

Treatment Options for Complicated/Severe Asthma

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Asthma Epidemiology

- World Health Organization, Asthma is one of the most common non-communicable diseases worldwide
- The Global Asthma Network in 2014 estimated that worldwide 334 million individuals were affected by asthma
- Annually 250,000 premature deaths
- 38%-54% of patients with asthma have uncontrolled asthma
- The majority of individuals in the world that have asthma are not diagnosed, and the majority being treated for asthma are not receiving the right treatment

Asthma

- The smooth muscle of the bronchioles constrict causing the airway to close, this is called “bronchial constriction”
- The smooth muscle will relax and this is called “bronchodilation”
- Asthma is a disease where the bronchioles open and close
- The more the bronchioles open and close will determine how active or severe the asthma is. Or how much inflammation is present
- The opening and closing of the bronchioles is ultimately inflammation
- Inflammation leads to collagen build up in the bronchioles, goblet cells enlarge, and bronchiole hyperreactivity (more constriction)
- 35% of asthmatics may develop COPD

Asthma

- Triggers for an asthma attack, flare up or exacerbation:
 - The number one trigger for asthma is a virus or cold
 - The second biggest trigger are allergies, if the individual has allergies
 - Approximately 60% of asthmatics have allergies
 - An asthmatic may be allergic to grass pollen causing itching and sneezing, but typically an allergic trigger for asthma needs to be more specific like a cat, or dog
 - The third biggest trigger can be exercise, GERD, odors, fumes, anxiety

Asthma

- There are various tools to assess the degree of asthma control
 - GINA Symptom Control Tool (Global Initiative for Asthma)
 - ACT (Asthma Control Test)
 - ACQ (Asthma Control Questionnaire)
 - ATAQ (Asthma Therapy Assessment Questionnaire)
- Low FEV1/Forced Vital Capacity Ratio, Low FEV1% predicted, Low FEF25-75
- Elevated Nitrous Oxide
- Intermittent asthma: the individual rarely requires albuterol and has normal spirometry and nitrous oxide readings
- Persistent asthma: the individual is suffering with inflammation in the bronchioles and potentially scarring the lungs also called “remodeling” --- leading to COPD

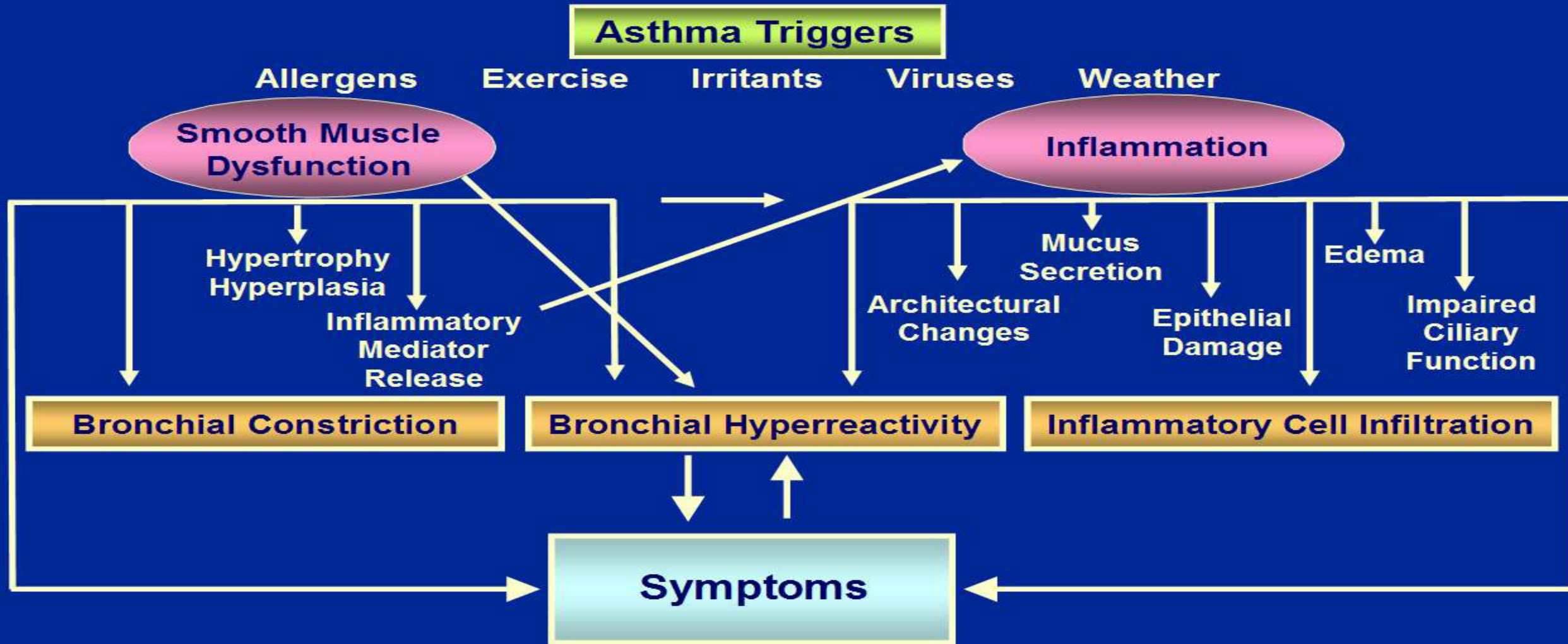
Asthma

- In persistent asthma the most important medication is the inhaled corticosteroid (ICS)
- Determining if the individual has persistent asthma is key:
 - A small infant can have persistent asthma
 - If a child or adult requires 4 albuterol treatments per day for 3-4 days in a row to treat an asthma exacerbation, twice in 12 months
 - If the child or adult requires 5 doses of oral steroids in a year
 - If the child or adult requires 4 doses of albuterol in a week outside of sports
- Treat this individual, no matter what age, with a daily inhaled corticosteroid to reduce frequent exacerbations and avoid developing COPD

Asthma

- The following slides show how asthma is an inflammatory disease
- The more inflammation involving the bronchioles the more permanent damage will occur, the more exacerbations will occur
- Inflammation leads to collagen depositing in the bronchioles reducing airflow and lung function
- Inflammation in the bronchioles leads to remodeling and Chronic Obstructive Pulmonary Disease (COPD), Emphysema and Chronic Bronchitis

