New Therapeutic Options in Asthma

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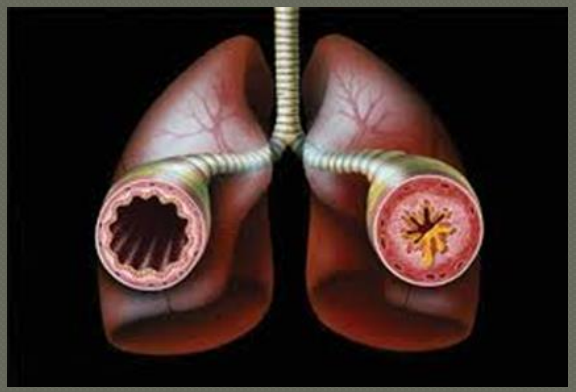
Objectives / Outline

- What is asthma?
- History
- Epidemiology
- Pathophysiology
- NIH Classifications of Severity
- NIH Step Up Therapy
- Severe Persistent Asthma, Step 6
- Current Basic Treatment Options
- Current Advanced Treatment Options
- Looking ahead
- Summary

Introduction to Asthma

- "A common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper-responsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment."

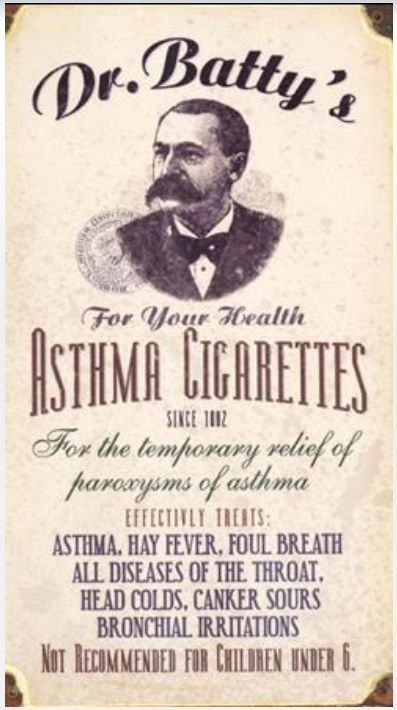


National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051) www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm

Then

- 450 BC — Hippocrates named respiratory problem
- 200 BC — "Related to the emotions"
- 1872 — "Cured" with Chloroform
- 1880 — IV Pilocarpin
- 1886 — F.H. Bosworth: connection with Hay Fever
- 1905 — Epinephrine
- 1950's — Oral Steroids
- 1960's — Inhaled Steroids
- 2015 — ???

