UPDATE ON ASTHMA MEDICATIONS
INCLUDING BIOLOGICS FOR SEVERE PERSISTENT ASTHMA

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## OBJECTIVES

<table>
<thead>
<tr>
<th>Describe</th>
<th>Describe asthma medications that have been added to the GINA and NAEPP guidelines in the recent year.</th>
</tr>
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<tr>
<td>Compare</td>
<td>Compare the mechanism of action and effectiveness of inhaled steroids and bronchodilators for the management of persistent asthma; including device characteristics.</td>
</tr>
<tr>
<td>Discuss</td>
<td>Discuss the key features and management of severe asthma including the use of biologics.</td>
</tr>
</tbody>
</table>
What is Asthma?

- A common and complex disease
- Chronic inflammation of the airways
- Heterogeneous nature

Characterized by:

- Variable and recurrent symptoms
- Airflow obstruction
- Bronchial hyperresponsiveness
- Underlying inflammation
Common View of Asthma

- Allergen plus pre-disposition
- Th2
- Inflammation and damage
- Airway hyper-responsiveness plus mediators
- Symptoms

“Asthma” may be due to different biological pathways
Asthma guidelines

GINA
Updated yearly

EPR-3 2007
Treatment steps – changes in 2018

- **Step 1**
  - It is explained that the reason ICS should be considered for patients with mild asthma (rather than prescribing SABA alone) is to reduce their risk of serious exacerbations *(Pauwels, Lancet 2003; O’Byrne AJRCCM 2001; Reddel Lancet 2017)*

- **Steps 3-4**
  - From the large FDA LABA safety studies: adding LABA to ICS in a combination inhaler reduces risk of exacerbations and improves symptoms and lung function, compared with the same dose of ICS alone, but with only a small reduction in reliever use *(Stempel NEJM 2016, Peters NEJM 2016)*

- **Step 5 and Box 3-14: management of severe asthma**
  - Subcutaneous benralizumab (monoclonal anti-IL5 receptor α antibody) is another add-on treatment for patients aged ≥12 years with severe eosinophilic asthma
Children aged ≤5 years – key changes

- **Step 2 (initial controller treatment) for children with frequent viral-induced wheezing and with interval asthma symptoms**
  - A trial of regular low-dose ICS should be undertaken first
  - As-needed (prn) or episodic ICS may be considered
  - The reduction in exacerbations seems similar for regular and high dose episodic ICS *(Kaiser Pediatr 2015)*
  - LTRA is another controller option

- **Step 3 (additional controller treatment)**
  - First check diagnosis, exposures, inhaler technique, adherence
  - Preferred option is medium dose ICS
  - Low-dose ICS + LTRA is another controller option
    - Blood eosinophils and atopy predict greater short-term response to moderate dose ICS than to LTRA *(Fitzpatrick JACI 2016)*
    - Relative cost of different treatment options in some countries may be relevant to controller choices
Common treatments for the medical management of Asthma

Quick-relief “rescue”
- Short-acting bronchodilators prn
  (beta 2 agonists - SABAs - preferred)
- “Burst” of systemic corticosteroids

Long-term control
- Inhaled corticosteroids (ICS)
- Long-acting muscarinic antagonist (LAMA)
- Combination therapy (inhaled corticosteroids and long-acting beta 2 agonists (ICS/LABA)
- Leukotriene modifiers
- Biologic agents
Dry powder albuterol
Proair Respикlick Open-Click-Inhale

Quick-relief “rescue”

SABAs: proclerch (in. Proventil), Proair MDI and Respilette, ALBUTEROL,
Xopenex (LEVABUTEROL)
Atrvent (IPRATROPIUM), Duoneb,
Combivent (BOTH ALBUTEROL &
IPRATROPIUM), Spireva (TIOPLIPIUM)

OCS: Prednisone, Medrol, Prelone
Common treatments for the medical management of Asthma

Introduction of generic fluticasone propionate: ArmonAir

- Long-term control
  - Inhaled corticosteroids (ICS)
  - Long-acting muscarinic antagonist (LAMA)
  - Combination therapy (inhaled corticosteroids and long-acting beta 2 agonists (ICS/LABA))
  - Leukotriene modifiers
  - Biologic agents
Introduction of QVAR RediHaler breath-actuated MDI device

QVAR REDIHALER

STILL AN HFA, NOT A DPI
DIFFERENT FLUTICASONE ESTERS FUROATE VS. PROPRIONATE

FF confers higher affinity for lung tissue compared with FP.

