The other secondary end points were not included in the plan to adjust for multiple testing results and are reported with 95% confidence intervals, without P values; the 95% confidence intervals are not adjusted for multiple testing and should not be used to infer treatment effects.

OUTMATCH, NEJM 25-28 February 2024

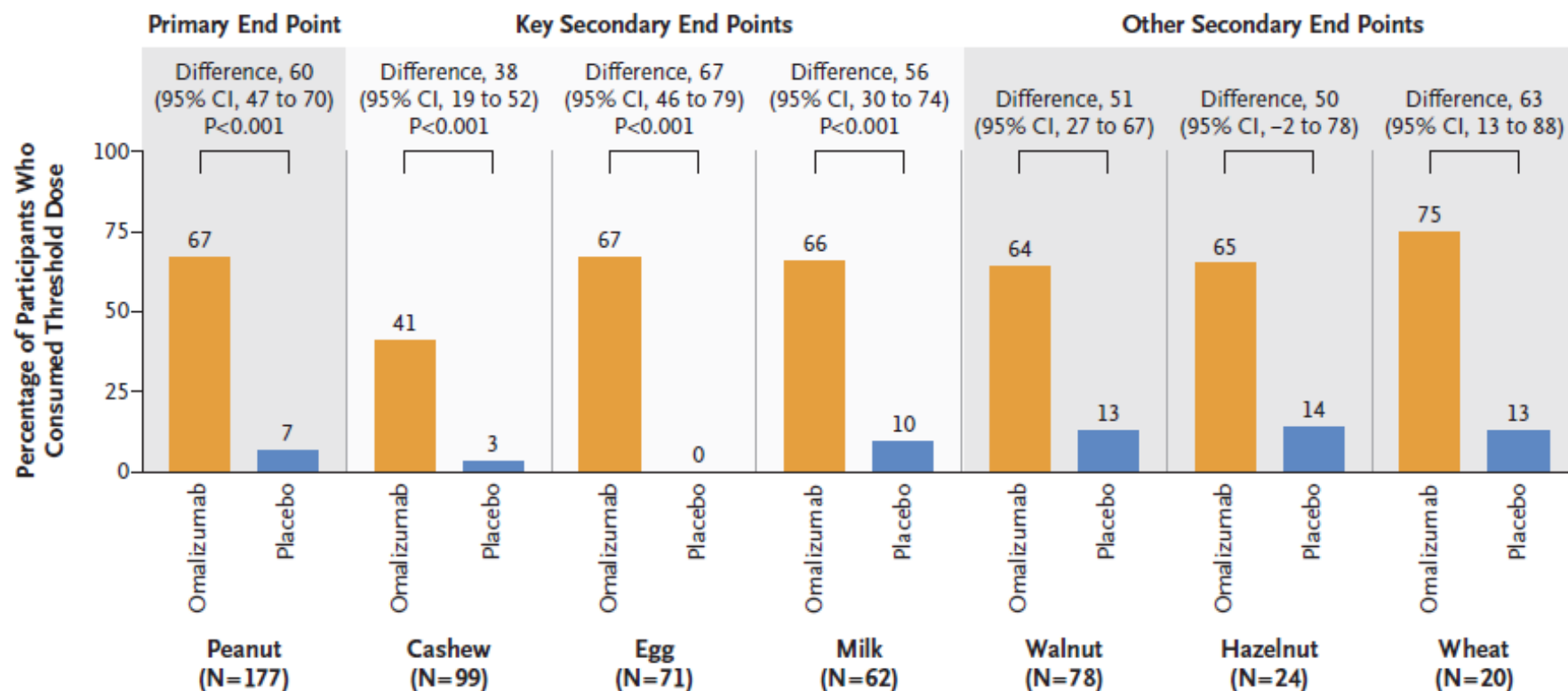
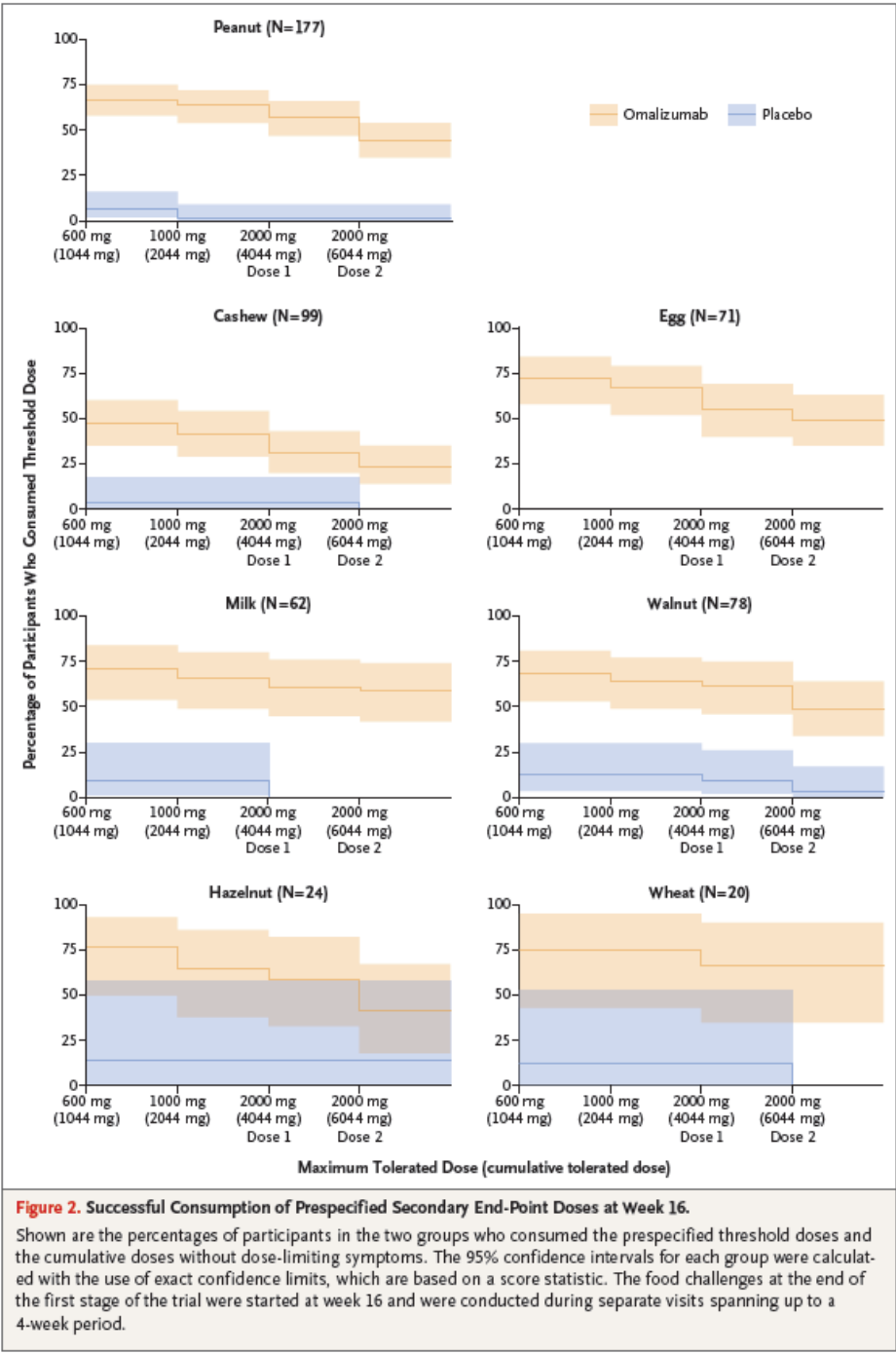


Figure 1. Successful Consumption of Prespecified Threshold Dose at Week 16.

Shown are the percentages of participants in the two groups who consumed the prespecified threshold doses without dose-limiting symptoms during food challenges at the end of the first stage of the trial; these food challenges were started at week 16 and were conducted during separate visits spanning up to a 4-week period. The prespecified threshold dose of peanut protein was a single dose of at least 600 mg; for cashew, egg, milk, walnut, hazelnut, and wheat protein, the prespecified threshold was a single dose of at least 1000 mg. The 95% confidence intervals for the differences were calculated with the use of exact unconditional confidence limits. The P values for the primary and key secondary end points are unadjusted, two-sided values derived from Fisher's exact test.