Now

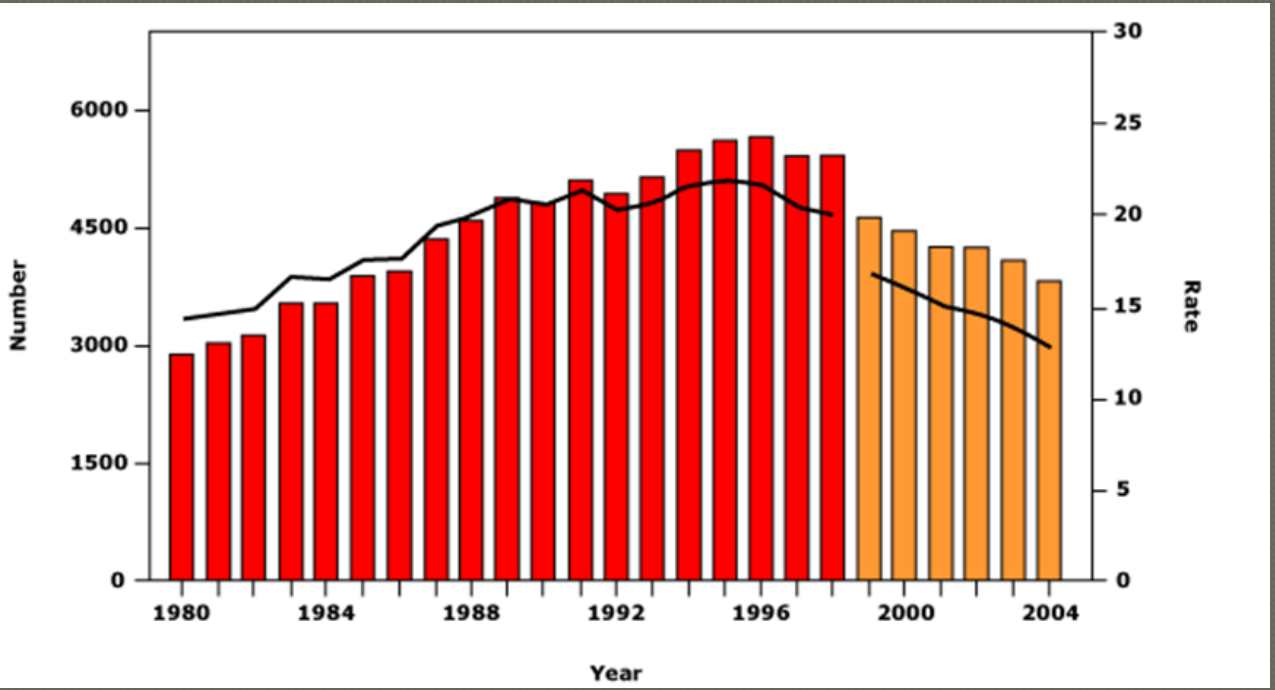


Epidemiology

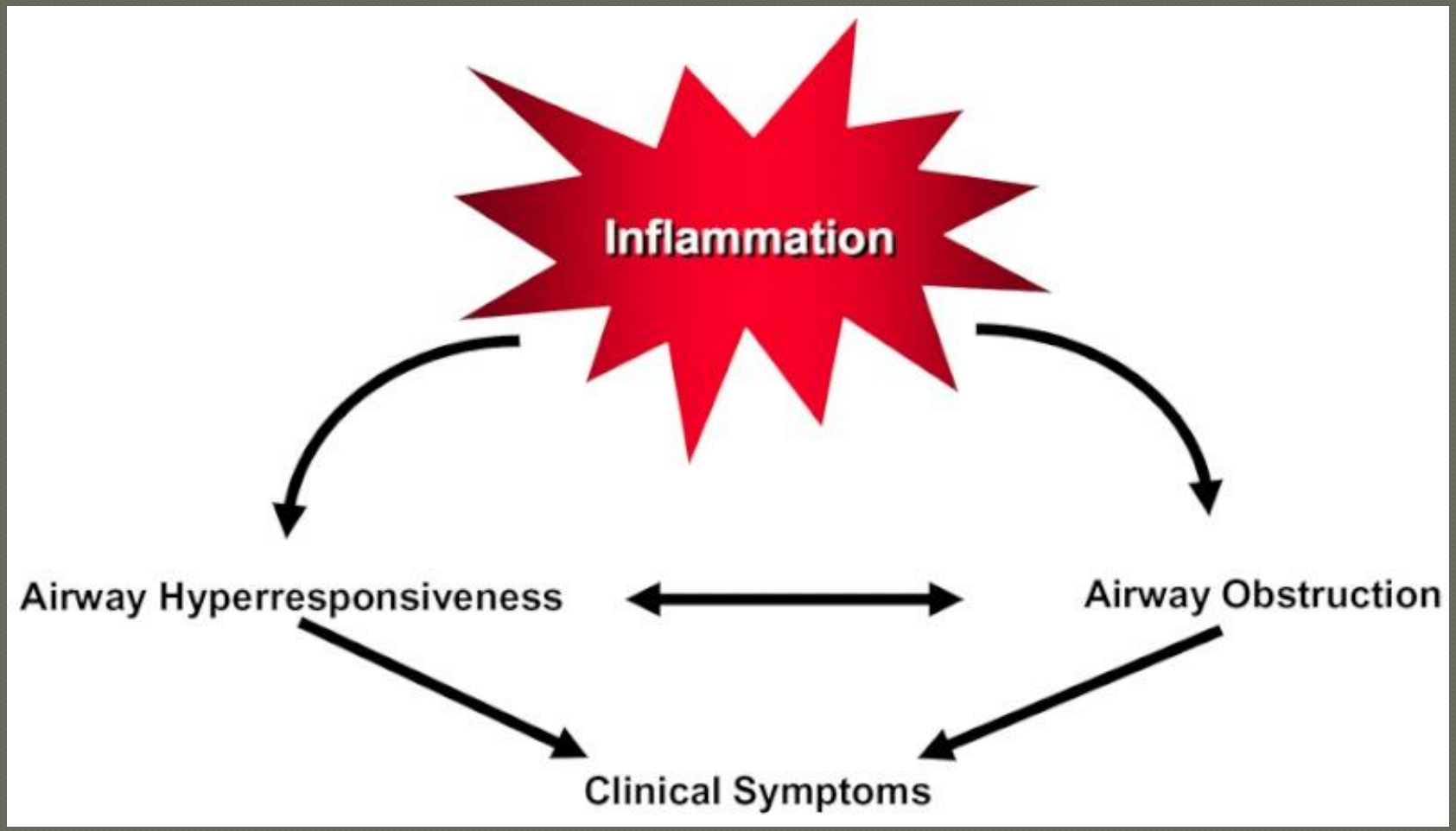
- Affects all ages
- 300 million worldwide as of 2004
- By 2025 → 400 million worldwide
- Rate of asthma increasing with urbanization
- 1/250 deaths worldwide.
- Expensive