Translates to enhanced lung residency and once daily efficacy.

May result in superior symptom control compared with FP.
LAMA'S FOR
STEP 4
THERAPY

Spiriva (tiotropium)
FDA approved for 6+ Feb 2017
2 inhalation once daily

• 15 trials confirmed that adding LAMA (usually tiotropium) to ICS reduces exacerbations
SPIRIVA - ASTHMA INDICATION

- Spiriva Respimat (tiotropium)
- FDA approved for 6+ Feb 2017
- 2 inhalation once daily
- Not a DPI
MECHANISM OF ACTION OF LAMA'S

- Compete with acetylcholine at the muscarinic receptors
- Bronchodilation occurs mostly in the larger airways
- Both ipratropium and tiotropium stay in lung tissue and are not readily absorbed into systemic circulation
- Therefore not likely to cause significant systemic anticholinergic side effects

- Does not inhibit mucociliary clearance
- Not as effective bronchodilating as Beta 2 agonists
- Slower onset of action
Mechanism of Action: long-acting muscarinic antagonist (LAMA)
Soft mist inhaler
Technique for use of soft mist inhalers (SMIs)

The first time you use a soft mist inhaler,* you will need to insert the cartridge.
- Press the safety catch on the side and pull off the clear plastic base.
- Push the narrow end of the cartridge into the inhaler until it clicks.
- Push the cartridge against a firm surface or table top to be sure it has gone all the way in.
- Do not remove the cartridge after it has been inserted.
- Put the clear base back on. Press until you hear a click.
- Do not remove the clear base again.

Prime the inhaler before the first dose.
- Hold the inhaler upright. Turn the clear base clockwise (to the right) until it clicks.
- Open the cap and point the inhaler towards the floor.
- Press the button on the side until you see a mist or cloud.
- Repeat 3 more times.
- If you do not use the inhaler for more than 3 days, repeat 1 time.
- If you do not use the inhaler for more than 3 weeks, repeat 4 times.

To take a dose of medicine, hold inhaler upright with the cap closed. There is no need to shake it.
- Hold the top of the inhaler with 1 hand. With the other hand, turn the clear base clockwise (to the right) until it clicks. This prepares the dose of medicine.
- Open the cap.
- Breathe out slowly and fully.
- Put the mouthpiece in your mouth, and hold the inhaler horizontally, pointing toward the back of your throat.
- Seal your lips around the inhaler, but do not cover the air vents on the side.
- As you take a slow deep breath in, press and hold the button on the side of the inhaler. This releases the medicine in a soft mist.
- Breathe in to a full deep breath to get all the medicine into your lungs.
- Hold your breath for a count of 10.
- Remove inhaler from your mouth and breathe out slowly.

The inhaler has a dose indicator on the side. When the arrow is in the red zone, the inhaler is almost empty. When the inhaler is completely empty, the arrow will point to "0," and you will not be able to turn the base of the inhaler.

* Soft mist inhalers are also known as Respinat inhalers.
Respimat Daily Use  T-O-P (Turn, Open, Press)
OTHER LAMA’S

- Incruse-Umeclidinium
- Tudorza Pressair-Aclidinium
- Seebri Neohaler-Glycopyrrolate
FDA lifted warning as of December 2017

After a review of 4 large clinical trial using ICS/LABA

Does not increase asthma related adverse events compared to ICS alone

Boxed warning removed for all combinations

Warning remains on single agent LABA medication
AIR DUO

Generic fluticasone/salmeterol

Respiclick
COMBINATION ICS/LABA APPROVED FOR PEDIATRICS

Children 5-11 years of age
Symbicort 80/4,5 mcg 2 puffs
twice a day.

Children- 4-11 Can continue
to use Advair 100/50 mcg 1
puff twice daily
BREO ELLIPTA
(FLUTICASONE - FUROATE AND VILANTEROL).

Approved for treatment of asthma.

