Asthma - Part 2

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Disclosure: **I have the following financial disclosures- Contracted Research with American Lung Association and Regeneron**

KEY POINTS: MANAGING ASTHMA LONG TERM

- The goal for therapy is to control asthma by (Evidence A):
  - Reducing impairment
    - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, in the night, or after exertion)
    - Require infrequent use (≤2 days a week) of inhaled short-acting beta$_2$-agonist (SABA) for quick relief of symptoms (not including prevention of exercise-induced bronchospasm (EIB))
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care
  - Reducing risk
    - Prevent recurrent exacerbations of asthma and minimize the need for emergency department (ED) visits or hospitalizations
    - Prevent progressive loss of lung function; for children, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects

NHLBI NAEPP EPR 3 Guidelines, 2007

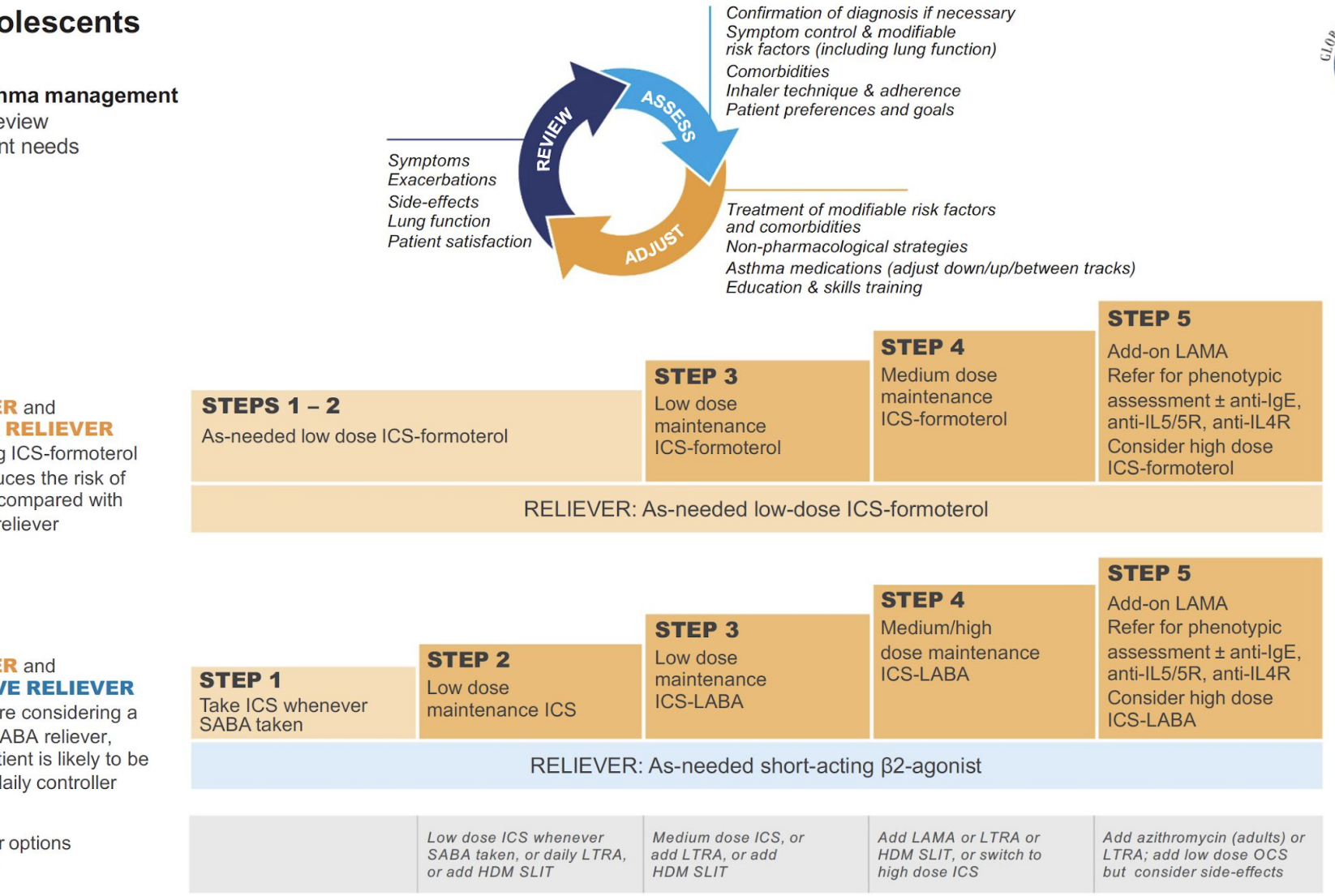
Controversy: ICS/formoterol rescue

GINA 2021:

- Strongly prefer prn ICS-formoterol for rescue
- “mild intermittent” definition is removed, asthma is persistent (mild-mod-severe)
  - Further definition planned 2021

EPR4:

- Strong recommendation for ICS/formoterol rescue steps 3+



GINA 2021

International perspective (GINA)

Background - the risks of SABA-only treatment

- Regular use of SABA, even for 1–2 weeks, is associated with adverse effects
  - β-receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response *(Hancox, Respir Med 2000);* increased allergic response, and increased eosinophilic airway inflammation *(Aldridge, AJRCCM 2000)*
- Higher use of SABA is associated with adverse clinical outcomes
  - Dispensing of ≥3 canisters per year (i.e. daily use) is associated with higher risk of severe exacerbations *(Stanford, AAAI 2012; Nwaru, ERJ 2021)*
  - Dispensing of ≥12 canisters per year is associated with much higher risk of death *(Suissa, AJRCCM 1994; Nwaru, ERJ 2021)*
- Inhaled corticosteroids reduce the risk of asthma deaths, hospitalization and exacerbations requiring oral corticosteroids (OCS) *(Suissa, NEJM 2000 & 2002; Pauwels, Lancet 2003)*
  - BUT adherence is poor, particularly in patients with mild or infrequent symptoms

→ A safe and effective alternative was needed for mild asthma

OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist

International perspective (GINA)

Background - the risks of 'mild' asthma

- Patients with apparently mild asthma are still at risk of serious adverse events
  - 30–37% of adults with acute asthma
  - 16% of patients with near-fatal asthma
  - 15–20% of adults dying of asthma

  } had symptoms less than weekly in previous 3 months *(Dusser, Allergy 2007)*
- Exacerbation triggers are unpredictable (viruses, pollens, pollution, poor adherence)
- Inhaled SABA has been first-line treatment for asthma for 50 years
  - Dating from an era when asthma was thought to be a disease of bronchoconstriction
  - Its role has been reinforced by rapid relief of symptoms and low cost
  - Starting treatment with SABA trains the patient to regard it as their primary asthma treatment

SABA: short-acting $beta_2$-agonist

GINA Track 1 (preferred): the reliever is low dose ICS-formoterol

- Why is this preferred for adults and adolescents?
  - Because using low dose ICS-formoterol as reliever reduces the risk of severe exacerbations compared with regimens with SABA as reliever, with similar symptom control
- How is it used?
  - When a patient at any treatment step has asthma symptoms, they use low dose ICS-formoterol in a single inhaler for symptom relief
  - In Steps 3–5, patients also take ICS-formoterol as their daily controller treatment. Together, this is called 'maintenance and reliever therapy' or 'MART'
- When should it not be used?
  - ICS-formoterol should not be used as the reliever in patients prescribed a different ICS-LABA for their controller therapy

Novel START, PRACTICAL

ICS: inhaled corticosteroids; SABA: short-acting beta$_2$-agonist

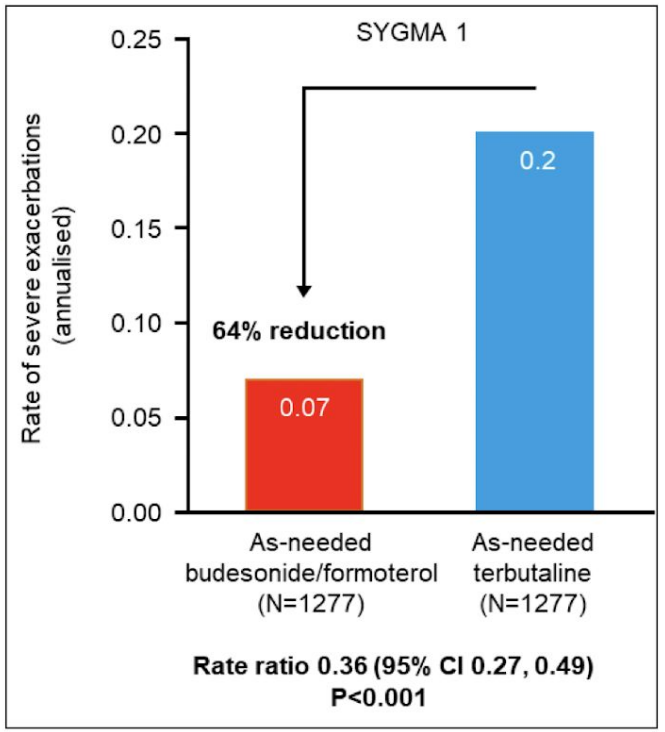
As-needed low dose ICS-formoterol in mild asthma (n=9,565)