Number & Rate of Asthma Deaths

US, 1980 to 2004

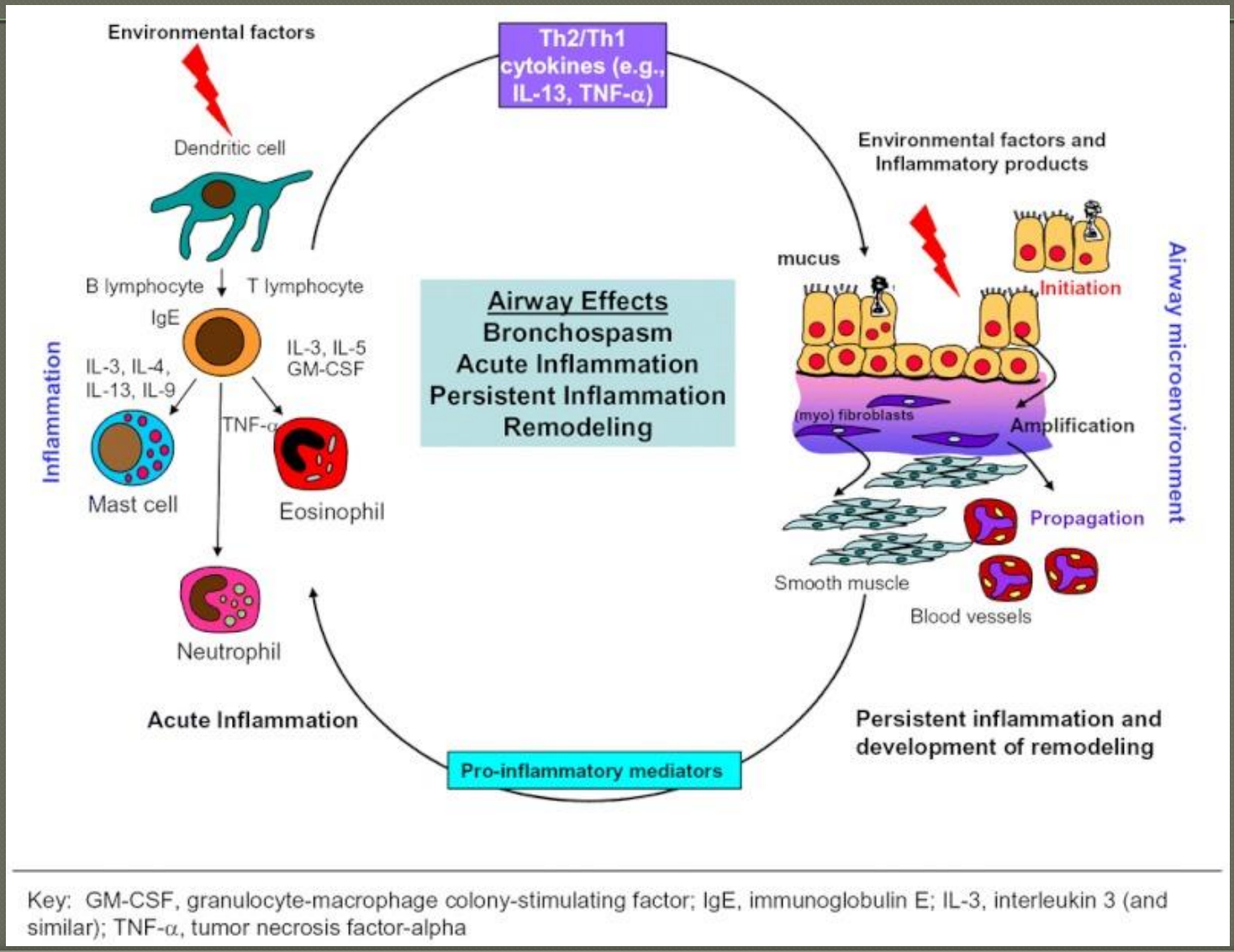


Pathophysiology

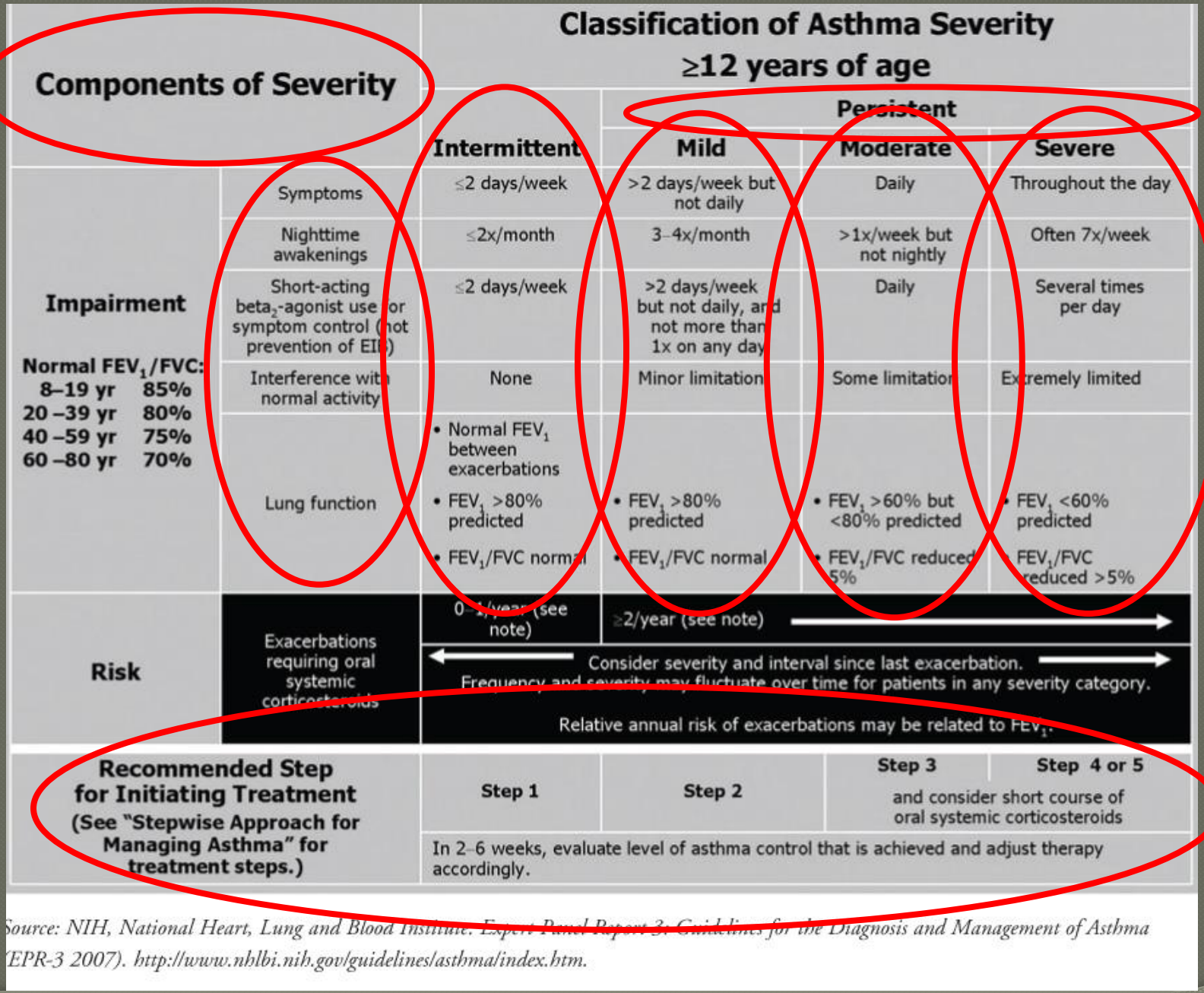


Expert Panel Report 3

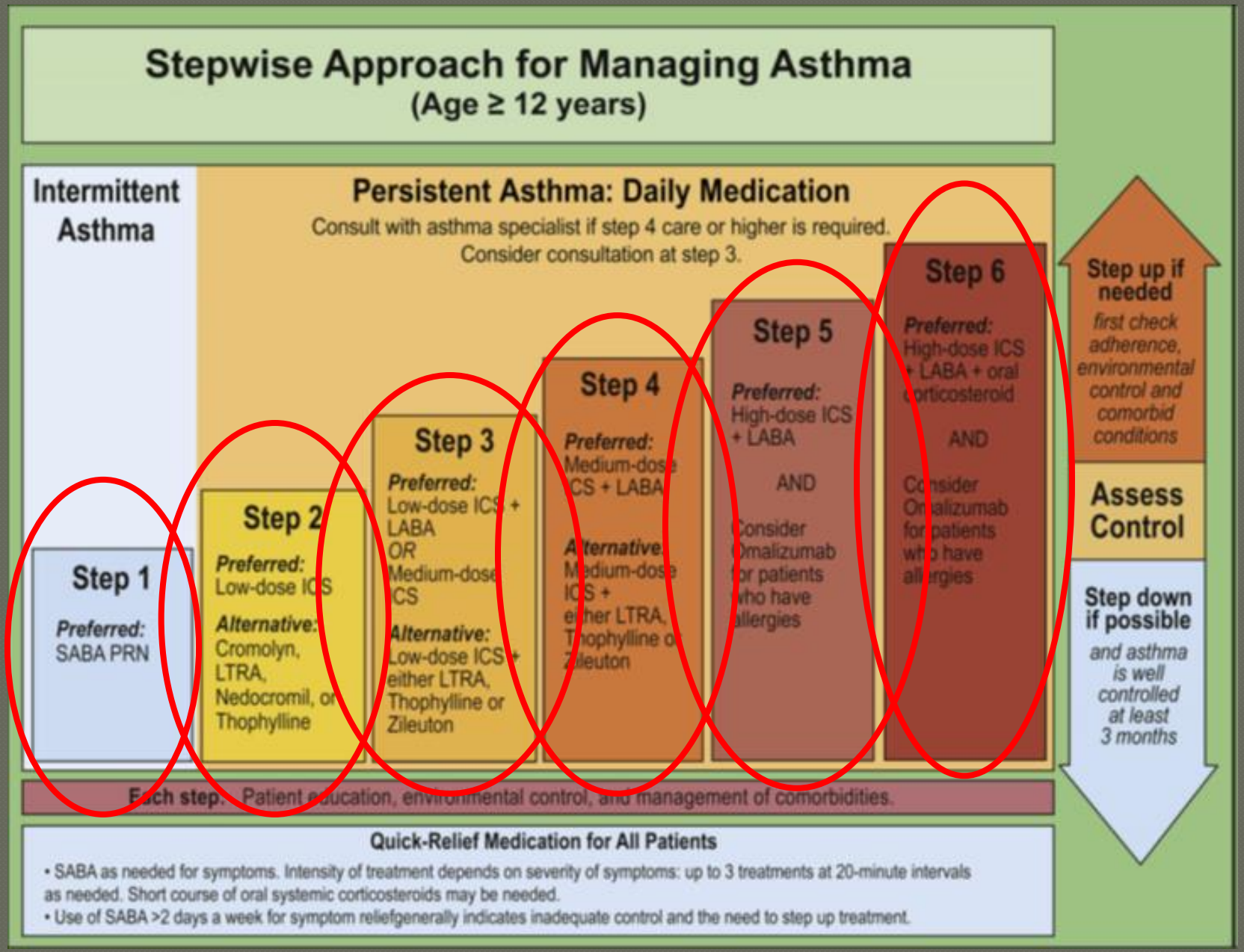
Factors Limiting Airflow



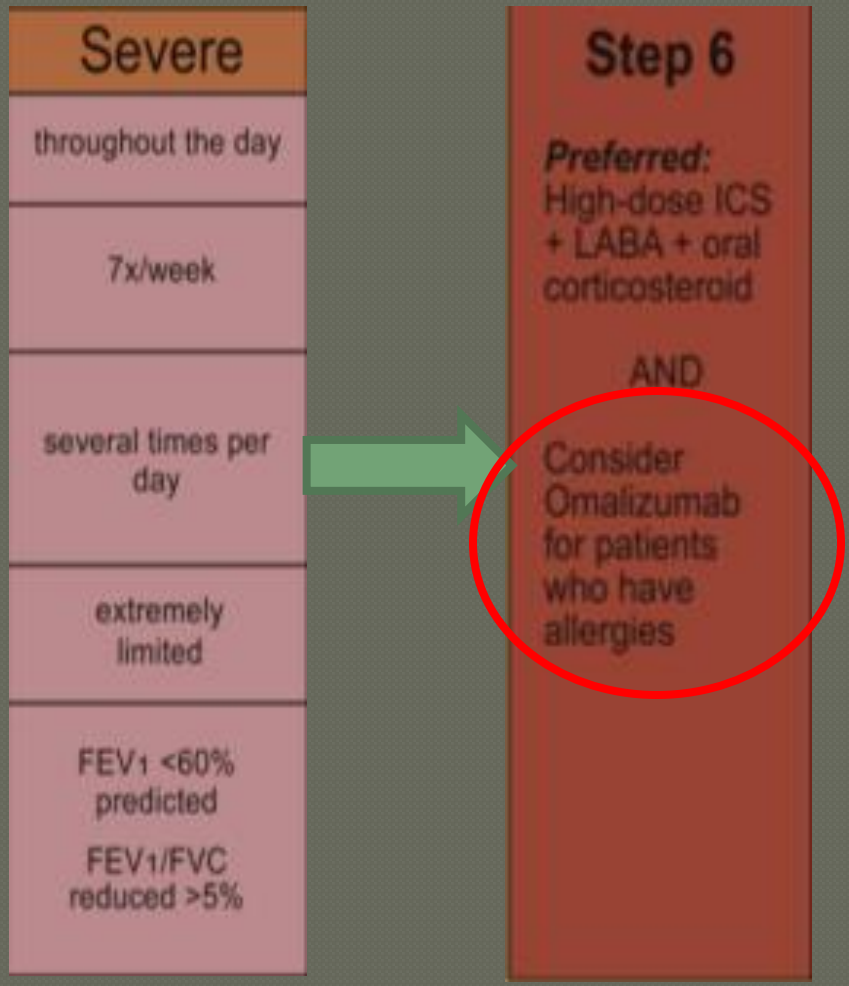
Key: GM-CSF, granulocyte-macrophage colony-stimulating factor; IgE, immunoglobulin E; IL-3, interleukin 3 (and similar); TNF-α, tumor necrosis factor-alpha



Source: NIH, National Heart, Lung and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (EPR-3 2007). http://www.nhlbi.nih.gov/guidelines/asthma/index.htm.