Mechanisms of Asthma Leading to Symptoms



Asthma: Pathophysiologic Features and Changes in Airway Morphology

Airway lumen narrowing

Mucous gland hypertrophy and hyperplasia

Edema

Mucus hypersecretion

Thickening of basement membrane

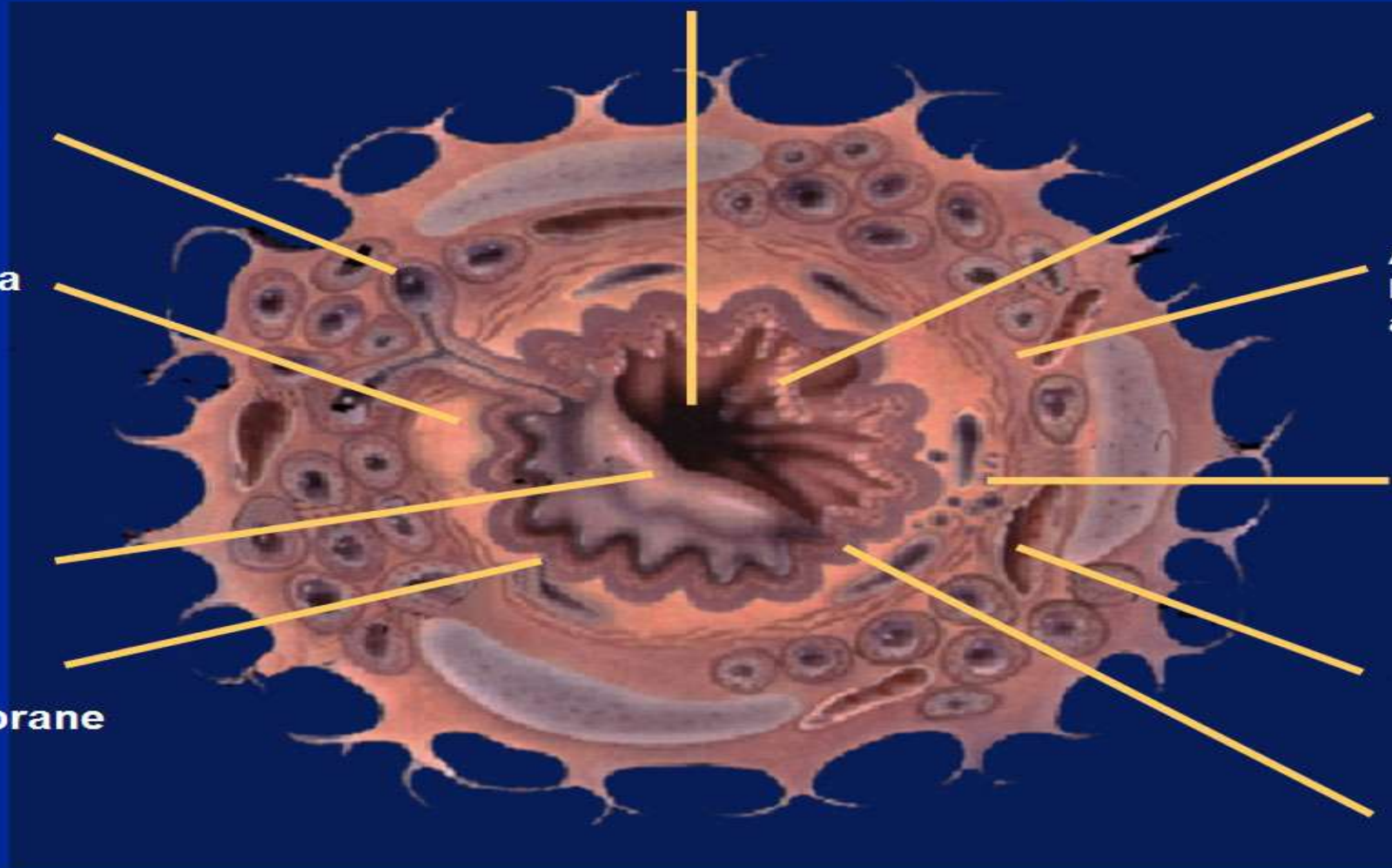
Epithelial damage

Airway smooth-muscle hypertrophy, hyperplasia, and bronchoconstriction

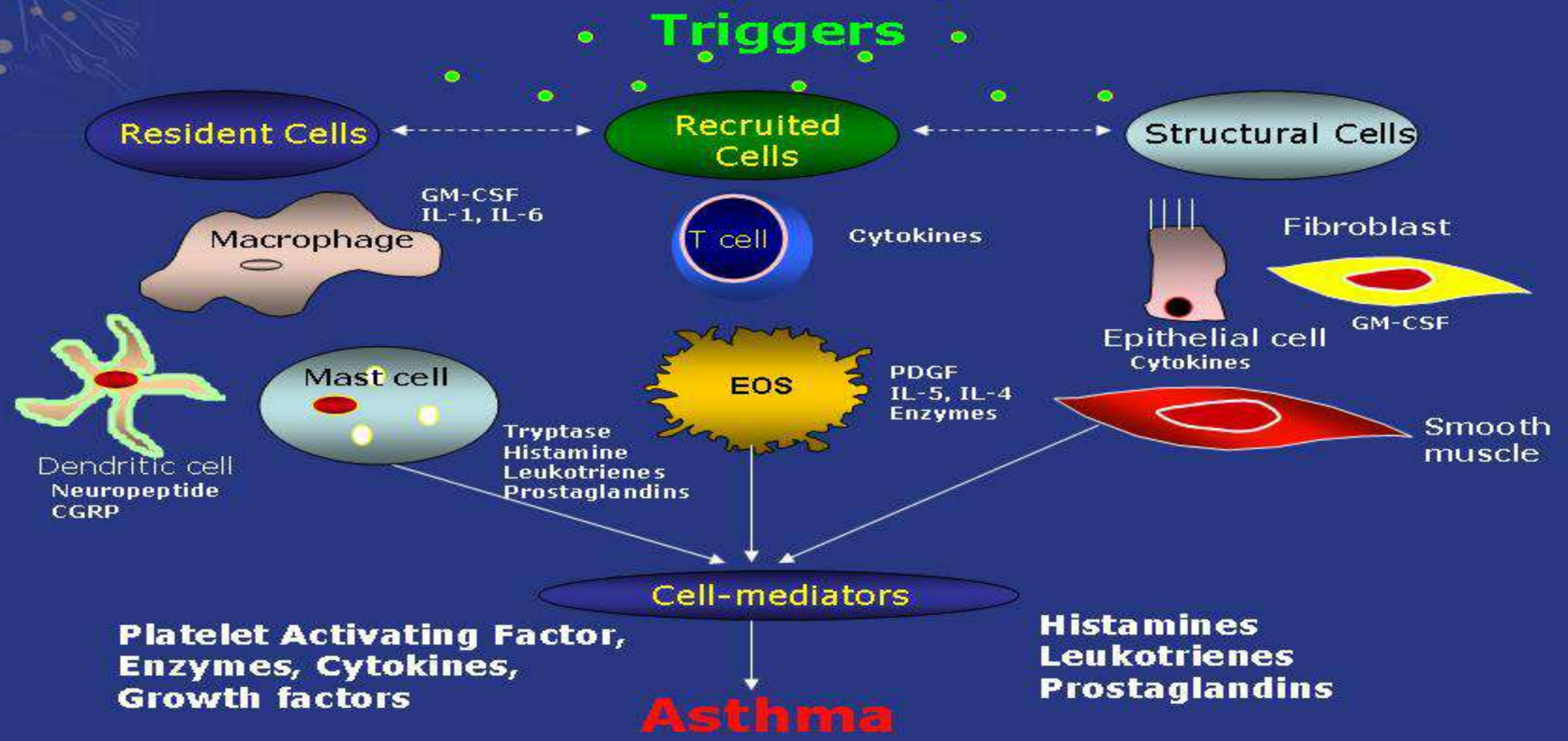
Inflammatory cell infiltration

Vascular dilation

Goblet cell hyperplasia



Cells and Cell Mediators Involved in the Asthmatic Inflammatory Response



Asthma Control Test™ (ACT)

1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?

SCORE

All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5
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2. During the past **4 weeks**, how often have you had shortness of breath?

More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5
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3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5
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4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5
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5. How would you rate your **asthma** control during the **past 4 weeks**?

Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5
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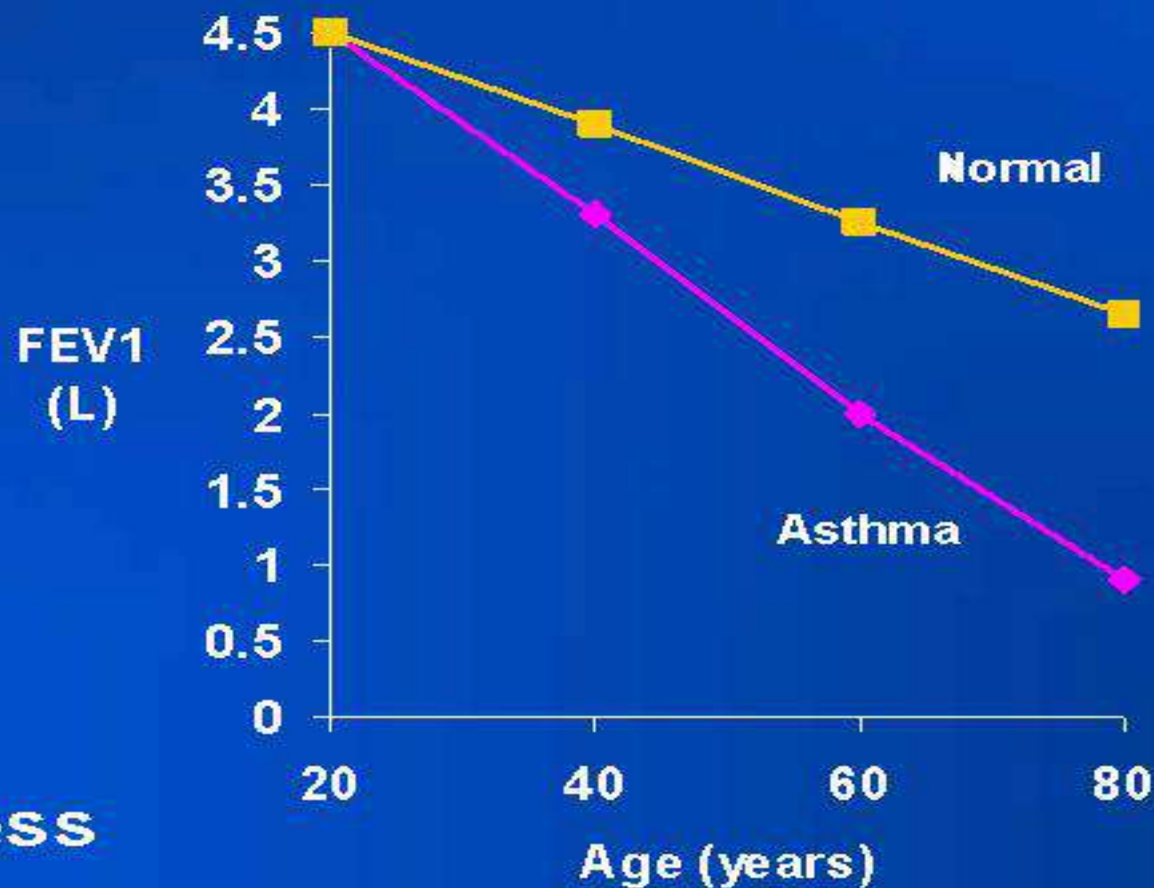
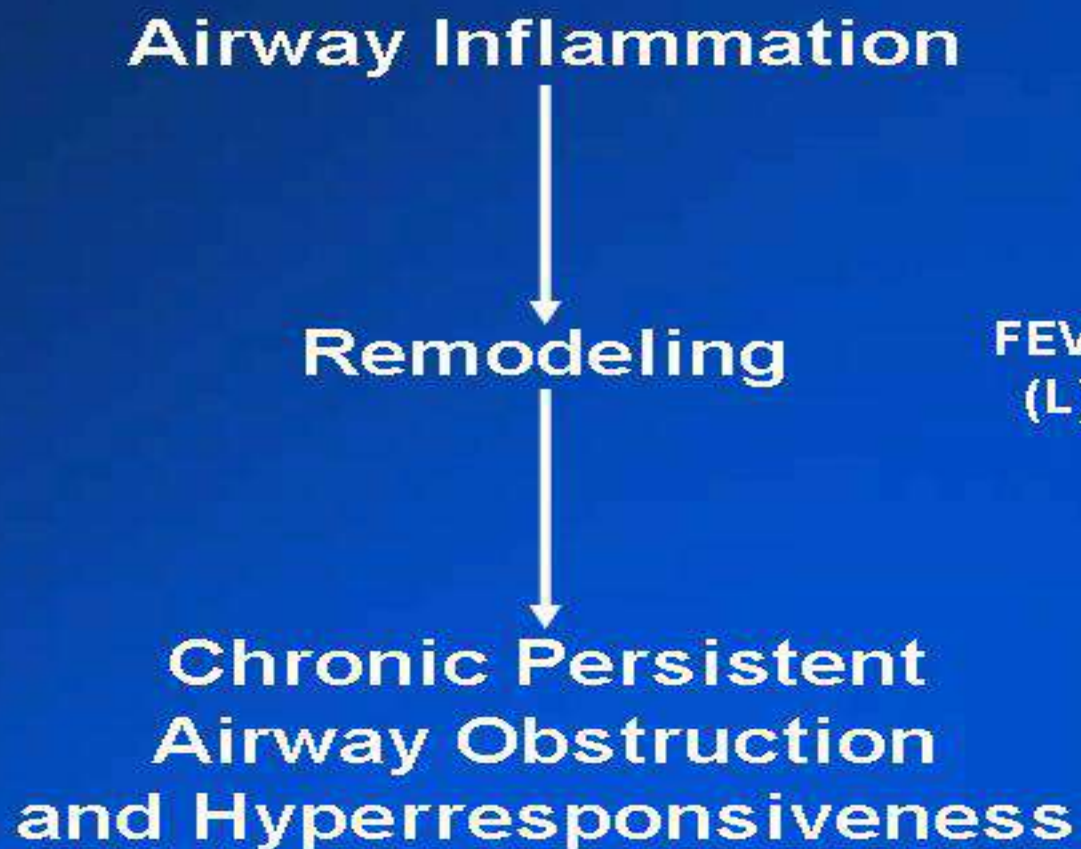
A score of ≤ 19 means your patient's asthma may not be under control.