OUTMATCH,
NEJM 25-28
February 2024



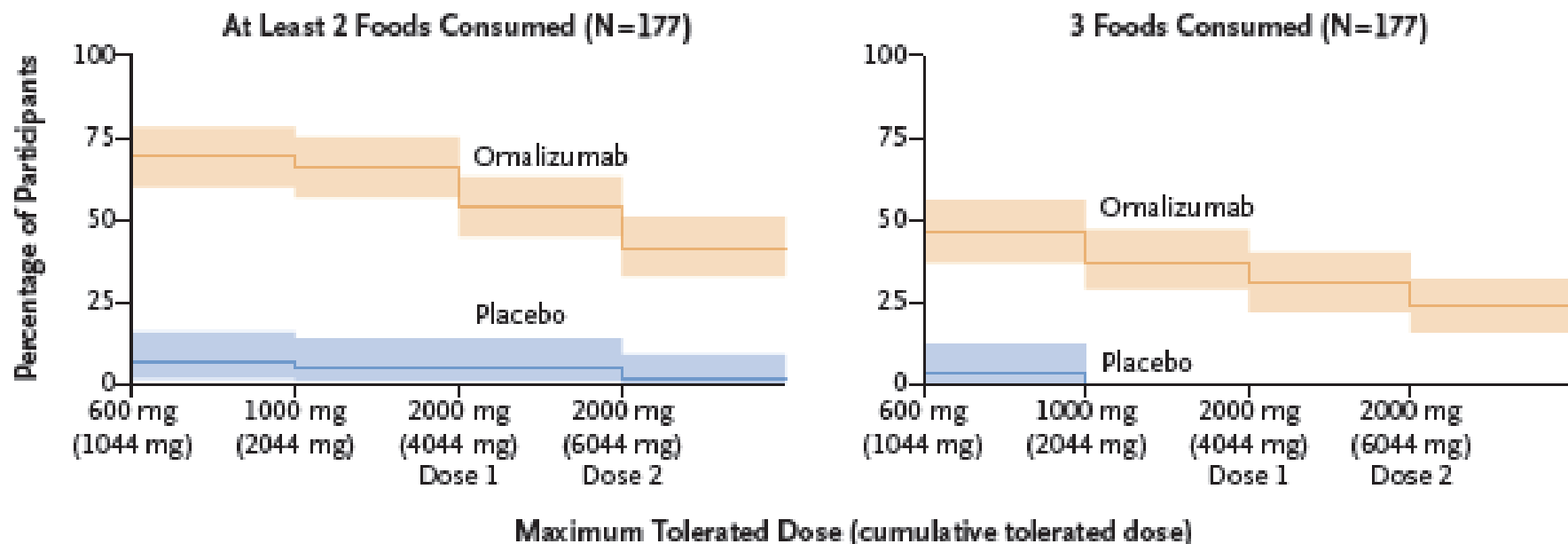


Figure 3. Successful Consumption of Multiple Foods at Prespecified Secondary End-Point Doses at Week 16.

Shown are the percentages of participants who consumed prespecified doses and cumulative doses of at least two foods and of all three foods without dose-limiting symptoms. The 95% confidence intervals for each group were calculated with the use of exact confidence limits, which are based on a score statistic. The food challenges at the end of the first stage of the trial were started at week 16 and were conducted during separate visits spanning up to a 4-week period.

Omalizumab Dosing Nomogram: food allergy vs asthma

Food Allergy

Figure S1: Omalizumab Dosing Table.
Values are milligrams per dose.

Baseline IgE (IU/mL)	Body Weight (kg)												
	≥10-12	> 12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75	75	75	75	75	75	150	150	150	150	150	300	300
>100-200	75	75	75	150	150	150	300	300	300	300	300	450	600
>200-300	75	75	150	150	150	225	300	300	450	450	450	600	375
>300-400	150	150	150	225	225	300	450	450	450	600	600	450	525
>400-500	150	150	225	225	300	450	450	600	600	375	375	525	600
>500-600	150	150	225	300	300	450	600	600	375	450	450	600	
>600-700	150	150	225	300	225	450	600	375	450	450	525		
>700-800	150	150	150	225	225	300	375	450	450	525	600		
>800-900	150	150	150	225	225	300	375	450	525	600			
>900-1000	150	150	225	225	300	375	450	525	600				
>1000-1100	150	150	225	225	300	375	450	600					
>1100-1200	150	150	225	300	300	450	525	600					
>1200-1300	150	225	225	300	375	450	525						
>1300-1500	150	225	300	300	375	525	600						
>1500-1850		225	300	375	450	600							

Dosing frequency:

	Dose every 4 weeks
	Dose every 2 weeks
	Do not dose

Asthma

Table 1. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Patients 12 Years of Age and Older with Asthma

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight			
		30–60 kg	>60–70 kg	>70–90 kg	>90–150 kg
		Dose (mg)			
≥30–100	Every	150	150	150	300
>100–200	4	300	300	300	225
>200–300	weeks	300	225	225	300
>300–400	Every	225	225	300	
>400–500	2	300	300	375	
>500–600	weeks	300	375	Insufficient Data	
>600–700		375	to Recommend a Dose		

*Dosing frequency:

- ☐ Subcutaneous doses to be administered every 4 weeks
- ☐ Subcutaneous doses to be administered every 2 weeks

Table 2. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Pediatric Patients with Asthma Who Begin XOLAIR Between the Ages of 6 to <12 Years

Pre-treatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight										
		20-25 kg	>25-30 kg	>30-40 kg	>40-50 kg	>50-60 kg	>60-70 kg	>70-80 kg	>80-90 kg	>90-125 kg	>125-150 kg	
		Dose (mg)										
30-100	Every 4 weeks	75	75	75	150	150	150	150	150	300	300	
>100-200		150	150	150	300	300	300	300	300	225	300	
>200-300		150	150	225	300	300	225	225	225	300	375	
>300-400		225	225	300	225	225	225	300	300			
>400-500		225	300	225	225	300	300	375	375			
>500-600		300	300	225	300	300	375					
>600-700		300	225	225	300	375						
>700-800	Every 2 weeks	225	225	300	375							
>800-900		225	225	300	375							
>900-1000		225	300	375	Insufficient Data to Recommend a Dose							
>1000-1100		225	300	375								
>1100-1200		300	300									
>1200-1300		300	375									

*Dosing frequency:

- ☐ Subcutaneous doses to be administered every 4 weeks
- ☐ Subcutaneous doses to be administered every 2 weeks

