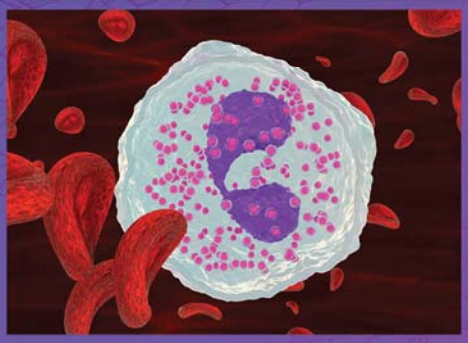
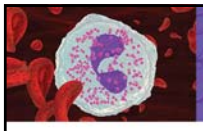
Severe Asthma and Related Eosinophilic Diseases:



The Role of IL-5 in Diagnosis and Treatment

National Jewish Health®
Breathing Science is Life.®



Severe Asthma and Related Eosinophilic Diseases:
The Role of IL-5 in Diagnosis and Treatment

Pathophysiology, identification, diagnosis, biomarkers and subtypes

Chapter 1

Learning Objectives

1. Describe the role of eosinophils and type 2 inflammation in severe asthma and eosinophil-associated diseases.

2. Identify the mechanisms of action of biologic therapies for severe asthma and eosinophil-associated diseases.

3. Distinguish severe asthma and related eosinophilic diseases from one another using clinical presentation, diagnostic test results, and input from subspecialty consultants.

4. Apply the results of clinical studies that examine the tolerability, efficacy, and safety of approved agents when selecting and monitoring therapy for severe asthma and associated eosinophilic diseases.

Epidemiology of Severe Asthma

- About 5-15% of asthma patients have severe disease, not controlled by available therapies.
- This group accounts for > 50% of health care utilization related to asthma and is at increased risk of asthma-related death.

Chambers et al. JACI 2015;136: 628-3
Chung et al. Eur Respir J 2014;43: 343-73
Jarjour et al. AJRCCM 2012;185: 356-62
Desai et al. Clin & Exp Immun 2009;158: 10-19

"Severe" Asthma

Difficult-to-treat asthma

Lack of asthma control is due to factors other than asthma itself (non-adherence, incorrect inhalation technique, comorbidities)

True refractory asthma

Causes of difficult asthma addressed or excluded, but still have poor asthma control or ≥ 2 exacerbations/year despite high-intensity treatment & verified adherence

Task force International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma Eur Respir J 2014; 43: 343–373

Severe Asthma and Related Eosinophilic Diseases:
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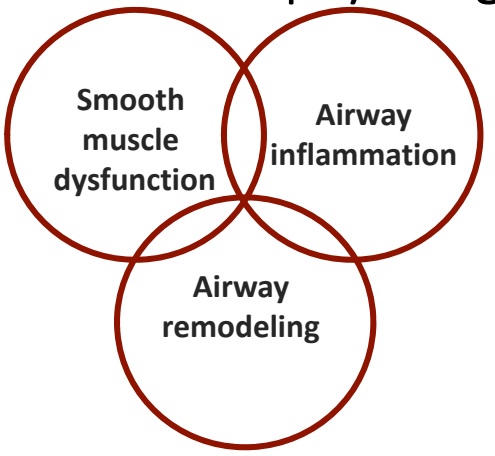
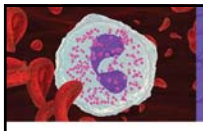
Asthma Pathophysiology



Adapted from Bousquet et al. *Am J Respir Crit Care Med.* 2000;161:1720-1745.

Peripheral Eosinophilia: Differential diagnosis

- Allergy/Asthma
- Drug allergy
- Eosinophilic esophagitis/eosinophilic gastrointestinal disease
- Some connective tissue/rheumatologic disorders
- Parasitic infections
- Some cancers
- Acute or chronic eosinophilic pneumonia
- **Hypereosinophilic syndrome**
- **Chronic sinusitis with nasal polyposis**
- **Eosinophilic granulomatosis polyangiitis (EGPA)**
- Other conditions (HIV, hypoadrenalism, Loeffler's syndrome)



Severe Asthma and Related Eosinophilic Diseases:
The Role of IL-5 in Diagnosis and Treatment