Stepwise Approach for Managing Asthma
(Age ≥ 12 years)
Intermittent Asthma
Persistent Asthma: Daily Medication
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.
Step 1
Preferred:
SABA PRN
Step 2
Preferred:
Low-dose ICS
Alternative:
Cromolyn, LTRA, Nedocromil, or Thophylline
Step 3
Preferred:
Low-dose ICS + LABA
OR
Medium-dose ICS
Alternative:
Low-dose ICS + either LTRA, Thophylline or Zileuton
Step 4
Preferred:
Medium-dose ICS + LABA
Alternative
Medium-dose ICS + either LTRA, Thophylline or Zileuton
Step 5
Preferred:
High-dose ICS + LABA
AND
Consider Omalizumab for patients who have allergies
Step 6
Preferred:
High-dose ICS + LABA + oral corticosteroid
AND
Consider Omalizumab for patients who have allergies
Step up if needed
first check adherence, environmental control and comorbid conditions
Assess Control
Step down if possible
and asthma is well controlled at least 3 months
Each step: Patient education, environmental control, and management of comorbidities.
Quick-Relief Medication for All Patients
• SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
• Use of SABA >2 days a week for symptom reliefgenerally indicates inadequate control and the need to step up treatment.

Severe Persistent Asthma, Step 6



Overview of basic treatment options

- Short acting beta agonists – rescue
- Inhaled corticosteroids – low, medium, high doses
- Cromolyn – alternative at Step 2
- Long acting beta agonists – add on therapy at Step 3
- Theophylline – alternative at Step 2-3
- Oral steroid – Steps 5-6

J Allergy Clin Immunol. 2011 Nov;128(5):915-24; quiz 925-6. doi: 10.1016/j.jaci.2011.07.014. Epub 2011 Sep 8.

Currently Available Advanced Treatment Options:

- Anti-Leukotriene Agents
  - Montelukast (Singulair)
  - Zafirlukast (Accolate)
  - Zilueton (Zyflo)
- Monoclonal Antibodies
  - Omalizumab (Xolair)
- Bronchial Thermoplasty

Leukotrienes

- Inflammatory mediators
- Produced in leukocytes from arachidonic acid
- Cysteinyl leukotrienes (cysLTs) contribute to asthma
- Smooth muscle contraction
- Bronchoconstriction
- Vascular leakage, mucous secretion
- Synthesized within minutes
- Stimulate smooth muscle cell & fibroblast proliferation

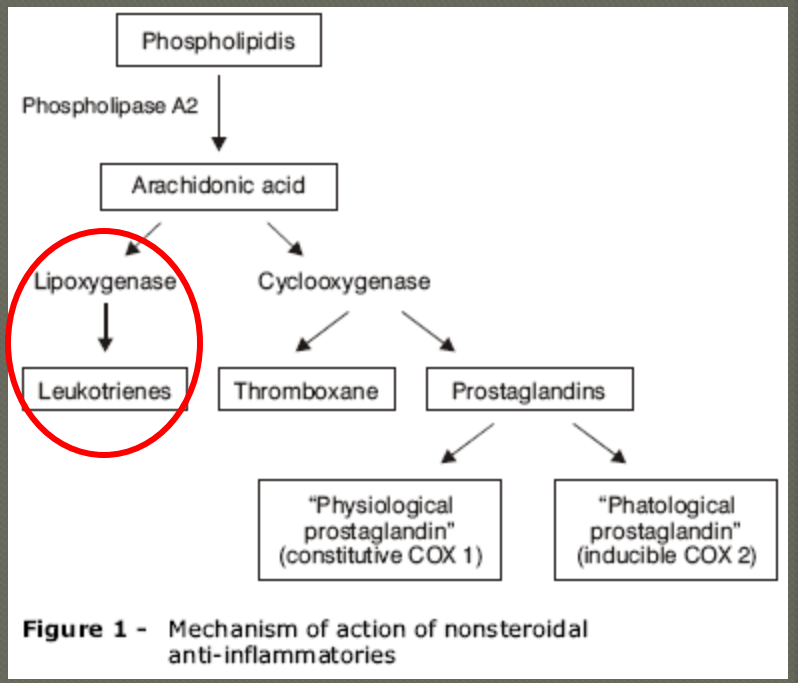


Figure 1 - Mechanism of action of nonsteroidal anti-inflammatories

Montelukast (Singulair), Zafirlukast (Accolate)

"Leukotriene Receptor Antagonists"

Antagonize cysteinyl leukotrienes (cysLTs) at the cysLT1 receptor

Singulair

1x/ day

> 1 year old

Good choice for allergic asthmatics

Alternative in Step 2

Accolate

2x/ day

> 5 years old

Side Effects:
anaphylaxis, dizziness, dyspepsia, muscle weakness, elevated LFTs, suicidal thinking, behavior or mood changes

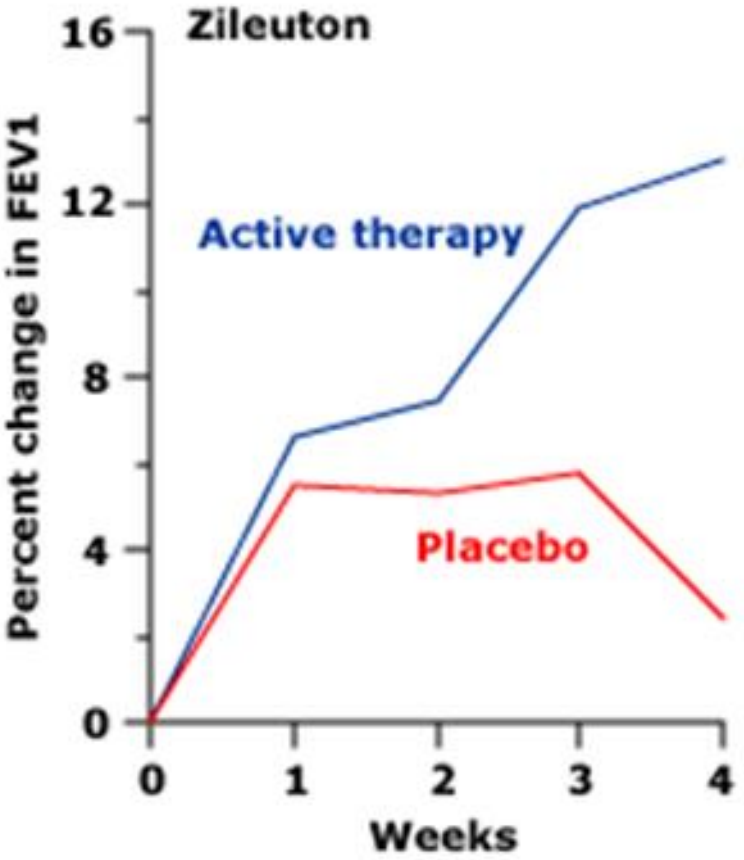
Zilueton (Zyflo)