OUTMATCH,
NEJM 25-28 February 2024

Peanut OIT: Anaphylaxis

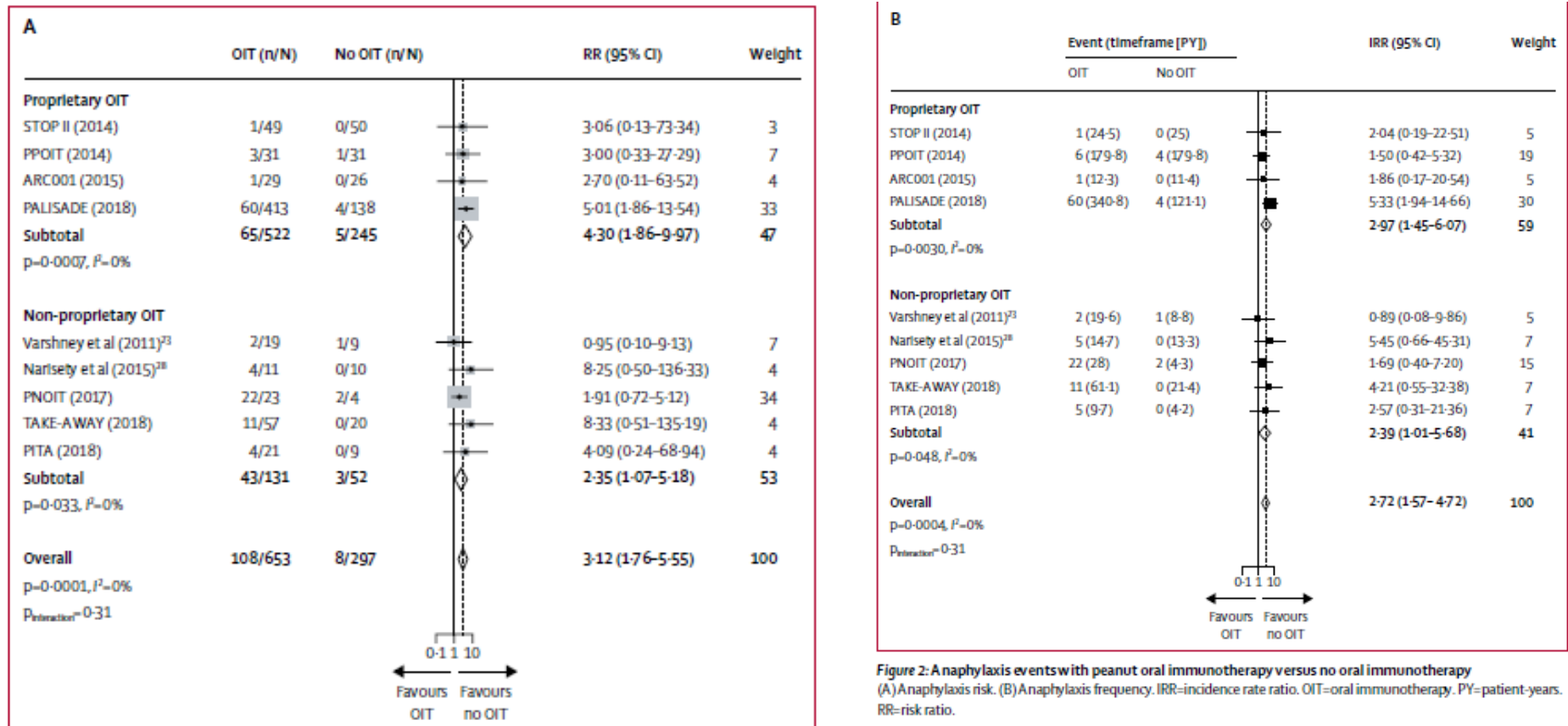


Figure 2: Anaphylaxis events with peanut oral immunotherapy versus no oral immunotherapy (A) Anaphylaxis risk. (B) Anaphylaxis frequency. IRR=incidence rate ratio. OIT=oral immunotherapy. PY=patient-years. RR=risk ratio.

Peanut OIT: Other Allergic Reactions

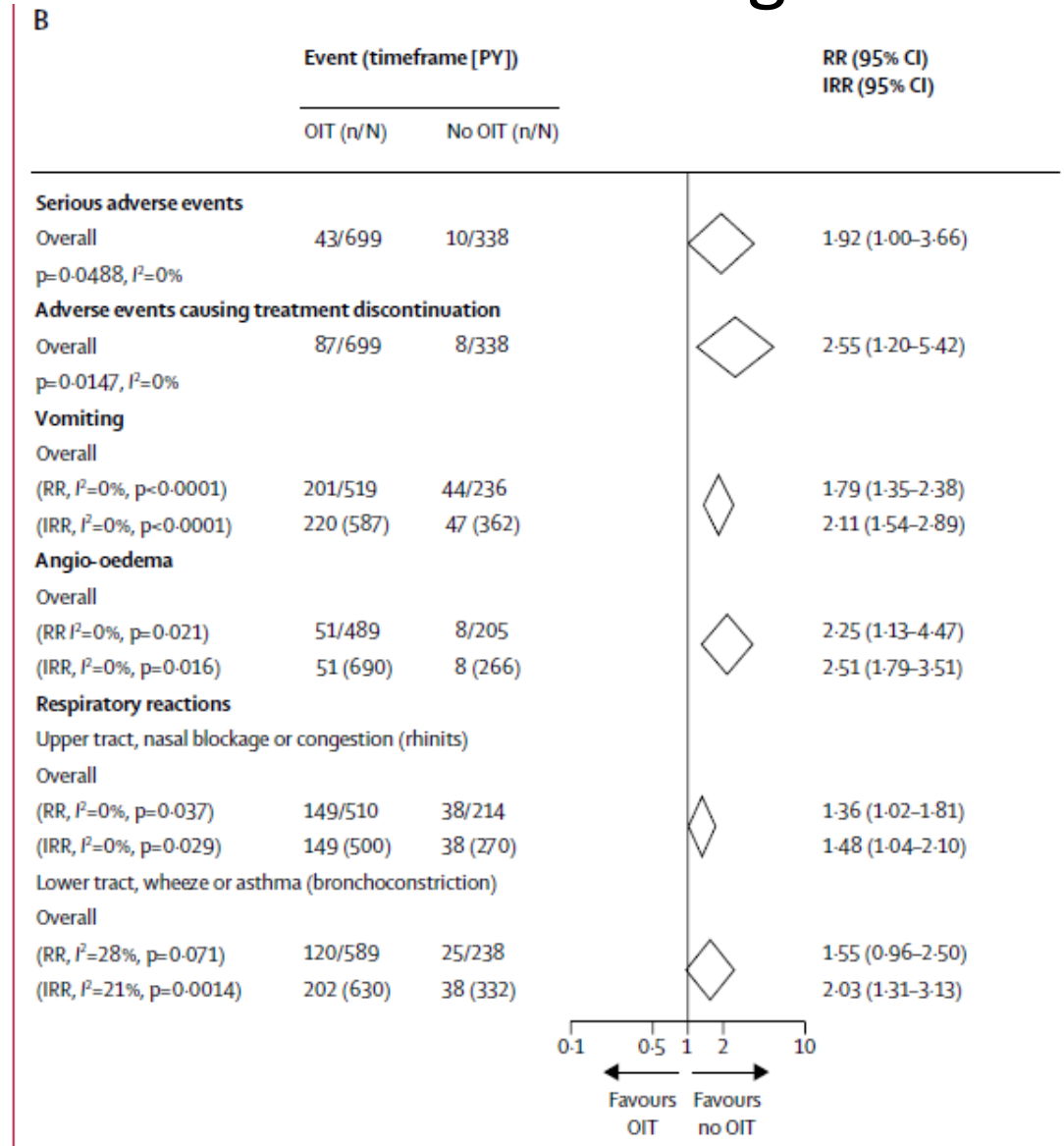


Figure 4: Serious adverse events, reactions causing study discontinuation, and allergic reactions by organ system involvement with peanut oral immunotherapy versus no oral immunotherapy
(A) Any allergic or adverse reaction. (B) Subgroups of allergic or adverse reactions. IRR=incidence rate ratio. OIT=oral immunotherapy. PY=patient-years. RR=risk ratio.

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

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

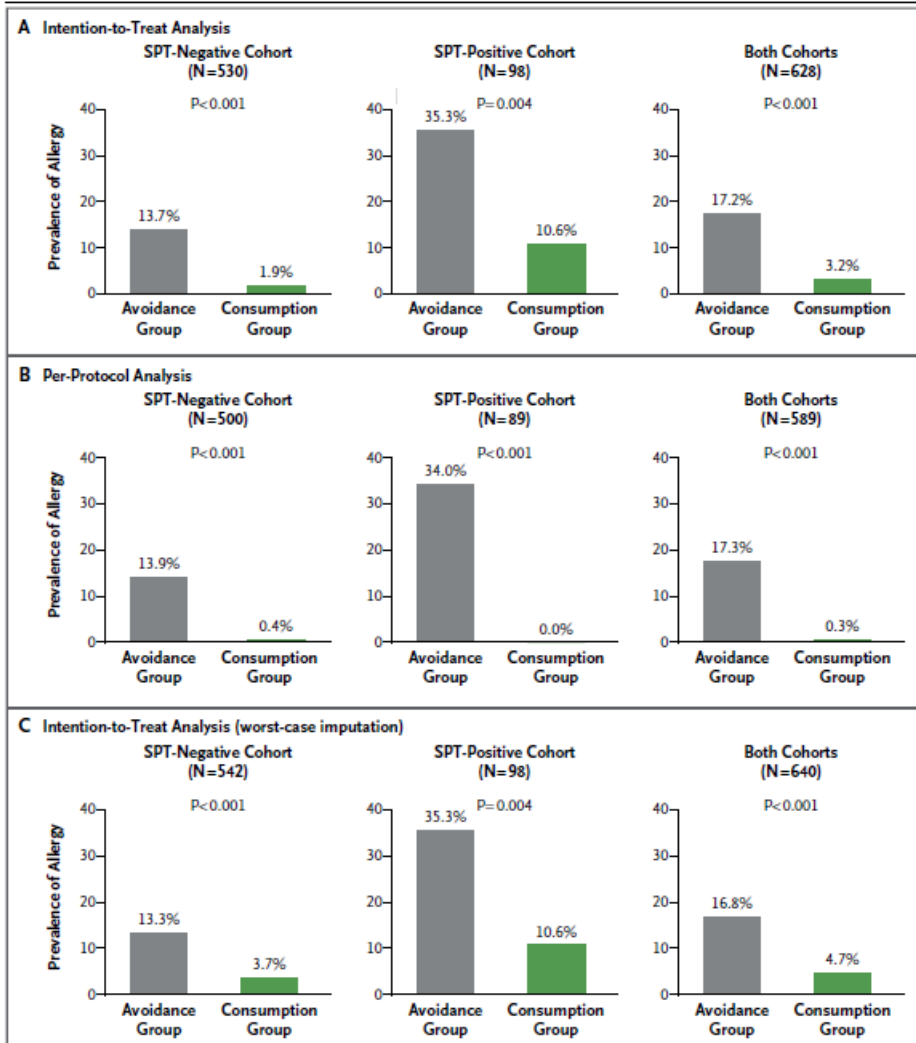


Figure 2. Primary Outcome.