Thoracic and extrathoracic manifestations of Churg-Strauss syndrome	
Anatomic location	Manifestations
Lung	Pulmonary vasculitis, pleural effusions, hilar lymphadenopathy, cavitary lesion
Heart	Acute pericarditis, constrictive pericarditis, cardiac failure, myocardial infarction
Central nervous system	Mononeuritis complex
Gastrointestinal tract	Eosinophilic gastroenteritis, polyarteritis nodosa
Kidney	Focal segmental glomerular nephritis
Muscles and	Myalgia joint pain
Skin	Purpura, macular or papular erythematous rash, urticaria, subcutaneous nodules

Eosinophilic Granulomatosis with Polyangiitis

- Respiratory tract
- Nervous system
- Heart
- Kidney
- GI tract
- Vascular system
- Skin

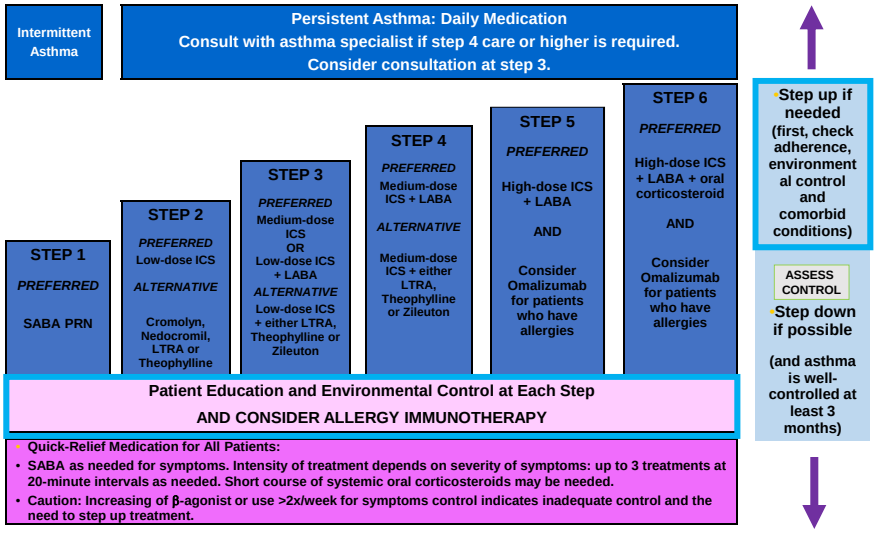
Morbidity

- Those with higher FeNO and/or AEC compared to those without had worsened airflow obstruction, increased bronchial hyperresponsiveness, worsened asthma control, increased frequency of asthma exacerbations

Malinovschi A, et al JACI 2016
Mogensen I, at al. Clin Exp Allergy 2018

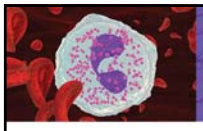
When to Refer to Specialist

Stepwise Approach for Managing Asthma in Patients ≥12 Years of Age



NHLBI. National Asthma Education and Prevention Program. Expert Panel Report 3: page 517. Available at: http://www.nhlbi.nih.gov/guidelines/index.htm. Accessed 2.8.07.

Refer to an asthma specialist for consultation or comanagment if there are difficulties achieving or maintaining control; step 4 care or higher is required (step 3 care or higher for children 0–4 years of age); immunotherapy or omalizumab is considered; or additional testing is indicated; or if the patient required 2 bursts of oral systemic corticosticosteroids in the past year or a hospitalization. Consider referral to an asthma specialist if signs and symptoms are atypical, if there are problems with a differential diagnosis, or if additional testing is indicated.



Severe Asthma and Related Eosinophilic Diseases:
The Role of IL-5 in Diagnosis and Treatment