COMPARED WITH AS-NEEDED SABA

- The risk of severe exacerbations was reduced by 60–64% (SYGMA 1, Novel START)

COMPARED WITH MAINTENANCE LOW DOSE ICS

- The risk of severe exacerbations was similar (SYGMA 1 & 2), or lower (Novel START, PRACTICAL)
- Small differences in other asthma outcomes, favoring maintenance ICS, but all were less than the minimal clinically important difference
  - ACQ-5 mean difference 0.15 (MCID 0.5)
  - FEV_1 mean difference ~54 mL
  - FeNO mean difference ~10ppb (Novel START, PRACTICAL)
  - No evidence of progressive worsening over 12 months
- In Novel START and PRACTICAL, outcomes were independent of baseline features including blood eosinophils, FeNO, lung function, and exacerbation history
- Average ICS dose was ~50–100mcg budesonide/day

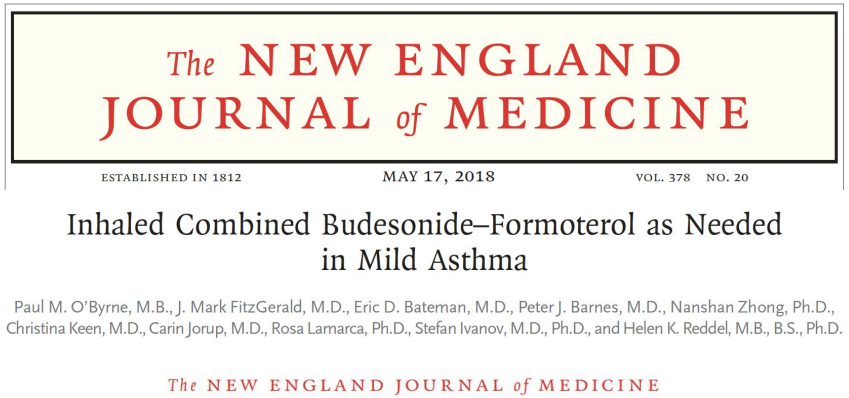


O'Byrne et al, NEJM 2018

*Budesonide-formoterol 200/6 mcg, 1 inhalation as needed for symptom relief

Key studies of SMART approach

SYGMA1
NEJM 2018


The NEW ENGLAND JOURNAL of MEDICINE

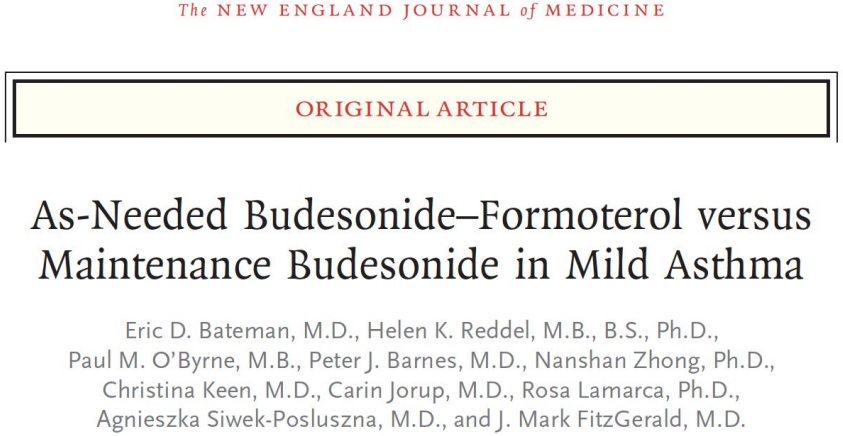
ESTABLISHED IN 1812 MAY 17, 2018 VOL. 378 NO. 20

Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

SYGMA2
NEJM 2018


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D., Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.

Novel START
NEJM 2019


ORIGINAL ARTICLE

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

Richard Beasley, D.Sc., Mark Holliday, B.Sc., Helen K. Reddel, Ph.D., Irene Braithwaite, Ph.D., Stefan Ebmeier, B.M., B.Ch., Robert J. Hancox, M.D., Tim Harrison, M.D., Claire Houghton, B.M., B.S., Karen Oldfield, M.B., Ch.B., Alberto Papi, M.D., Ian D. Pavord, F.Med.Sci., Mathew Williams, Dip.Ex.Sci., and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

PRACTICAL
Lancet 2019


Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

Jo Hardy, Christina Baggott*, James Fingleton, Helen K Reddel, Robert J Hancox, Matire Harwood, Andrew Corin, Jenny Sparks, Daniela Hall, Doñah Sabbagh, Saras Mane, Alexandra Vohlidkova, John Martindale, Mathew Williams, Philippa Shirtcliffe, Mark Holliday, Mark Weatherall, Richard Beasley, on behalf of the PRACTICAL study team†*

Meta-analysis of 4 RCTs: Crossingham, *Cochrane* 2021

EPR4, GINA, FDA and insurance in the US

- Controller inhalers are expensive
- Most patients can’t afford out-of-pocket cost of inhalers for off-label use
  - prn ICS/formoterol is off-label
- Most patients are covered by insurance for one ICS/LABA inhaler per month