The prevalence of peanut allergy at 60 months of age is shown among participants who had a negative result on the skin-prick test at baseline, among those who had a positive result at baseline, and in both groups combined, in the intention-to-treat analysis (Panel A) and the per-protocol analysis (Panel B). Among the 640 participants who underwent randomization, peanut-allergy status was determined by means of an oral food challenge in 617 (96.4%) and by means of a diagnostic algorithm in 11 (1.7%). Peanut allergy could not be evaluated with the use of the diagnostic algorithm in 2 participants (0.3%). A total of 10 participants (1.6%) voluntarily withdrew or were lost to follow-up. The worst-case imputation analysis (Panel C) assumes that participants with missing data in the peanut-consumption group would have been allergic to peanuts and that participants with missing data in the peanut-avoidance group would have been nonallergic. P values are based on chi-square analyses.

Du Toit G et al.
NEJM 2015;372(9): 803-13

On the way:
Epicutaneous Immunotherapy
For Toddlers with Peanut
Allergy
N Engl J Med 2023;
388:1755-66.

Food Allergy: Mast cells in IBS?!

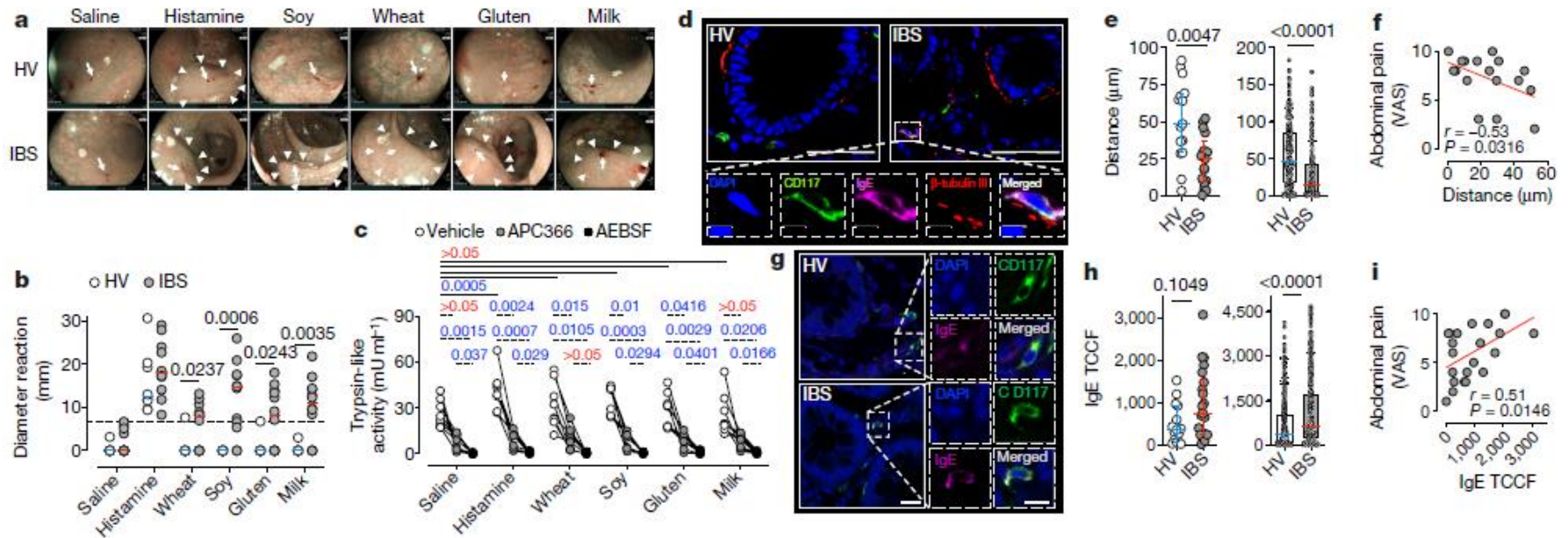
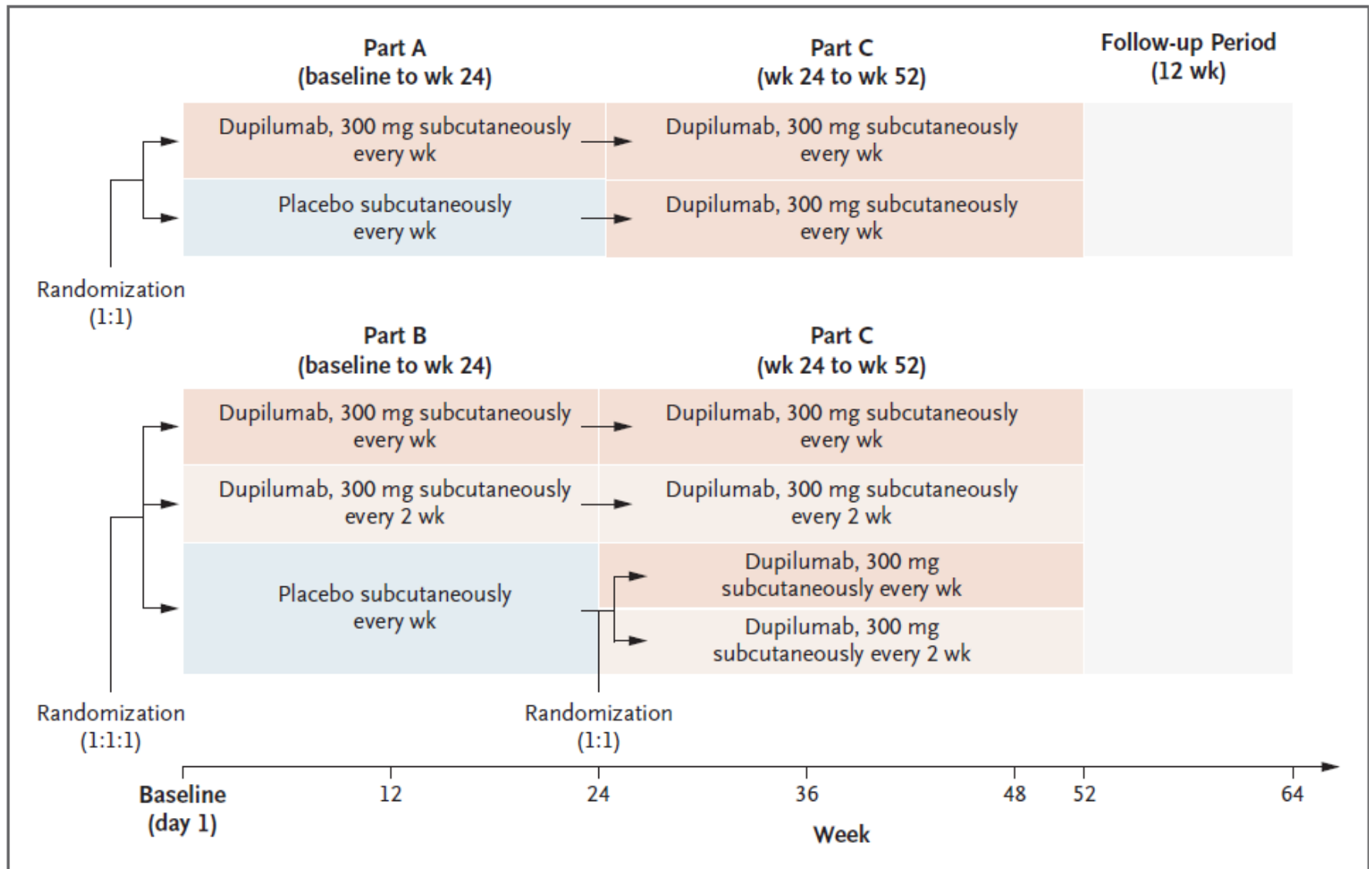


