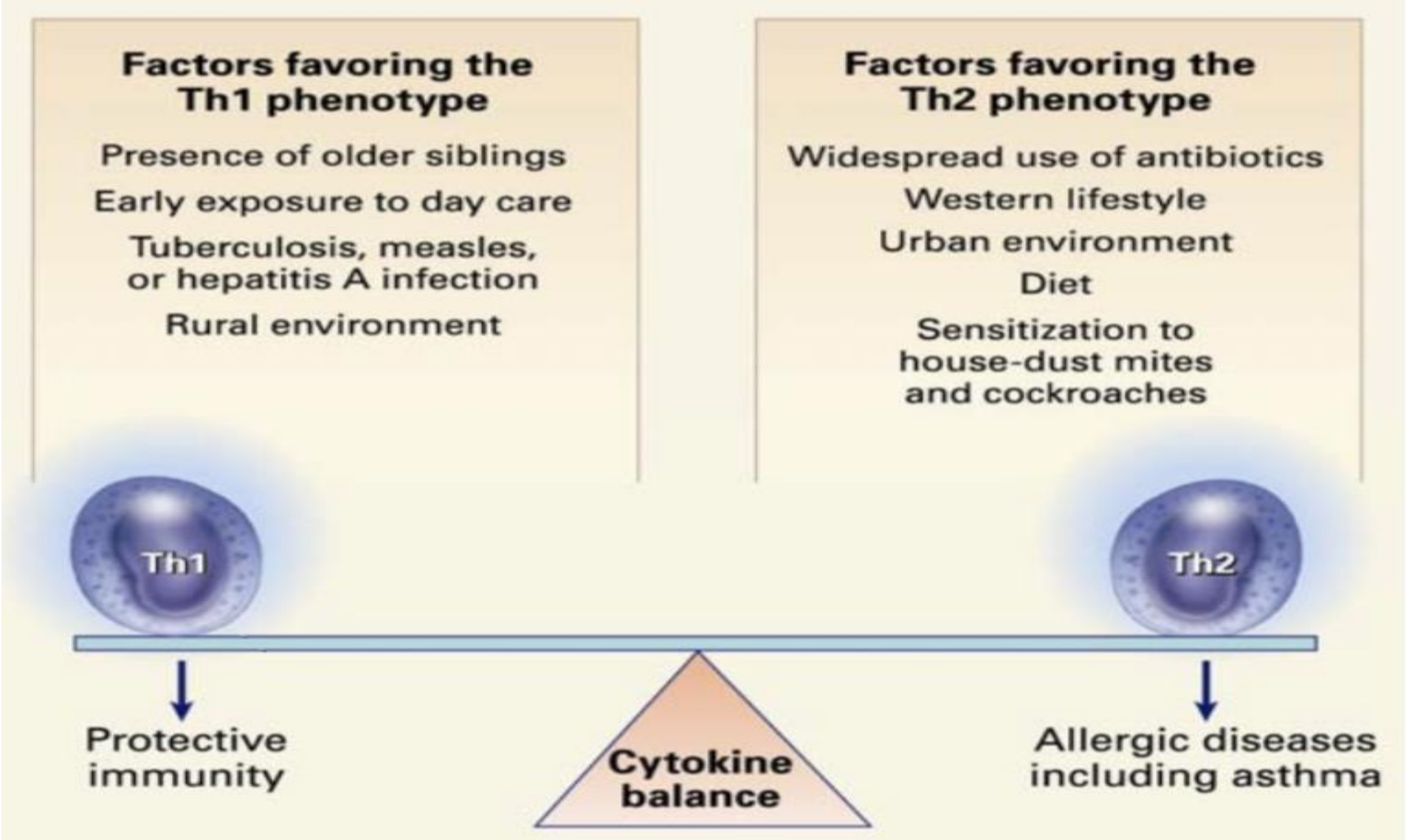
Asthma

Current approaches and management

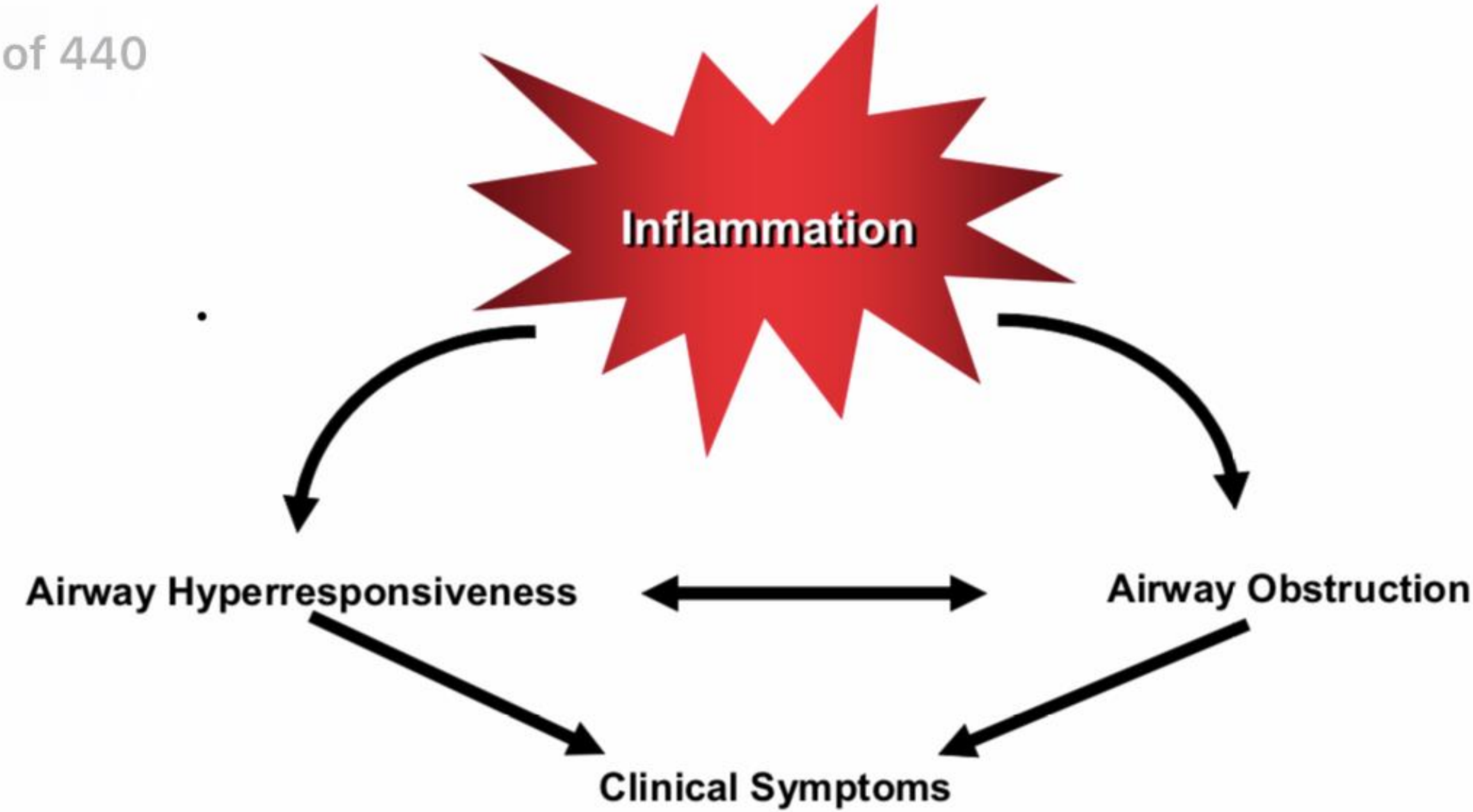
Definition