Ultra- long acting inhaled steroid and long acting beta agonist.
SEVERE ASTHMA
Severe Asthma Definition
European Respiratory Society and American Thoracic Society (ERS/ATS) Guidelines

ERS/ATS Severe Asthma Definition (2014)

Asthma that requires use of high-dose inhaled corticosteroids (ICS) plus a long-acting beta₂-agonist (LABA) or leukotriene modifier/theophylline for the previous year or systemic corticosteroids for ≥50% of the previous year (Global Initiative for Asthma [GINA] steps 4-5 therapy) to prevent it from becoming uncontrolled, or that remains uncontrolled despite this therapy

– Historically, a wide variety of criteria have been used inconsistently to define “severe asthma.”
– Severe asthma is estimated to have a prevalence of 5% to 10% of the total asthma population.

Common Causes of Uncontrolled Asthma That is Not Severe

- Nonadherence to therapy
- Incorrect inhaler technique
- Comorbidities and psychosocial factors
- Ongoing exposure to asthma triggers

Understanding a patient’s adherence to therapy is always a prerequisite when assessing severe asthma.
ADHERENCE

Over half of patients with asthma appear to be poorly controlled largely due to poor adherence.

80% of patients with difficult to treat asthma have poor adherence with their regular inhaled therapy.

In patients with steroid dependent asthma only half take oral corticosteroids regularly.
NHLBI Asthma Guidelines*

- High-dose inhaled corticosteroid (ICS) in combination with long acting beta₂-agonists (LABAs) with or without oral corticosteroid (OCS) and anti-IgE treatment are recommended for severe persistent asthma (Steps 5 – 6).
- No therapies specifically recommended for patients with severe asthma with eosinophilic phenotype.†

**Persistent Asthma: Daily Medication**
Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Preferred:</th>
<th>SABA PRN</th>
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<tbody>
<tr>
<td>Step 2</td>
<td>Preferred:</td>
<td>Low-dose ICS</td>
</tr>
<tr>
<td></td>
<td>Alternative:</td>
<td>Cromolyn, LTTRA, Nedocromil, or Theophylline</td>
</tr>
<tr>
<td>Step 3</td>
<td>Preferred:</td>
<td>Medium-dose ICS + LABA</td>
</tr>
<tr>
<td></td>
<td>Alternative:</td>
<td>Low-dose ICS + LABA OR Medium-dose ICS</td>
</tr>
</tbody>
</table>

- **Step 4**
  - **Preferred:** High-dose ICS + LABA
  - **Alternative:** Consider Omalizumab for patients who have allergies

- **Step 5**
  - **Preferred:** High-dose ICS + LABA + Oral corticosteroid AND
  - Consider Omalizumab for patients who have allergies

- **Step 6**
  - **Preferred:** (first, check adherence, inhaler technique, environmental control and comorbid conditions)

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*Each step: Patient education, environmental control, and management of comorbidities
Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

**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 systemic oral corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

*Patients ≥12 Years of age; †The NHLBI guidelines were published prior to the availability of mepolizumab.
WHY THEY WORK
ORAL STEROIDS
Cellular effects of corticosteroids

**Inflammatory cells**
- Eosinophil
  - Numbers (apoptosis)
  - Cytokines
  - Numbers
  - Cytokines

**Structural cells**
- Epithelial cell
  - Cytokines
  - Mediators
- Endothelial cell
  - Leak
- Airway smooth muscle
  - $\beta_2$-Receptors
  - Cytokines
- Mucus gland

CORTICOSTEROIDS
Era of Precision Medicine

- Target molecule(s) involved in persistent airway inflammation in severe asthma by biological agents
Global INitiative for Asthma (GINA) Report (cont’d): STEP 5