O'Byrne, NEJM, 2018

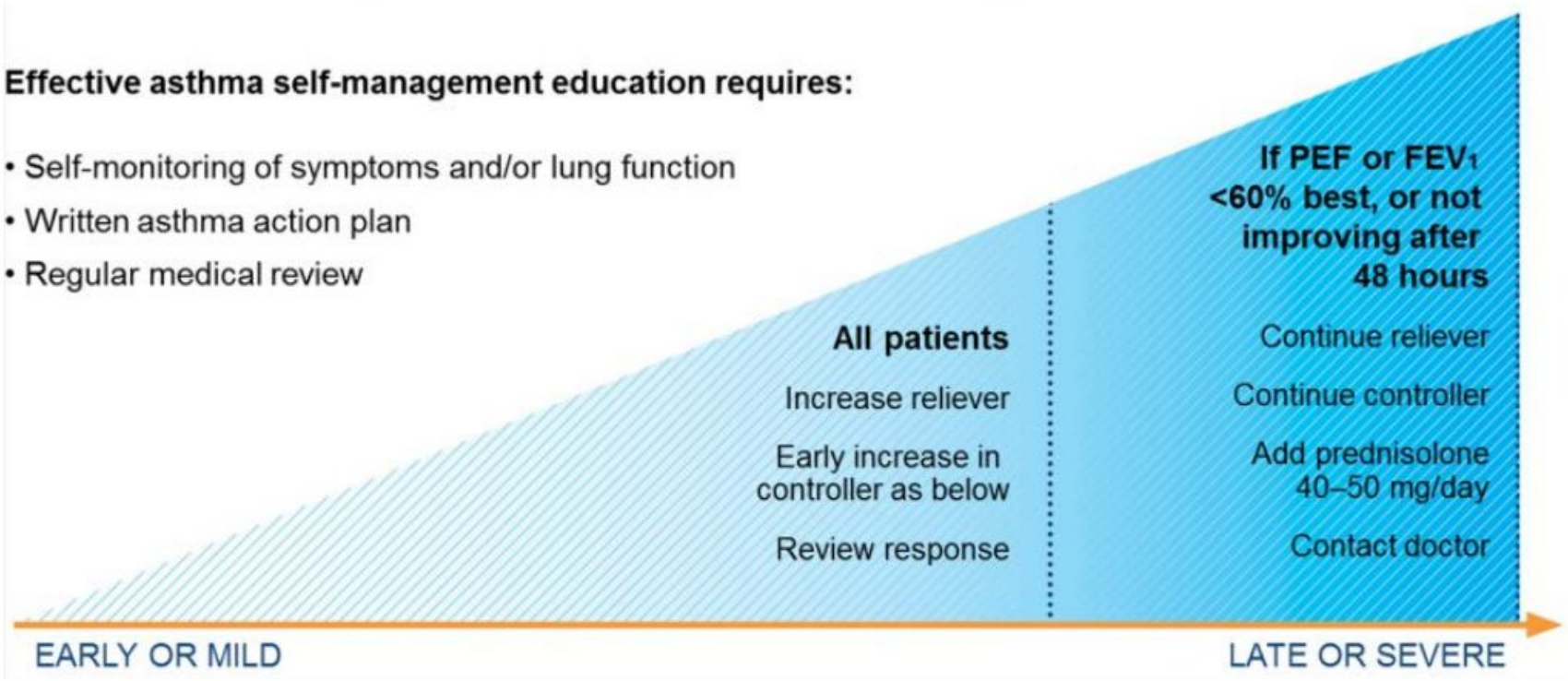
Outline

- What is asthma
  - Defining asthma
  - Diagnosing asthma
  - Staging asthma

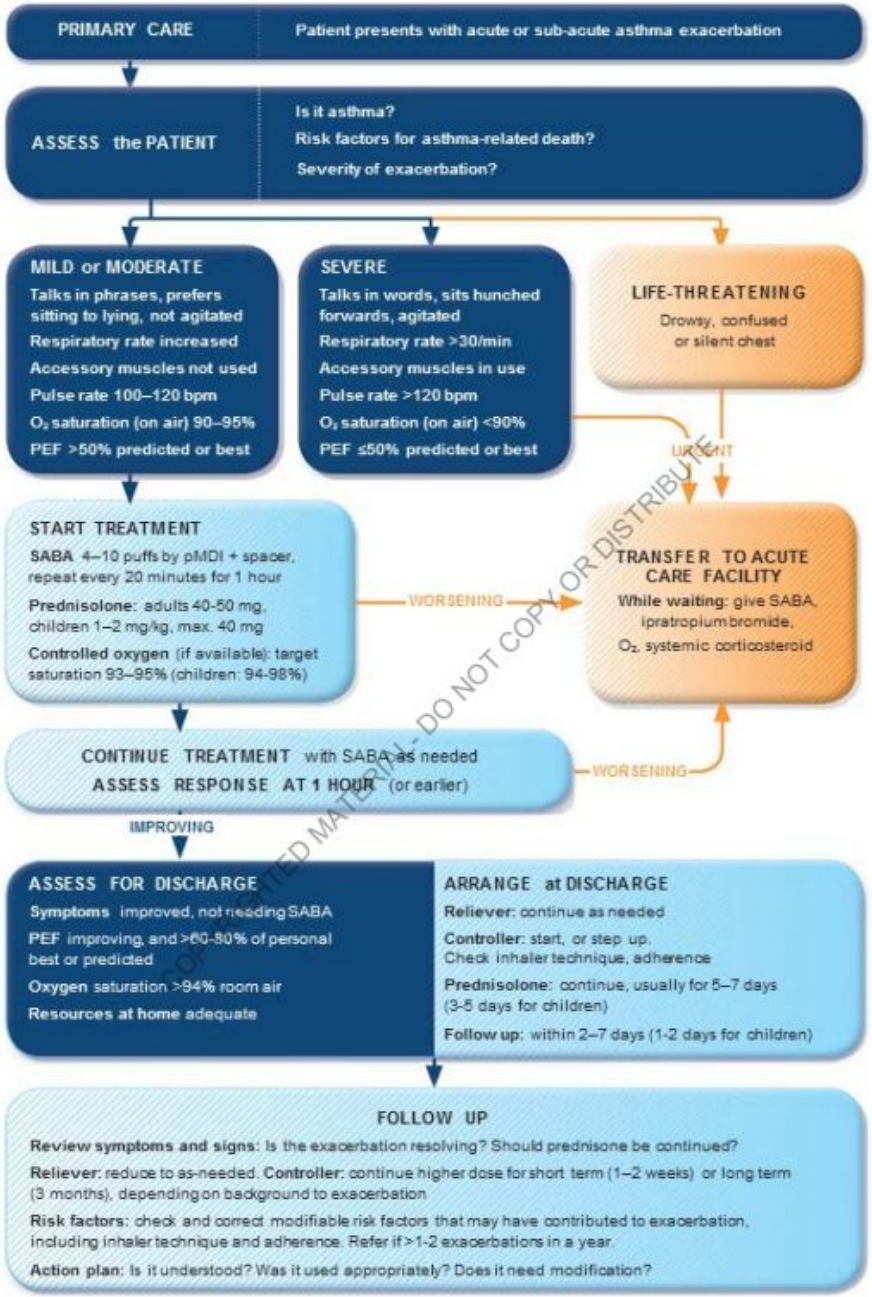
- How is asthma managed
  - Baseline asthma (EPR3 v EPR4)
    1. Measures of asthma assessment and monitoring
    2. Education
    3. Control of environmental triggers and comorbidities that affect asthma
    4. Medications
  - Acute exacerbations

- How is severe or refractory asthma managed
  - What is an asthma endotype?
  - What do I do with these abnormal labs in my severe asthma patient?

Acute exacerbations



Per GINA 2019 guidelines, can quadruple ICS dose (including ICS/formoterol up to 72mcg/24h) or treat with OCS (40-50 mg) for 5-7 days.



O_2: oxygen; PEF: peak expiratory flow; SABA: short-acting beta$_2$-agonist (doses are for salbutamol)

Acute exacerbations

- EPR4:
  - for patients 12yo and up likely to be adherent to ICS therapy, *conditional* recommendation against temporarily increasing ICS for increased asthma symptoms
    - "increasing" = doubling, quadrupling or quintupling the ICS dose
      - Did not reduce asthma exacerbations or hospitalizations
    - Potential benefit for quadrupling ICS if 16 yo or up and not adherent to ICS
  - SMART therapy (see above)
  - Systemic steroids for severe exacerbations

- GINA 2021
  - SMART therapy (see comments re: FDA and prn formoterol/ICS in US)
  - Prednisone 40-50 mg x 5-7 days preferred if OCS is needed

Future strategies for rescue regimens

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reliever-Triggered Inhaled Glucocorticoid in Black and Latinx Adults with Asthma

E. Israel, J.-C. Cardet, J.K. Carroll, A.L. Fuhlbrigge, L. She, F.W. Rockhold, N.E. Maher, M. Fagan, V.E. Forth, B.P. Yawn, P. Arias Hernandez, J.M. Kruse, B.K. Manning, J. Rodriguez-Louis, J.B. Shields, B. Ericson, A.D. Colon-Moya, S. Madison, T. Coyne-Beasley, G.M. Hammer, B.M. Kaplan, C.S. Rand, J. Robles, O. Thompson, M.E. Wechsler, J.P. Wisnivesky, M.D. McKee, S.P. Jariwala, E. Jerschow, P.J. Busse, D.C. Kaelber, S. Nazario, M.L. Hernandez, A.J. Apter, K.-L. Chang, V. Pinto-Plata, P.M. Stranges, L.P. Hurley, J. Trevor, T.B. Casale, G. Chupp, I.L. Riley, K. Shenoy, M. Pasarica, R.A. Calderon-Candelario, H. Tapp, A. Baydur, and W.D. Pace

Phase 3 RCT (PICORI)
PRACTAL
NEJM 2/26/22

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 2, 2022 VOL. 386 NO. 22

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma

Alberto Papi, M.D., Bradley E. Chipps, M.D., Richard Beasley, D.Sc., Reynold A. Panettieri, Jr., M.D., Elliot Israel, M.D., Mark Cooper, M.Sc., Lynn Dunsire, M.Sc., Allison Jeynes-Ellis, M.D., Eva Johnsson, M.D., Robert Rees, Ph.D., Christy Cappelletti, Pharm.D., and Frank C. Albers, M.D.

Phase 2 trial

NEJM 6/02/22

FDA has not specifically approved addition of prn ICS to prn SABA

Outline

- What is asthma
  - Defining asthma
  - Diagnosing asthma
  - Staging asthma

- How is asthma managed
  - Baseline asthma (EPR3 v EPR4)
    1. Measures of asthma assessment and monitoring
    2. Education
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  - Acute exacerbations

- How is severe or refractory asthma managed
  - What is an asthma endotype?
  - What do I do with these abnormal labs in my severe asthma patient?