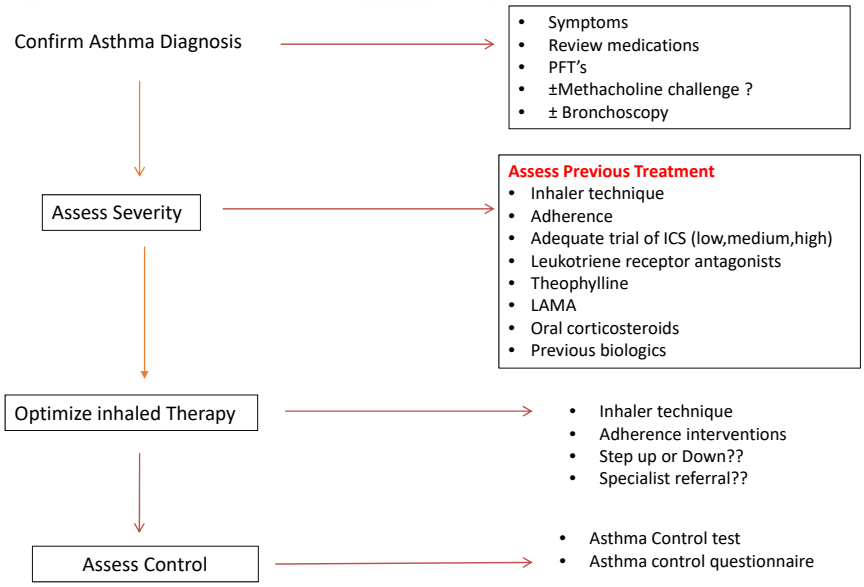
Differential diagnosis of Severe Asthma and associated Eosinophilic diseases

Chapter 2

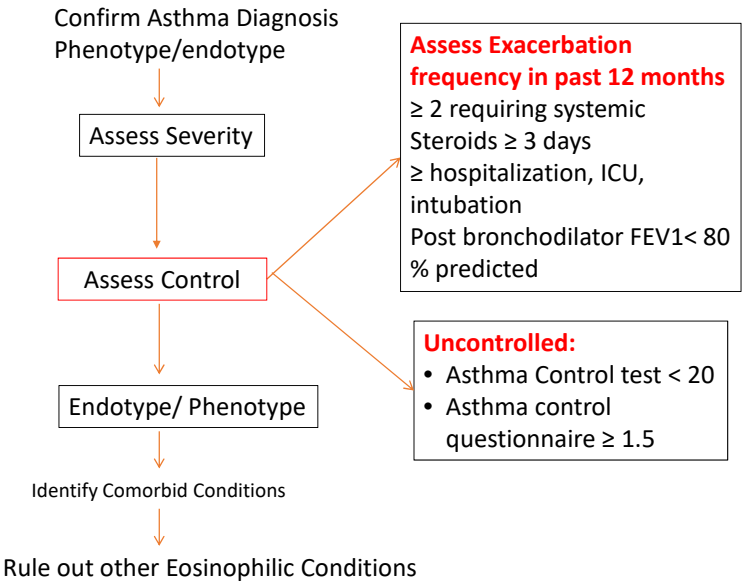
Differential Diagnosis of Severe Asthma and associated Eosinophilic Diseases

- Clinical Evaluation of Severe Asthma
- Differentiating Severe Asthma from other Eosinophilic Conditions
  - Chronic rhinosinusitis and nasal polyposis
  - Allergic bronchopulmonary Aspergillosis
  - Eosinophilic granulomatosis and polyangiitis
  - Hypereosinophilic syndrome