- Preferred option is referral for specialist investigation and consideration of add-on treatment¹
  - If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring
  - Add-on tiotropium for patients ≥12 years with history of exacerbations
  - Add-on anti-IgE (omalizumab) for patients with severe allergic asthma
  - Add-on anti-IL5 (mepolizumab (SC) or benralizumab (SC) for ages ≥12 yrs, or reslizumab (IV) for ages ≥18 yrs) in severe eosinophilic asthma
- Other add-on treatment options at Step 5 include:
  - Sputum-guided treatment: this is available in specialized centers; reduces exacerbations and/or corticosteroid dose
  - Add-on low dose oral corticosteroids (≤7.5 mg/day prednisone equivalent): this may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis
  - See ERS/ATS Severe Asthma Guidelines (Chung et al, ERJ 2014) for more detail
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Association</th>
<th>Specifically target treatments</th>
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</thead>
<tbody>
<tr>
<td>Severe allergic asthma</td>
<td>Blood and sputum eosinophils</td>
<td>Anti-IgE (adults and children)</td>
</tr>
<tr>
<td></td>
<td>High serum IgE</td>
<td>Anti-IL-4/IL-13</td>
</tr>
<tr>
<td></td>
<td>High FeNO</td>
<td>Anti-IL-4 receptor</td>
</tr>
<tr>
<td>Eosinophilic asthma</td>
<td>Blood and sputum eosinophils</td>
<td>Anti-IL-5</td>
</tr>
<tr>
<td></td>
<td>Recurrent exacerbations</td>
<td>Anti-IL-4/IL-13</td>
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<tr>
<td></td>
<td>High FeNO</td>
<td>Anti-IL-4 receptor</td>
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<tr>
<td>Neutrophilic asthma</td>
<td>Corticosteroid insensitivity</td>
<td>Anti-IL-8</td>
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<tr>
<td></td>
<td>Bacterial infections</td>
<td>CXCR2 antagonists</td>
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<tr>
<td></td>
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<td>Anti-LTB4 (adults and children)</td>
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<td></td>
<td></td>
<td>Macrolides (adults and children)</td>
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<tr>
<td>Chronic airflow obstruction</td>
<td>Airway wall remodeling as increased</td>
<td>Anti-IL-13</td>
</tr>
<tr>
<td></td>
<td>airway wall thickness</td>
<td>Bronchial thermoplasty</td>
</tr>
<tr>
<td>Recurrent exacerbations</td>
<td>Sputum eosinophils in sputum</td>
<td>Anti-IL5</td>
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<tr>
<td></td>
<td>Reduced response to ICS and/or OCS</td>
<td>Anti-IgE (adults and children)</td>
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<tr>
<td>Corticosteroid insensitivity</td>
<td>Increased neutrophils in sputum</td>
<td>p38 MAPK inhibitors</td>
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<tr>
<td>Chung et al. ETS/ATS Guidelines. Eur</td>
<td></td>
<td>Theophylline</td>
</tr>
<tr>
<td>Respir J 2011/2013/33</td>
<td></td>
<td>Macrolides</td>
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</table>
BIOLOGICS

- Biologic treatments aim to treat T2 high
- Therapies that target key cells and mediators that drive inflammatory responses in asthma
- Moderate or severe persistent asthma with particular phenotypes
- Heterogeneity of asthma results in varying responses to therapies
IgE is produced by B lymphocytes under direction of the cytokines IL-4 and IL-13.

IgE specific to allergens and binds to the receptor on the mast cell, basophils and other cells.

These cells then release mediators such as histamine, prostaglandins and eos, which lead to bronchoconstriction and plasma exudation.
XOLAIR

**Anti IgE humanized recombinant monoclonal antibody**

**Binds to free circulating IgE at the same site as high affinity IgE receptor**

**Reduces circulating IgE levels by 95% and leads to a reduction in the number of receptor binding sites on mast cells.**

**Small risk of delayed anaphylaxis.**

**Administration is subcutaneous every 2-4 weeks based on IgE level and weight.**

**Need to carry epinephrine device for 48 hours after injection.**
• Moderate to severe asthma > 6 years of age
• + skin test or serum IgE test to a perennial allergen
• Symptoms not adequately controlled with Step 4 therapy
• The dose and frequency is based on body weight and the level of serum IgE
• 150 — 375 mg every 2-4 weeks.
• IgE 30- 1300 for 6-12
• IgE 30- 700 for 12 and up
SHEENA

45 year old female

Allergies to tree, grass, weeds and ragweed pollen, dust mites mold and animal dander.

Prescribed Breo 200 mcg 1 puffs daily

Patient was needing 2-3 bursts of prednisone per year.

Levalbuterol HFA 2 puffs as needed.

Montelukast 10 mg daily.

Frequently triggered by seasonal allergies.