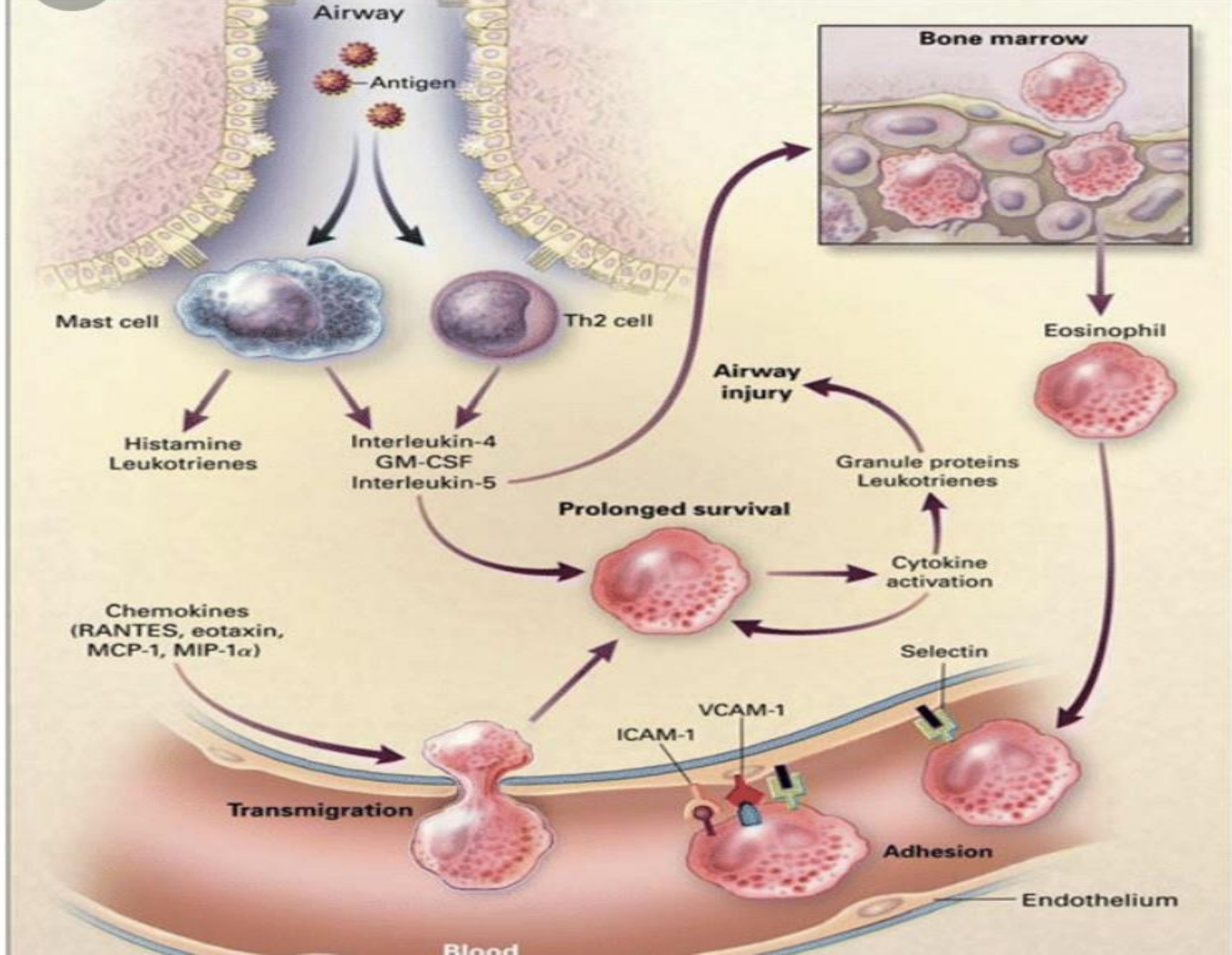
- Obstructive airflow that is Reversible
- Atopic relationship of allergy
- Genetic