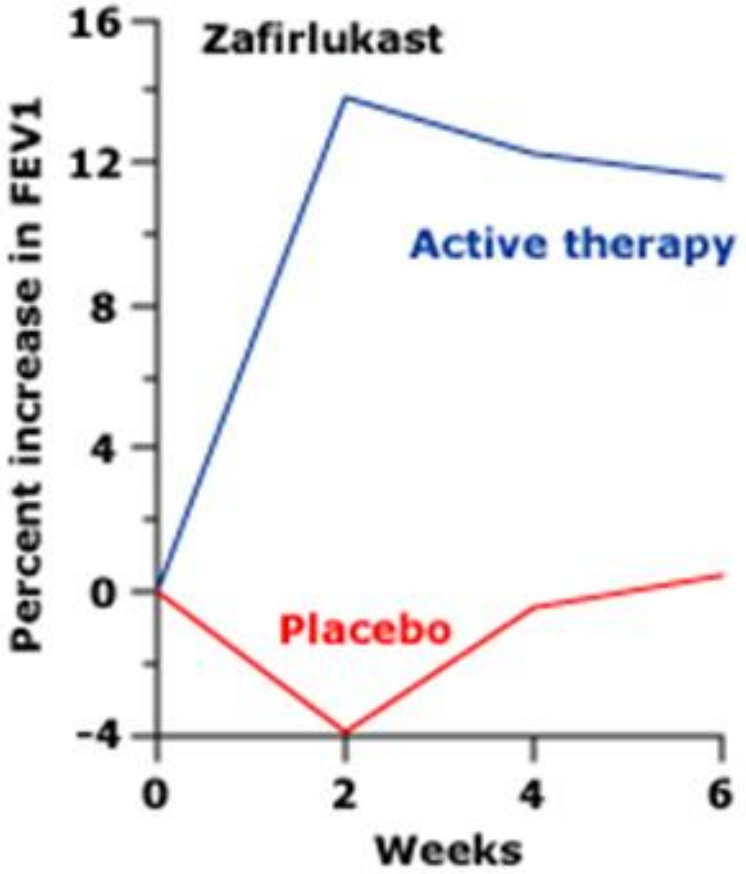
- Direct leukotriene antagonist
- Inhibits 5-lipoxygenase, inhibiting formation of leukotrienes
- Good choice for nasal polyps
- For more severe airflow obstruction

- Monitor ALT
- Avoid alcohol
- Monitor theophylline levels – can increase

Side effects:
headache, dyspepsia, myalgias, leukopenia, elevated LFTs, sleep disorders & behavior changes

Anti leukotriene vs Placebo



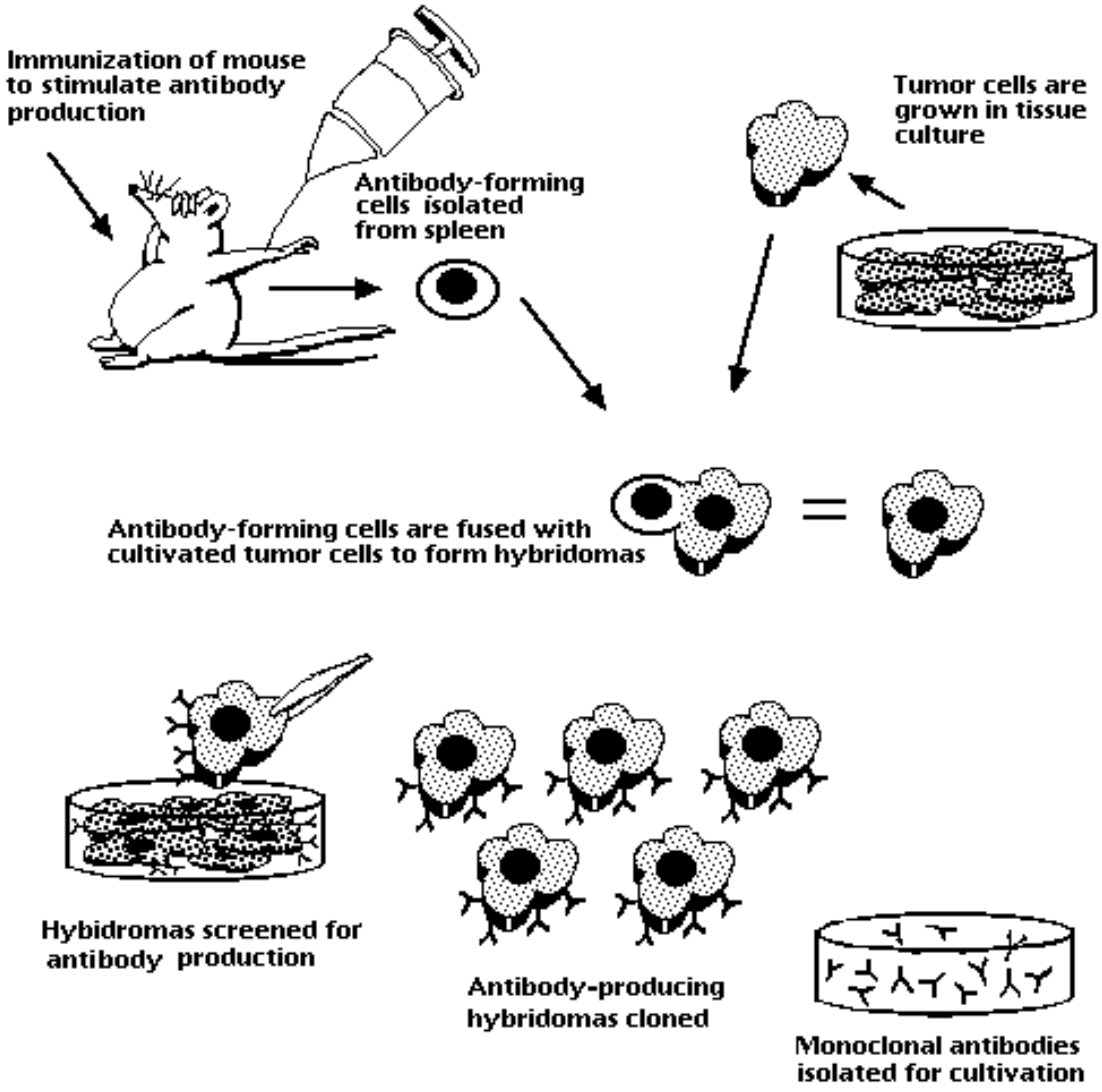


Monoclonal Antibodies

Immunoglobulin E (IgE)