TOTAL

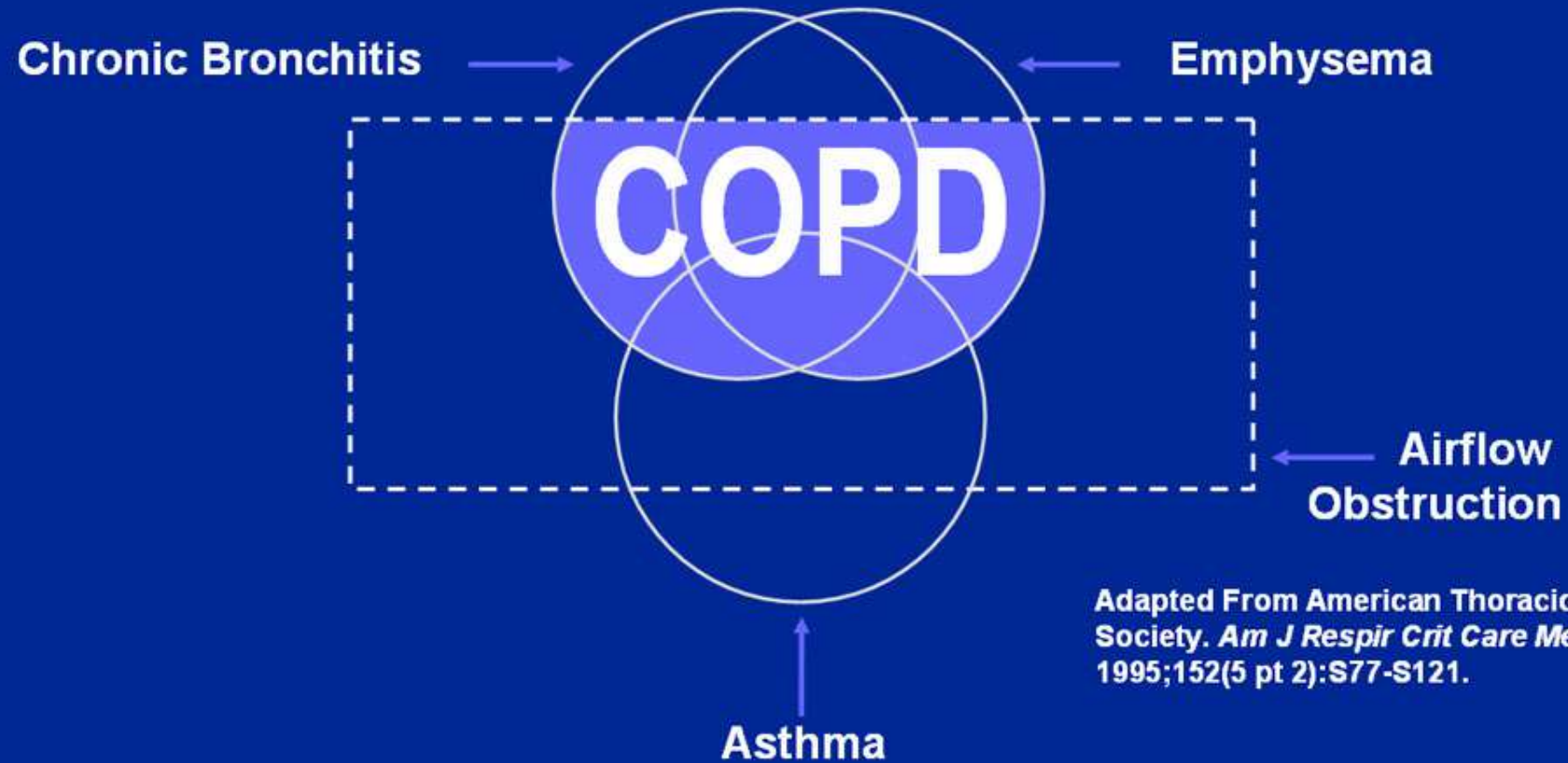
ACT is for patients with asthma 12 years and older.

Asthma Control Test is a trademark of QualityMetric Incorporated.
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Asthma and Airway Remodeling



Spectrum of COPD

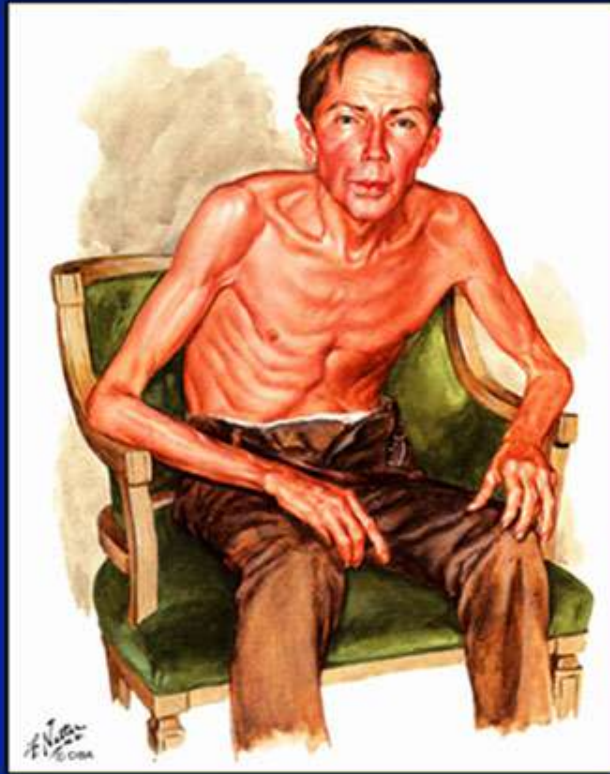


Adapted From American Thoracic Society. *Am J Respir Crit Care Med.* 1995;152(5 pt 2):S77-S121.