GP OR SPECIALIST CARE

Investigate and manage difficult-to-treat asthma in adults and adolescents

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS: *"Difficult-to-treat asthma"*

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

1 Confirm the diagnosis (asthma/differential diagnoses)

2 Look for factors contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

3 Optimize management, including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza and COVID-19 vaccination)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, LAMA, LTRA, if not used)
- Consider trial of high dose ICS-LABA, if not used

4 Review response after ~3-6 months

Is asthma still uncontrolled?

yes

DIAGNOSIS: *"Severe asthma"*

If not done by now, refer to a specialist, if possible

no

Consider stepping down treatment, OCS first, (if used)

Does asthma become uncontrolled when treatment is stepped down?

yes

Restore previous dose

no

Continue optimizing management

Key

- decision, filters
- intervention, treatment
- diagnosis, confirmation

Severe asthma definition: risk + control

TABLE 3 Definition of severe asthma for patients aged ⩾6 years

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS[#] and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ⩾50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy

Uncontrolled asthma defined as at least one of the following:

1) Poor symptom control: ACQ consistently >1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)
2) Frequent severe exacerbations: two or more bursts of systemic CS (>3 days each) in the previous year
3) Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year
4) Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)

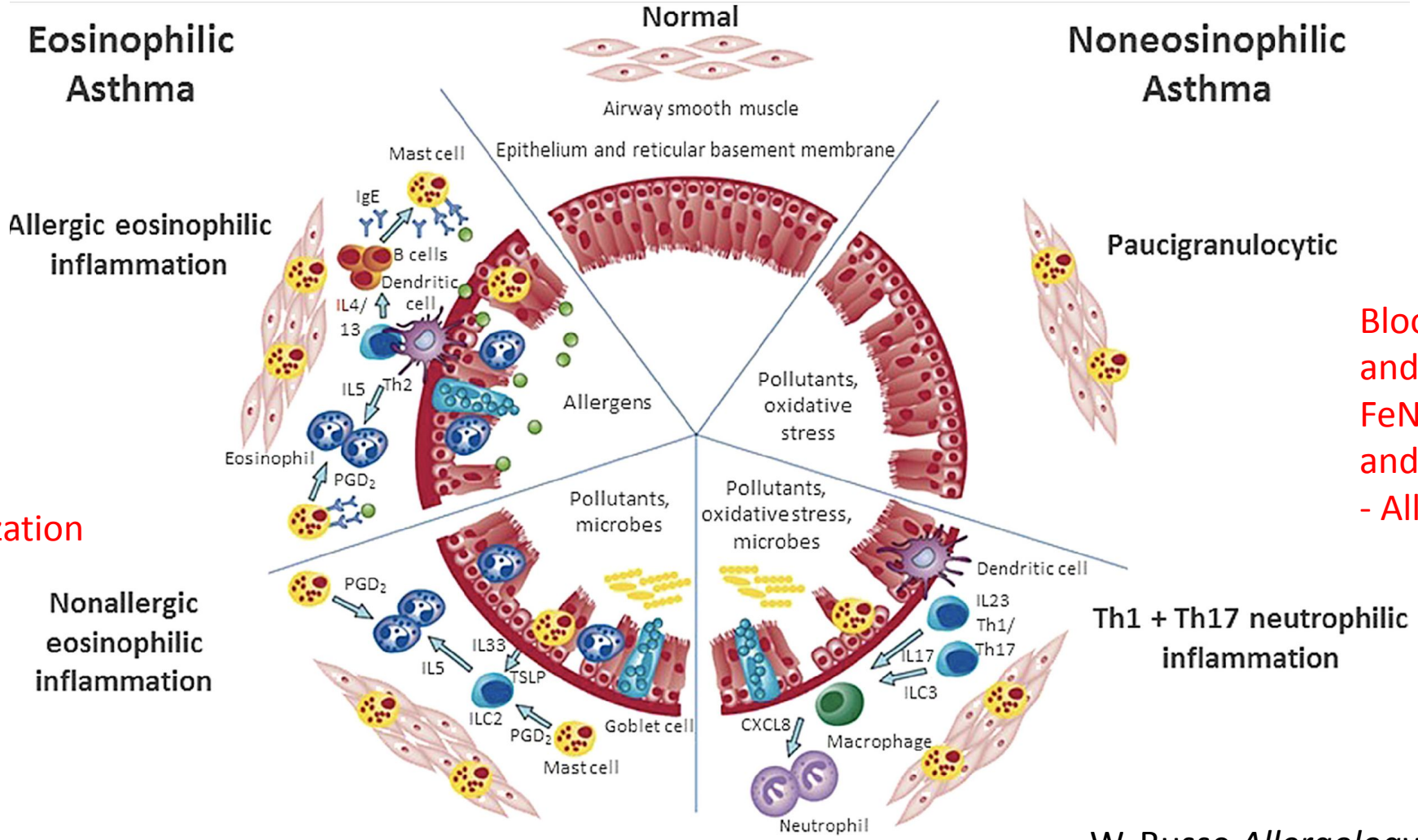
Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)

#: the definition of high dose inhaled corticosteroids (ICS) is age-specific (table 4). GINA: Global Initiative for Asthma; LABA: long-acting β_2-agonists; CS: corticosteroids; ACQ: Asthma Control Questionnaire; ACT: Asthma Control Test; NAEPP National Asthma Education and Prevention Program.

Chung et al. ATS/ERS statement severe asthma, 2013

What we think is happening vs. what we can measure in clinic

Blood eos > 150
or
FeNO > 25
or
+ Allergen sensitization



Blood eos < 150
and
FeNO < 25
and
- Allergen sensitization

W. Busse *Allergology International* 2019

Severe asthma: it's all about the endotype

- T_H2^{hi} or T_H2^{lo}
  - Peripheral eosinophils #
    - Sputum eos # (use for clinical research but not available for routine clinical care)
  - Serum IgE
  - Aeroallergen specific IgE
  - Fractional exhaled nitric oxide (FENO)
  - Candidacy for biologics?
    - Biologics are not addressed in EPR4, they are addressed in GINA

- Additional descriptors we note and address (but do not contribute to defining endotype):
  - Age of onset (childhood, adult, elderly)
  - Triggers (viral URI, allergens, alcohol)
  - NSAID-triggered acute bronchospasm or sinusitis
  - Obesity
  - Chronic rhinitis/rhinosinusitis/nasal polyposis
  - Fixed airway obstruction
  - Bronchiectasis
  - VCD
  - A1AT

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

5 *Investigate* further and provide *patient support*

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO; DEXA scan
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Consider screening for adrenal insufficiency in patients taking maintenance OCS or high dose ICS
  - If blood eosinophils ≥300/µl, look for and treat non-asthma causes, including parasites (e.g. Strongyloidus serology, or stool examination)
  - If hypereosinophilia e.g. ≥1500/µl consider causes such as EGPA
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- Consider need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

6 Assess the *severe asthma phenotype*

Could patient have Type 2 airway inflammation?

Type 2 inflammation

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)

Note: these are not the criteria for add-on biologic therapy (see **8***)*

7 Consider *other* treatments

Type 2 airway inflammation

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes, e.g. AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

Is add-on Type 2 biologic therapy available/affordable?

If add-on Type 2-targeted biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider other add-on therapy (e.g. LAMA, LM/LTRA, low dose azithromycin)
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

Go to section **10**

Not currently eligible for T2-targeted biologic therapy

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4R* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

Go to section **10**

** Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

Monitor / Manage severe asthma treatment

Continue to optimize management

9 Review response

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side effects, affordability
- Patient satisfaction

If good response to Type 2-targeted therapy

- Re-evaluate the patient every 3-6 months*
- For **oral treatments:** consider decreasing/stopping OCS first (and check for adrenal insufficiency), then stopping other add-on medication
- For **inhaled treatments:** consider decreasing after 3-6 months, continue at least moderate dose ICS-LABA
- Re-evaluate need for ongoing biologic therapy
- Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference

If no good response to Type 2-targeted therapy

- Stop the biologic therapy
- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects, emotional support
- Consider high resolution chest CT (if not done)
- Reassess phenotype and treatment options
  - Induced sputum (if available)
  - Consider add-on low dose azithromycin
  - Consider bronchoscopy for alternative/additional diagnoses
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Consider bronchial thermoplasty (if registry)
- Stop ineffective add-on therapies
- Do not stop ICS

yes

no

No evidence of Type 2 airway inflammation. Go to section **10**

10 Continue to **optimize management** as in section **3**, including:

- Inhaler technique
- Adherence
- Comorbidity management
- Non-pharmacologic strategies
- Patients' social/emotional needs
- Two-way communication with GP for ongoing care

Notes:

**Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

Asthma and eosinophilia

- Eosinophil # > 1500 (current or historic)
  - Confirmed present over at least 30 days?

