Brigham and Women's Hospital
Founding Member, Mass General Brigham

Asthma Update

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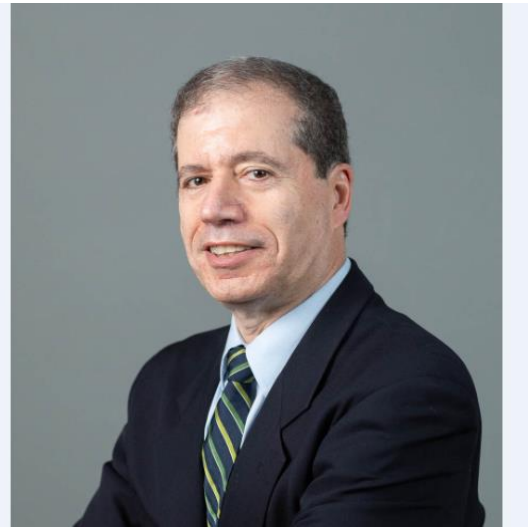
CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Elliot Israel, M.D.



Medical School: Johns Hopkins University School of Medicine
Medicine Residency – Johns Hopkins Hospital, New York Hospital/Cornell
Pulmonary/Critical Care Fellowship - BWH
Allergy & Immunology Fellowship - BWH
Professor of Medicine, Harvard Medical School
Gloria M. and Anthony C. Simboli Distinguished Chair in Asthma Research
Clinical focus: Severe Asthma
Research focus:

- Clinical and Translational Research related to severe asthma
- Pharmacogenetics of asthma therapy
- Precision medicine and adaptive trial design in asthma
- Asthma in disadvantaged communities

DISCLOSURES

Amgen	Consultant and Clinical Research Support
Anaptys Bio	Consultant
Apogee Therapeutics	Consultant
Arrowhead Pharmaceuticals	Consultant
AstraZeneca	Consultant and Clinical Research Support
Bain Capital	Consultant
Cowen	Consultant
GlaxoSmithKline	Consultant
Jasper Therapeutics	Consultant
Leerink Partners	Consultant
Orbimed	Consultant
Regeneron	Consultant
Sanofi	Consultant
TEVA	Consultant and Clinical Research Support
Yuhan	Consultant

Objectives

- Understand paradigm shift discouraging the use of beta-agonist reliever medication without inhaled corticosteroid in asthma
- Understand the concept of type 2 (T2) inflammation and how we clinically assess for its presence in asthma
- Review the biologics available in asthma that mostly target T2 inflammation, how they work, and how they are used

Definition of Asthma

Chronic inflammatory disorder of the airways

Characterized by:

- Airflow limitation,
  - reversible either spontaneously or with treatment
- Airway inflammation
- Increased responsiveness to a variety of stimuli

Rule of 2's for Lack of Control and Escalation of Medications

- Lack of Control
  - Nighttime awakenings >2/mo
  - SABA use for sxs (not pre-exercise) >2/wk
  - Sx >2 wk
  - ACT / ACQ ≤20 / >1.5
  - Lung function Reduced by >20%
  - Exacerbations >2/yr

Control on ACT or ACQ

- ACT
  - 20 or more
  - 3 point change is considered MCID
- ACQ
  - ≤1.5
  - MCID 0.5

NAEPP Major Change in 2021 Update
AIR

- The use of as needed inhaled corticosteroids with a short-acting beta-agonist or a long-acting beta agonist (formoterol ONLY) in all severity levels

- Now Referred to as

AIR (Anti-Inflammatory Reliever)

43 yo woman with hypertension and mild asthma seeking f/u of her hypertension

- One steroid requiring exacerbation in the past and it was in the last year with a cold
- She has several unopened/unexpired salmeterol/fluticasone inhalers at home from the exacerbation and they are her insurer's preferred ICS/LABA with a low co-pay
- Needs her albuterol inhaler once a week or so and sometimes after exercise
- ACT is 21
- Asks you to renew her albuterol (she has refilled it once in the last year)

Would you?

A. Renew albuterol
B. Suggest that she use her low-cost salmeterol/fluticasone inhaler as needed instead of albuterol
C. Prescribe formoterol/ICS inhaler and tell her to use it prn instead of the albuterol
D. Prescribe albuterol/budesonide inhaler and tell her to use prn instead of albuterol
E. Prescribe an ICS and tell her to use it whenever she uses her prn albuterol (use a rubber band to connect them both)

Anti-Inflammatory Reliever Therapy AIR

- Paradigm Shift
- Concept that reliever bronchodilator therapy should almost always be accompanied by an anti-inflammatory drug (inhaled corticosteroid)
  - Increased beta agonist use without concomitant ICS is associated with increased asthma morbidity
  - Using ICS every time you use a reliever reduces asthma exacerbations