Approximately 80% of patients with COPD have associated chronic bronchitis¹

1. American Lung Association Web site. Available at: <http://www.lungusa.org>. Accessed March 1, 2005.

Classic Representations of Patients with COPD

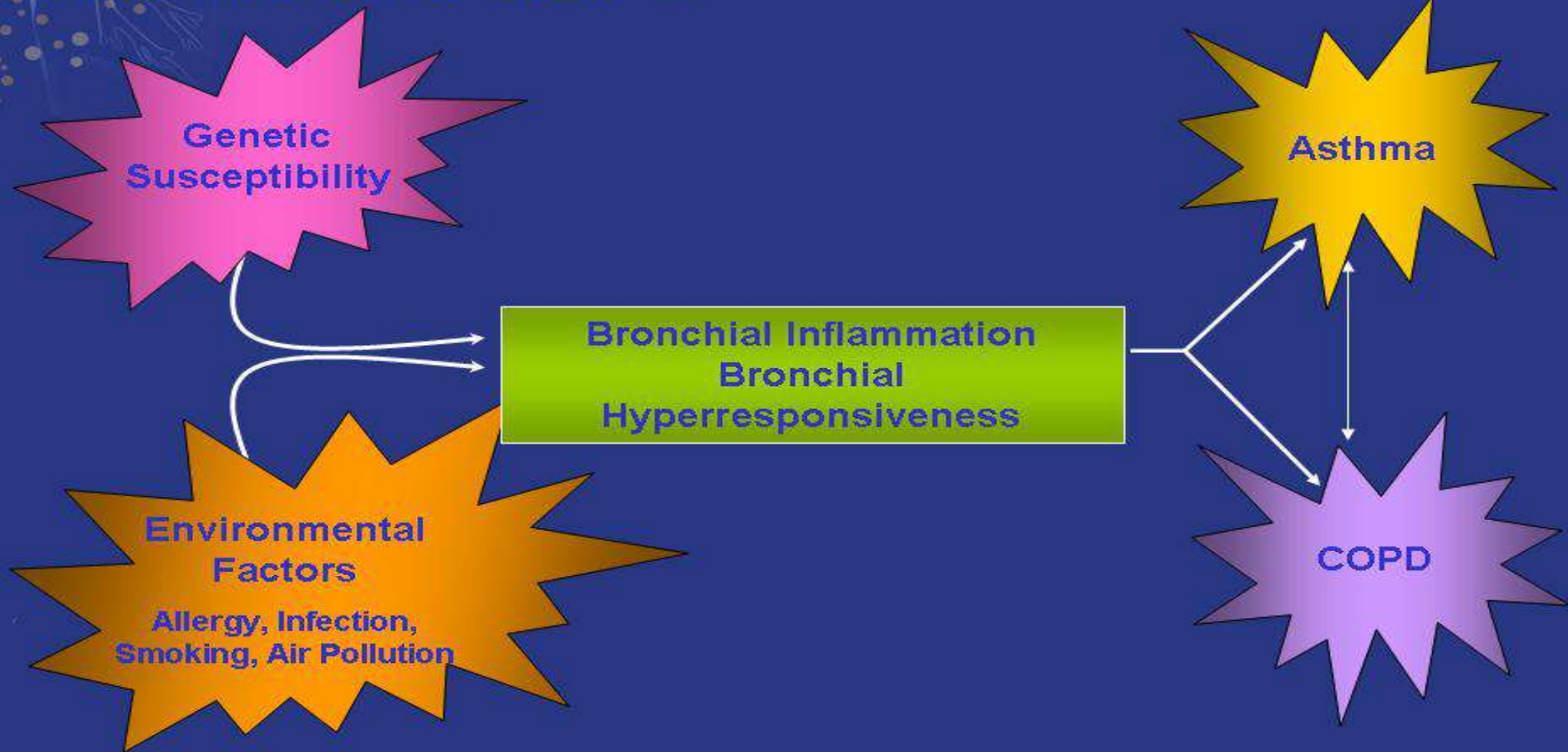


Emphysema

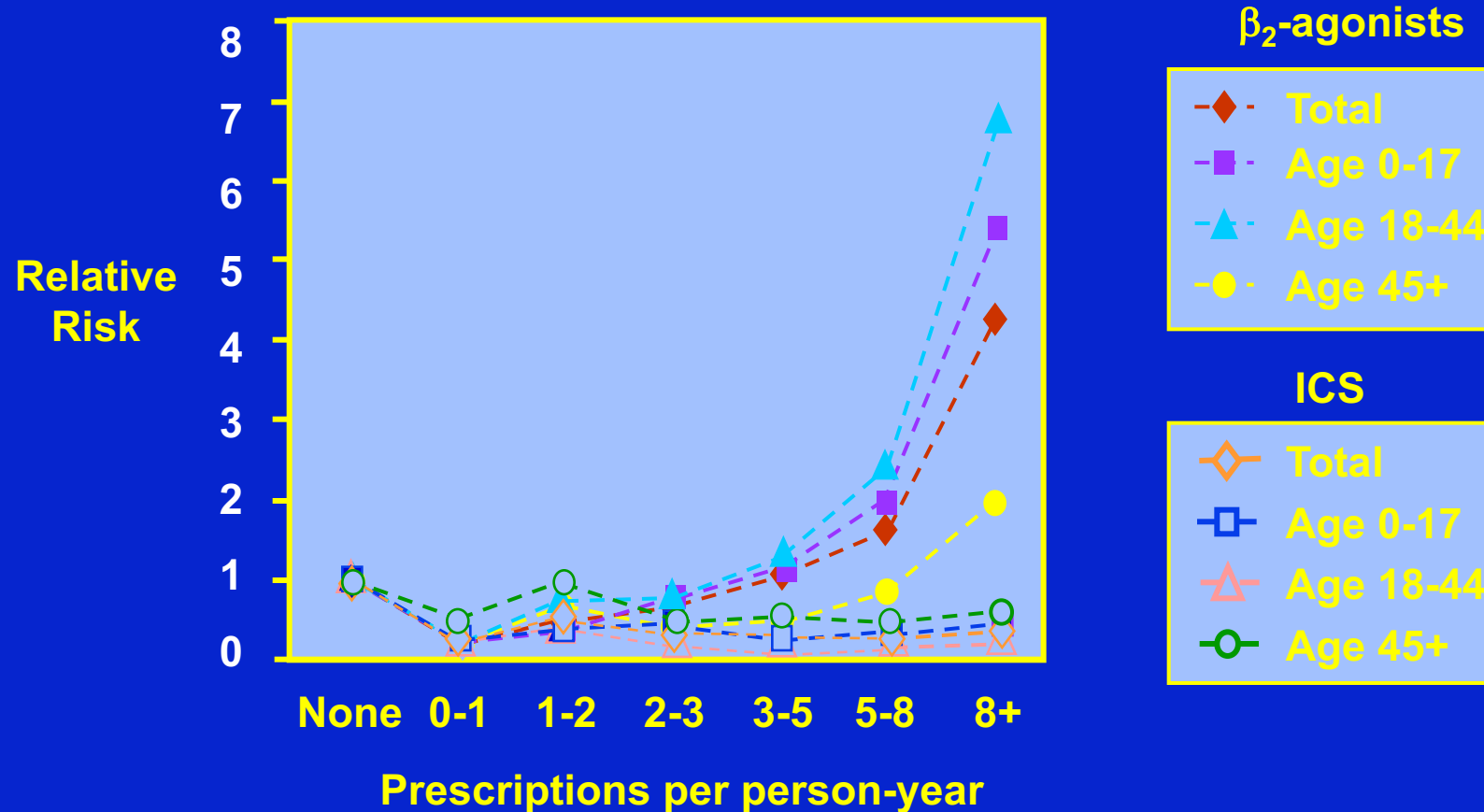


Chronic Bronchitis

Potential Interactions Between Asthma and COPD



Relative Risk of Hospitalization in the United States



Asthma: Treatment Options

- Inhaled Corticosteroids (ICS), sometimes doubling or tripling the dose
- Inhaled ICS/LABA combinations (long acting beta agonists)
- Inhaled LABA/LAMA combinations (long acting Muscarinic antagonists)
- Inhaled ICS/LABA/LAMA combinations
- Leukotriene Receptor Antagonists (overused and of questionable benefit)
- Oral Steroids
- Bronchial Thermoplasty
- Biologics

Severe Persistent Asthma

- Most asthma individuals can achieve good control with the various medications commercially available
- When the individual is not well controlled requiring the higher doses of inhaled medications, and requiring multiple inhaled medications
- When the individual requires frequent doses of oral steroids in a year, such as twenty days in a 12 month period
- Frequent emergency visits, hospitalizations, missing work or school
- Decreased quality of life due to frequent attacks and poor lung function
- These individuals are considered to be suffering severe persistent asthma

Severe Persistent Asthma

- Many factors can cause poor control of lung function
- Treat GERD with proton pump inhibitors, sometimes a prokinetic such as Metoclopramide or Domperidone may be needed
- Environmental issues such as allergies, smoking, obesity, home and occupation air quality
- Chronic sinusitis can cause poor response to therapy
- Immune deficiency
- Rule out autoimmune diseases, sarcoidosis, interstitial lung disease, infectious disease like tuberculosis, alpha one antitrypsin, etc.

GERD Gastro esophageal reflux disease

- As we eat food the lower esophageal sphincter (LES) opens allowing everything to enter the stomach
- As the acid mixes with the food the LES may become irritated, this is called erosion of the LES
- Erosion of the LES allows air, food, water to come up into the esophagus. Most often silently, so it is not felt or causing pain
- The vagal nerve innervates the LES and the nerve sends signals to plug the ears and the nose, cause sneezing, tightening of the throat, hoarse voice, chest tightness, bronchial spasm, even drop the heart rate causing passing out

Severe Persistent Asthma

- Differentiate patients into one category:
 - TH2 phenotype (T Helper cell type 2)
 - Low TH2 phenotype
- TH2 phenotype are generally responsive to inhaled corticosteroids, may have elevated eosinophils, may be candidates for biologics
- TH2 low individuals
 - Generally will not respond to Inhaled Corticosteroids
 - May respond to antimuscarinics and long acting beta agonists
 - Environmental measures, social issues, obesity, GERD, Chronic Sinusitis
 - Bronchial Thermoplasty
 - It is important to evaluate immune status

Evaluation of Severe Persistent Asthma

- Spirometry
- Nitrous Oxide
 - When elevated use ICS, possibly biologics
 - If not elevated ICS may not be beneficial, but a trial is warranted
- Immunoglobulin G,A,M,E
 - Elevated IgE and atopy consider Omalizumab
 - Low IgG investigate for immune deficiency
- CBC/Differential
 - Eosinophils 150 cells/ul or greater consider use of biologics

Immune Deficiency

- CVID: Common Variable Immune Deficiency
 - Bronchiectasis: not responsive to asthma medication
 - Chronic Sinusitis
 - Irritable Bowel with severe diarrhea
 - Anemia, low platelets
- Diagnosis: CBC/Diff, Immunoglobulins G,A,M,E, pneumococcal titers
- Low IgG, low IgA or IgM, low streptococcus pneumoniae titers. If low then vaccinate with Pneumovax #23 and repeat measurement of titers in 4 weeks