  - No
    - monitor, remember this when making selections on biologics
    - Serum IgE: screen for ABPA
    - Screen for parasitic infections (*Strongyloides, Toxocara* IgG serologies)

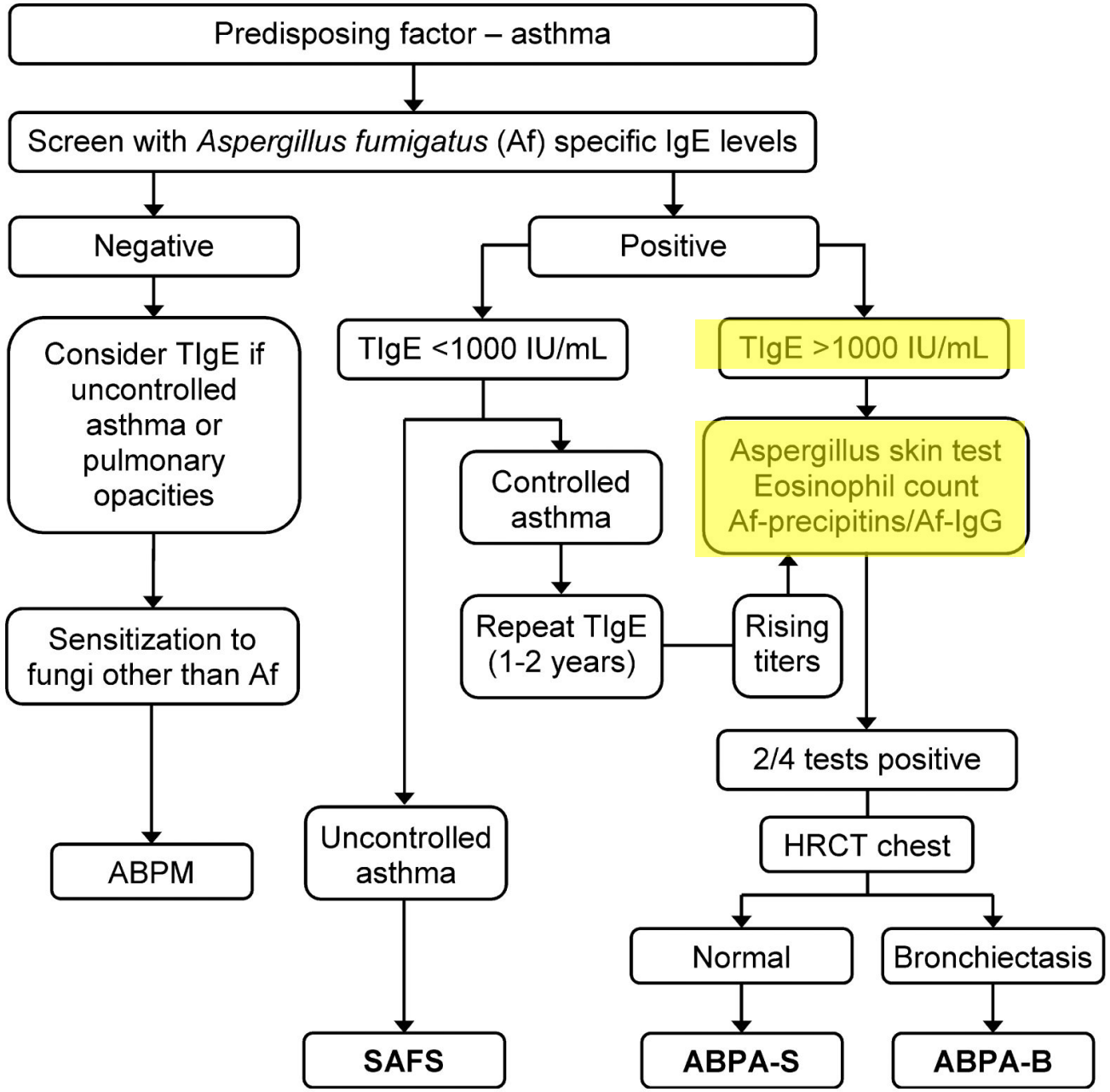
  - Yes: Hypereosinophilic syndrome
    - Screen for parasitic infections (*Strongyloides, Toxocara* IgG serologies)
    - Urgently need to determine if malignancy is present
      - ↑B12 or ↑ tryptase or peripheral smear with dysmorphic eos: oncologist referral for bone marrow biopsy
    - Need to determine if EGPA is present
      - Asthma + sinusitis +/- other organ involvement: involve EGPA specialists early

Asthma and serum IgE

- Allergic bronchopulmonary aspergillosis (ABPA) or mycosis (ABPM) diagnosis
- Obligatory criteria (3/3)
  - pre-existing asthma or cystic fibrosis
  - Total serum IgE > 1000
    - EGPA often causes serum IgE to exceed this level
  - Mold allergy (skin test or Immunocap)
- Minor criteria
  - Peripheral eos >500
    - If peripheral eos # > 1500 then need to consider EGPA
  - Aspergillus IgG > 27
  - HRCT transient findings (opacities, nodules, high-attenuating mucus) OR bronchiectasis OR fibrosis (if longstanding ABPA)
    - EGPA can also cause fleeting opacities, nodules and bronchiectasis

Radiologic Classification by HRCT

ABPA-S	normal HRCT
ABPA-B	bronchiectasis
ABPA-HAM	high attenuation mucus
ABPA-CPF	fibrosis, scarring, aspergilloma, or pleural thickening w/o HAM



R. Agarwal *et al. Clin. Exp. Allergy* 2013

Biologic agents targeting T_H2^{hi} asthma

- Adherant to at least ICS/LABA + LTRA and/or LAMA
- At least 2 exacerbations in past 12 months requiring systemic steroids

- Anti-IgE
  - omalizumab
- Anti-IL5/5Rα (Eos >150 in last 6 months)
  - mepolizumab, reslizumab, benralizumab
- Anti-IL4rα/IL13 (Eos>150 in last 6 months or FeNO > 25)
  - dupilumab
    - *Not suggested if eos # (current or historic) > 1500/μL*
- Anti-TSLP
  - tezepelumab

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

8 Consider *add-on biologic Type 2-targeted* treatments

- Consider add-on Type 2-targeted biologic therapy for patients with exacerbations or poor symptom control on high dose ICS-LABA, who have evidence of Type 2 inflammation*
- Consider local payer **eligibility criteria***, **comorbidities** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Eligibility

Predictors of asthma response

Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl +–
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / no

Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?**

- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/µl or ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult onset of asthma ++
- Nasal polyposis ++

no / no

Anti-IL4R *(dupilumab)*

*Is the patient eligible for **anti-IL4R** for severe eosinophilic/Type 2 asthma?**

- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

What factors may predict good asthma response to anti-IL4R?

- Higher blood eosinophils +++
- Higher FeNO +++

no / no

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

- Exacerbations in last year

What factors may predict good asthma response to anti-TSLP?

- Higher blood eosinophils +++
- Higher FeNO +++

Eligible for none? Return to section **7**

Choose one if eligible*; trial for at least 4 months and assess response

*Good asthma response?**

- *yes* → Good response to T2-targeted therapy
- *unclear* → Extend trial to 6-12 months*
- *no* → **STOP add-on**