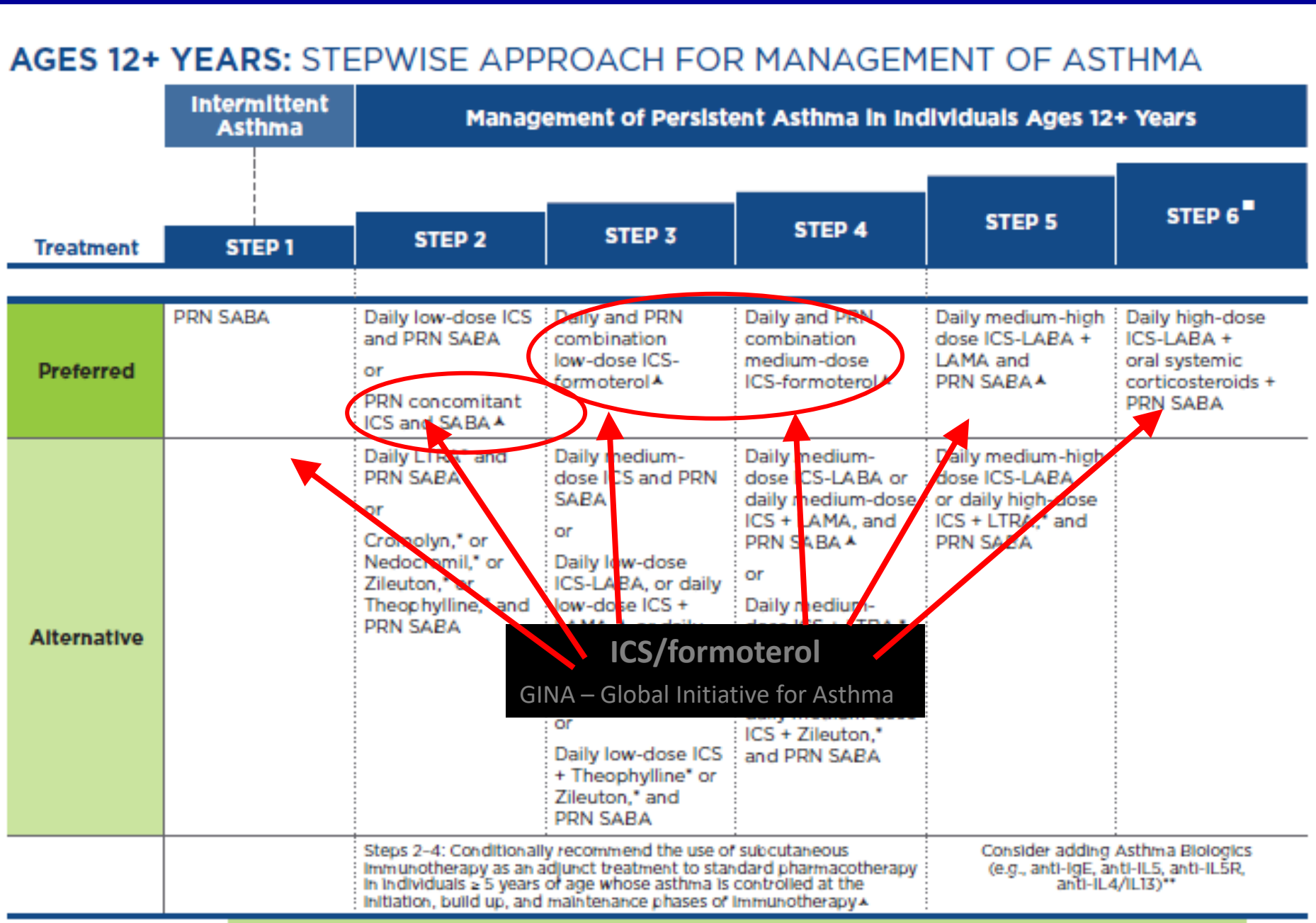
ICS/formoterol and the evolution to (S)MART (Single) Maintenance And Reliever Therapy

- While formoterol is a long-acting beta-agonist (LABA), as compared to the other LABA (salmeterol), formoterol has a quick onset of action
- Studies were undertaken to examine whether ICS/formoterol could be used instead of albuterol and simultaneously as background therapy
- Studies showed that ICS/formoterol prn was as effective as regularly used ICS in preventing exacerbations and resulted in a 50 to 75% reduction in ICS exposure

AIR Instead of a SABA Alone

- Further it was shown that substituting ICS/f for SABA reduced exacerbations by 30% or more
- Studies also showed that using ICS/f instead of SABA was as, or more, effective than increasing the ICS dose of ICS/f while decreasing ICS exposure
- .

NAEPP 2020


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

Except possibly for mildest cases of asthma the general consensus is that albuterol should not be used without an ICS

In most cases of mild asthma AIR approach should be used

Three Ways to Administer AIR

- Single inhaler with beta-agonist and ICS
  - Formoterol/ICS inhaler
    - Formoterol/budesonide (Breyna or Symbicort)
    - Formoterol/mometasone (Dulera)

    Cannot use Salmeterol containing combination (Advair) since salmeterol in not quick acting enough
  - Albuterol/ICS
    - Albuterol/budesonide (AirSupra)
- Instructing patient to take ICS every time they use their reliever (PARTICS) – Patient Activated Reliever Triggered ICS