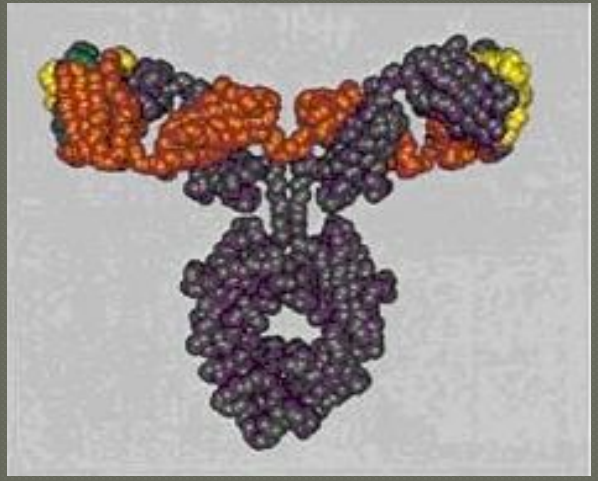
- Central to the pathogenesis of many allergic diseases
- Most asthmatics have increased circulating IgE
- Produced by Plasma Cells
- Defends against parasitic diseases
- Receptors on mast cell & basophils; binding leads to degranulation

Monoclonal Antibody Production

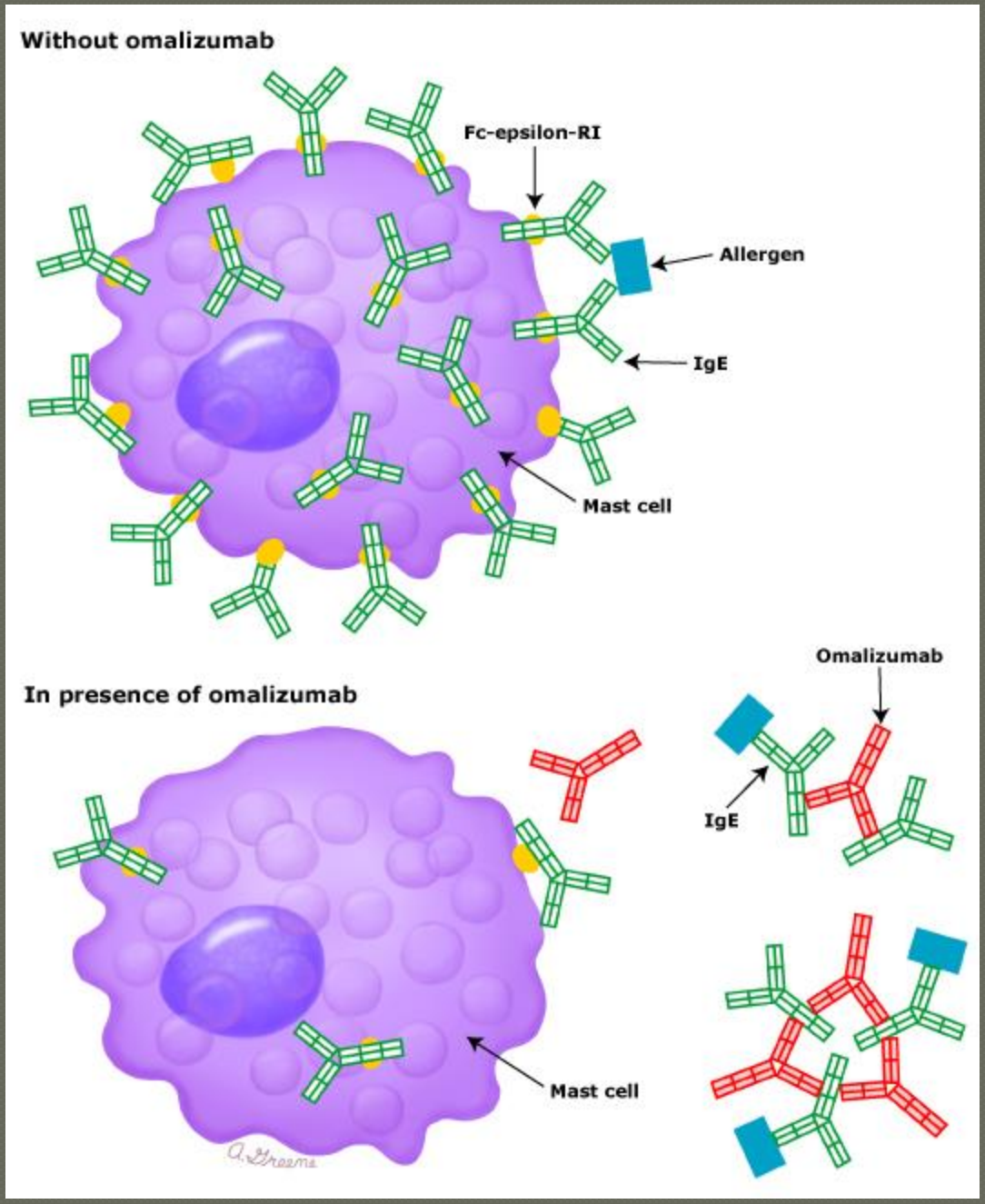


Omalizumab (Xolair)

- Recombinant humanized IgG1 monoclonal antibody
- Binds IgE
- Moderate to severe asthma
  - Step 5 or 6
- IgE levels 30-700 IU prior to treatment
- > 12 years old
- Significantly reduces severe exacerbations