Missing work due to asthma flares.

IgE level of 144 IU/ml
SHEENA’S RESULTS

Patient started on Xolair 300 mg monthly

After 6 months, asthma under markedly improved control.

Able to discontinue Montelukast after 1 year.

Stepped down Breo I inhalation daily.

No need for Levalbuterol inhaler at all.

No need for any bursts on prednisone.

Patient reports significant improvement in activity level and quality of life.
EOSINOPHILIC ASTHMA
ASTHMA PATHOGENESIS: ALLERGIC AND NONALLERGIC ASTHMA\(^1\) WITH DOWNSTREAM EOSINOPHILIC EFFECTS\(^2\)


IL=interleukin; ILC=innate lymphoid cell; EOS=eosinophil; MHC=major histocompatibility complex; TCR=T cell antigen receptor; TSLP(R)=thymic stromal lymphopoietin (receptor).

1. Pollutants, microbes
2. Allergic eosinophilic airway inflammation
3. Nonallergic eosinophilic airway inflammation
4. Airway epithelium
5. Mast cells
6. T cell
7. Eosinophils
8. Epithelial damage and activation
9. Bronchial smooth muscle cell contraction and proliferation
10. Mast cell activation/survival
11. Histamine, prostaglandin, cytokine release
12. T cell proliferation, differentiation, and apoptosis
13. Pathways of EOS Trafficking
Measuring Eosinophils in Clinical Practice

Sputum Eosinophils
- Accurate predictor of steroid response
- Time-consuming
- Labor-intensive
- Not readily available

Peripheral Blood Eosinophils
- Common blood test\(^1\)
- Widely available (CBC with differential)\(^1,2\)
- Increased levels can correlate with exacerbations and loss of control\(^3\)
- Accuracy varies; levels fluctuate throughout the day\(^1\)

Peripheral blood eosinophils are a practical biomarker to detect eosinophilic asthma in routine clinical practice and can be used to inform clinical decisions\(^4\)

CBC = complete blood count.
SUMMARY: INCREASED EOSINOPHILS IN ASTHMA

Increased asthma severity\(^1\) and worsening lung function\(^3-5\) are also correlated with elevated sputum eosinophil levels.

Elevated blood eosinophils were correlated with:

- Increased asthma severity\(^1,\dagger\)
- Worsening lung function\(^3,\dagger\)
- Increased risk of exacerbations\(^6,7\)
- Increased rates of hospitalizations and ED visits\(^6\)

\(^1\)Increased asthma severity\(^2\) and worsening lung function\(^3-5\) are also correlated with elevated sputum eosinophil levels.

EMERGING CHARACTERISTICS OF EOSINOPHILIC ASTHMA

- Can be late onset
- Equal gender distribution
- No or limited allergies to common allergens
- Risk of severe exacerbations
- Low FEV₁ with persistent airflow limitation
- Elevated blood eosinophils
- Normal or moderately elevated IgE
- Rhinosinusitis with nasal polyps
- May be aspirin sensitive
- Dynamic hyperinflation and air trapping

FEV₁ = forced expiratory volume in 1 second; IgE = immunoglobulin type E.

IL-5 antagonists are monoclonal antibodies that reduce the production and survival of eosinophils by preventing IL-5 from binding to its receptors.
How Can IL-5 Be Targeted?

Mepolizumab
Reslizumab

\[ \text{IL-5} \]

\[ \text{Survival} \]
\[ \text{Recruitment} \]
\[ \text{Activation} \]

Benralizumab

\[ \text{IL-5} \]

ADCC
WHO ARE CANDIDATES FOR IL-5 BIOLOGICS?

<table>
<thead>
<tr>
<th>Patient's with poor symptom control- symptoms throughout the day</th>
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</thead>
<tbody>
<tr>
<td>Coughing, wheezing, difficulty breathing</td>
</tr>
<tr>
<td>Frequent use of rescue inhaler throughout the day.</td>
</tr>
<tr>
<td>Waking up at night</td>
</tr>
<tr>
<td>Limitations of normal activity</td>
</tr>
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</table>

Worsening of Asthma despite

- following plan of care, and needing Step 4-5 therapy
- and frequent bursts of steroids or daily steroids.