Implementation Considerations Regarding AIR

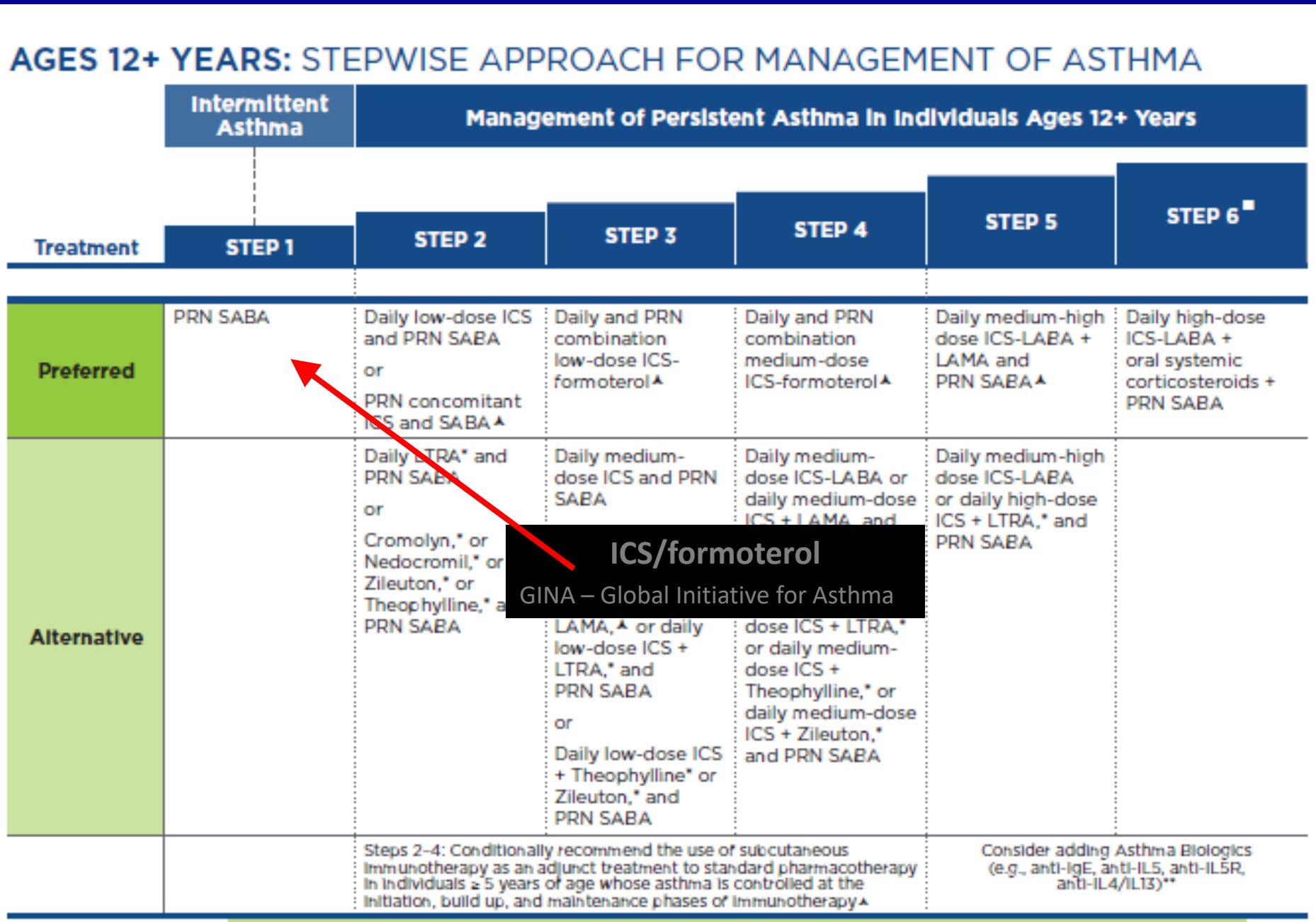
- Formoterol is the ONLY LABA for use due to its rapid onset of action
- FDA package insert warns against using budesonide/formoterol prn
  - Many insurers will not cover the extra ICS//f inhaler
- Studies of MART were almost exclusively performed with budesonide/formoterol;
  - Theoretically, other ICS/formoterol combinations such as mometasone/formoterol could be effective but they have not been studied
- Albuterol/budesonide is approved in the USA but may not be covered by all insurance
- MART may not be effective in patients who use a nebulizer during exacerbations (those patients may benefit from PARTICS)
- Telling patients to use their ICS every time they use their albuterol (tying a rubber band around them), PARTICS, is also effective

  -Can only use PARTICS or budesonide/albuterol if person on therapy

iCARE

- We are conducting a real-life study comparing MART to PARTICS in patients on ICS/LABA with a history of an exacerbation
- 1 888 99 ASTHMA

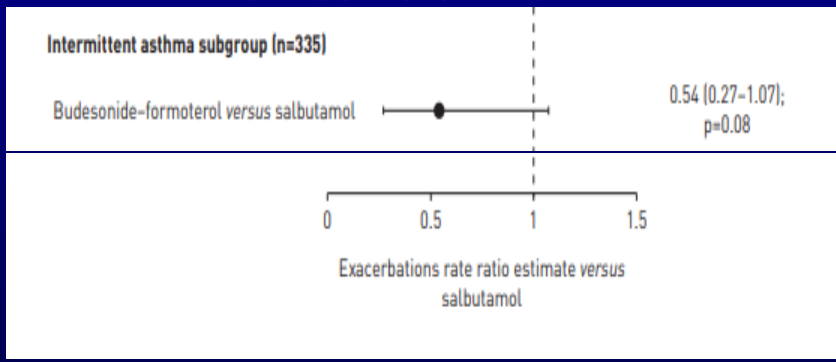
What about AIR for the mild intermittent patient?



In Mild Intermittent Patients Air Appears to Reduce Exacerbations by 50% (NS) but Absolute Rate is Low

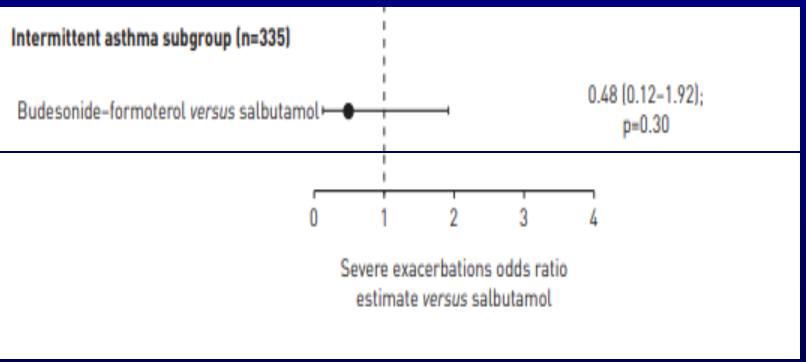
All Exacerbations

0.265 vs 0.143



Severe Exacerbations

6.1% vs. 3.1%



25.5 mg of budesonide/yr (0.35 puffs/d)

- Post-Hoc Analysis Novel Start ICS/f in Mild Intermittent Patients (≤2 puff/wk and no exacerbations)

Papi et al, ERJ, 2021

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Considerations for AIR in Intermittent Asthma vs. PRN SABA

- Shared decision making
- Even if well controlled, still at risk for an exacerbation especially if had an exacerbation in the past 1-2 years
- Reduces but does not eliminate risk of an exacerbation
- May be less appropriate for patients who are well controlled but use SABA frequently prophylactically e.g before exercise since may get more ICS than they need
- Can consider any of the 3 methods of AIR

Pt with 1 exacerbation using albuterol 1x/week Would you?