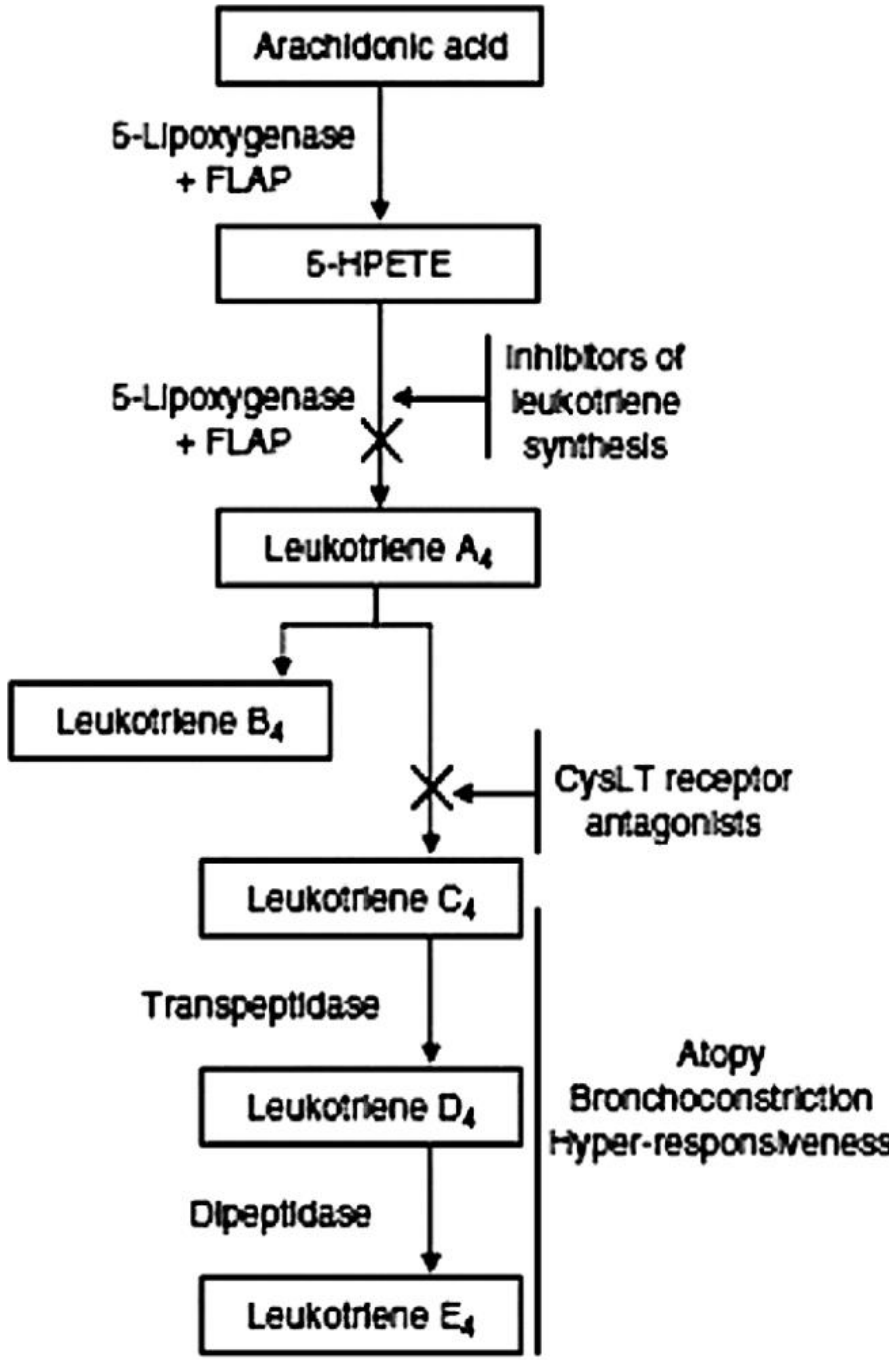
Inflammation



As a guide to describing asthma and identifying treatment directions, a working definition of asthma put forth in the previous Guidelines remains valid: *Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma* (EPR 1991; EPR—2 1997).


Inflammation
Airway Hyperresponsiveness
Airway Obstruction
Clinical Symptoms


Airway
Antigen
Bone marrow
Mast cell
Th2 cell
Eosinophil
Airway injury
Histamine
Leukotrienes
Interleukin-4
GM-CSF
Interleukin-5
Granule proteins
Leukotrienes
Prolonged survival
Cytokine activation
Chemokines
(RANTES, eotaxin,
MCP-1, MIP-1α)
Selectin
VCAM-1
ICAM-1
Transmigration
Adhesion
Endothelium
Blood


Arachidonic acid
5-Lipoxygenase
+ FLAP
5-HPETE
Inhibitors of
leukotriene
synthesis
5-Lipoxygenase
+ FLAP
Leukotriene A4
Leukotriene B4
CysLT receptor
antagonists
Leukotriene C4
Transpeptidase
Leukotriene D4
Atopy
Bronchoconstriction
Hyper-responsiveness
Dipeptidase
Leukotriene E4

- Airway inflammation contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity.

- In some patients, persistent changes in airway structure occur, including sub-basement fibrosis, mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis.

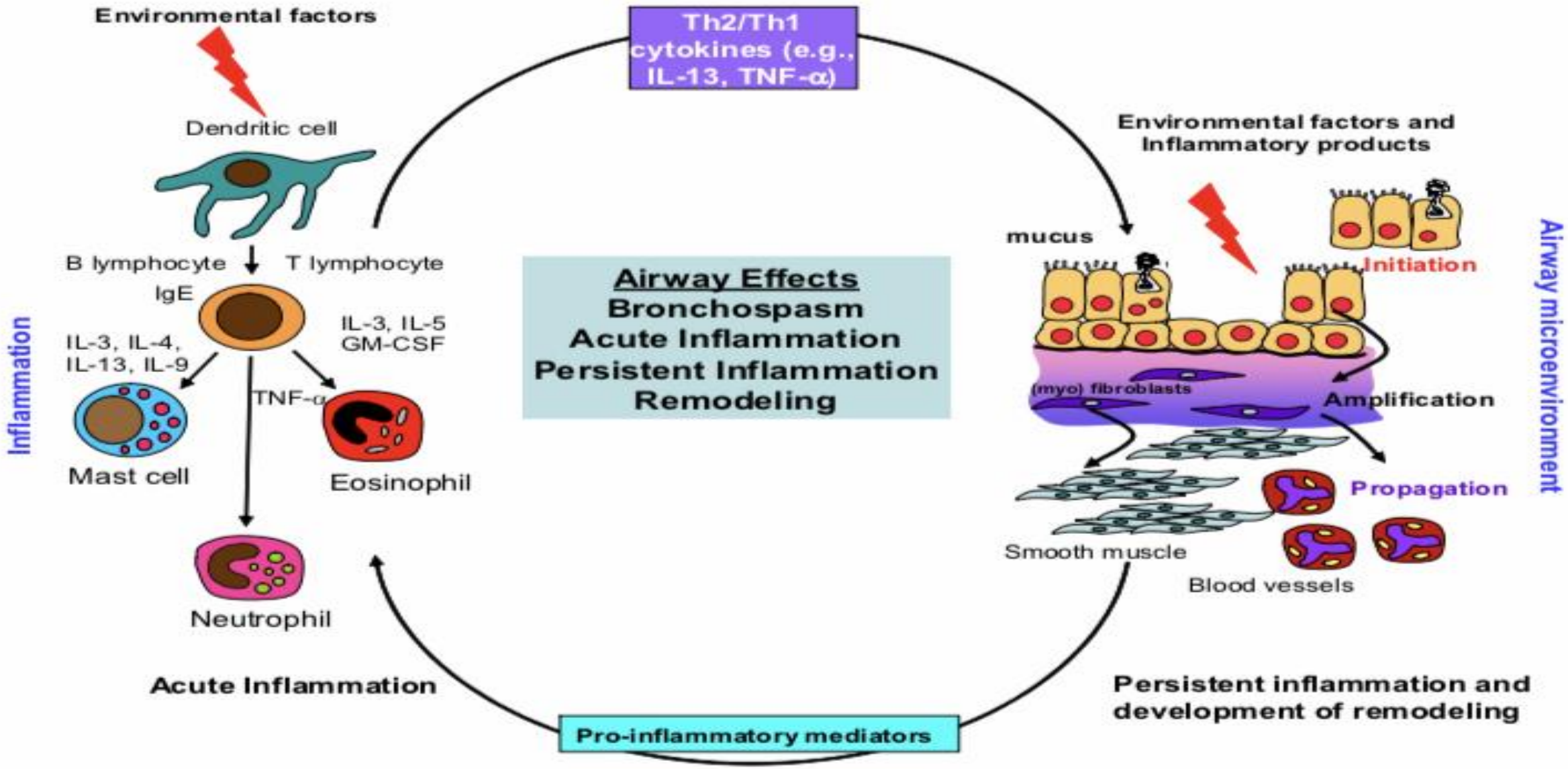
- Gene-by-environment interactions are important to the expression of asthma.

- Atopy, the genetic predisposition for the development of an immunoglobulin E (IgE)-mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma.

  — Viral respiratory infections are one of the most important causes of asthma exacerbation and may also contribute to the development of asthma.