STOP add-on

Consider switching to a different Type 2-targeted therapy, if eligible*

no → Little/no response to T2-targeted therapy

No evidence of Type 2 airway inflammation

No evidence of Type 2 airway inflammation. Go to section **10**

* *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

Omalizumab

WARNING: Anaphylaxis

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

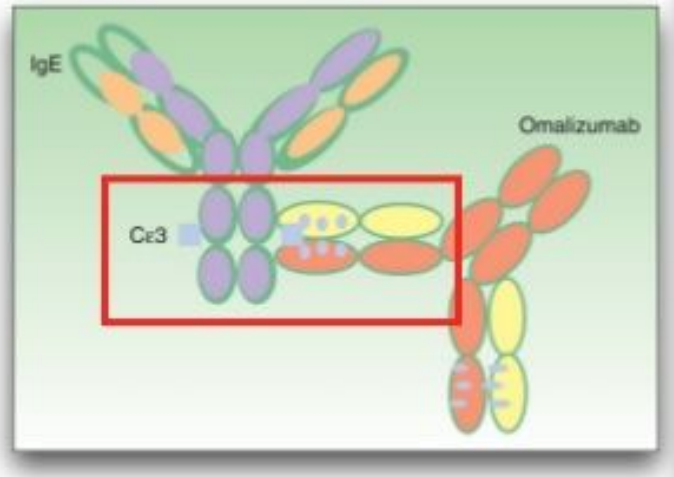
2 mechanisms

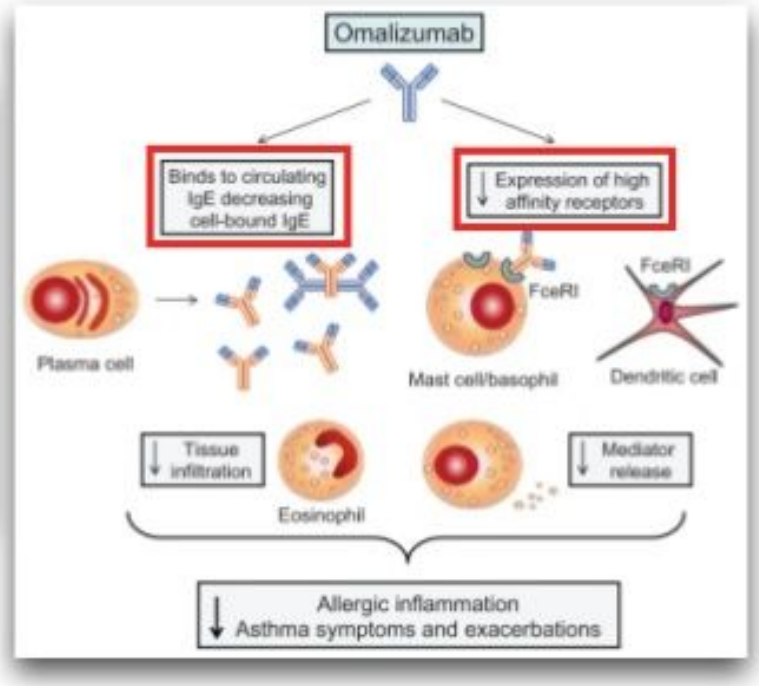
1.) Blockage of free IgE

: binds the **Cε3** domain of the free IgE heavy chain

2.) Downregulation of FcεRI receptors

: decrease FcεRI receptor density on mast cells and basophils





J.B. Bice et al. / Ann Allergy Asthma Immunol 112 (2014) 108e115

sc q2 or 4 week

Anaphylaxis risk
- Home admin after doses 1-3 in clinic is FDA approved

4 month trial needed before efficacy is assessed

also for chronic urticaria and CRS + nasal polyps

Asthma nomogram (6yo+):
+ Perennial aeroallergen
*** IgE 30 - 700 IU/mL**
*** weight 66 lb – 331 lb**

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: Pounds 66-132 lb	>132-154 lb	>154-198 lb	>198-330 lb
		Kilograms 30-60 kg	>60-70 kg	>70-90 kg	>90-150 kg
		Dose (mg)			
≥30-100	Every 4 weeks	150	150	150	300
>100-200		300	300	300	225
>200-300		300	225	225	300
>300-400	Every 2 weeks	225	225	300	
>400-500		300	300	375	
>500-600		300	375	Insufficient data to recommend a dose	
>600-700		375			

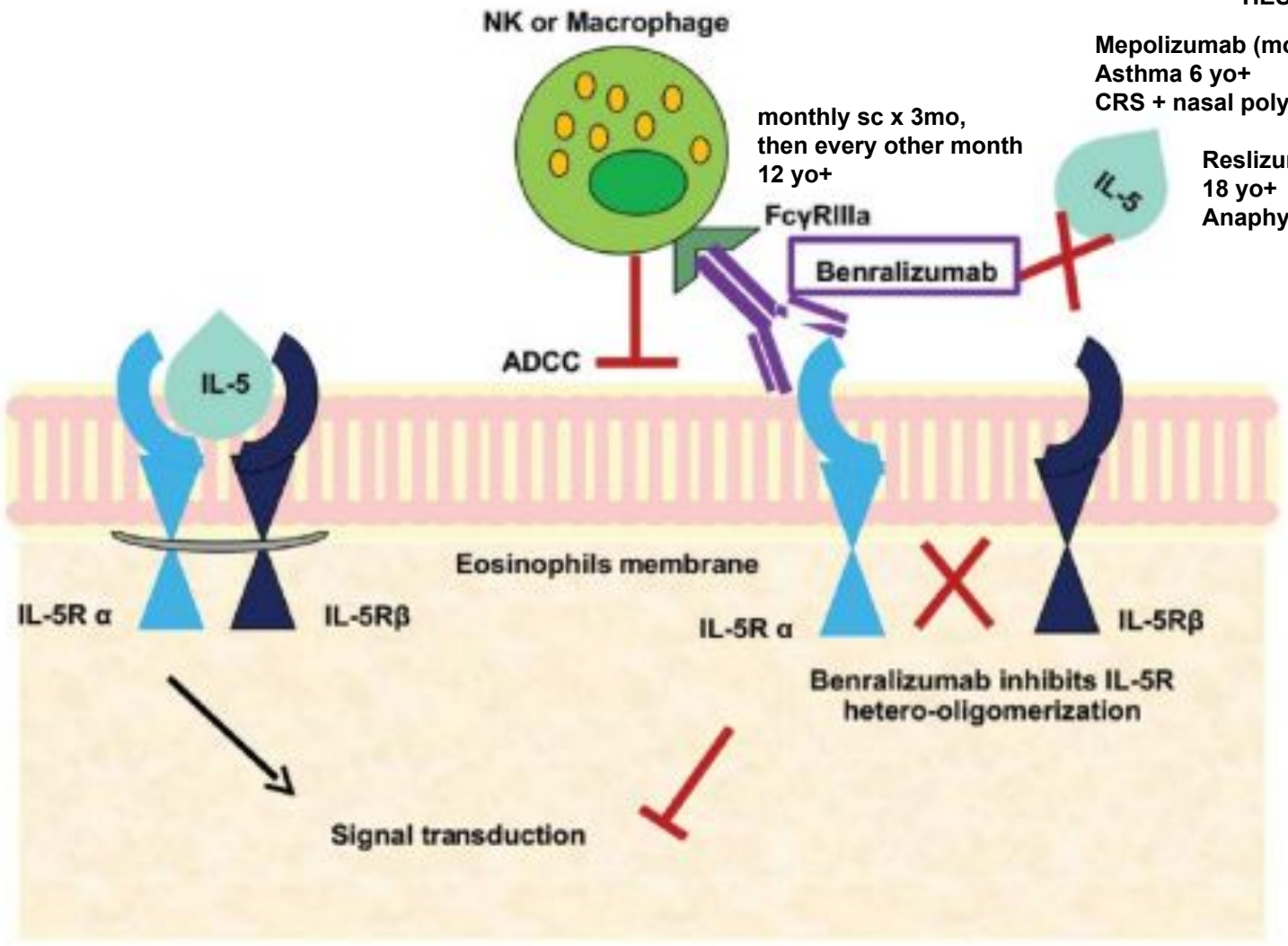
*Dosing frequency:
- Subcutaneous doses to be administered every 4 weeks
- Subcutaneous doses to be administered every 2 weeks

Anti-IL5Rα

Also for EGPA and HES, 3x dose
EGPA 18 yo+
HES 12 yo+

Mepolizumab (monthly sc)
Asthma 6 yo+
CRS + nasal polyposis 18yo+

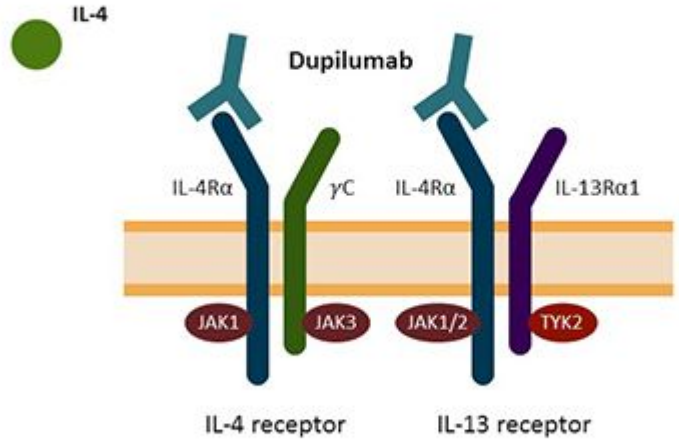
Reslizumab (monthly iv)
18 yo+
Anaphylaxis risk