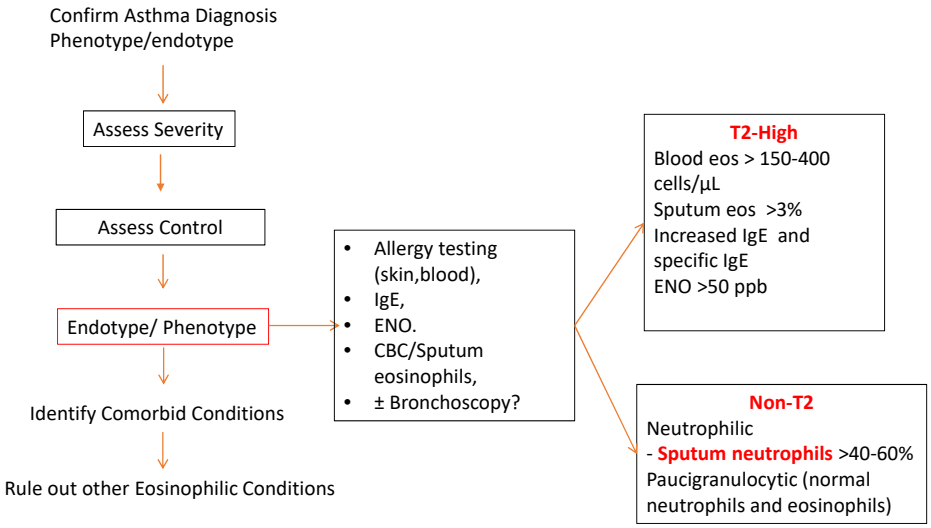
Assessment of Severe Asthma



Assessment of Asthma Control



Phenotype/Endotype



Identify Comorbid conditions

Identify Comorbid Conditions

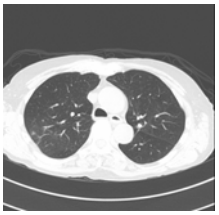
- Gastro-esophageal reflux disease/Aspiration
- Dysbiosis/chronic infection
- Obesity
- Asthma/COPD Overlap
- Paradoxical Vocal Fold Motion Disorder
- Bronchiolitis
- Tracheobronchomalacia

Rule out other Eosinophilic Conditions

Identify Comorbid Conditions

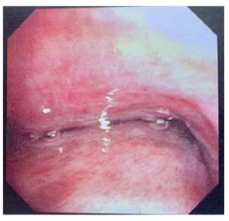
Identify Comorbid Conditions

1



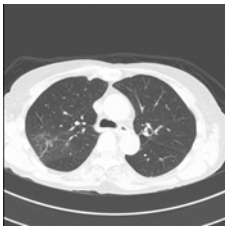
Hiatal Hernia/GERD

3



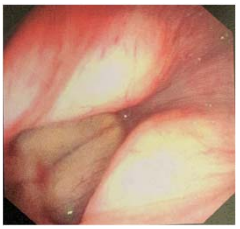
Tracheobronchomalacia

2



Aspiration??

4



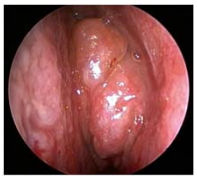
Inducible laryngeal obstruction

Rule out other Eosinophilic Conditions

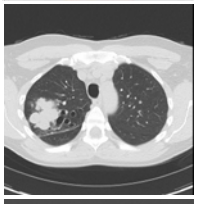
Rule Out Other Eosinophilic Conditions

Rule out other Eosinophilic Conditions

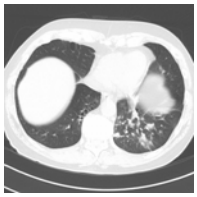
- CRSwNP



- (ABPM)



- EGPA
- HES



Ruling out Other Eosinophilic Lung Diseases

- History and physical
  - History of asthma
    - EGPA
    - Allergic bronchopulmonary mycosis
    - Bronchogenic granulomatosis
    - Hypereosinophilic syndrome
  - Travel history
    - Parasitic infections
  - Multiorgan involvement
    - EGPA
    - HES

Clinical Lab evaluation

CBC eosinophils , ANCA, MPO, PR3, ABPM Screen, urinalysis

Stool and serological testing for parasites

Bone Marrow biopsy and karyotyping (HES)

Pulmonary function test

- **Restrictive pattern**
  - **Acute eosinophilic pneumonia, chronic eosinophilic pneumonia, tropical pulmonary eosinophilia**
- **Obstructive pattern**
  - **Asthma, allergic bronchopulmonary mycosis, EGPA**

CT Scan, Echo

Bronchoscopy

Ruling out Other Eosinophilic Lung Disease: Allergic Bronchopulmonary Aspergillosis/Mycosis

- **Clinical features**
  1. History of asthma, C.F. Rarely have neither
  2. Systemic and airway eosinophilia
  3. Elevated IgE Levels
  4. Lung infiltration
  5. Bronchiectasis
  6. Mucoid impaction
  7. Lung Fibrosis

- **Diagnostic Criteria**

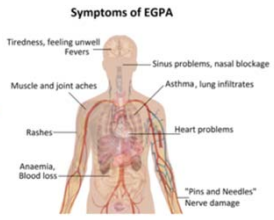
1. Asthma or C.F. Aspergillus skin test positive or Specific IgE (>35 kU/L
2. IgE typically > 1000 (can be less if meets other criteria)
3. At least 2 of the following:
   1. Precipitating Antibodies to A fumigatus or other fungi
   2. Radiographic pulmonary opacities c/w ABPA,
   3. Total eosinophil count > 500 in steroid naïve patients

Eosinophilic Granulomatosis with Polyangiitis

Multiorgan Eosinophilic Vasculitis

Associations

Adult onset Asthma (90%)
Allergic Sinus disease
Nasal polyps
Multi-organ involvement



