Allergic Asthma Treatment 2021
…It's a "mab, mab" world

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Overview…

- The world of immunology has entered a new and incredibly exciting era in the 21st century…and one of the biggest reasons?
- The approval of numerous targeted biologic therapies for the prevention and treatment of many conditions/diseases including specific types of severe asthma
- Two “old” standard treatments for severe asthma? Target the acute and chronic symptoms of bronchoconstriction with short- and long-acting bronchodilators and targeting the acute and chronic inflammatory response with inhaled and oral corticosteroids—
- NOTE: We’re still using the “old, standard treatments mentioned above BUT…

ADD-ON drugs as GAME CHANGERS!!

- The new monoclonal antibody treatments target the underlying pathophysiology that triggers the bronchoconstriction and inflammatory response

But first…let's define asthma…things have changed considerably since my nursing school days

- "Back-in-the-day" asthma was divided into 2 types
- Extrinsic asthma (kids and allergens—cat dander and crustaceans, dog dander and dust mites, roach dander and ragweed, peanuts and pollen); we discussed avoiding allergens and we prescribed puffers and steroids…
- Intrinsic asthma (adult-onset and we were clueless (aka idiopathic) as to the triggers)—bronchodilators and high-dose oral steroids anchored the treatment
- FAST FORWARD…

So what is the 2021 definition of severe asthma?

- Definition: based on Rx that requires high dose, inhaled glucocorticoids with a second controller (Long-acting inhaled beta agonist)—(examples: budesonide + formeterol (Symbicort); fluticasone + salmeterol (Advair); fluticasone + vilanterol (Breo Ellipta); and/or may also…
- Severe asthmatics may also require a leukotriene modifier (Montelukast/Singulair; zafirlukast/Accolate; zileuton/Zyflo; or theophylline (who remembers that old, tired, but effective drug?)
- and finally, the definition includes taking systemic oral glucocorticoids for greater than 50% of the year to prevent “uncontrolled” asthma
- And, now? There are more than 2 “types” of asthma based on disease characteristics—there are 4 asthma phenotypes in today’s world

Phenotypes (disease characteristics of asthmatics)…may overlap in some instances

1) **Childhood-onset allergic asthma beginning before the age of 12 vs. later onset after age 12; strong allergic history; family history** (this is the type we're talking about today, but for the sake of being thorough…)**
2) Adult-onset atopic asthma—very mixed group of patients; 34% with severe asthma are less likely to be atopic (allergen-induced); 52% with mild-to-moderate persistent asthma w/ allergies

Phenotypes (continued)…

3) Adult-onset NON-atopic asthma (over age 12)—asthma onset after a viral illness, occupational exposure, ingestion of aspirin

4) Hyper-eosinophilic adult-onset asthma and ASA exacerbated respiratory disease (AERD)—require systemic GC (glucocorticoids) early in disease; high levels of blood and tissue eosinophils; severe sinus disease; nasal polyps and in a minority of patients, aspirin and other COX-1 inhibitors (NSAIDs) exacerbate respiratory disease; 30-50% are atopic (allergic)

A quick review of the innate inflammatory response and the acquired immune response

- As related to childhood-onset allergic asthma…
- Starting with the white blood cells that are involved with **inflammation**
- Collectively these WBCs are known as granulocytes because they have “granules” in their cytoplasm –
- When triggered by a specific pathogens or allergens, these granulocytes ”degranulate” – releasing vasoactive and bronchospastic agents in the airways

The WBCs of the innate inflammatory response—

- Neutrophils (and again, for the sake of being thorough, I added these—but these are NOT part of the asthma inflammatory response in kids)—however, the NEXT 2 are:
- Eosinophils
- Basophils
- “phil” means “an affinity for”
- The Wright’s stain differentiates these cells under the microscope – the granules stain with either the basic dye (blue) or basophil, or the acid /eosin dye (red) or eosinophil, or they don’t take up any stain at all and are “neutral” or neutrophil