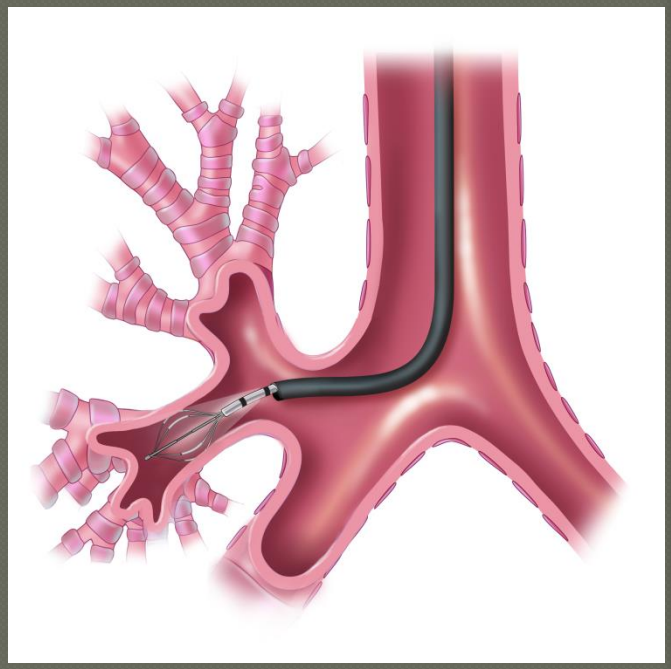


Anaphylaxis occurs in1 per 1000 patients


Without omalizumab
Fc-epsilon-RI
Allergen
IgE
Mast cell
In presence of omalizumab
Omalizumab
IgE
Mast cell

Bronchial Thermoplasty

- Applies heat to airways during bronchoscopy
- Reduces mass of smooth muscle
- Many risks
- Modest improvement
- Long term effects unknown
- Alair approved for adults with severe asthma… but safety and efficacy unknown for FEV1 < 50%

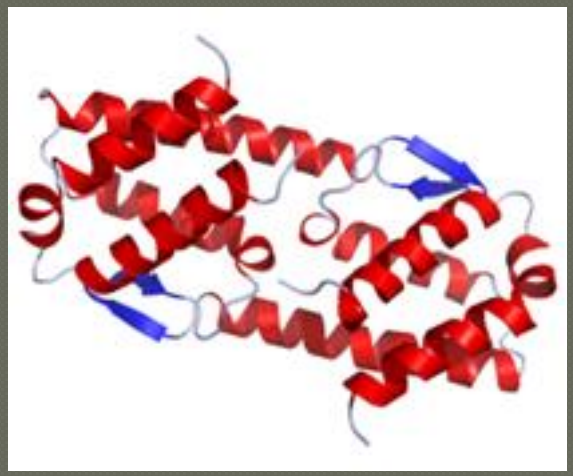


Looking Ahead

- Anti IL-5 treatment (pending FDA Approval)
- Anti IL-13

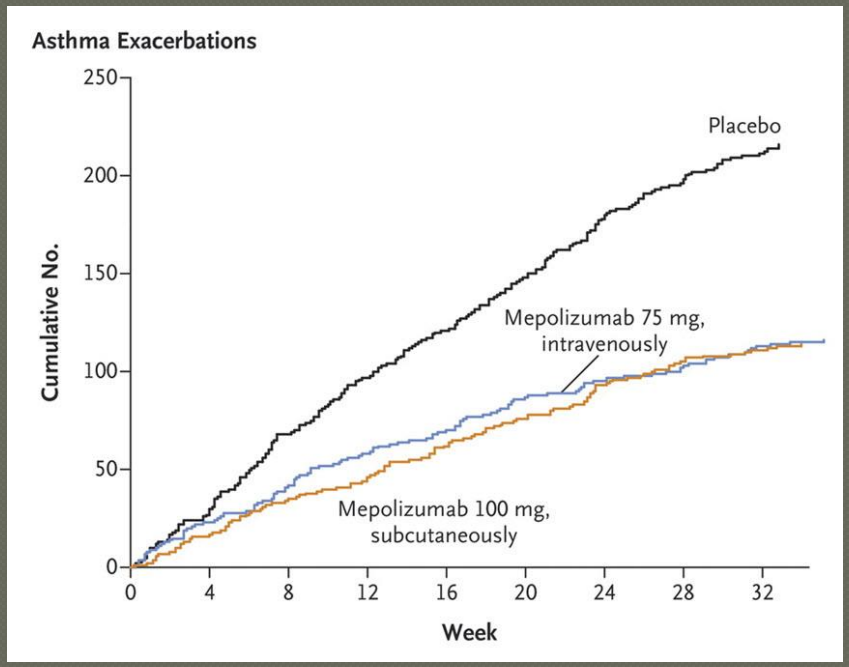
Interleukin 5

- Pro-inflammatory cytokine
- Also known as eosinophil differentiation factor (EDF)
- Regulates eosinophil growth, maturation & activation
- Plays an important role in diseases associated with increased levels of eosinophils (asthma, allergic rhinitis)
- Secreted by Mast Cells/ T h2 Cells



Mepolizumab (Anti IL-5)

- Directed at immuno-inflammatory response
- Anti IL-5
- Decreases eosinophil recruitment
- May reduce exacerbations and decrease steroid use in severe asthma
- SIRIUS, MENSA and DREAM trials all show positive results
- FDA approval is pending



NEJM 2014.

Interleukin 13

- Promotes:
  - IgE production by B Cells
  - Generation of eosinophil chemoattractants
  - Contractility of airway smooth muscle cells

Anti IL-13

- Anti IL-13 vs placebo
- 3 trials, ~200 patients each
- Increased FEV1 at 12 weeks, no difference at 24 weeks
- Additional trials have not been successful at improving outcomes with Anti IL-13
- More work is needed

Final Thoughts

- Exciting scientific discoveries have occurred recently in the field of allergic diseases including asthma.
- It is necessary that general practitioners keep abreast of this knowledge to familiarize oneself with newer modalities of therapy that will be rapidly introduced within the near future.

Summary

- Asthma is a chronic lung disease marked by variable symptoms, obstruction & bronchial hyperresponsiveness with inflammation.
- It is classified based on severity & therapy is tailored to degree of symptoms
- Mainstays of therapy include inhaled glucocorticoids & beta agonists, however there are many alternative treatments available, and many exciting new treatment options to look forward to in the near future.

Questions? Thank you!