Fig. 4 | Intramucosal injection of food antigens induces an immediate mucosal response in patients with IBS. a, b, Representative images (a; arrows, antigen injection sites; arrowheads, reaction areas) and diameters of reactions to food antigens injected into healthy volunteers (HV) and individuals with IBS ($n = 8$ and 12 , respectively; dotted line in **b** represents the threshold for positive reactions). **c,** Trypsin-like activity in supernatants from rectal biopsies taken after antigen injection in individuals with IBS ($n = 8$). **d, e,** Examples of micrographs (**d**) used to measure distance from IgE⁺ mast cells to nerve fibres (**e**) in healthy volunteers ($n = 15$ individuals (left), 206 cells (right)) and individuals with IBS ($n = 17$ individuals (left), 296 cells (right)). Scale bars, 50 μm (top), 5 μm (bottom). **f,** Correlation between distance from IgE⁺ mast cells to nerve fibres and abdominal pain severity in individuals with IBS

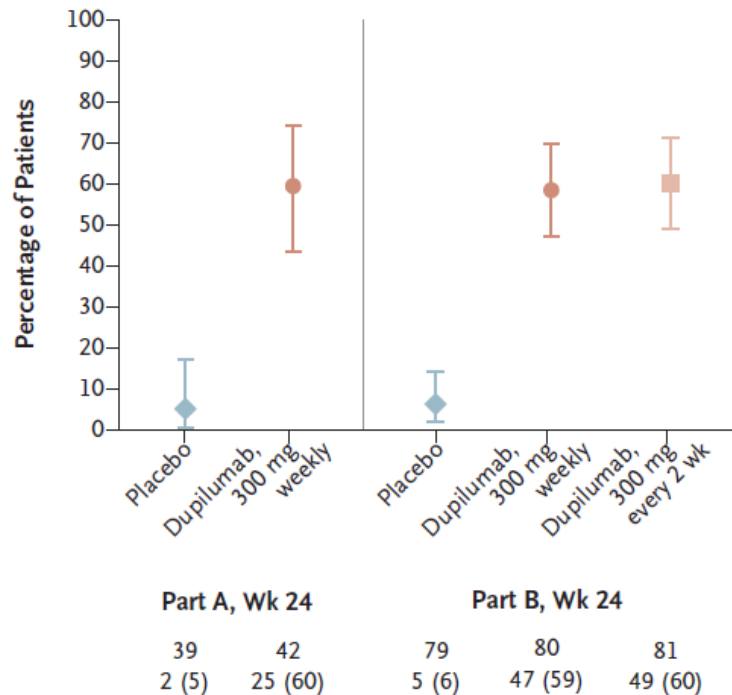
($n = 17$). VAS, visual analogue scale. **g, h,** Examples of micrographs (**g**) used to quantify IgE intensity (TCCF) in mast cells (**h**) in mucosal rectal biopsies from healthy volunteers ($n = 15$ individuals (left), 261 cells (right)) and individuals with IBS ($n = 22$ individuals (left), 315 cells (right)). Scale bars, 20 μm (left), 10 μm (right). **i,** Correlation between the IgE TCCF and abdominal pain severity in individuals with IBS ($n = 22$). *P* values shown in plots. **b, e, h,** Two-tailed Mann-Whitney test; **c,** two-way ANOVA with Sidak's multiple-comparisons test; **f,** two-tailed Spearman's correlation; **i,** two-tailed Pearson's correlation. **b,** Individual data points and median; **e** (left), **h** (left), median \pm IQR; **e** (right), **h** (right), box plots (centre line, median; box, 25th–75th percentiles; whiskers, 10th–90th percentiles).

Dupilumab for Eosinophilic Esophagitis



Dupilumab for Eosinophilic Esophagitis

A Histologic Remission at Wk 24 in Parts A and B



B Histologic Remission in the Part A–C Group Wk 52 in Part C

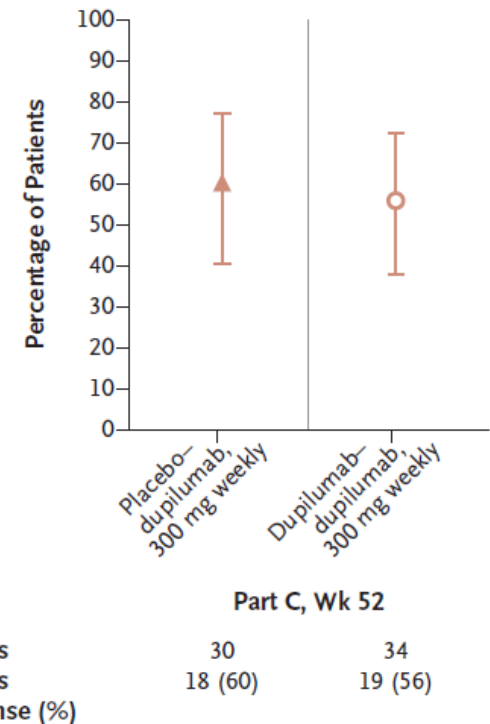


Figure 2. Histologic Remission at Weeks 24 and 52.

Shown are the percentages of patients with histologic remission at week 24 in Parts A and B of the trial (Panel A) and at week 52 in the Part A–C group, which comprised the eligible patients from Part A who continued the trial in Part C (Panel B). Histologic remission was defined as a peak esophageal intraepithelial eosinophil count of six or fewer eosinophils per high-power field. In Part C, placebo–dupilumab indicates the patients who received placebo in Part A and weekly dupilumab in Part C, and dupilumab–dupilumab indicates the patients who received dupilumab weekly in Parts A and C. The 95% confidence intervals (indicated by I bars) were calculated with the use of Rubin's method in Parts A and B of the trial and with the use of exact binomial distribution in Part C.