Eosinophils

- Eosinophilic phenotype occurs in atopic and non-atopic individuals
- Eosinophilic Inflammation affects 40-60% of patients with severe asthma
- Eosinophils release various products that can damage the airway
 - Cytokines
 - Lipid mediators
 - Proteins
 - Oxidative activities
- Eosinophils cause airway hyper-responsiveness, excess mucous secretion and collagen deposition

Biologics

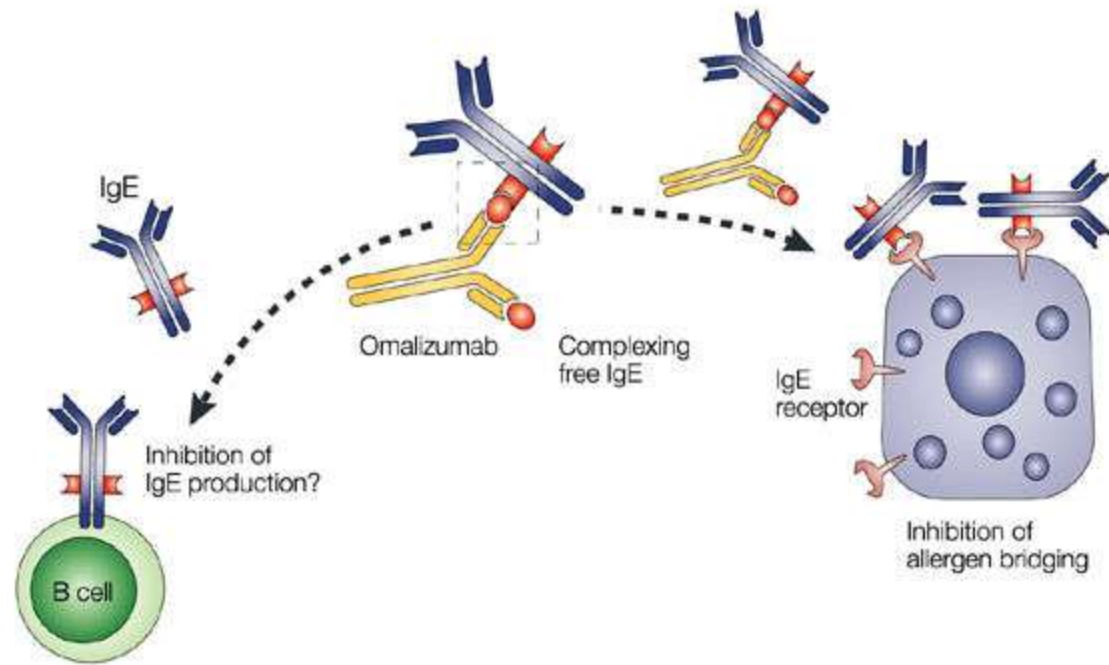
- The following slides introduce the biologics and show the complicated pathways that are involved in asthma and other inflammatory disorders
- The control of inflammation is the key to managing asthma. Inflammation is the problem, whether it is in the joints leading to arthritis, or in the lungs leading to chronic scarring of the bronchioles
- Biologics are used to stop the disease process early on, this minimizes all damage
- Biologics appear to be much more effective in controlling the disease as compared to pharmacologics, like inhalers

Biologics For Asthma and Allergic Disease

- Reslizumab: (Cinqair) Anti-interleukin-5: Severe Asthma
- Mepolizumab: (Nucala) Anti-interleukin-5: Severe Asthma
- Benralizumab: (launch date in 2017) Anti-interleukin-5, Apoptosis of eosinophil: Severe Asthma
- Dupilumab: (Dupixent) Anti-interleukin-4 and interleukin-13: Atopic Dermatitis, studies show some asthma affect
- Omalizumab: (Xolair) In use since 2003, Anti-IgE: Moderate-Severe Allergic Asthma, Chronic Idiopathic Urticaria since 2016