Here, take a look…basophils and eosinophils (and the neutrophil)

- Neutrophil—cytoplasm with granules is clear…(top left)
- Basophils—granules that stain dark blue … (top right)
- Eosinophils—granules that stain red…looks like the cell has the measles)… (lower right)

The eosinophil

- The recruitment of eosinophils into the lungs plays an REALLY important role in the pathophysiology of allergic diseases such asthma
- Once recruited into the lungs, eosinophils are instrumental in modulating the characteristic immune and inflammatory responses and inducing airway bronchoconstriction

- Possa SS, Leick EA, Prado CM, Martins MA, Tibério IF. Eosinophilic inflammation in allergic asthma. *Front Pharmacol*. 2013;4:46. Published 2013 Apr 17. doi:10.3389/fphar.2013.00046

The $64,000,000 question is?

- How do eosinophils congregate in the lungs in kids with severe asthma?
- Two major proteins produced by the immune system are instrumental in recruiting eosinophils to the lungs –
- **These two pro-inflammatory proteins are IL-5 and IL-13**…(IL is the abbreviation for “interleukin”)
- Stay tuned for more about these interleukins

FYI: Eosinophils are not just recruited in patients with asthma

- Eosinophils also play a major role in several other "eosinophilic" allergic diseases, including allergic rhinitis, nasal polyps, and idiopathic eosinophilic syndromes including eosinophilic esophagitis, and atopic dermatitis (eczema)
- All of the above have prominent inflammatory components characterized by pronounced eosinophilic infiltration and high levels of eosinophils in the blood (eosinophilia)