Dupilumab for Eosinophilic Esophagitis

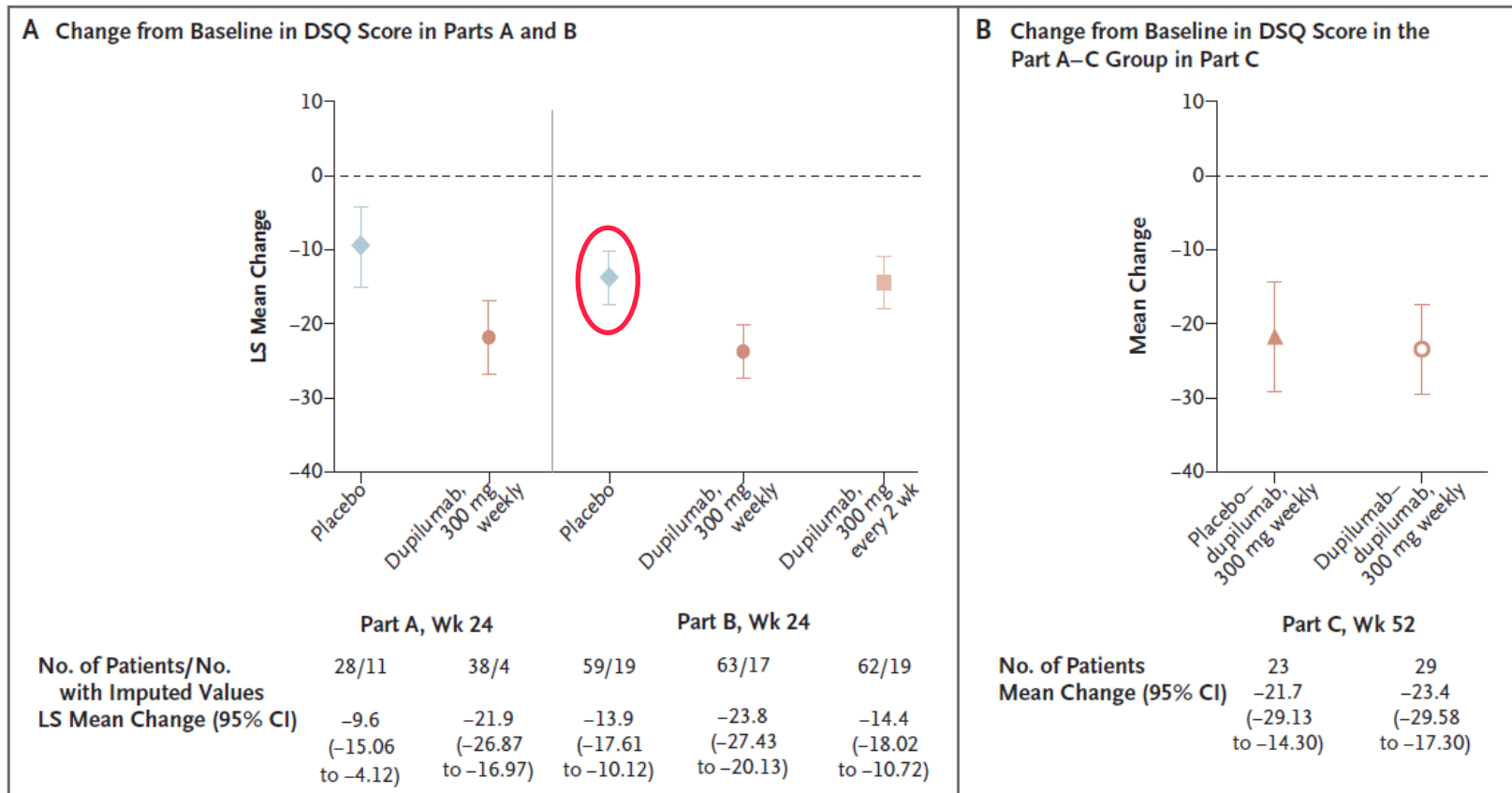


Figure 3. Change in DSQ Score at Weeks 24 and 52.

Shown are the least-squares (LS) mean changes from baseline in the Dysphagia Symptom Questionnaire (DSQ) score at week 24 in Parts A and B of the trial (Panel A) and the mean changes in the DSQ score at week 52 in the Part A–C group, which comprised the eligible patients in Part A who continued the trial in Part C (Panel B). Scores on the DSQ range from 0 to 84, with higher values indicating more frequent or more severe dysphagia. In Part C, placebo–dupilumab indicates the patients who received placebo in Part A and weekly dupilumab in Part C, and dupilumab–dupilumab indicates the patients who received dupilumab weekly in Parts A and C. I bars indicate 95% confidence intervals, which were calculated with the use of Rubin's method for the least-squares mean changes in Parts A and B and with the use of normal approximation for the mean changes in Part C.

Systemic Mastocytosis: Diagnostic Criteria

Major Criteria :

multifocal infiltrates of 15 or more mast cells in bone marrow and/or extracutaneous organs

Minor Criteria:

1. > 25% spindle shaped mast cells
2. c-kit mutations (codon D816V)
3. aberrant expression of CD2 and CD25
4. Tryptase >20 ng/ml

- Classification of Disease associated with Mast Cell Activation (Akin, Metcalf, Valent et al. J All Clin Immun 2010)
- **Non-Clonal** Mast Cell Activation Syndrome (MCAS: Hamilton et al JACI 2011)

TABLE II. Signs and symptoms of patients with MCAS

Sign or symptom	Total (%), n = 18
Abdominal pain	17 (94)
Dermatographism	16 (89)
Flushing	16 (89)
Headache	15 (83)
Poor concentration and memory	12 (67)
Diarrhea	12 (67)
Naso-ocular	7 (39)
Asthma	7 (39)
Anaphylaxis	3 (17)

ORIGINAL ARTICLE

Avapritinib versus Placebo in Indolent Systemic Mastocytosis

- ISM is the most common subtype of systemic mastocytosis
- ISM is primarily driven by *KIT* D816V mutation
- Avapritinib = an oral, highly selective, potent inhibitor of the c-kit D816V mutated tyrosine kinase.

Avapritinib for ISM

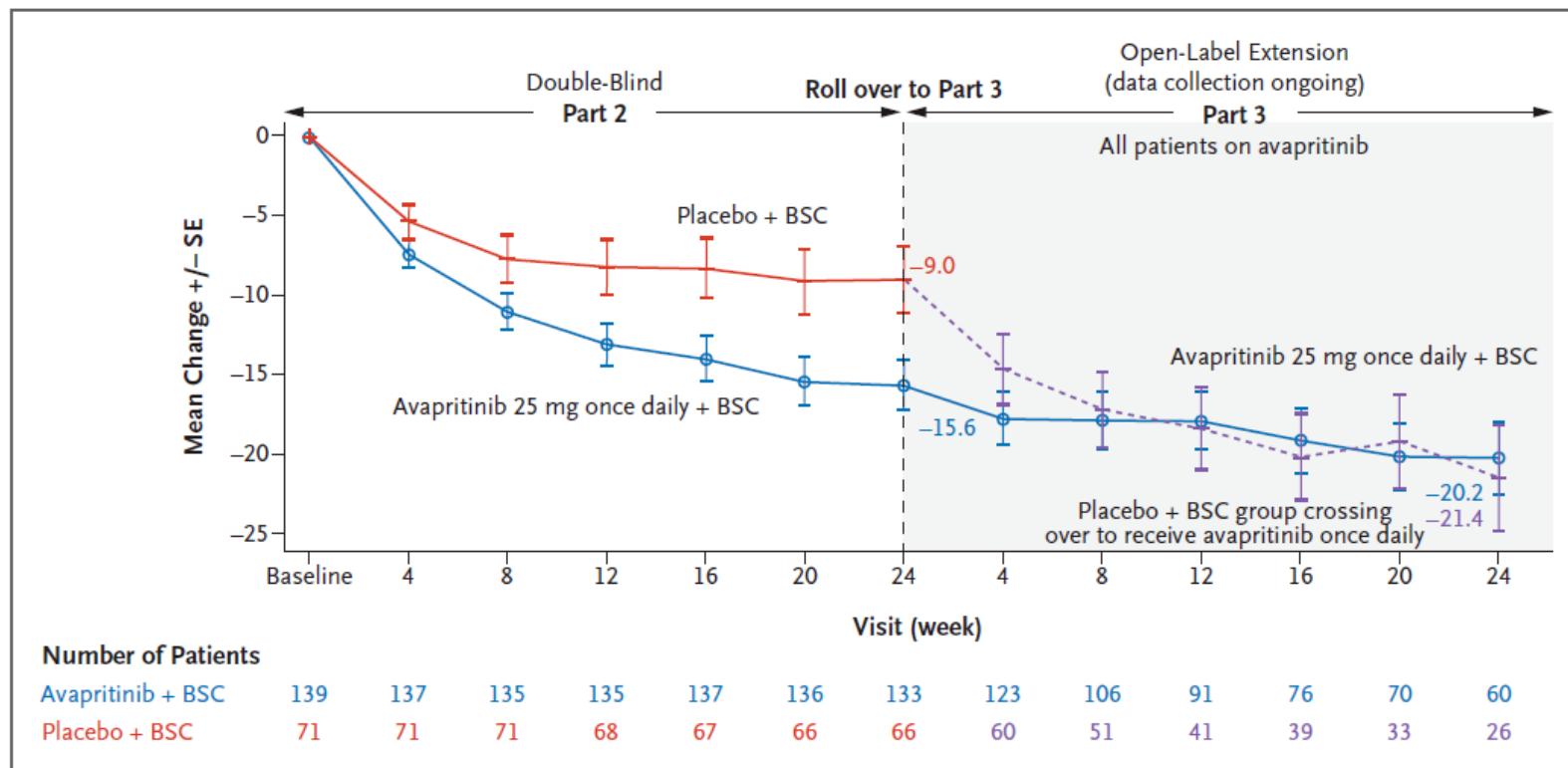
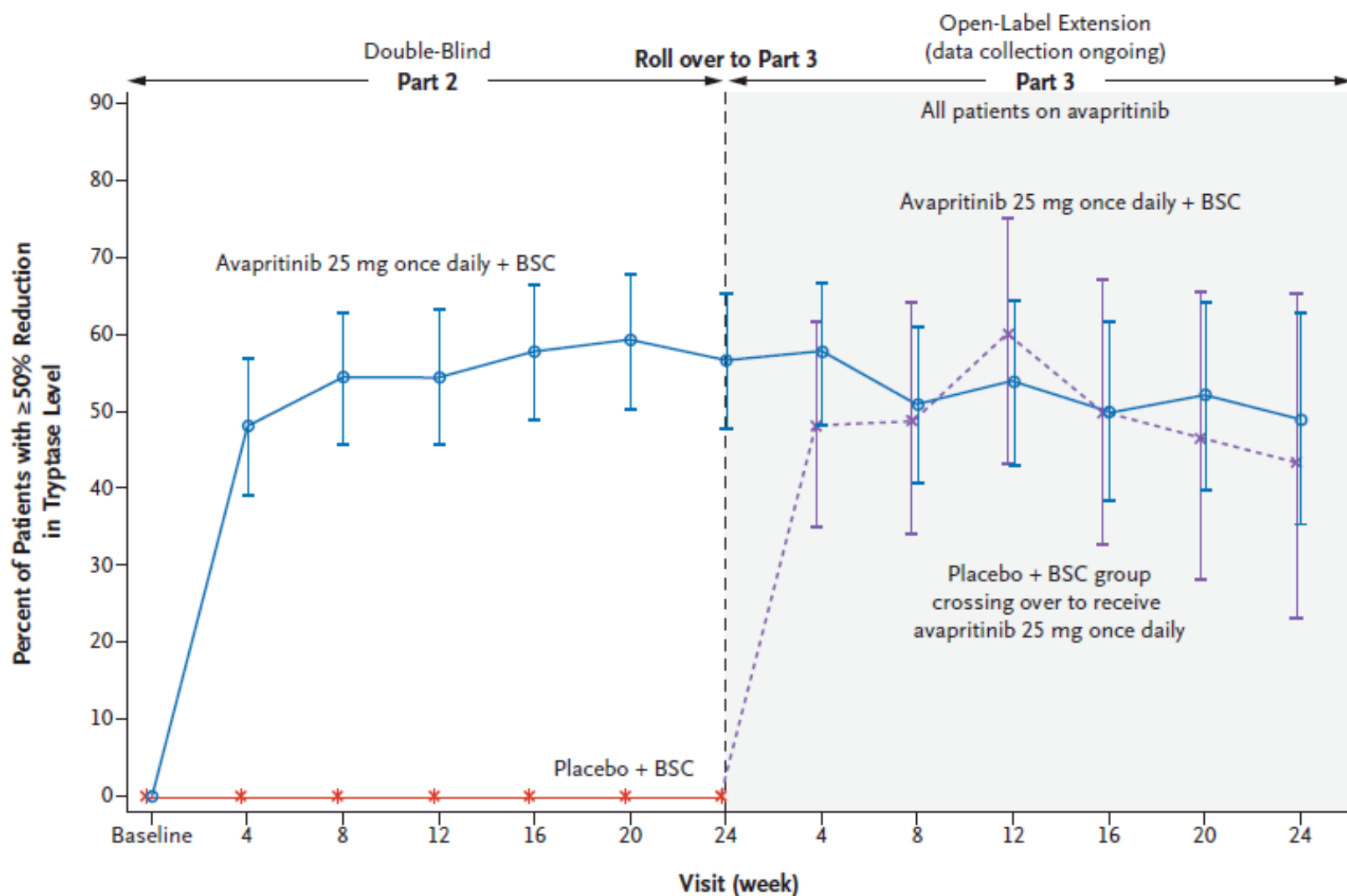