A. Renew albuterol

B. Suggest that she use her low-cost salmeterol/fluticasone inhaler as needed instead of albuterol

C. Prescribe formoterol/ICS inhaler and tell her to use it prn instead of the albuterol

D. Prescribe albuterol/budesonide inhaler and tell her to use prn instead of albuterol

E. Prescribe an ICS and tell her to use it whenever she uses her prn albuterol (use a rubber band to connect them both)

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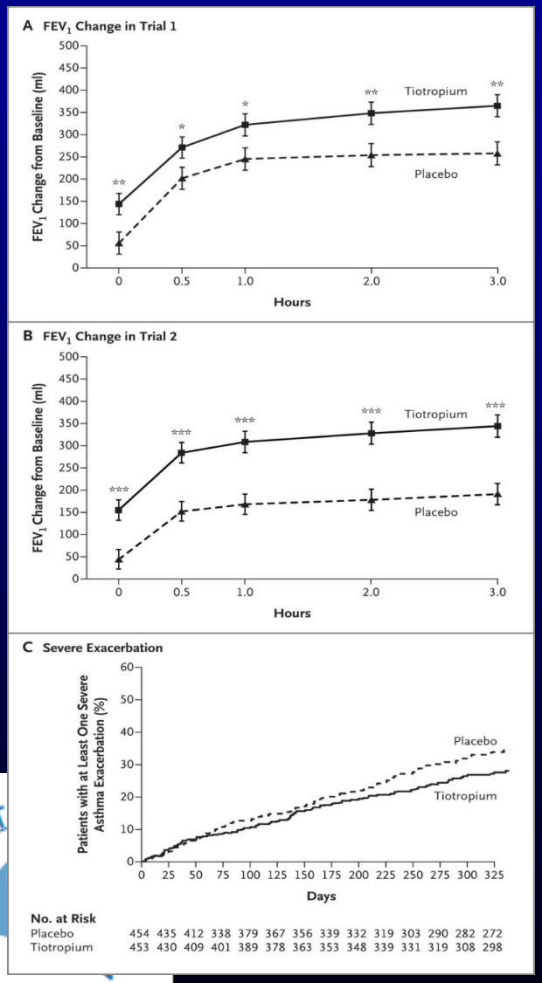
Super long-acting beta-agonist combinations for once a day

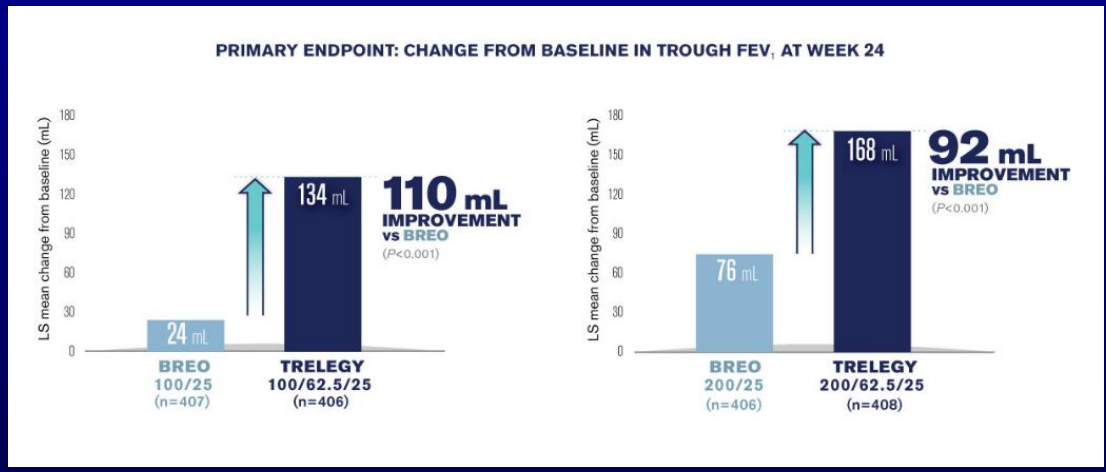
- Fluticasone furoate 100/vilanterol 25 and 200/25
  - Combined long-acting ICS and super-long acting (LA)BA.
  - Only approved in 18 yo and above
  - Dose equivalency
    - 1 puff 100/25 qd = 1 puff bid FP250/Salm 50 BID
    - 1 puff 200/25 qd = 1 puff bid FP500/Salm50 BID

Additional NAEPP Updates

- LAMA can be used in addition to ICS/LABA for some potential additional control in Step 5
- Allergy shots can be used in mild-moderate asthma with clinical worsening due to allergens but NOT in severe asthma
  - SLIT is not recommended for asthma
- Indoor allergen mitigation not that effective
  - Consider only for those with documented allergy to indoor substances
    - Pest control provides some benefit
    - Multi-strategy dust control provides some be

Triple Inhaler Approved for Asthma





Kerstjens HAM et al. N Engl J Med 2012;367:1198-1207

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Currently Approved Triple Inhalers ICS/LAMA/LABA

- F furoate/umeclidinium/vilanterol) (Trelegy Ellipta)
  - 1 puff daily (100/62.5/25 and 200/62.5/25)
- Bud/glycopyrroate/F fumarate – Breztri Aerosphere
  - 2 puffs bid (160/18/4.8)
- Beclo/Glycopyrrolate/F fumarate – Trimbow
  - 2 puffs bid (86//10,6/4.9 or 172/10.6/4.9

PROGRESSION in USA

- SABA (+/- ICS)
- Daily ICS + SABA +/- ICS

  or

  Lower dose daily ICS/formoterol +/- prn ICS/f or SABA/ICS
- As above but with higher dose ICS/f
- Add LAMA
- Consider biologic