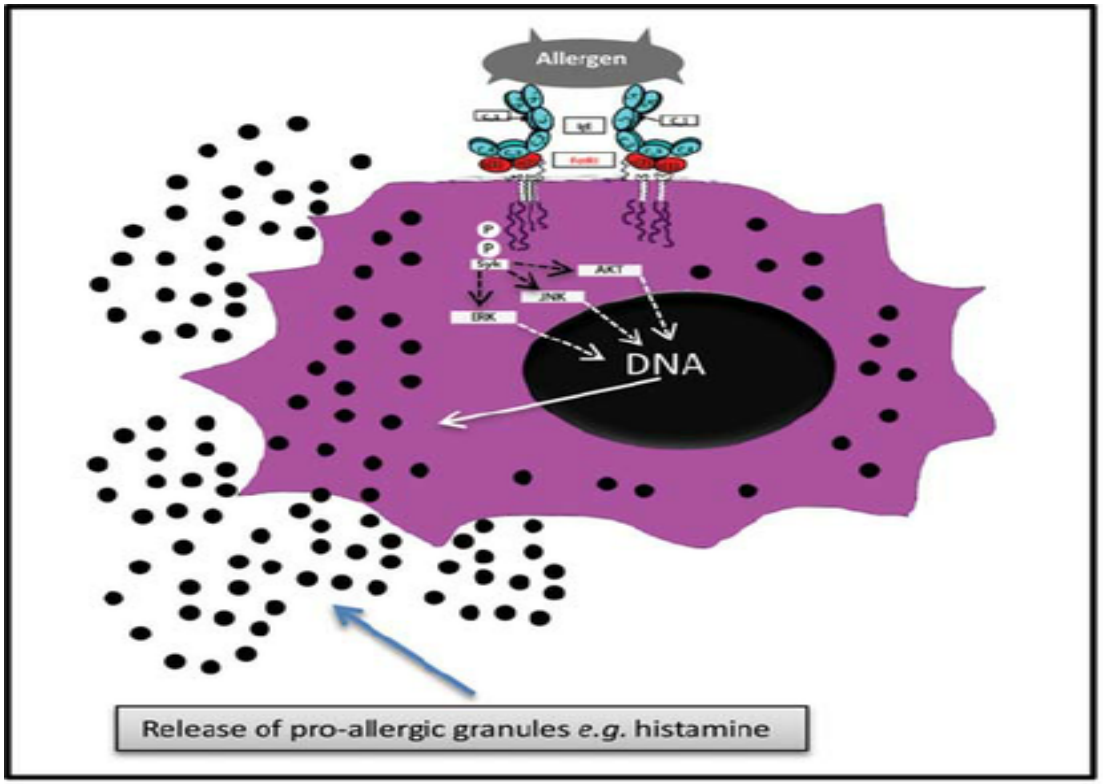
The basophil

- Also plays a critical role in allergic disease by infiltrating sites of allergic inflammation (nose, respiratory tract) and degranulating
- The degranulation process releases histamine and other “cytokines” (proteins) that trigger asthma
- Degranulation is preceded by the interaction of allergen with a specific antibody formed by the immune system – IgE (aka immunoglobulin epsilon)—
- Who calls IgE immunoglobulin epsilon? NOBODY!! (more in a moment)
- OK, so we have ONE more cell involved that comes from the bone-marrow but isn’t found in blood…it’s ONLY found in tissues

The mast cell

- Mast cells are packed with histamine and other vasoactive amines responsible for itchy, scratchy, drippy, sneezy, coughy and wheezy symptoms
- Mast cells are located in the dermis at the junction point of the host and external environment at places of entry of foreign antigens (mouth--gastrointestinal tract, eyes, skin, nose--respiratory tract). Mast cells are also located in connective tissue surrounding vasculature, smooth muscle, mucous, and hair follicles.
- Mast cells (like basophils) degranulate via the immunoglobulin, IgE

Mast cell and basophil degranulation



IgE antibody

Let's add the effector cells of the immune system to the response-- 2 major types of lymphocytes

- T lymphocytes – thymus-derived; love to circulate in the blood—there are lots of subsets of T lymphocyte but for today's lecture we'll focus on helper T cells (Th) (also known as T4 lymphocytes)
- But there's always more to it than that. There are two types of T4 lymphocytes that modulate the immune response – Th1 and Th2
- The Th1 lymphocyte pathway modulates the "normal" immune cell-mediated pathways for the response to foreign antigens
- The Th2 lymphocyte pathway is involved in the "abnormal" inflammatory cell-mediated immune pathways leading to the allergic asthma response in children—in other words, it's the predominant pathway in eosinophilic diseases (this is also the pathway taken in patients with autoimmune diseases)—(but that presentation is for another day)

Th2 inflammation

- Th2 inflammation is mediated by eosinophils, mast cells, and basophils
- The majority of patients with severe allergic eosinophilic asthma have evidence of high levels of T2 inflammation (referred to as T2-high)
- The newest treatments are specific T2-targeted therapies with considerable efficacy – and we'll get to these shortly!

When the Th1 and Th2 pathways are triggered…

- Cytokines are produced and released; **What are cytokines? Various types of proteins produced by cells of the immune system**
- One group of cytokines is the “Interleukin” group— “inter”= between and “leukins”—white blood cells (leukocytes); there are 36 of them…SERIOUSLY?? Abbreviated IL-1, IL-2, IL-3...get it? Aren’t you happy we won’t be talking about ALL of them? LOL (but if you want to stay an extra 3 hours, we can... (and, there are other ‘cytokines’ but that’s for another day...or never. ☺)