Figure 2. Indolent Systemic Mastocytosis Symptom Assessment Form Total Symptom Score over Time with Avapritinib versus Placebo.

Analysis was on the basis of the intent-to-treat population; however, patients using high-dose glucocorticoids (three patients treated with avapritinib and one in the placebo group) were included in this analysis, but per the prespecified statistical analysis plan, these patients were not included in the primary end point calculation because of the potential for high-dose glucocorticoids to influence symptoms. Total symptom score ranges from 0 to 110, with higher numbers indicating more severe symptoms. The “I” bars represent the standard error. BSC denotes best supportive care; and SE, standard error.

Avapritinib for ISM

A

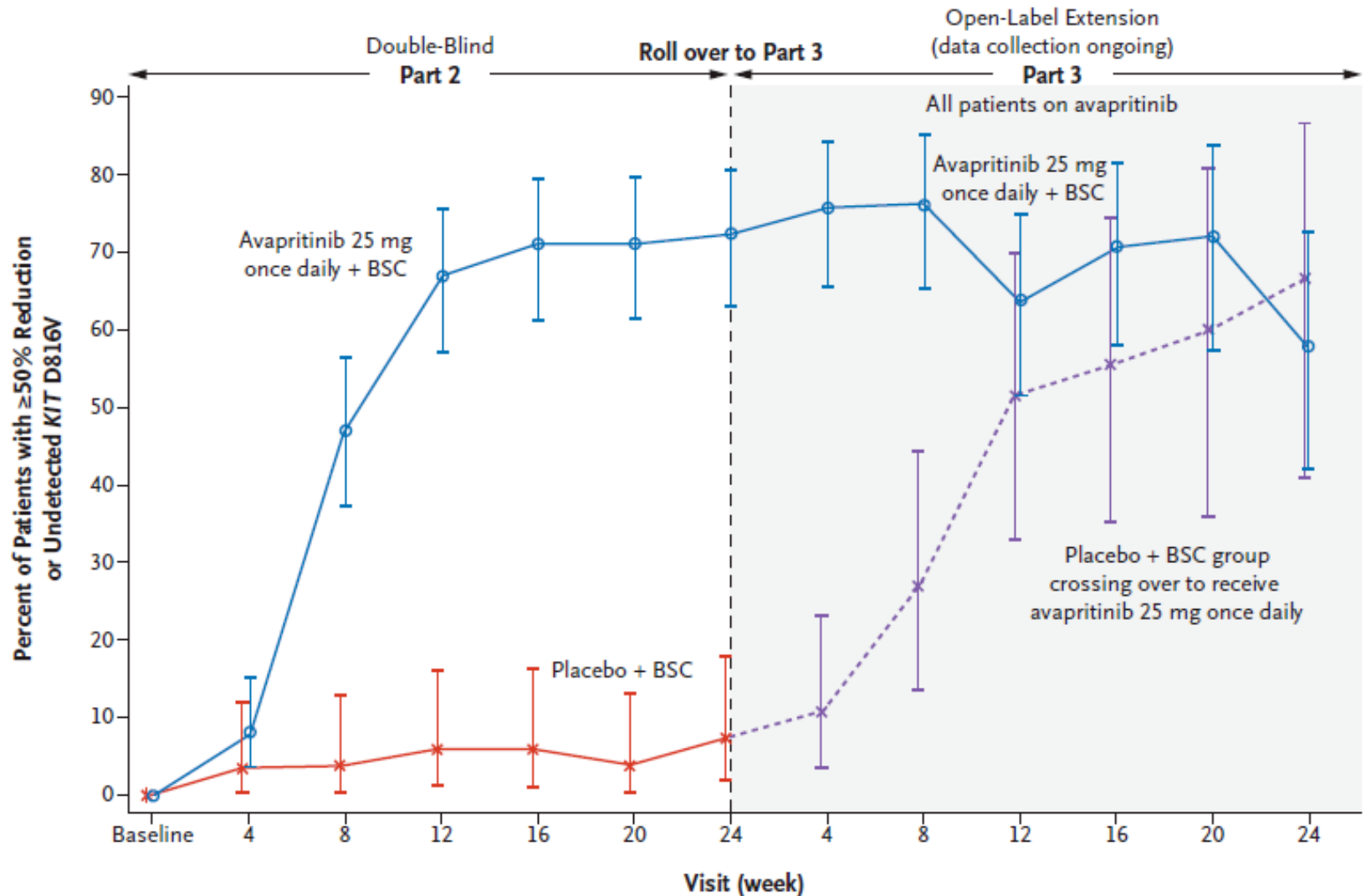


Number of Patients

Avapritinib + BSC	141	133	136	132	133	128	134	116	102	89	76	69	55
Placebo + BSC	71	66	62	61	60	62	64	58	47	40	36	30	23

Avapritinib for ISM

B



Number of Patients

Avapritinib + BSC	118	110	113	109	107	104	109	91	80	72	65	50	45
Placebo + BSC	63	57	54	52	51	53	54	47	37	31	27	20	18

Common Variable Immunodeficiency

- Sinusitis (>2) , Pneumonia (>2), UTI (>3-4), Deep seated infections
- Low IgG, IgA, IgM (– 2 SD)
- Poor response to vaccines : Pneumovax, H.Influenza, Hepatitis, Strep pneumo (Pevnar-13 or Pevnar-20)
- Gammaglobulin replacement:
IVIG or SQ 400mg/kg q 3-4 weeks
(TACI defect, association with autoimmune diseases and lymphoma)

Idiopathic CD4 Lymphopenia

Natural History

- CD4+ T cell concentration of <300 cells/ μ cL on at least two occasions at least 6 weeks apart.
- No other explanation such as HIV or medication or an already characterized inborn error of immunity (e.g., *NFKB1*, *PI3KCD*, *DOCK8*, *CD4*)
- Typically, normal NK, B cell, IgG, IgM, and IgA concentrations.
- Patients have opportunistic infections with HPV, Cryptococcus, VZV, Non-TB mycobacteria.