BIOLOGICS

- For patients with recurrent exacerbations despite adherence to high dose ICS/LABA
- Effects
  - Reduce exacerbations
  - Improve symptoms
  - May improve FEV_1
- Mostly target type 2 (T2) (allergic/eosinophilic) inflammatory processes and patients most likely to respond have evidence of T2 inflammation
  - Eosinophils (>300/ul)
  - Nitric oxide

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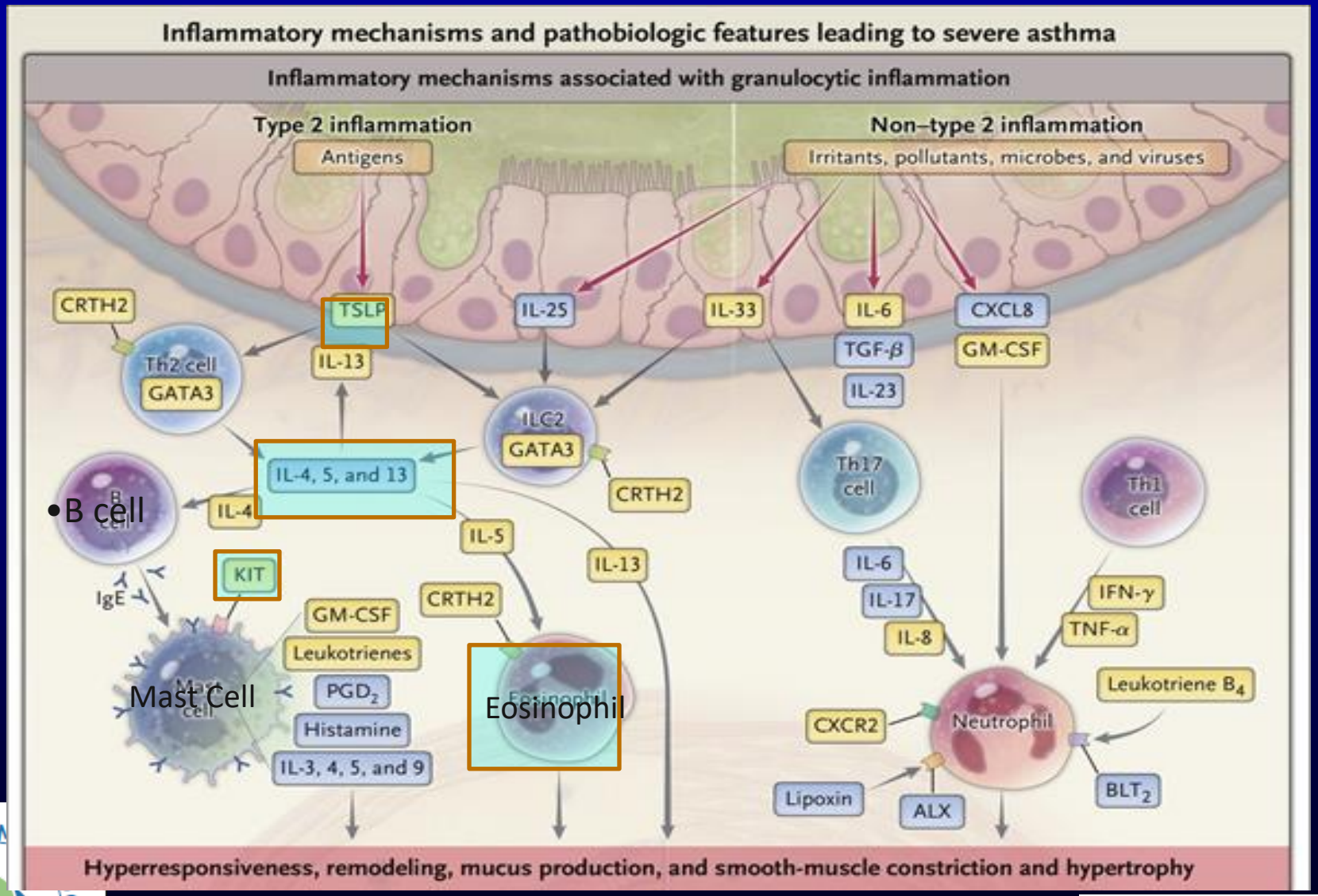
Type 2 Inflammatory Targets