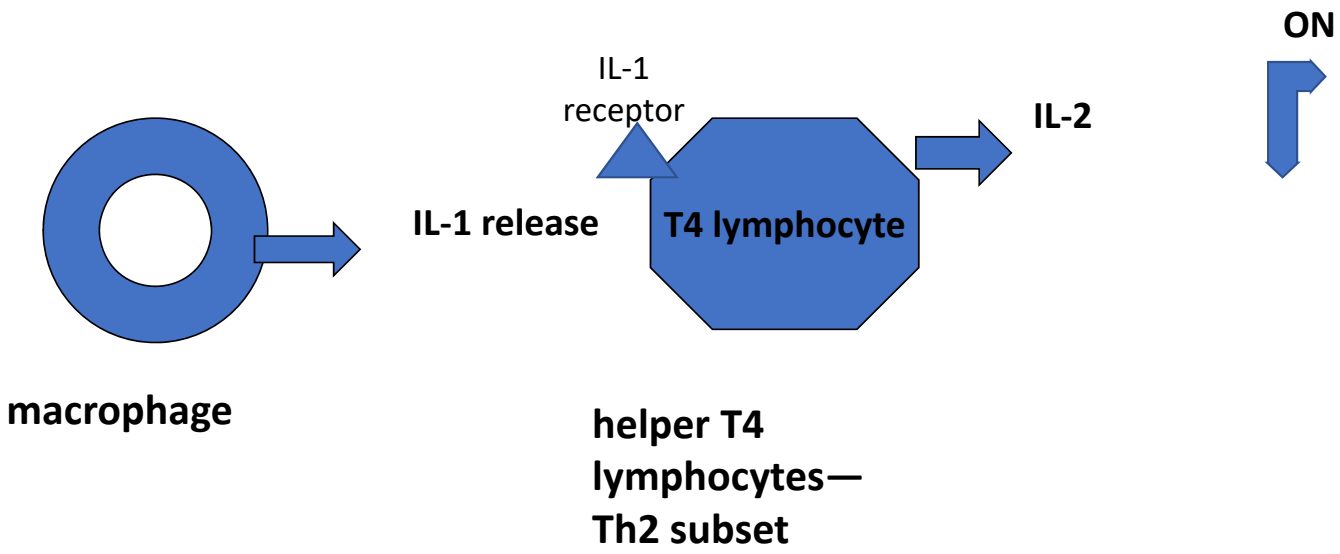
Interleukin of importance in severe asthma

- IL-1, IL-2 are interleukins that “turn on” the immune system…
- IL-4, IL-5, and IL-13 are normal interleukins but produced in much higher amounts if the Th2 pathway is activated. These are important **pro-inflammatory** interleukins involved in severe childhood **eosinophilic** asthma

Interleukins, continued.

- Each interleukin has a receptor it has to interact with;
- IL-1 is produced by the macrophage, and is the first interleukin in the cascade of immune activation; interacts with IL-1 receptors on the Helper T4 lymphocytes to activate the “resting” T lymphocyte

Take a look: IL-1 is the first IL and starts the immune response…macrophage to T4 lymphocyte



Why is IL-1 clinically important?

- Prednisone/Prednisolone are oral corticosteroids that inhibit IL-1 (interleukin-1) release—and suppresses the immune response
- Prednisone is a “general” inhibitor of immune activation and oral steroids are potent “general” immunosuppressants as well as anti-inflammatory drugs
- It also inhibits the migration, engulfment and degranulation by the eosinophils; hence, its **potent** anti-inflammatory properties
- Corticosteroids decrease eosinophil responses in severe asthma
- Oral steroids come with a lot of “baggage”—side effects, especially in kids

Corticosteroids (oral and topical) are used in inflammatory/immune conditions

- Oral forms—prednisone, prednisolone, methylprednisolone
- Inhaled – beclomethasone (QVAR), budesonide (Pulmicort flexhaler), fluticasone (Flovent*), etc.
- Inhaled steroid with a long-acting beta 2 agonist (bronchodilator)– budesonide + formeterol (Symbicort); fluticasone + salmeterol (Advair); fluticasone + vilanterol (Breo Ellipta)
- Liquid—oral budesonide viscous liquid (used for eosinophilic esophagitis)
- Nasal sprays for allergic rhinitis—OTC (Flonase*, Nasacort, Rhinocort); prescription (Beconase/beclomethasone Nasal; Nasonex/mometasone furoate); Vancenase/beclomethasone dipropionate, etc)
- ***NOT FLOMAX** ☺