- **Bronchoconstriction.** In asthma, the dominant physiological event leading to clinical symptoms is airway narrowing and a subsequent interference with airflow. In acute exacerbations of asthma, bronchial smooth muscle contraction (bronchoconstriction) occurs quickly to narrow the airways in response to exposure to a variety of stimuli including allergens or irritants. Allergen-induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that includes histamine, tryptase, leukotrienes, and prostaglandins that directly contract airway smooth muscle (Busse and Lemanske 2001). Aspirin and other nonsteroidal anti-inflammatory drugs (see section 3, component 3) can also cause acute airflow obstruction in some patients, and evidence indicates that this non-IgE-dependent response also involves mediator release from airway cells (Stevenson and Szczeklik 2006). In addition, other stimuli (including exercise, cold air, and irritants) can cause acute airflow obstruction. The mechanisms regulating the airway response to these factors are less well defined, but the intensity of the response appears related to underlying airway inflammation. Stress may also play a role in precipitating asthma exacerbations. The mechanisms involved have yet to be established and may include enhanced generation of pro-inflammatory cytokines.

FIGURE 2–2. FACTORS LIMITING AIRFLOW IN ACUTE AND PERSISTENT ASTHMA



Symptoms

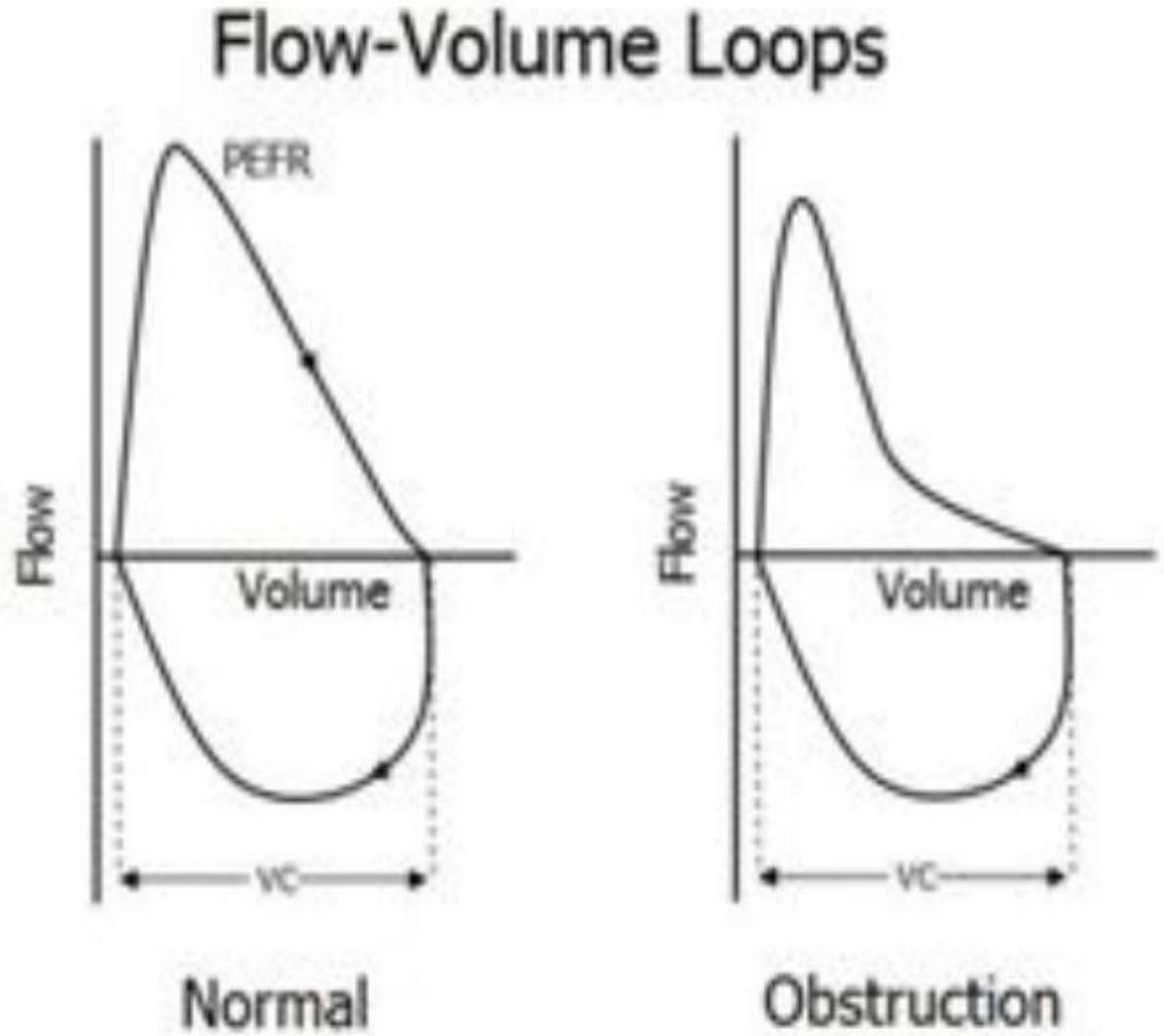
- Wheeze
  - Airway inflammation
- Fatigue
- Chest Tightness
- Cough
  - Nocturnal
  - Exertional
  - Nonspecific irritants

Diagnosis

- Clinical exam
- History
  - Environment
  - Family history
- Spirometry
  - Reversibility
  - Methacholine
  - FeNO2
- Atopy