Signs and Symptoms

- Prodrome: asthma, allergies, sinus disease
- 2nd phase: high eos in blood and tissue, eosinophilic pneumonia , GI
- 3rd life threatening vasculitis
  - Renal, Cardiac, GI, Neuro

Testing:

- CT Chest: Lung opacities, Nodular disease, pleural effusions
- Peripheral blood eosinophilis
  - >1500 eos/µL (5k to 9K)
- ANCA ANCA +ve (30-60%): MPO (P-ANCA)(70-75%) of +ve ANCA
- BAL lavage eos > 33%
- Sputum cultures
- Surgical lung biopsy (skin, kidney, lung or peripheral nerve)
- Urinalysis
- Echocardiogram

Eosinophilic Granulomatosis with Polyangiitis

Multiorgan Eosinophilic Vasculitis

Diagnostic Criteria (American College of Rheumatology):

Must have 4/6 criteria

1. History of asthma
2. > 10% eosinophils on differential Leukocyte count
3. Migratory/transient lung opacities
4. Mononeuropathy or polyneuropathy
5. Paranasal sinus abnormality
6. Biopsy containing a blood vessel showing an accumulation of eosinophils in extravascular areas

Thoracic and Extrathoracic manifestations of Eosinophilic Granulomatosis with Polyangiitis

Anatomic location	Manifestations
Lung	Asthma, Pulmonary vasculitis, pleural effusions, hilar lymphadenopathy
Heart	Acute pericarditis, constrictive pericarditis, cardiac failure, myocardial infarction
Peripheral nervous system	Mononeuritis complex/Polyneuropathy
Gastrointestinal tract	Eosinophilic gastroenteritis, polyarteritis nodosa
Kidney	Focal segmental glomerular nephritis
Muscles and	Myalgia joint pain
Skin	Purpura, macular or papular erythematous rash, urticaria, subcutaneous nodules

Hypereosinophilic Syndrome

Hypereosinophilia

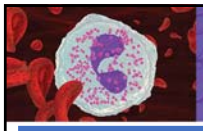
- Peripheral blood (> 1500 cell/µL)
  - On at least 2 occasions
  - At least month apart
- Pathologic Confirmation of tissue hypereosinophilia
  - Bone marrow
    - > 20% of all nucleated cells
    - Extensive eosinophilic infiltration in Pathologist opinion
    - Marked deposition of eosinophilic granule proteins in tissue

↓

Eosinophilic infiltration, degranulation and mediator release

↓

Multiorgan damage



Severe Asthma and Related Eosinophilic Diseases:
The Role of IL-5 in Diagnosis and Treatment

Thoracic and extrathoracic manifestations of Hypereosinophilic Syndrome

Anatomic location	Manifestations
Lung	Pulmonary infiltrates, pleural effusions, Asthma, Sinus disease, cough, recurrent infections
Heart	Cardiomyopathy, pericardial effusion, cardiac failure, **myocarditis,** Valvular disease
Nervous system	Vertigo, paresthesia, **change in mentation, aphasia, visual changes**
Gastrointestinal tract	Abdominal pain, vomiting and diarrhea
Constitutional	Fever, weight loss, malaise, fatigue, night sweats, flulike illness
Rheumatologic	Myalgia, joint pain, myositis
Skin	Urticaria, angioedema, dermatitis, eosinophilic vasculitis, bullous lesions
Hematologic	**Deep venous thrombosis**, anemia, superficial thrombophlebitis

Hypereosinophilic Syndrome

Hypereosinophilia (> 1500 cell/µL)

History: symptoms, Drugs, Travel, Exposure
Physical: skin, pulmonary, heart, nasal neurological signs

Screen for Secondary causes
Parasites, Allergic, Pulmonary, Connective Tissue,

Reactive Eosinophilia

Screen for FIP121-PDGFRA gene mutation

Positive

Myeloproliferative
Clonal eosinophilia
Chronic eosinophilic Leukemia
(CEL)

Negative

Familial: Mutation not identified as yet

Clonal cytogenetic abnormality or increase in Marrow blasts (CEL NOS)

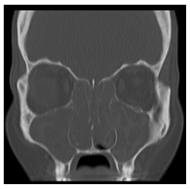
Lymphocytic HES
Abnormal T –cell associated HES
Increased IL-5 production?