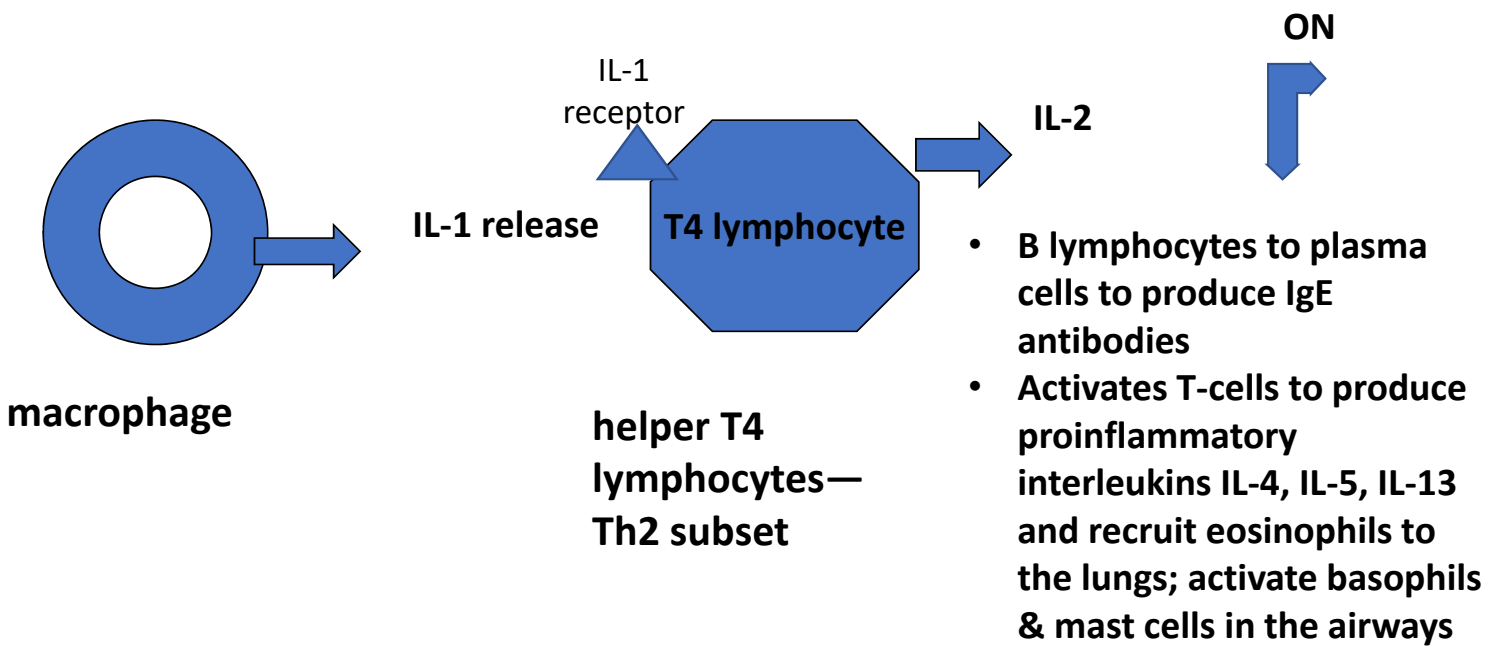
Interleukins

- IL-2 is the second interleukin and it triggers B-lymphocyte antibody production, more T lymphocyte activation, eosinophil recruitment, and eosinophil and basophil activation

WHAT OTHER INTERLEUKINS are involved for severe eosinophilic diseases?