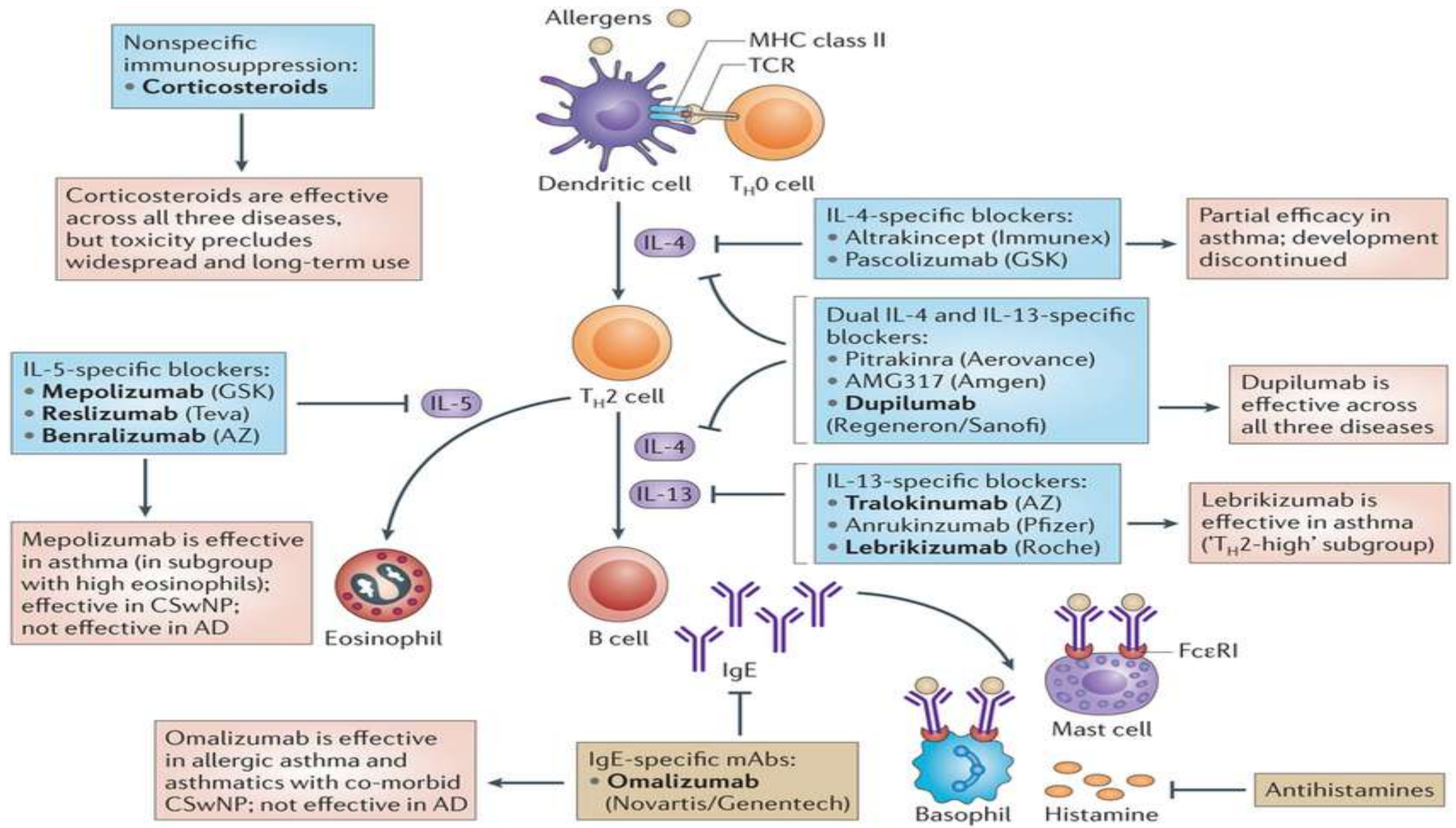
Biologics For Severe Persistent Asthma

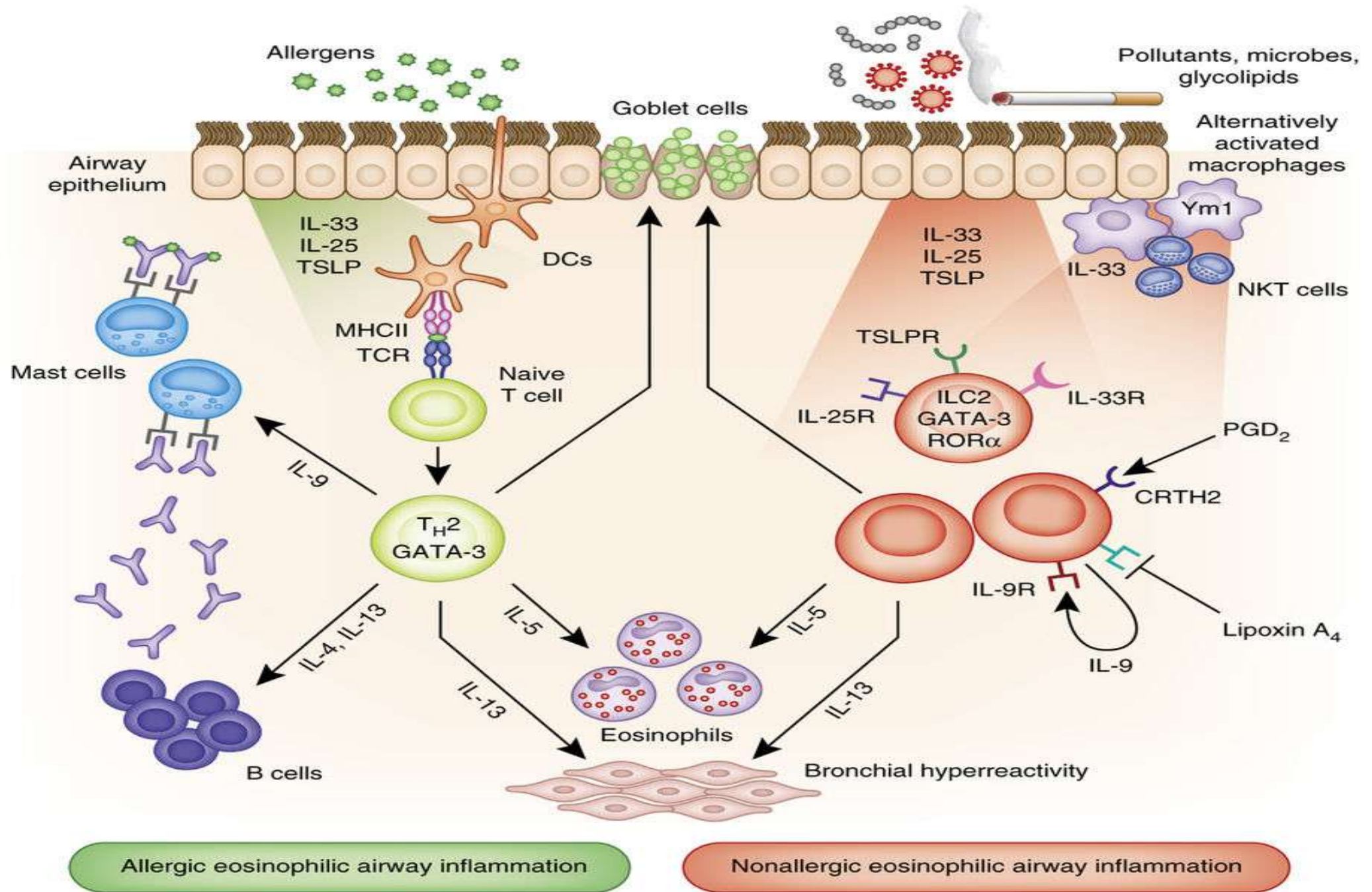
- Omalizumab (Xolair):
- Severe Allergic IgE mediated asthma: IgG1 fraction
 - Anti-IgE monoclonal antibody, approved for use in allergic asthma and Chronic Idiopathic Urticaria
 - IgE levels between 30 and 1,300 IU/ml and show allergy by skin test or blood test, 6 years of age and older
 - Prevents IgE from binding to the high-affinity IgE receptor
 - Blocking free IgE will disrupt the allergic signaling cascade and inflammation
 - May have efficacy in non-atopic individuals by down regulating the high-affinity IgE receptor on basophils and dendritic cells
 - Chronic Idiopathic Urticaria, no atopy required, no IgE level required