•Israel & Reddel, NEJM, 2017

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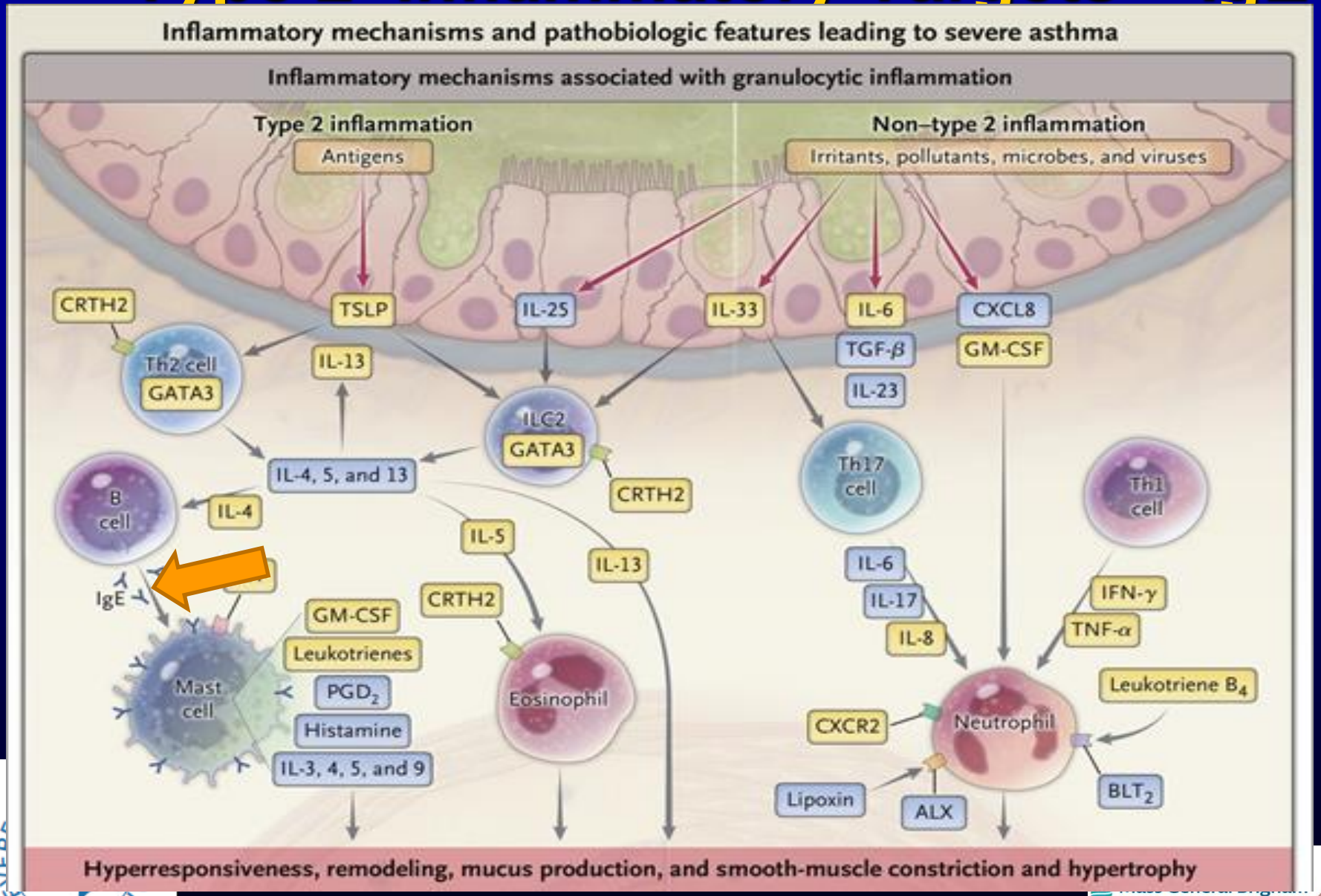
Type 2 Inflammatory Targets – IgE