Idiopathic HES

When to Refer

Rule out other Eosinophilic Conditions

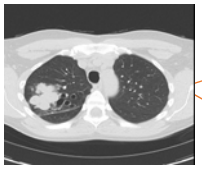
CRSwNP



ENT: Surgery?

Allergist (AERD)

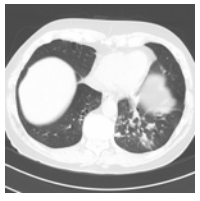
(ABPM)



Allergist

Pulmonologist (Bronchoscopy)

EGPA



Rheumatologist (Vasculitis)

HES

Hematologist (Bone Marrow Bx)

Treatment Selection for the spectrum of Eosinophilic diseases

Chapter 3

Inhaled Corticosteroids Adverse Effects

Adverse effect	Mechanism	Potential Minimizing Factors	Notes
Dysphonia	Local deposition leading to myopathy of laryngeal muscles, candidiasis, mucosal irritation	Spacer devices may help to reduce risk	
Oropharyngeal candidiasis	Local deposition	Spacer devices may help to reduce risk	
Contact hypersensitivity	Local deposition on skin. Most commonly budesonide	Confirm with patch testing then switch to ICS that does not cross-react with budesonide	ICS that do not cross-react with budesonide include: beclomethasone, mometasone, fluticasone
Adrenal insufficiency	Systemic absorption	Screen asymptomatic children at higher risk	
Pneumonia	Systemic absorption	Possible avoidance of fluticasone propionate	Risk of mortality not increased
Growth deceleration	Systemic absorption	Further research needed to determine whether certain ICS have different effects	Effect on adult height appears small

Systemic Corticosteroid Adverse Effects

Organ system	
Ophthalmologic	Cataracts, glaucoma, exophthalmos
Cardiovascular	Hypertension, arteriosclerosis, arrhythmias
Gastrointestinal	Gastritis, peptic ulcer disease, steatohepatitis
Immune	Increased susceptibility to infections
Hematologic	Leukocytosis
Neuropsychiatric	Insomnia, mania, psychosis, dysphoria, depression, euphoria
Musculoskeletal	Osteopenia/osteoporosis, avascular necrosis, myopathy
Dermatologic	Acne, hirsutism, striae, skin thinning, purpura, ecchymosis
Endocrinologic	Diabetes mellitus/hyperglycemia, adrenal insufficiency, weight gain, cushingoid appearance, fluid retention

Asthma Approved Biologic Agents

Drug	Target	Approval in US	Age	Dosing and Frequency		Route	Biomarker Criteria	Phase 3 Clinical Trial Results		
								Exacerbation Reduction	Increased FEV1	Steroid Reduction
Omalizumab	IgE	2003 Asthma 2016 C.I.U.	≥6 y.o	75-375 mg (based upon weight, IgE level, age)	Q2W Q4W	s.q. office	IgE: 30-1300	✓	Not done/no change	✓
Mepolizumab	IL-5	2015Asthma 2019 EGPA	≥ 12 6-11	100 mg 40 mg 100 mg x 3	Q4W X3	s.q. Office Home-prefilled (> 11y.o.)	CBC eos 150 ≤6 weeks 300 ≤12 months	✓	Minimal increase	✓
Resilizumab	IL-5	2016	≥ 12	3.0 mg/kg	Q4W	i.v. Clinic/ Infusion center	CBC eos >400	✓	✓	Not done
Benralizumab	IL-5Rα	2018	≥ 12		Q4W (x3) → Q8W	s.q. prefilled Office	CBC eos: All comers 300 for primary 150 for OCS red.	✓	✓	✓
Dupilumab	IL-4Rα (impacts IL-4 and IL-13)	2017 A.D. 2018: Mod-Severe Asthma 2019: CRSwNP	≥ 12	200 mg or 300 mg 300 if O.C.D.	Q2W	s.q. prefilled Home office	No minimum eos	✓	✓	✓