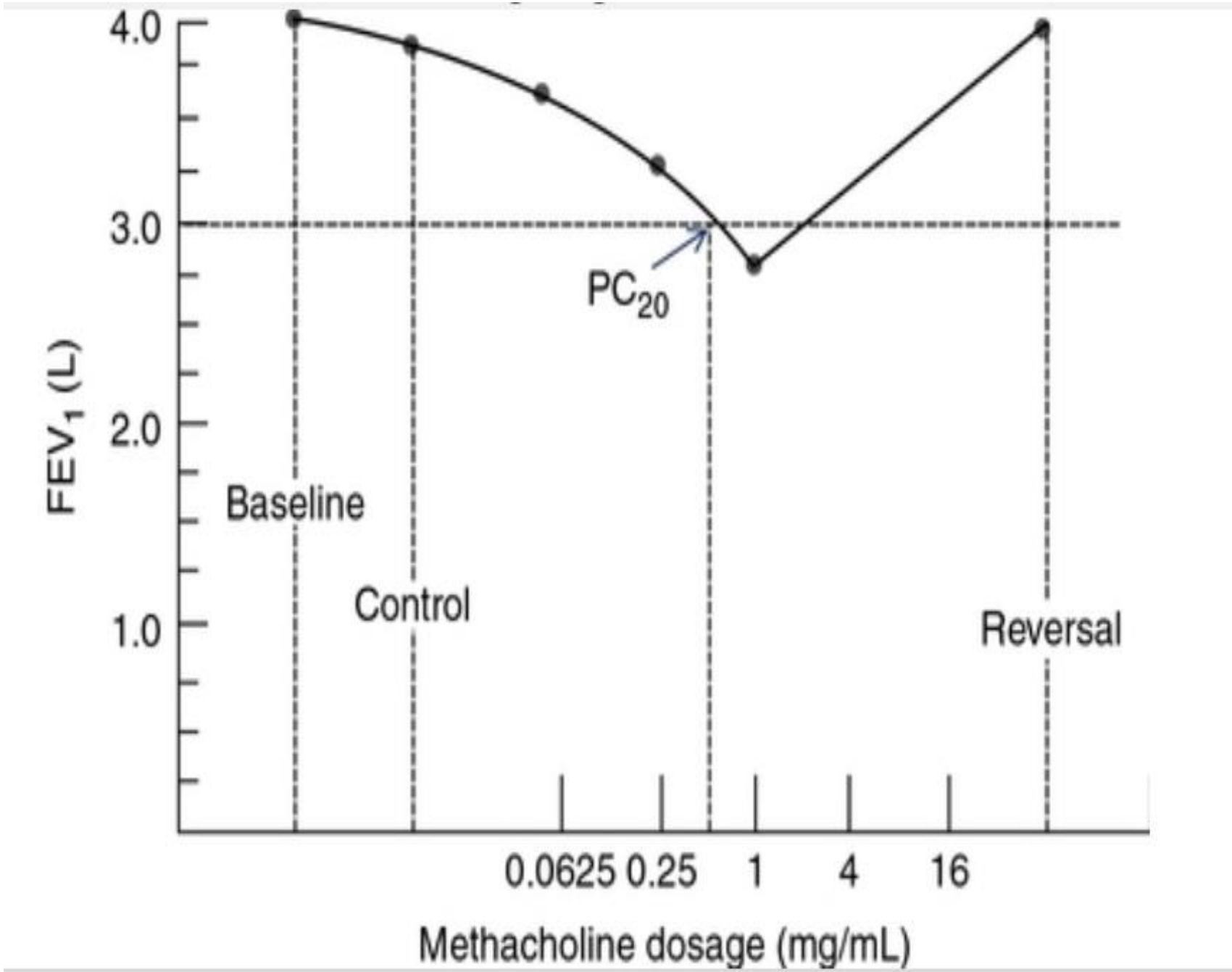
Spirometry

- FEV1
- FEF 25-75
- Reversibility
- Serial measurements


Flow-Volume Loops
PEFR
Flow
Volume
VC
Normal
Flow
Volume
VC
Obstruction

	Pre-Bronch			Post-Bronch		
	Actual	Pred	%Pred	Actual	%Pred	%Chng
--- SPIROMETRY ---						
FVC (L)	*4.00	4.86	*82	4.31	88	+7
FEV1 (L)	3.32	3.83	86	3.42	89	+3
FEV1/FVC (%)	83	79	104	79	100	-4
FEF 25% (L/sec)	*6.11	7.50	*81	*4.09	*54	-32
FEF 75% (L/sec)	1.53	1.71	89	*3.06	*179	+100
FEF 25-75% (L/sec)	3.55	3.56	99	3.52	98	+0
FEF Max (L/sec)	*6.18	9.60	*64	*4.21	*43	*-31
FIVC (L)	3.90			3.59		-7
FIF Max (L/sec)	3.21			4.13		+28
MVV (L/min)	*113	153	*73	140	91	+23

	Pre-Bronch			Post-Bronch		
	Actual	Pred	%Pred	Actual	%Pred	%Chng
--- SPIROMETRY ---						
FVC (L)	*1.85	4.27	*43	*1.90	*44	+2
FEV1 (L)	*1.02	3.14	*32	*1.18	*37	+16
FEV1/FVC (%)	*55	74	*74	62	84	+13
FEF 25% (L/sec)	*1.17	7.06	*16	*1.78	*25	+53
FEF 75% (L/sec)	*0.25	1.18	*21	*0.44	*37	+77
FEF 25-75% (L/sec)	*0.50	2.39	*20	*0.74	*30	+47
FEF Max (L/sec)	*2.36	8.15	*28	*2.61	*31	+10
FIVC (L)	1.82			2.20		+21
FIF Max (L/sec)	2.24			2.04		-8
MVV (L/min)	*37	125	*29	*37	*29	+0


4.0
3.0
2.0
1.0
FEV1 (L)
PC20
Baseline
Control
Reversal
0.0625 0.25 1 4 16
Methacholine dosage (mg/mL)

Exhaled Nitric Oxide

Conclusions:

In the setting of chronic inflammatory airway disease including asthma, conventional tests such as FEV1 reversibility or provocation tests are only indirectly associated with airway inflammation. FeNO offers added advantages for patient care including, but not limited to (1) detecting of eosinophilic airway inflammation,(2) determining the likelihood of corticosteroid responsiveness,(3) monitoring of airway inflammation to determine the potential need for corticosteroid, and (4) unmasking of otherwise unsuspected nonadherence to corticosteroid therapy.

What Do the Results Mean?

The measurements are used to determine:

- If you should take steroids to manage your asthma.
- If you are already taking steroids, the results will show how effective your medications are.
- If you are following your asthma treatment plan.
- If you should modify your therapy plan; you might be asked to do the test three to four times a year.
- In some cases, the results are used to diagnose asthma, along with results of other diagnostic tests.

Long term management

- Reduce Risk
  - Prevent exacerbations
  - Minimize need for emergency care, hospitalization
  - Prevent loss of lung function
  - Minimize adverse effects of therapy

- Reduce impairment
  - Prevent chronic symptoms
  - Require infrequent use of short acting beta agonist
  - Maintain normal lung function and normal activity

Assessment and Monitoring

- Following long term at each clinic visit
  - Asthma control
  - Proper medication technique
  - Written asthma plan
  - Spirometry every year, more frequent if control being achieved
  - Patient adherence
  - Patient concerns