•Israel & Reddel, NEJM, 2017

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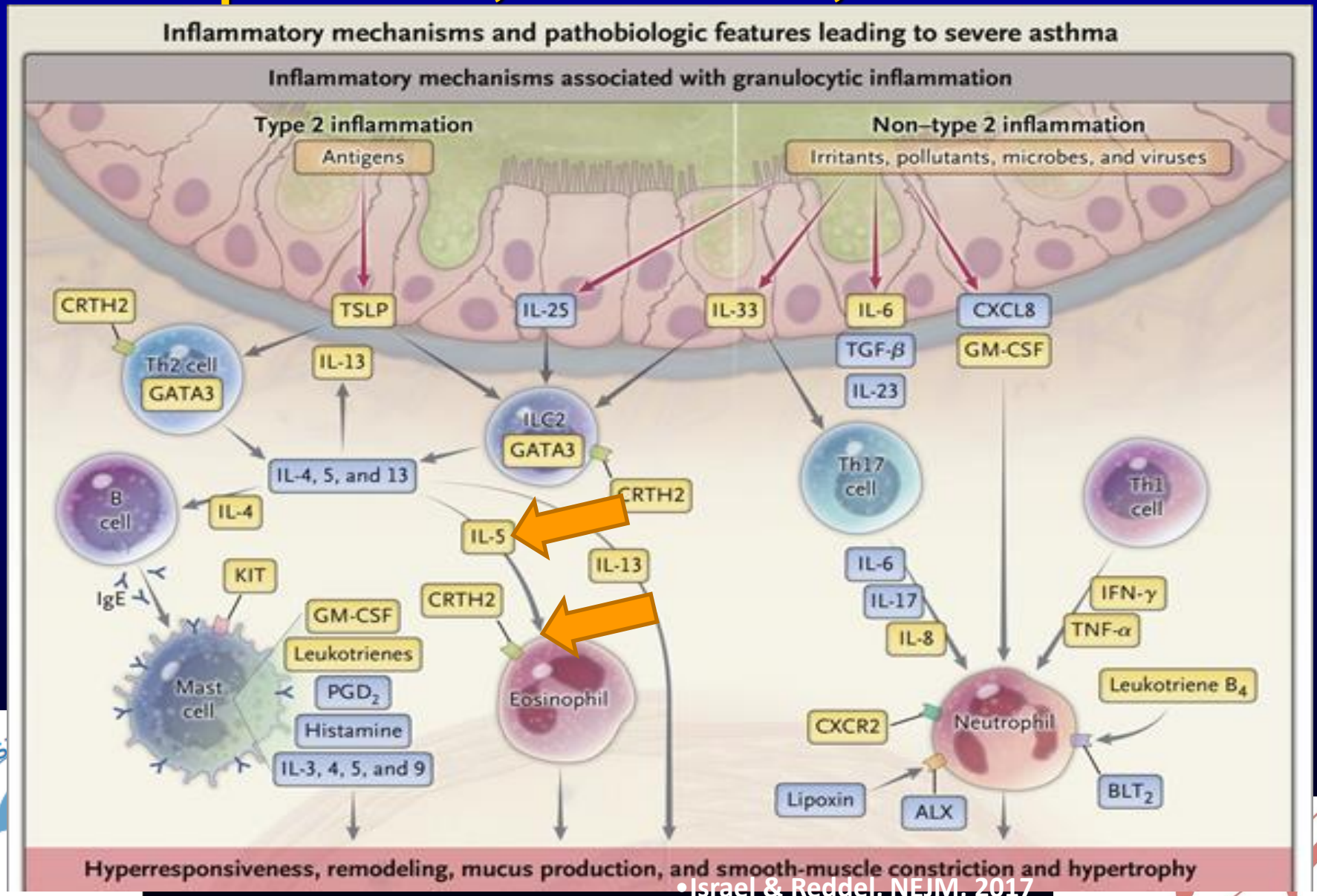
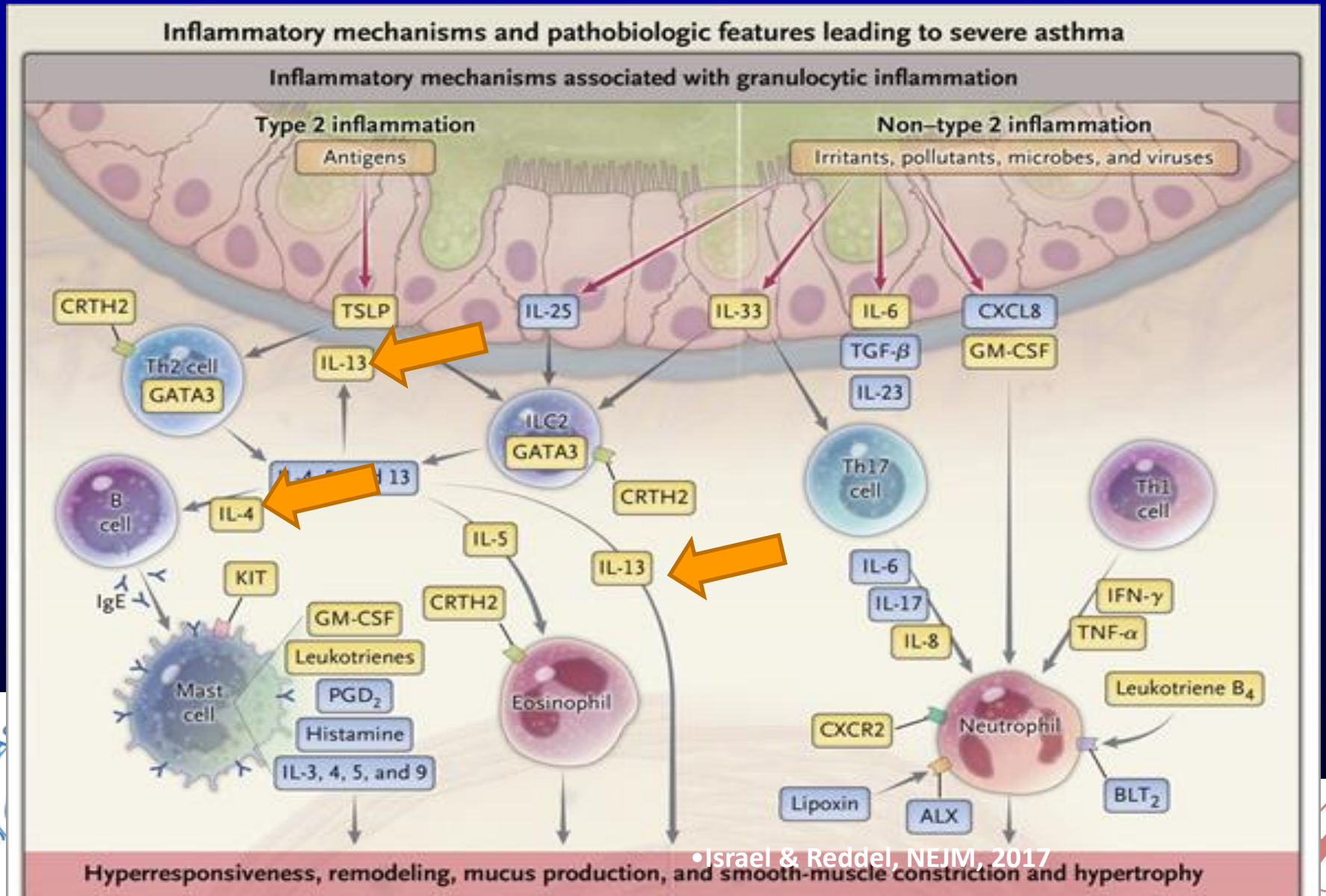
Type 2 Inflammatory Targets – IL5 Mepolizumab, Reslizumab, Benralizumab