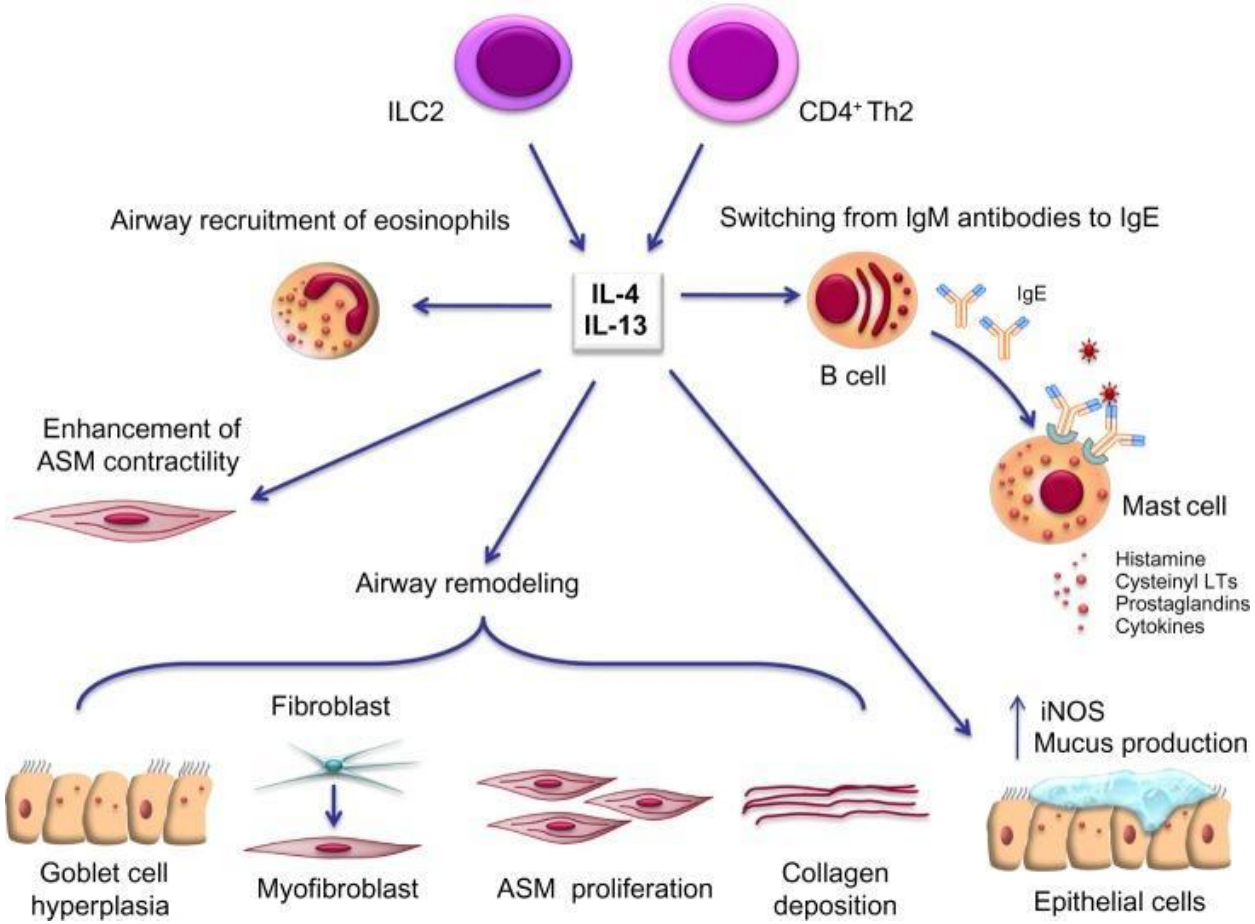
Anti-IL4 and IL-13 activity

sc q2 week for asthma, atopic dermatitis or CRS + nasal polyps
sc q1 week for eosinophilic esophagitis
Hypersensitivity rxn risk (conjunctivitis/ketatitis)
recc avoid live vaccines
FDA approval 6+ yo (asthma), 6+ mo (severe atopic dermatitis), 18yo+ (CRSwNP), 12yo+ EoE)
Monitor asthma patients for symptomatic hyperoesinophilia

Dupilumab
IL-4 Receptor α Inhibitor



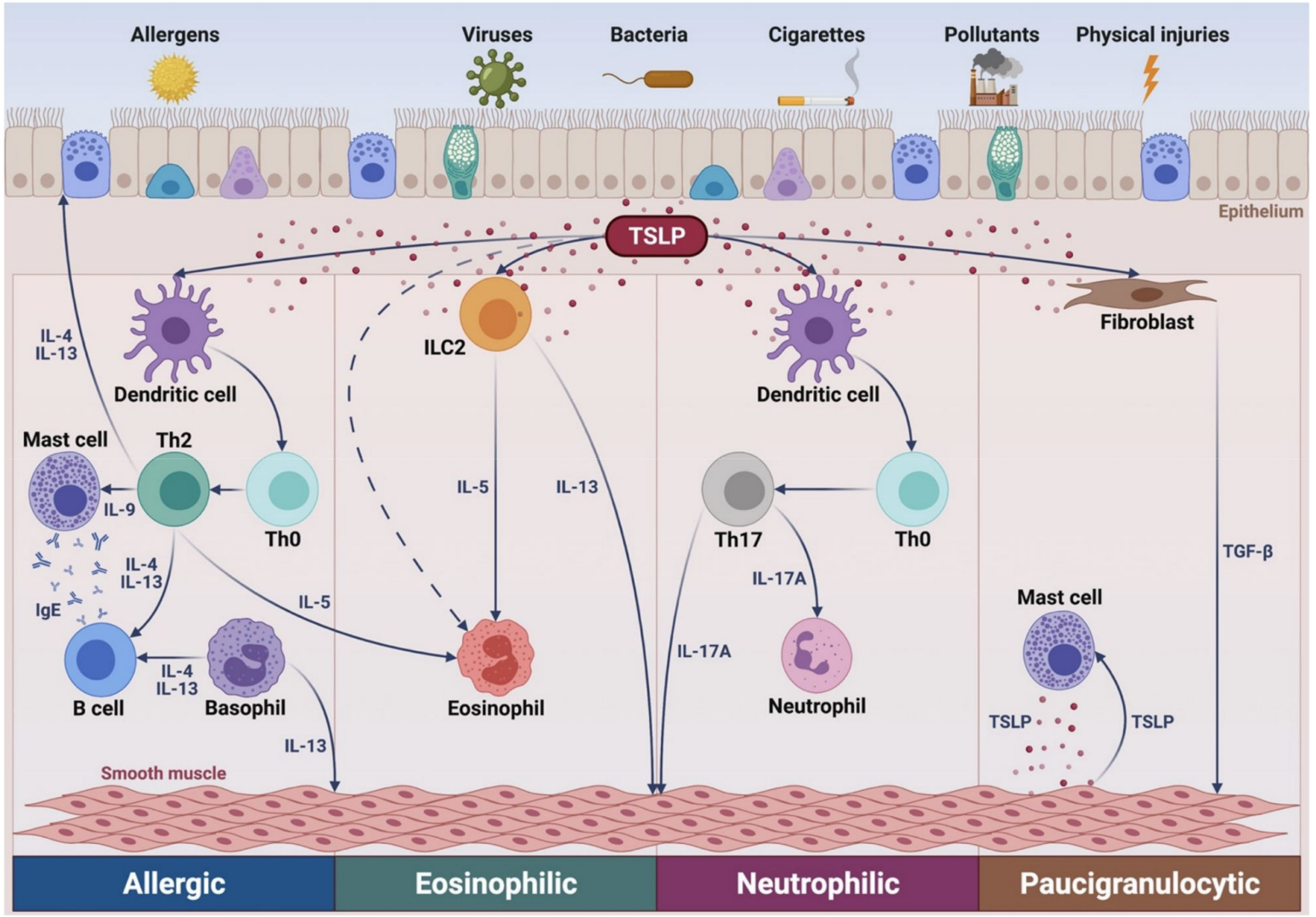
Monoclonal antibody directed against the IL-4 receptor α