N Engl J Med 2023;388:1680-91.

Idiopathic CD4 Lymphopenia

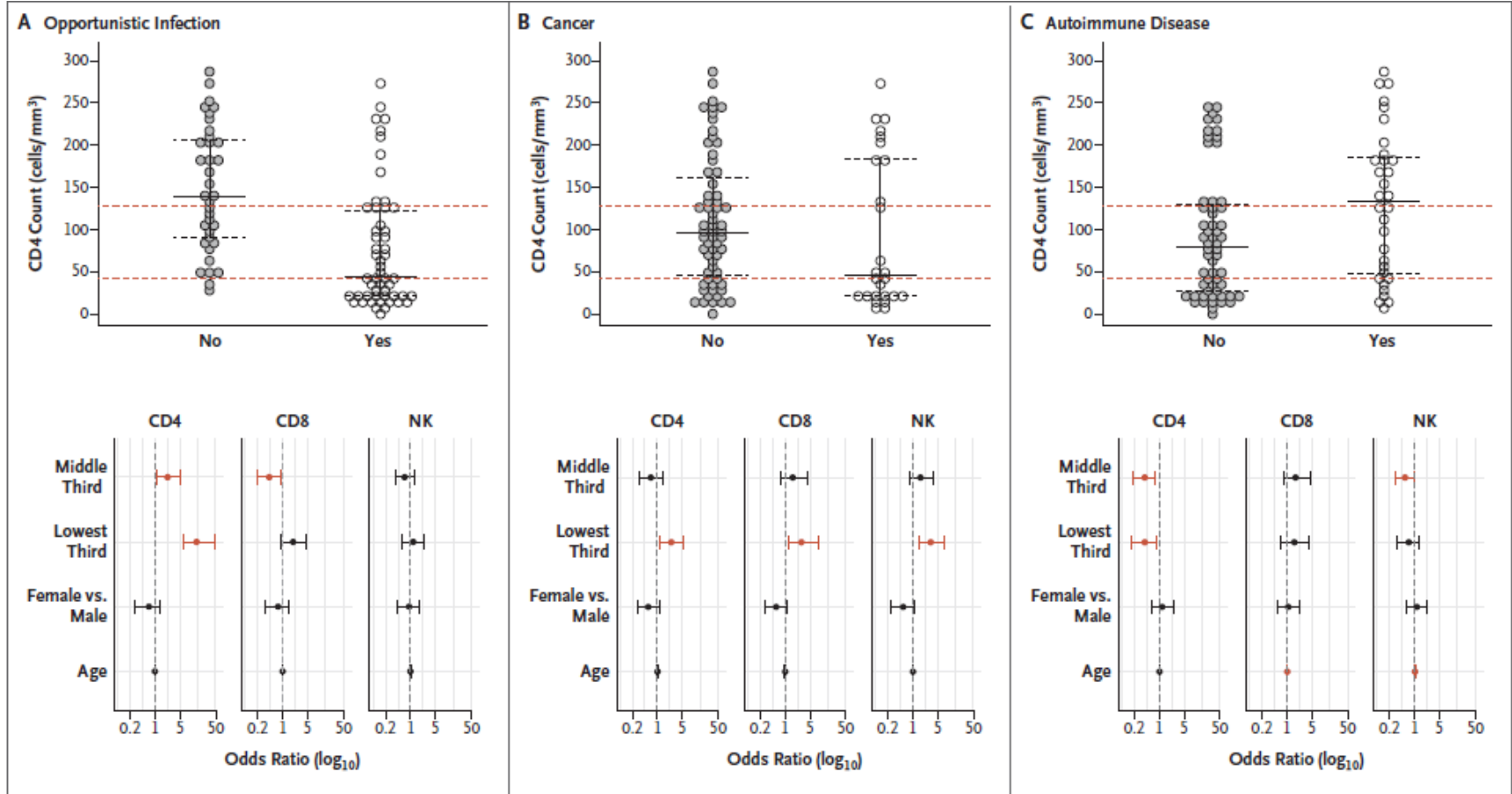


Figure 1. Distribution of CD4, CD8, and NK Cell Counts in Patients with Opportunistic Infections, Cancers, and Autoimmune Diseases.

Shown are the median absolute numbers of CD4+ and CD8+ T cells and natural killer (NK) cells in the study patients, according to the presence or absence of opportunistic infection of clinical significance (Panel A), cancer (Panel B), and autoimmune disease (Panel C) (upper panels). The red dashed lines show the cutoffs for the lowest third, middle third, and highest third of the values. In each graph, the horizontal black bar indicates the median value, and the dashed black bars indicate the interquartile range. The lower panels show log-transformed odds ratios for opportunistic infection, cancer, or autoimmune disease among the study patients in the lowest third and middle third of values as compared with the highest third after adjustment for age and sex. Data points in red indicate the odds ratios in which the 95% confidence intervals (represented by error bars) exclude the null value of 1, indicating a significant increase or decrease in the risk of the specified outcome.

Board Question 1

An 18 yo patient presents with an episode of angiodema of his face and abdominal pain. He has no itching or associated hives. Which test would be most appropriate?

- a) Serum tryptase
- b) Serum C4
- c) CT abdomen
- d) CBC

Explanation: Correct answer = B. The clinical presentation of angioedema without associated pruritus, in conjunction with this family history, suggests hereditary angioedema (HAE). The best single test for HAE is the serum C4 concentration.

Board Question 2

A 50 yo male with CAD presents to the ER with hypotension , tachycardia, SOB and generalized hives after a wasp sting. The most important action in the acute setting is:

- a) Perform skin test to Hymenoptera venom
- b) Obtain a serum tryptase
- c) Administer epinephrine
- d) Administer venom immunotherapy

Explanation: Correct answer = C. While all these measures are appropriate, the most pressing issue acutely is patient safety. Timely administration of epinephrine is life saving, while a delay in administration is the most important risk factor for death from anaphylaxis.

Allergy/Immunology: Reflections

- Asthma:
 - there are multiple endotypes and highly specific biologic therapies are starting to address them
- Urticaria and Angioedema
 - Start with high dose H1 and H2 antagonists; if this fails, anti-IgE is often highly effective.
- Anaphylaxis
 - Giving Epinephrine is the most important thing. Obtain a serum tryptase!
- Drug Hypersensitivity
 - Know a SCAR when you see one and don't try to desensitize or challenge to this. Most patients with a history of antibiotic allergies are not allergic.
- Food Allergy
 - Omalizumab is now FDA approved for true IgE mediated food allergies. Some patients with IBS-like symptoms appear to have mast cell involvement. Whether mast cell directed therapies will be effective for them remains to be seen
- Mastocytosis and Mast Cell Activation Syndromes
 - Avapritinib is effective for indolent systemic mastocytosis
- Primary Immunodeficiency
 - If you think a patient has more than a reasonable number of infections, check IgA, IgG, and IgM

References

- Rapid Drug Desensitization: Castells et al JACI 2008, 2012
- Food Allergies: Boyce et al JACI 2009
- Omalizumab use in Urticaria: NEJM Maurer et al. 2013
- Mastocytosis: Escribano et al. 2009
- Common Variable Immunodeficiency: Cunningham Rundles 2007
- Anaphylaxis Practice Parameter update: Shaker MS et al. J Allergy Clin Immunol 2020;145:1082-123
- LEAP peanut allergy study: NEJM 2015
- OUtMATCH, omalizumab in food allergy NEJM 25-28 February 2024
- Mast Cell Anaphylactoid Receptor: Nature 2015