Follow up care

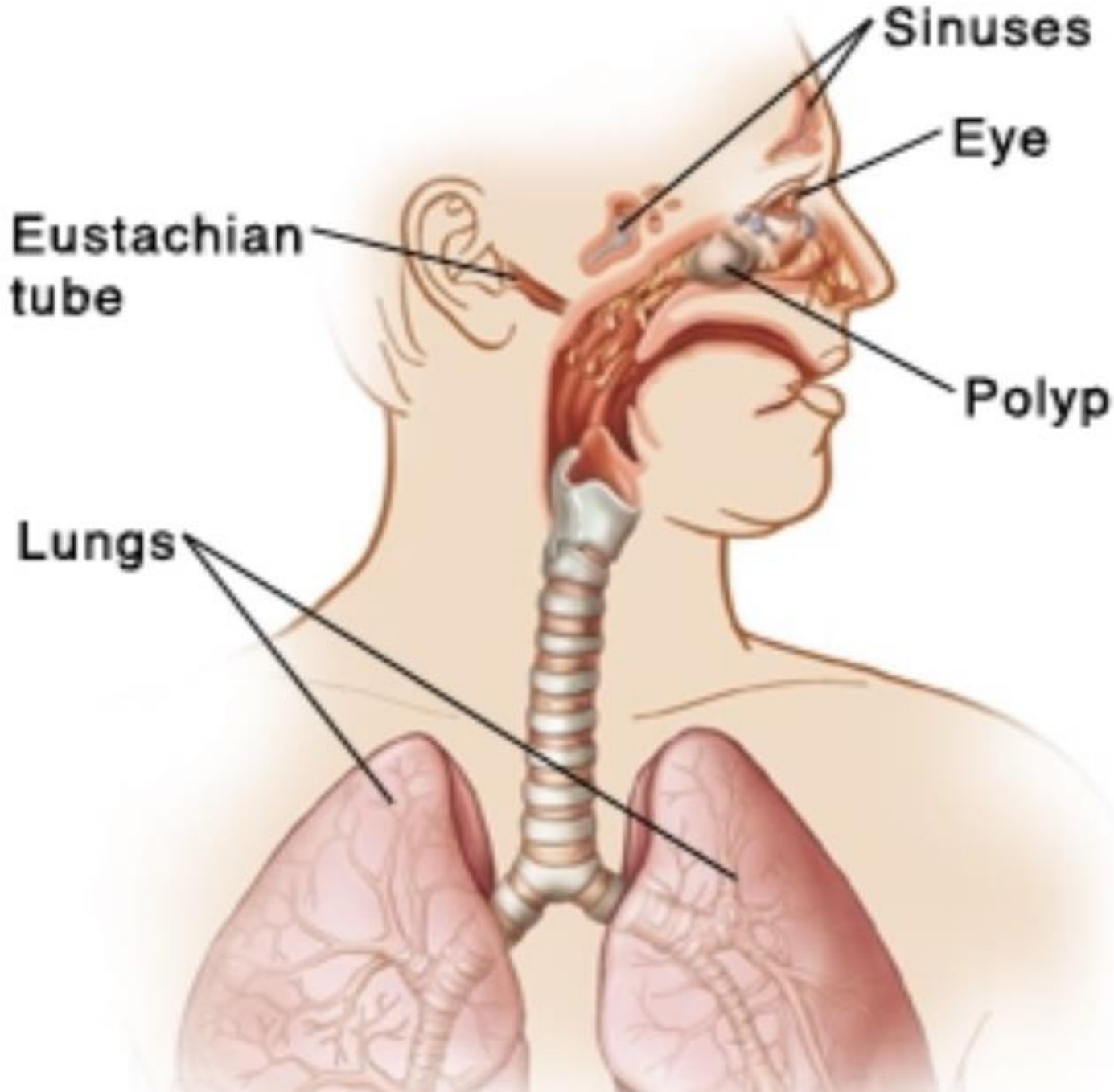
- Asthma is highly variable over time, See Patients:
  - Every 2-6 weeks while gaining control
  - Every 1-6 months to monitor control
  - Every 3 months if step down is anticipated

Teach patients how to manage their asthma

- Self monitoring (Peak Flow)
- Encourage praise, which builds confidence.
- Encourage family involvement
- Taking medication appropriately
  - Maintenance therapy
  - Recovery inhaler
  - Written asthma action plan
    - Daily control
    - Response to worsening asthma
    - Seek medical care

Exposure concerns

- Allergen concerns
- Tobacco exposure
- Co-morbidities
  - Sinus
  - GERD
  - Dietary
  - Sleep apnea
  - Exercise exacerbation (Leukotriene C, D)
    - SABA
    - Cromolyn
    - Leukotriene inhibitors (Cysteinyl pathway)
    - Warm up


Sinuses
Eye
Eustachian tube
Polyp
Lungs

Therapeutic Options

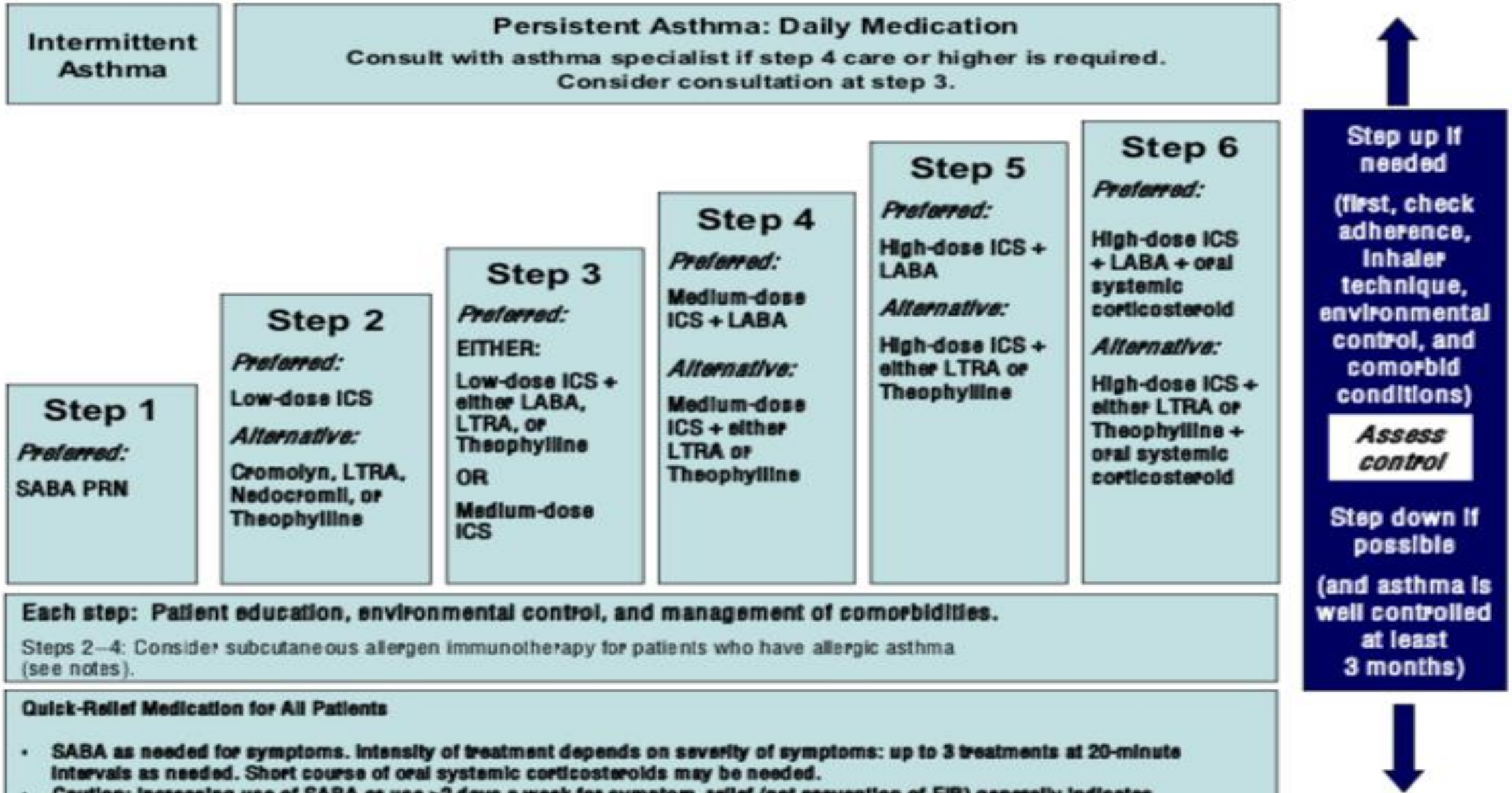
- Allergy assessment and therapy
  - RAST/IgE
  - Skin Testing
  - Antileukotriene
  - Antihistamine
  - Environmental Control