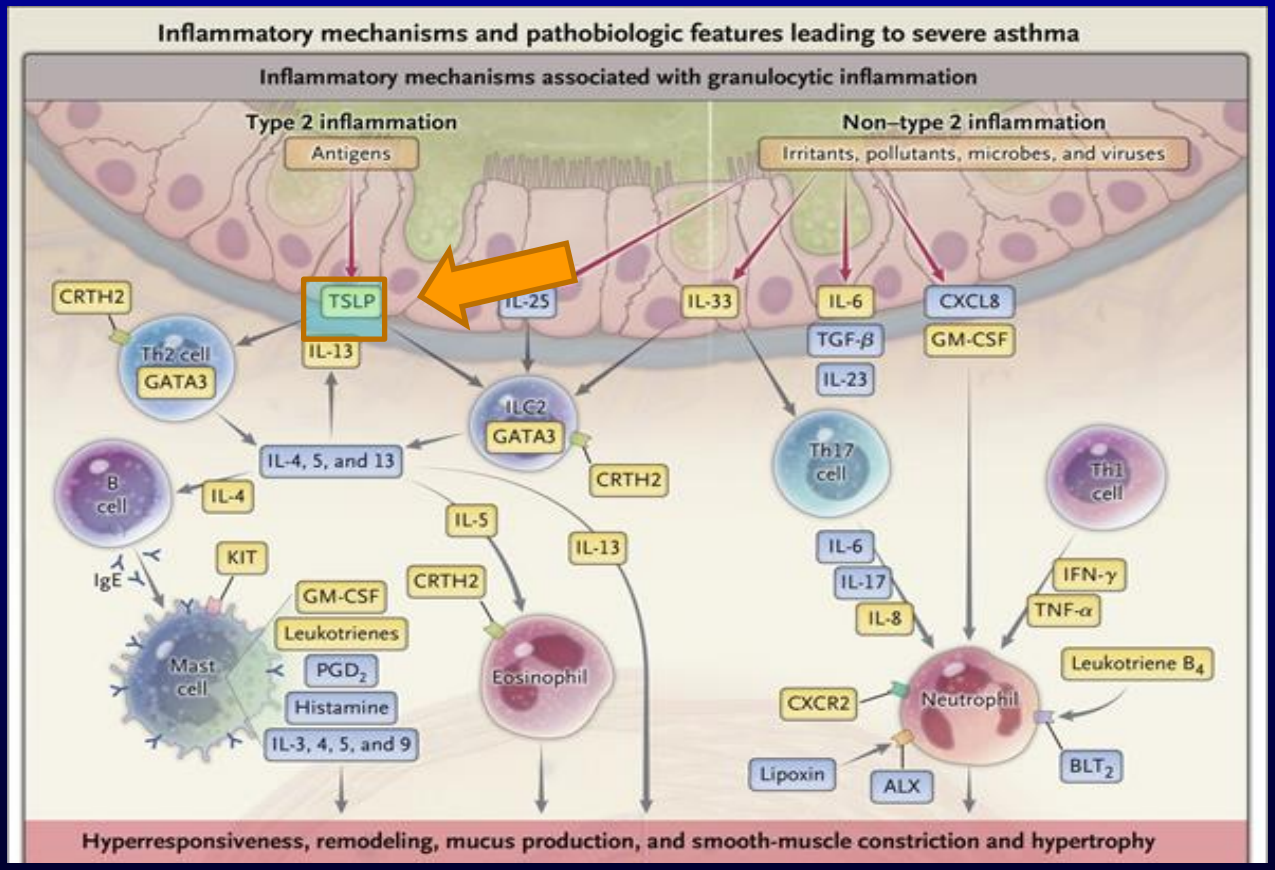
•Israel & Reddel, NEJM, 2017

Type 2 Inflammatory Targets – IL4RA Dupilumab



•Israel & Reddel, NEJM, 2017

Type 2 Inflammatory Targets – TSLP Tezepelumab



•Israel & Reddel, NEJM, 2017

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Outcomes in Patients with Eosinophils ≥300/ul

- (Studies Required 1-2 exacerbations, ≥12% Bronchodilator Response and ACQ ≥1.5 on Study Entry)

	IgE	IL5			IL4RA	TSLP
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
% Reduction in Exacerabation	32	61	~55 (In eos >400/ul)	~35	66	70
FEV1 (cc)	40	202	126	~138	~225	230
ACQ	0.36	~0.48	~0.24	~0.2	~0.4	0.33

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Effects on Co-Morbidities

- Omalizumab
  - CRSwNP
  - Chronic idiopathic urticaria (CIU)
  - Food allergies
- Mepolizumab
  - CRSwNP
  - COPD
  - EGPA
- Benralizumab
  - EGPA
- Dupilumab
  - CRSwNP
  - Eczema
  - COPD
  - CIU
  - Eosinophilic Esophagitis
  - Prurigo Nodularis
- Tezepelumab
  - CRSwNP

Neutrophilic or Non-Type 2 Asthma

- Forty to 50% of severe asthmatics may have neutrophilic or paucigranulocytic inflammation
  - May be less responsive to steroids

Definition of "High-Risk"

- Newly diagnosed asthma
- On daily prednisone prior to admission
- ≥2 E.D. visits in last 6 months
- ≥1 prior hosp'ns in last 12 months
- Ever intubated for asthma
- Severe psychosocial problems
- Drug addiction
- Lower socio-economic status

Points to Remember

- Rules of two's for initiation of controller and for step up
- Consider use of reliever combined with an ICS in nearly all asthma severities
- Patients who require regular background therapy should be considered for MART or should have a combination inhaler or be instructed in combining ICS with SABA for relief
- Patients with recurrent exacerbations despite high dose therapy should be considered for a biologic if they have evidence of T2 inflammation
  - Eosinophils > 300/ul
  - FeNO can be high even if eosinophils are not
- High risk patients should be considered for specialty referral

MGB Severe Asthma Program

State of the Art Multidisciplinary Evaluation and Treatment of Patients with Severe Asthma

- Pulmonary
- Allergy
- ENT
- GI
- Psychiatry
- Alternative Medicine

- severeasthma@bwh.harvard.edu or 1 844 BWH-LUNG

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Question

35 yo female with history of asthma using albuterol twice a week and an asthma exacerbation 2 years ago presents. Her ACT is 19

You would:

a. Leave meds unchanged
b. Start ICS/formoterol as needed
c. Start combination albuterol/budesonide as needed
d. Give her a prescription for an ICS and tell her to tie it onto her albuterol with a rubber band and use them together as needed
e. B,C, or D

Answer:E

Her ACT is below the desired level of 20. She should be on some type of anti-inflammatory reliever (AIR)

-In shared decision making with the patient and knowledge about insurance coverage any of the AIR approaches would reduce her risk of exacerbations in the future

Question

A 40 yo male with asthma presents to your office after his second steroid-requiring exacerbation in the past year on MART therapy. His eosinophil count is 450 cell/ul. His medication refill records suggest adherence

You would:

a. Add a long-acting anti-muscarinic
b. Start low dose oral corticosteroids
c. Refer for biologic therapy

Answer: A

- This patient needs additional therapy. LAMAs have been shown to decrease exacerbations and considering the cost of the biologics, addition of a LAMA could be the next step.
- With a high eosinophil counts this patient is likely to respond to a biologic. If the patient has another exacerbation on the LAMA or is uncontrolled, refer for biologic

References

- **Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*, 2025. Updated 15 November 2025. Available from:** www.ginasthma.org.
- **Israel E, Wechsler ME, Jackson DJ, et al. Anti-cytokine biologics for asthma in adults. *The Lancet*. 2025; 406(10516): 2282–2294.** DOI: 10.1016/S0140-6736(25)01625-3.