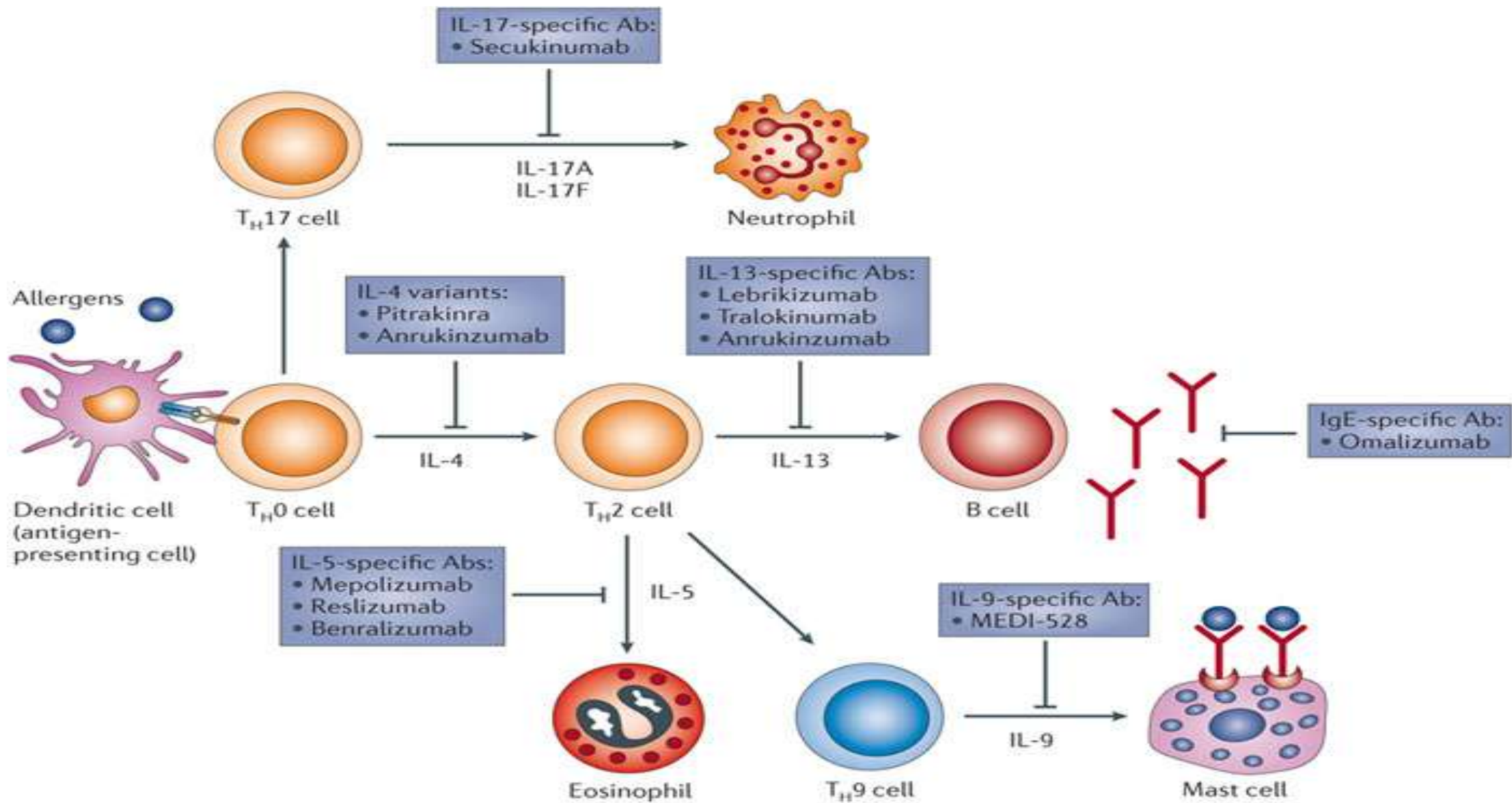


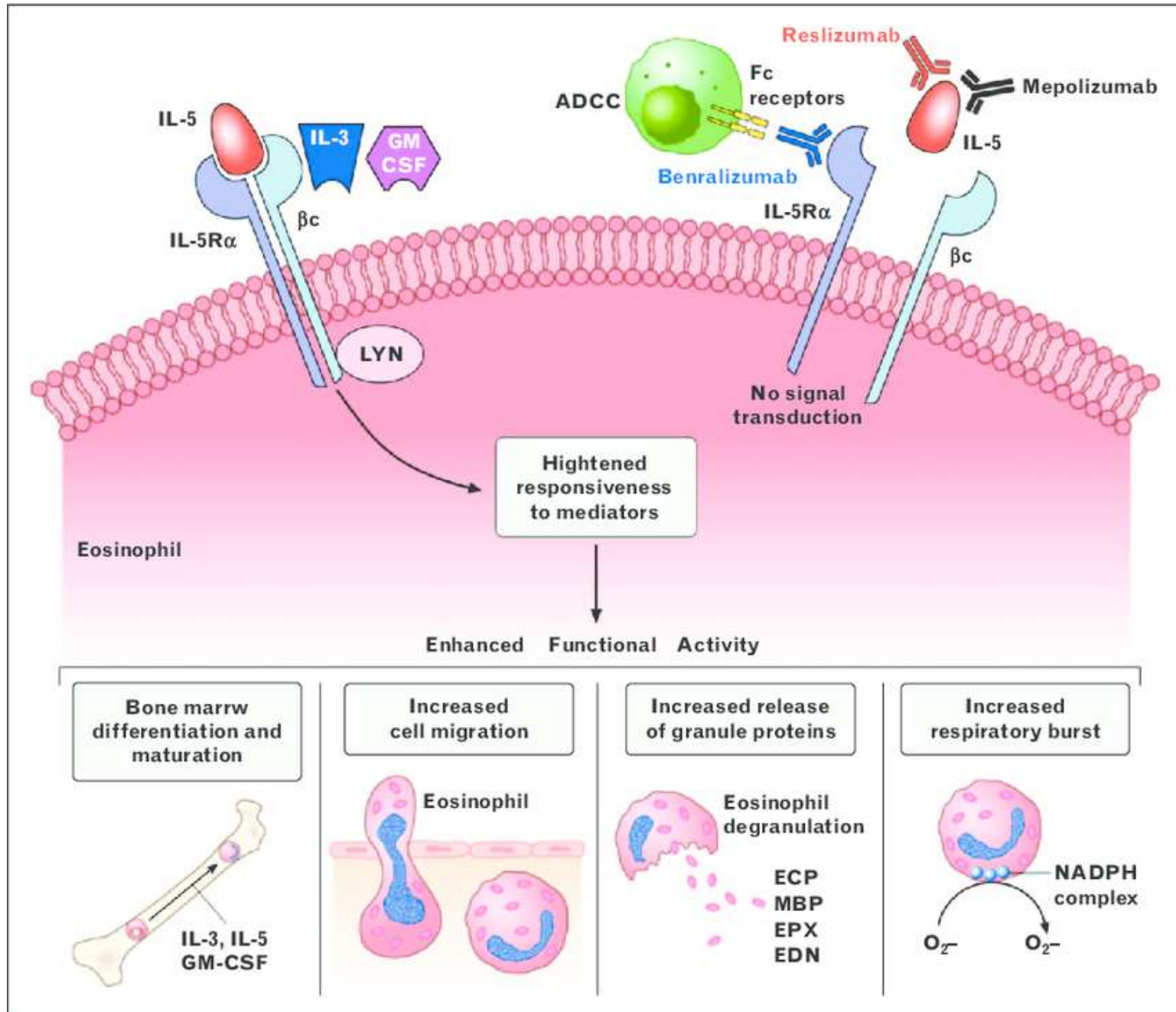
Biologics For Severe Persistent Asthma

- Mepolizumab (Nucala):
- Severe Persistent Asthma:IgG1 fraction
 - Eosinophils 150 or higher: Anti IL-5 monoclonal antibody
 - Reduces the frequency of asthma exacerbations
 - Improves lung function
 - Increases control of asthma in patients with severe eosinophilic asthma
 - Decreases eosinophils chemotaxis, maturation, survival
 - Subcutaneous 100 mg injection monthly
 - Was studied in intravenous form as well, but approved for subcutaneous









Biologics For Severe Persistent Asthma

- Reslizumab:(Cinqair)
- Severe Persistent Asthma:IgG4 fraction
 - Eosinophils 400 or higher: Anti IL-5 monoclonal antibody
 - Reduced frequency of asthma exacerbations
 - Improved lung function
 - Increased asthma control
 - Positive affect on quality of life
 - Decreases eosinophils chemotaxis, maturation, survival
 - Weight based, 10 mg/kg monthly, IV 20 minute infusion

Biologics for Severe Persistent Asthma

- Benralizumab:
- Severe Persistent Asthma: IgG1 fraction
 - FDA approval pending
 - Eosinophils 200 or higher: Anti IL-5 alpha receptor
 - Induces apoptosis in cells expressing the IL-5 receptor
 - Reduces asthma exacerbations
 - Glucocorticoid-sparing effect
 - Decreases Eosinophils chemotaxis, maturation, survival, in addition apoptosis
 - Subcutaneous 100 mg injection every 2 months

Asthma

- Determine if the asthma is intermittent or persistent
- Persistent asthma will lead to permanent lung damage
- Treat intermittent with albuterol as needed
- Treat persistent asthma with an inhaled steroid
- Determine lung function with spirometry and nitrous oxide and reevaluate every month to 3 months to 6 months until stable
- Address triggers when possible
- All asthmatics should have prednisone at home as part of their asthma action plan

Severe Persistent Asthma

- Measurement of lung function with spirometry and nitrous oxide
- Aggressive use of inhaled medications, including doubling or tripling the normal dose of the single inhaled corticosteroid. Inhaled steroids are always safer than oral steroids.
- Measurement of eosinophils and an immune work up to determine if a biologic may be of benefit or if immunodeficiency maybe the problem
- Address coexisting factors such as GERD (gastro esophageal reflux disease), allergies, lifestyle, compliance and proper use of medications

Asthma Action Plan

- If you have coughing, wheezing, chest tightness– use albuterol
- You may use albuterol inhaler or nebulizer again within 20 minutes
- May repeat albuterol again in 20 minutes
- If albuterol is needed 4 times in a 24 hour period then start oral prednisone
- Once you receive prednisone you may use albuterol every half hour to every hour, keep spreading out albuterol as needed
- You may need prednisone twice a day for 3 to 6 days
- Contact your medical provider to alert them of your asthma exacerbation