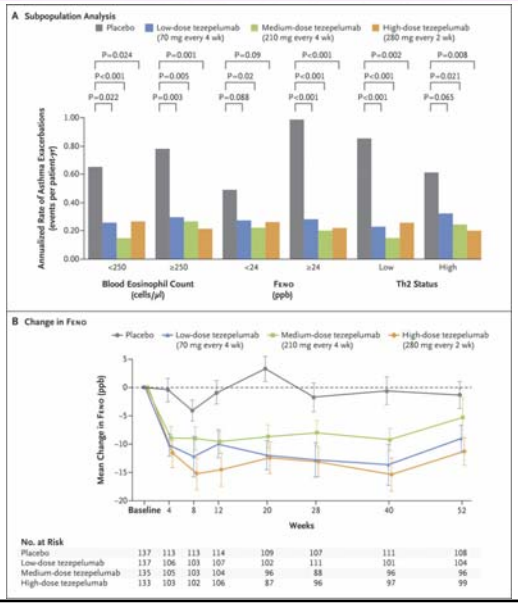
Newer Biologics Under Development

The Alarmins

- Anti- TSLP
- Anti-IL 33
- Anti-IL-25

Tezepelumab in Adults with Uncontrolled Asthma

- **Design:**
  - 52 weeks Phase II study RDBCT
  - Multicenter
  - 3 doses SQ vs placebo q 4 weeks
  - 137 patients each group on LABA and med/high dose ICS
  - Th2 high (IgE >100 Blood eos≥ 140 /mcL
- **Results**
  - All 3 doses 70 mg, 210 mg were 62%, 71%, 66% lower than in the placebo arm.(p<0.001)
  - FEV1 higher in all groups 120,130,150 ml compared to placebo (p< 0.015)
  - Results not influenced by baseline eosinophil count, FeNO



ALARMINS trials for Eosinophilic Diseases

Study Drug	Mechanism/ Target	Biomarkers	Route	Status
Tezepelumab	antiTSLP	FeNO, serum periostin	SC	Phase III
AREGN3500 GSK 3772847 ANB020	Anti-IL-33	FeNO, serum periostin, Blood eos, Sputum inflammatory markers	SC	Phase II
Anti-IL25	IL-25 also known as IL-17E	Blood and Sp eos	SC	None to date

Biologics that failed for Severe Asthma

Study Drug	Mechanism	Biomarkers	Route	Status
Lebrikizumab	IL-13	FeNO, serum periostin	SC	Failed
Tralokinumab	IL-13	FeNO, serum periostin	SC	Failed
Brodalumab	Anti- IL17	Blood and Sp eos	SC	Failed

Biologics Currently in Phase II or III Studies For Severe Asthma

Study Drug	Mechanism	Biomarkers	Route	Status
AREGN3500 GSK 3772847 ANB020	anti IL-33	Blood eos, FeNO, IgE	SC	ongoing
CJM112	Anti-IL-25	Blood eos, FeNO, IgE	SC	ongoing
Tezepelumab	Anti-TSLP	Blood Eos, IgE, FENO	SC	ongoing
Non T2 or T2 low Targets/Paucigranulocytic				
Navarixin	CXCR2	Blood + sp neutrophils	oral	ongoing
Fevipiprant	DP2 receptor	Sp Eos	oral	
Imatinib	KIT	Serum Tryptase	Oral	
Proposed Targets: IL-6, IL-9				

Biologics in Chronic Rhinosinusitis with nasal polyposis show encouraging results

- Biologics in active trials at current time
  - Dupilumab (approved 2019)
  - Mepolizumab
  - Benralizumab
  - Omalizumab
  - Tezepelumab
  - Anti-IL33
  - CRTH2 Antagonists
  - TP antagonist Ifetroban

Biologics Currently in Phase II or III Studies For Other Eosinophilic Diseases

Condition	Drug	Studies
EGPA	Mepolizumab (Approved 2017) Benralizumab	Clinical trials Clinical trials
Hyper-eosinophilic syndrome	Mepolizumab Benralizumab	Clinical trial Clinical trial
ABPA	Omalizumab Mepolizumab Benralizumab Dupilumab	RCT Case studies Case series Case series

Conclusions

- Asthma is a spectrum of diseases, with different pathologic and clinical phenotypes
- There has been an increased understanding of the immunology of asthma, leading to new therapeutic options
- Defining phenotypes/endotypes in asthma is a young field, but it is making progress.
- In the severe asthma population Investigating and managing comorbidities cannot be overemphasized
- Tailoring treatment to phenotypes/endotypes and/or treatable traits is the ultimate goal.