Vatrella A, et al. *J Asthma Allergy.* 2014;7:123-130

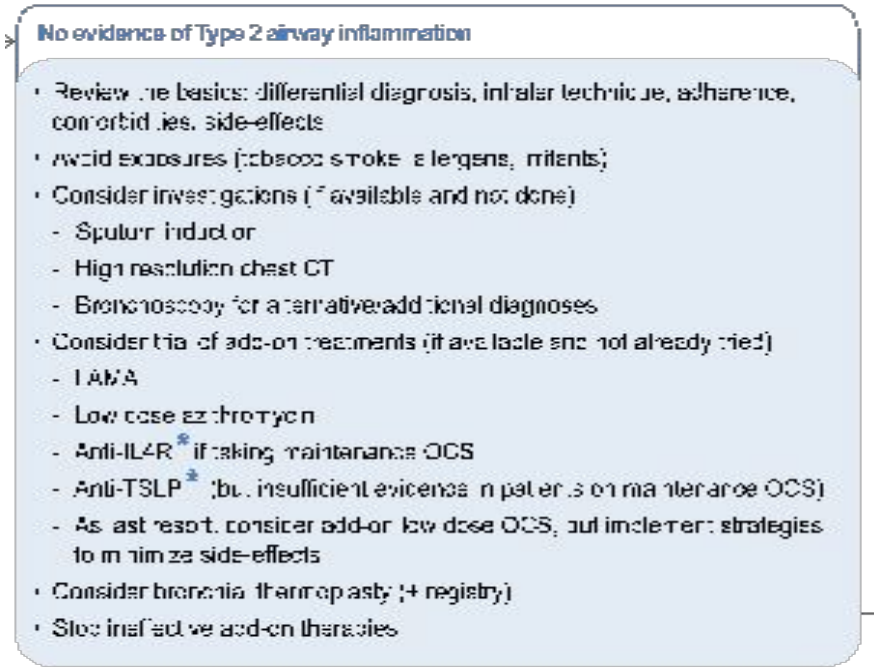
Anti-TSLP activity

sc q4 week
recc avoid live vaccines
FDA approval 12+ yo



C. Pelaia *et al. Int. J. Mol. Sci* 2021

Therapies for $T2^{lo}$ asthma



- Inhaler technique
- Adherence
- Comorbidity management
- Non-pharmacologic strategies
- Patients' social/emotional needs
- Two-way communication with GP for ongoing care

Maintenance OCS suppresses peripheral eos #s

dupilumab has FDA indication for OCS-dependent asthma

Tezepelumab approved for eos # < 150

HRCT is useful to exclude other concomitant pulmonary disease

Other management updates to be aware of: GOLD recommendations in COPD

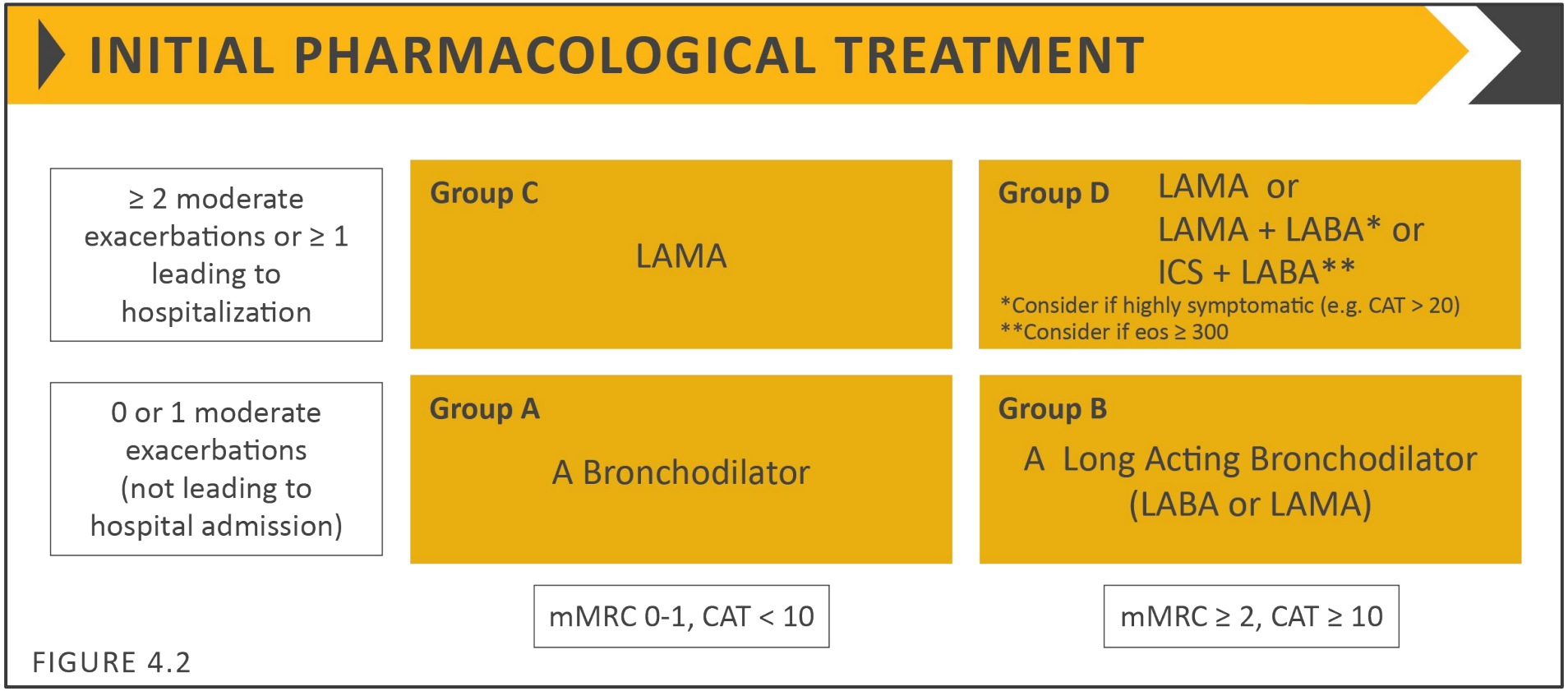
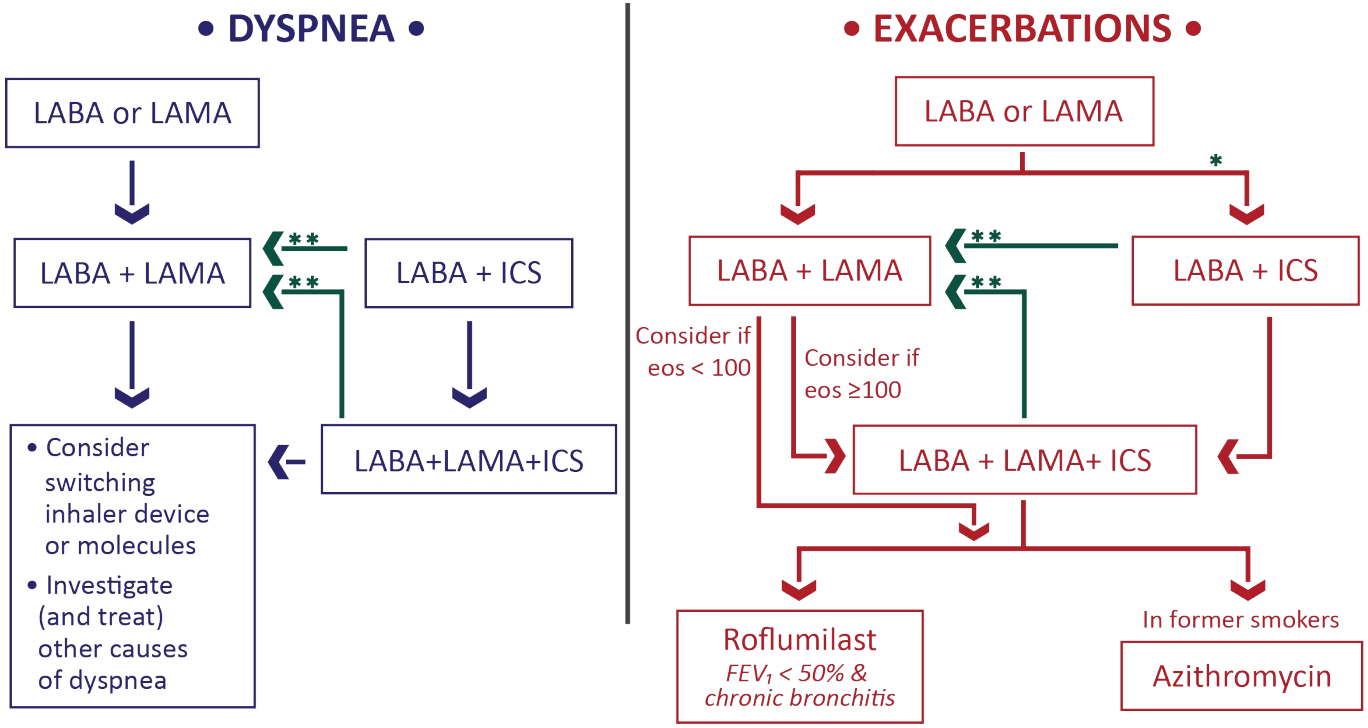


FIGURE 4.2

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis



eos = blood eosinophil count (cells/µL)
**** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization***
***** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS***

FIGURE 4.4

Additional reading

- GINA 2022
  - Asthma and COVID
  - Asthma and COVID vaccines
  - Asthma and COVID and biologics (ok to continue)
  - Asthma and COVID vaccines and biologics (administer different days)

Thank you for listening!