- IL-4, receptor IL-4R
- IL-5, receptor IL-5R
- IL-13, receptor IL-13R

Let's get back to the picture…IL-2 as the "ON" button and the activation of Th2 lymphocytes



One more cell to discuss: the second major type of lymphocyte—B lymphocytes

- B lymphocytes are bone-marrow derived; tend to stay in lymph tissues (spleen, lymph nodes, Peyer's patches in GI tract, bone marrow)—when stimulated by a foreign substance they change their appearance and turn into a plasma cell…plasma cells produce antibodies—the first time you "meet" the antigen/allergen it takes 7-21 days to produce antibodies;
- Five types of antibodies are produced to bazillions of antigens/allergens—IgA, IgG, IgM, IgD, and IgE
- IgE is the antibody of ALLERGIES (Why doesn't everyone have allergies?)
- So again, for today's lecture, IgE is the "bad guy"
- Why? REMEMBER…IgE drills a hole in both mast cells and basophils and releases histamine

B lymphocytes and “man-made” monoclonal antibodies (MABs)

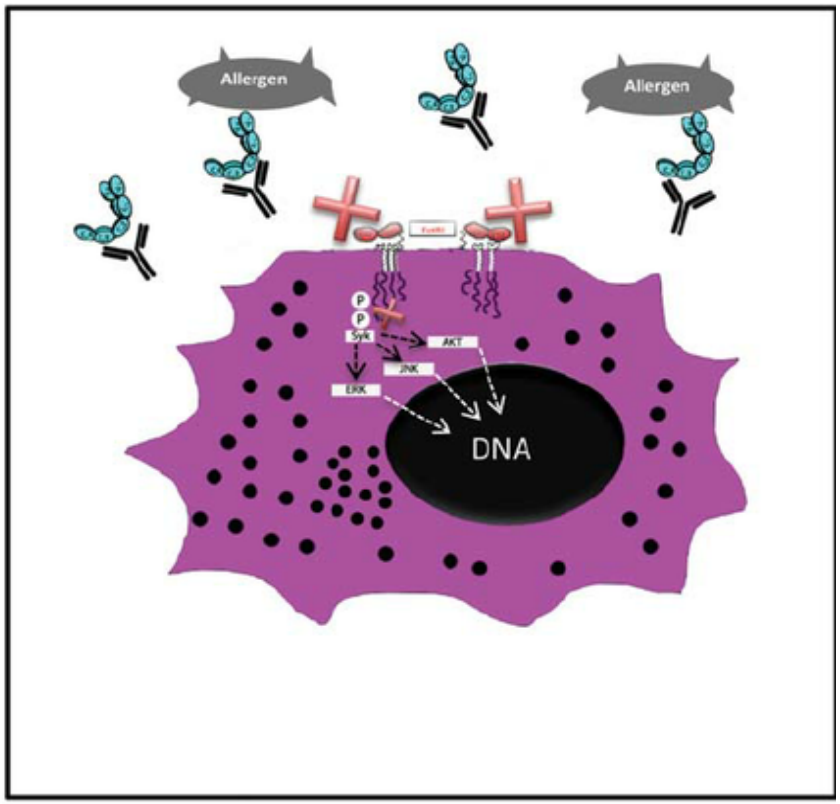
- We can manipulate the B lymphocyte in the laboratory—plasma cell differentiation in the lab to make “targeted” antibodies to ONE specific protein, ONE specific receptor
- These are called “monoclonal” antibodies and there are hundreds of them in use today
- Today? For severe allergic asthma? We have ***5*** monoclonal antibodies made in the laboratory

The “old” omalizumab/Xolair (15-years old); and the 4 “newbies” -- mepolizumab/Nucala; benralizumab/Fasenra/; reslizumab/Cinqair; and dupilumab/Dupixent