Need for frequent office visits, ER visits or hospitalizations.
In patients with blood eosinophil levels ≥ 150 cells/μL, NUCALA consistently reduced exacerbations\textsuperscript{4,5}

**MENSA (Trial 2) STUDY**
Primary Endpoint: Exacerbation Frequency at Week 32\textsuperscript{42}

**MUSCA STUDY**
Other Endpoint: Exacerbation Frequency at Week 24\textsuperscript{52}

![Graph showing reduction in exacerbation rate](image)
The NUCALA patient

Think NUCALA

In patients 12 years and older with severe asthma and:

2 or more controller therapies, including high-dose ICS and an additional controller(s)

2 or more exacerbations in the previous 12 months and/or daily OCS†

Test

Blood eosinophils: Conduct a complete blood count (CBC) with differential

Choose NUCALA

Baseline blood eosinophils $\geq 150$ cells/μL are predictive of efficacy for NUCALA

*According to the American Thoracic Society (ATS) and the European Respiratory Society (ERS), severe asthma is a type of asthma that requires treatment with high-dose inhaled corticosteroids (ICS), plus a second controller and/or systemic corticosteroid to prevent it from becoming uncontrolled, or asthma that remains uncontrolled despite this therapy.
NUCALA DOSING AND FREQUENCY

Administering NUCALA: Severe Asthma

- Fixed 100 mg dose independent of weight
- NUCALA should be administered by a healthcare professional
- SC injection into the upper arm, thigh, or abdomen once every 4 weeks
- In line with clinical practice, monitoring of patients after administration of biologic agents is recommended
KATHY - ASTHMA
SYMPTOMS OF WHEEZING, COUGHING, AND CHEST TIGHTNESS LIMITING ACTIVITIES

68 year old patient

On Symbicort 160 mcg 2 puffs BID

Montelukast 10 mg daily.

Allergic to grass pollen, ragweed and animal dander

Has need prednisone 5 x in the last year

Previously treated with Xolair for 1 year without improvement in symptoms.

Absolute eosinophils 0.2 K/UL
Blood Eosinophil Unit Conversion Calculator

If you receive blood eosinophil lab results that are not expressed as cells/µL use the calculator below to convert these results to µL.

**Blood Eosinophil Unit Conversion Calculator**

To convert blood eosinophil lab results to cells/µL, enter the following:

**Reported eosinophil result**

Please confirm that your entry matches your patient's lab results.

[CALCULATE]
CALCULATOR FOR EOSINOPHILS

0.2 \times 1000 = 200 CELLS PER MICROLITER
Kathy

Eosinophils 200- therefore candidate for Nucala 100mg/ml subcutaneously once a month.

Patient started on Nucala August of 2017.

Prednisone use down to 2 bursts in the last year triggered by URI’s.

No wheezing

Improved activity level and quality of life.

Improved FEV1
RON 45 YEAR OLD ENGINEER

- Severe persistent asthma
- Nasal polyposis
- Having daily dyspnea.
- Dulera 200 mcg 2 puffs BID
- Montelukast 10 mg daily.
- Needing frequent burst of steroids
- Absolute eosinophils 300 cells/microliter
- IgE 75

- Started on Nucala 100 mcg monthly 1 year ago
- No steroid bursts in past year.
- No daily asthma symptoms.
- Able to exercise without asthma symptoms.
- Nasal polyps are reduced and patients sense of smell has returned.
New Research on Nucala

COLUMBA study

Longest IL-5 therapy trial in severe eosinophilic asthma.

61% decrease in annual exacerbation rates at the end of the study. (3.5 years)
Consider CINQAIR for patients 18 years of age and older with:

- **Blood eosinophil count of ≥400 cells/mcL** within 3 to 4 weeks of dosing or other symptoms of an eosinophilic phenotype
- **Severe asthma that is inadequately controlled** despite standard of care (medium- to high-dose inhaled corticosteroids with long-acting beta agonists)
  - Symptoms >2 days a week
  - Short-acting beta agonist use for symptom control >2 days a week
  - Interference with daily activities
- **At least 1 asthma exacerbation requiring use of oral (systemic) corticosteroids** over the last 12 months
- **Compromised lung function** (FEV$_1$ <80% predicted)
CINQAIR DOSING

Dosing Calculator

Use the Dosing Calculator to quickly determine the appropriate weight-based dose of CINQAIR for your patient. You can also download a Dosing PDF.