Inhaler Use and Step Management

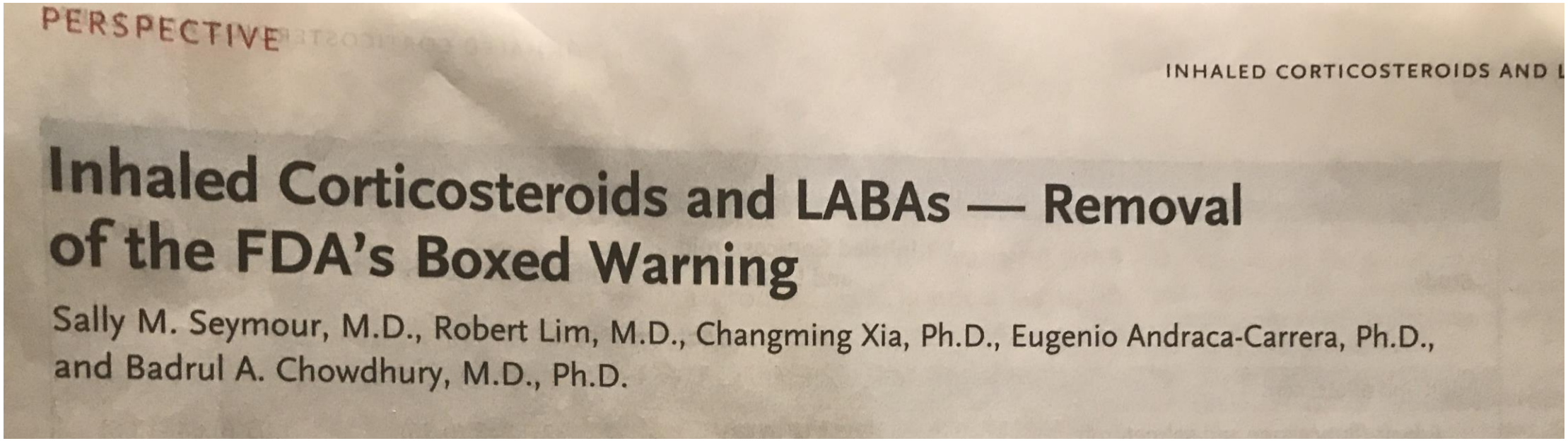
- Short Acting Beta Agonist (SABA)
- Inhaled Steroid
- Long Acting Beta Agonist (LABA)
- Intermittent inhaled steroid use

Lowest level of treatment required to maintain control (See figure 4–1a for treatment steps.)	Classification of Asthma Severity			
	Intermittent	Persistent		
	Step 1	Mild	Moderate	Severe
		Step 2	Step 3 or 4	Step 5 or 6

Components of Severity		Classification of Asthma Severity (Children 5–11 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV_1 between exacerbations • FEV_1 >80% predicted • FEV_1/FVC >85%	• FEV_1 = >80% predicted • FEV_1/FVC >80%	• FEV_1 = 60–80% predicted • FEV_1/FVC = 75–80%	• FEV_1 <60% predicted • FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2 in 1 year (see note) →		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →			
		Relative annual risk of exacerbations may be related to FEV_1			


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 Theophylline
Step 3
Preferred:
EITHER:
Low-dose ICS + either LABA, LTRA, or Theophylline
OR
Medium-dose ICS
Step 4
Preferred:
Medium-dose ICS + LABA
Alternative:
Medium-dose ICS + either LTRA or Theophylline
Step 5
Preferred:
High-dose ICS + LABA
Alternative:
High-dose ICS + either LTRA or Theophylline
Step 6
Preferred:
High-dose ICS + LABA + oral systemic corticosteroid
Alternative:
High-dose ICS + either LTRA or Theophylline + oral systemic corticosteroid
Step up if needed
(first, check adherence, inhaler technique, 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.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).
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.
• Caution: Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Black Box



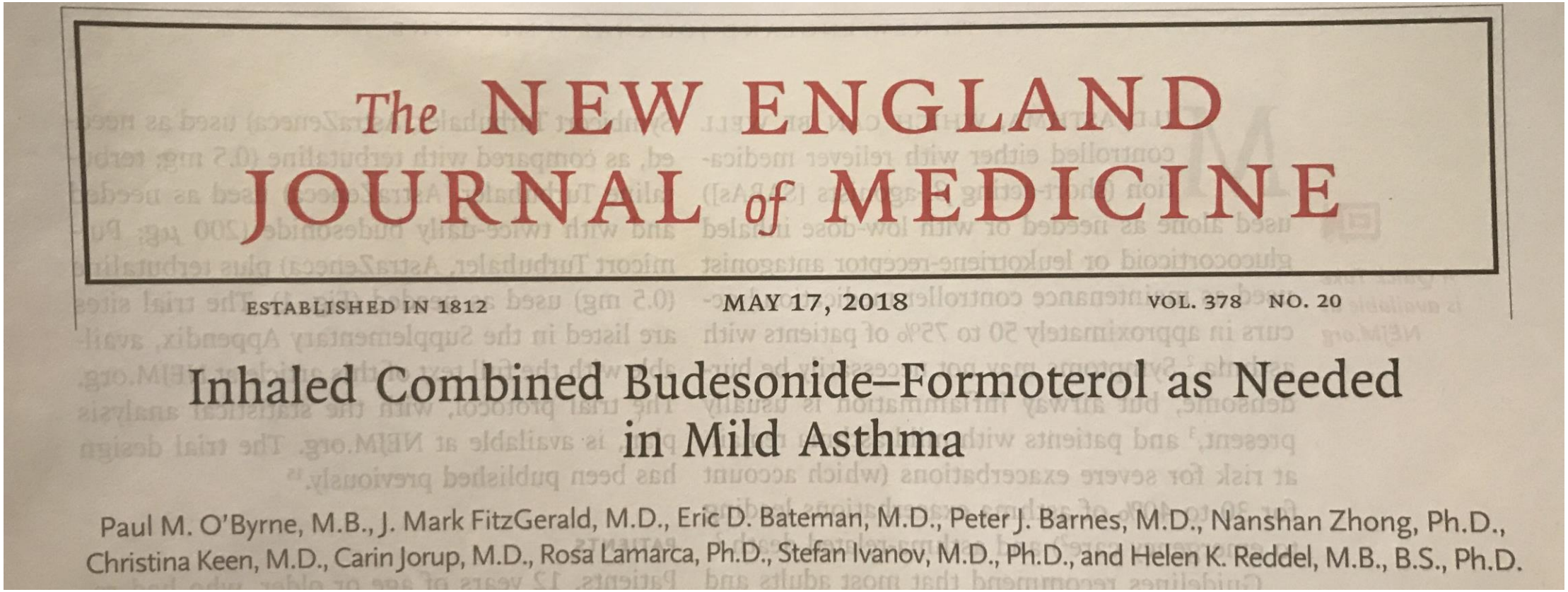
PERSPECTIVE

INHALED CORTICOSTEROIDS AND L

Inhaled Corticosteroids and LABAs — Removal of the FDA's Boxed Warning

Sally M. Seymour, M.D., Robert Lim, M.D., Changming Xia, Ph.D., Eugenio Andraca-Carrera, Ph.D., and Badrul A. Chowdhury, M.D., Ph.D.