Digressionn on naming monoclonal antibodies…

- Of course, “mab” is their last name…but…
- The “zu” or “u” before the mab means that made from a human plasma cell, instead of partially humanized or another species plasma cell (mouse, murine)…
- you may have some children on the monoclonal antibody infliximab/Remicade for Crohn’s disease; the “xi” before the mab means that it’s produced from a combo/man/mouse plasma cell in the lab, begging to ask the question—are you a man, or are you a mouse?
- The “li” before the “zu” or “xi” means that it’s made specifically to target some aspect of the immune system, so we’re back to …
- omalizumab/Xolair (15 years old); and the “newbies” -- mepolizumab/Nucala; benralizumab/Fasenra/; reslizumab/Cinqair; and dupilumab/Dupixent

Omalizumab (XOLAIR) blocks IgE antibodies from attaching to receptors on basophils, & mast cells



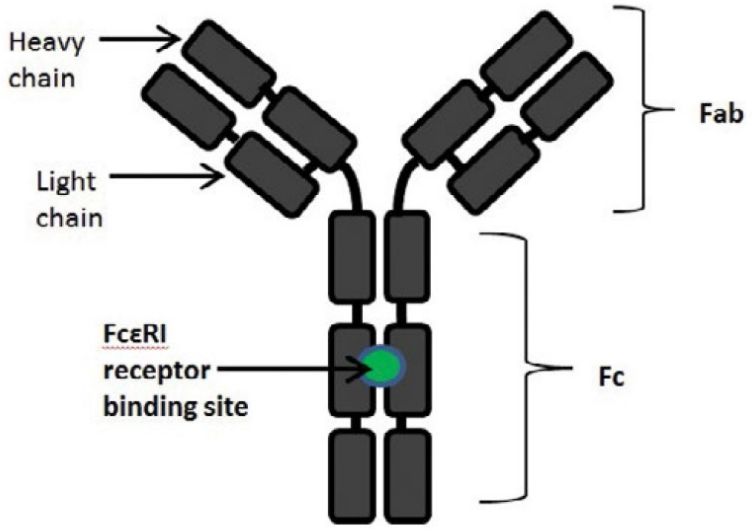


Figure 2. *The structure of Immunoglobulin E Antibody. It highlights the Fab and Fc portions, as well as the Fc□RI receptor binding site, which is the same site at which anti-IgE antibody binds.*

Omalizumab (Xolair) (2003)—SQ dosing

- Omalizumab -- approved for allergic asthma, If the patient doesn't have allergic asthma, they're not candidates for omalizumab. Given either every 2 weeks or every month, depending on the IgE level. Dosing is based on weight and IgE levels.
- Generally, adult levels of IgE are achieved by 5 to 7 years of age. Between the ages of 10 and 14 years, IgE levels may be higher than in adults. Reference range is 0 - 99 IU/mL.
- Eosinophilic asthma is likely if the total IgE level is 375 IU/mL or greater.
- It doesn't matter what their eosinophil and other T2 markers are; however, there some studies suggest that patients with high T2 markers may benefit with omalizumab. The effect on lung function is modest at best, but it has a small effect on reducing exacerbations. It's the only medication that targets IgE among the other biologics we have.
- Approved for age 6 and over
- FDA approved it for home administration. Black-box warning for possible anaphylaxis, so be aware of that possibility.

The “newbie mabs”…mepolizumab/Nucala or resliuzumab/Cinqair—ADD ONs to current Rx

- Bind to the IL-5 receptor and inhibit IL-5 signaling. Fancy way of saying that these two mabs inhibit the growth and differentiation of eosinophils, the recruitment of eosinophils to the site of the inflammation, activation, and survival of eosinophils
- INDICATIONS: For kids 6 and older who are taking a high-dose inhaler corticosteroid + add-on long-acting bronchodilator, or patients with 2 or more exacerbations (defined as worsening asthma requiring systemic corticosteroids or hospitalization or ED visit in the previous 12 months and/or daily oral corticosteroids; or for having to at least double the existing maintenance systemic corticosteroid dose for ≥3 days; or baseline blood eosinophils ≥ 150 cells/µL
- An elevation in blood eosinophil levels between 200 and 300/microL support an underlying active Type 2 immune response, and is a good predictor of response to these new targeted therapies
- Mepolizumab/Nucala is given once a month SQ; Reslizumab/Cinqair– IV dosing (based on weight) and fell out of favor during COVID

Case Study—8 year old with severe asthma—is she a candidate for meprolizumab? YEP!!