Weight-based Dosing: Individualized to Your Patients
Efficacy and Safety Profiles
CINQAIR is the anti-IL-5 proven in three important clinical measures¹

CINQAIR:
• 1. Reduced exacerbations in Studies I–II
• 2. Improved lung function in Studies I–IV
• 3. Improved quality of life in Studies I–III
JENNIFER

- Went to infusion center
- Receive infusion of 375 mg IV
- Able to come off daily steroids after 1 month on Cinqair
- Significant reduction in symptoms and improved quality of life
Binds to IL 5 receptor on the eosinophils

Blocks the IL5 from binding to the eosinophils.

Eosinophils start to die of and attract natural killer cells

Reduction in numbers of circulating eosinophils
FASENRA

Indicated as add on maintenance therapy for patients 12 years and older with severe eosinophilic asthma

Does not require a certain Eosinophil level on Prescribing Information.

Prefilled Syringe.

No mixing- Take out of refrigerator 30 minutes before administration.
FASENRA DOSING

Maintenance dosing schedule every 8 weeks

1 DOSE

Other Treatments

2-4 DOSES

FASENRA is a targeted asthma medicine given once every 8 weeks after the first 2 months.*

In 2 clinical trials, injection site reactions occurred at a rate of 2.2% in patients treated with FASENRA vs 1.9% in patients treated with placebo (e.g., pain, redness, itching, swelling near where the injection was given).

*First 3 doses given on day 1, week 4, and week 8.
<table>
<thead>
<tr>
<th>Reduce</th>
<th>Improve</th>
<th>Reduce</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce the occurrence of severe asthma exacerbations by up to 51%</td>
<td>Improve lung function making it easier to breathe</td>
<td>Reduce oral steroid use by 75% in people who are taking them every day</td>
</tr>
</tbody>
</table>
FEV1 had greater improvements in change from patients baseline FEV 1 compared with placebo at week 4.

Proven to reduce annual exacerbation rate and improve lung function.

Fasenra provides near complete depletion of blood eosinophils in 24 hours.
MARTHA

89 year old lady.

Patient previously very active despite severe asthma. Exercise class and line dancing.

In past 6 months has had to reduce her activity due to dyspnea and coughing and wheezing.

She is now needing daily Prednisone 15 mg per day.

Breo 200 mcg 1 puff daily.

Spiriva 2.5 mcg 2 puffs daily.

She is needing nebulized treatments 2-3 x a day.
MARTHA

- Ig E 39.2
- Absolute eosinophils 600 cells per microliter.
- Fasenra given in office.
- Patient called back after 2 days to report her wheezing was gone, coughing gone and chest heaviness gone.
- Patient has now received 3 doses and much more stable and with improved quality of life
CHRISTINE

• 79 year old female with severe asthma.
• Previously was on Xolair 225 mg every 2 weeks to treat Moderate Persistent asthma. She was well controlled up until last fall.
• She started having frequent coughing, wheezing and chest tightness.
• She required 3-4 bursts of prednisone in the past year.
• There has been a decline in her FEV 1 form 85% to 62%.
• She has need rescue meds on a daily to several times a day basis.
• She reports being afraid to go out due to her symptoms.
WHAT HAPPENED:

- IgE is 223
- Absolute Eosinophils – 260 cells per microliter.
- Patient started on Fasenra.
- After first dose, patient felt relief of wheezing and chest tightness.
- Coughing improved, but may be complicated by allergies and GERD.
- Able to discontinue oral prednisone.
- Able to go on trip with husband without fear.
EMERGING CHARACTERISTICS OF EOSINOPHILIC ASTHMA

- Can be late onset
- Equal gender distribution
- No or limited allergies to common allergens
- Risk of severe exacerbations
- Low FEV₁ with persistent airflow limitation
- Elevated blood eosinophils
- Normal or moderately elevated IgE
- Rhinosinusitis with nasal polyps
- May be aspirin sensitive
- Dynamic hyperinflation and air trapping

FEV₁=forced expiratory volume in 1 second; IgE=immunoglobulin type E.

Thank you for your attention!