- Mother called the school nurse with concern about current symptoms—the child has intermittent wheezing and dyspnea with frequent use of her rescue inhaler (albuterol—averaging 4 puffs per day); she's missing school due to asthma symptoms
- **Medical history:** Asthma duration: 4 years (diagnosed at age 4); She's had 2 exacerbations in the past year, including a hospitalization
- Atopic status: positive (prior subcutaneous immunotherapy for allergens)
- **Current asthma medications:** High-dose ICS/LABA (3 years)
- **Spirometry results:** FEV_1 68% predicted
- **Laboratory results:** Eosinophil count: 370 cells/µL; IgE concentration: 148 kU/L

Benralizumab/Fasenra, depletes IL-5 receptor-bearing cells

- The most recent biologic is benralizumab [Fasenra]. Instead of targeting IL-5, benralizumab targets the IL-5 receptor, so it's more directly anti-eosinophilic, because it has 2 effects: It blocks the interaction of IL-5 with its receptor, but it also brings in natural killer lymphocytes, which trigger direct cellular cytotoxicity. So there's apoptosis (preprogrammed suicide) of the eosinophils in the tissue.
- The clinical trials for benralizumab/Fasenra showed strong effects on reducing the exacerbation rates—SQ and 12 and over…
- Overall there appears to be better effects on improvement of lung function than with the other IL-5 biologics.

Interleukins IL-4 and IL-13 are two other proinflammatory interleukins in the Th2 pathway

- Basophils are a significant source of IL-4 and IL-13, two Th2 cytokines, whose expression is characteristic of allergic lesions and which are now considered critical components in the pathogenesis of allergic disease.
- IL-4 – a type 2 cytokine that plays a key role in allergy and asthma and it's receptor is IL-4R
- IL-13 promotes IgE production by B lymphocytes, it generates eosinophil chemoattractants (proteins that "call or attract" eosinophils to the 'scene of the crime', and contracts airway smooth muscle cells
- monoclonal antibodies to IL-13 have not been shown to benefit asthma symptoms, however…Dupilumab/Dupixent is a monoclonal antibody, binding to the alpha subunit of of the IL-4 receptor, inhibiting the activity of **both IL-4 and IL-13**

Dupilumab/Dupixent

- Has been approved as add-on maintenance treatment for patients 12 and over who have moderate-to-severe eosinophilic asthma or have oral steroid-dependent asthma that is not controlled with current asthma medicines. What can dupilumab do? It can:
- Improve lung function in as little as 2 weeks
- Help prevent severe asthma attacks
- Can reduce or completely eliminate the need for oral steroids (86% of patients reduced or eliminated their OCS dose
- ONE caveat: If the child cannot receive any attenuated, or "live vaccines" while being treated with dupilumab/Dupixant.

Important to know…

Dupilumab has also be approved for two more indications:

1. kids over 6 with moderate to uncontrolled atopic dermatitis
2. and patients 18 and older for inadequately controlled rhino-sinusitis and nasal polyposis

Dual monoclonal antibody therapy

- In some severe allergic asthma patients with persistently high eosinophil counts in peripheral blood and who are considered non- or mild responders to anti-IgE and anti-IL5 administered individually, a combination of the two antibodies covering the entire T2 spectrum may be effective—omalizumab and meprolizumab

- Domingo C, Pomares X, Morón A, Sogo A. Dual Monoclonal Antibody Therapy for a Severe Asthma Patient. *Front Pharmacol*. 2020;11:587621. Published 2020 Sep 30. doi:10.3389/fphar.2020.587621

Whew!! GOT IT??

- Thank you.
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