Step Therapy Adjustments



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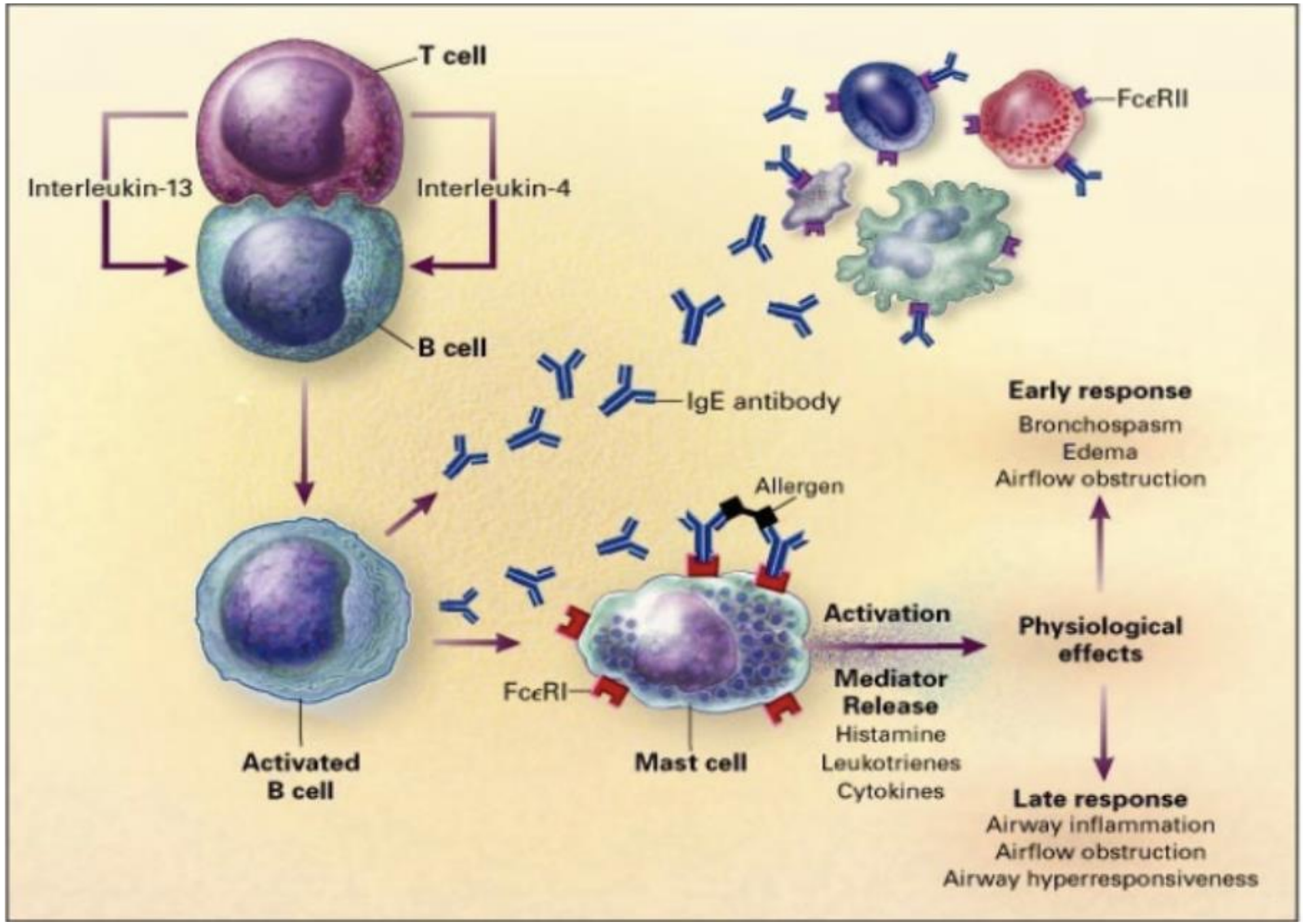
Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

Add on Management

- Xolair (IgE)
- Anti-eosinophilia biologics (IL5) (Fasenra, Nucala)
- IL4, IL13 (Dupixent)


T cell
Interleukin-13
Interleukin-4
B cell
FcεRII
IgE antibody
Allergen
Activated
B cell
FcεRI
Mast cell
Activation
Mediator
Release
Histamine
Leukotrienes
Cytokines
Physiological
effects
Early response
Bronchospasm
Edema
Airflow obstruction
Late response
Airway inflammation
Airflow obstruction
Airway hyperresponsiveness

Increasing confidence in the therapeutic relevance of eosinophils in severe asthma

Chronic airways diseases are a major burden globally, affecting all age groups and causing substantial morbidity, disability, and mortality worldwide.[1,2] In view of this challenging situation, the Lancet Commission after asthma: redefining airways diseases, chaired by Ian Pavord and Andrew Bush, proposes a major change in thinking about asthma that is generalisable to all airways diseases: the deconstruction of airways diseases into component parts that are identifiable and treatable.[3,4] Thus, identification of treatable traits would be the basis for future development

agents (mepolizumab and reslizumab, which are both monoclonal antibodies against interleukin 5, and benralizumab), have been developed for severe eosinophilic asthma.[5,7] Dupilumab, a monoclonal antibody against interleukin 4 receptor α that blocks the interleukin 4 and interleukin 13 pathways, has also been tested in severe asthma.[8] With various biologicals now approved as add-on therapies for severe asthma and without direct comparisons between these agents, prescribers will have difficulties in identifying the optimum agent for a given patient because of

KEY POINTS: DIAGNOSIS OF ASTHMA

- To establish a diagnosis of asthma, the clinician should determine that (EPR—2 1997):
  - Episodic symptoms of airflow obstruction or airway hyperresponsiveness are present.
  - Airflow obstruction is at least partially reversible.
  - Alternative diagnoses are excluded.
- Recommended methods to establish the diagnosis are (EPR—2 1997):
  - Detailed medical history.
  - Physical exam focusing on the upper respiratory tract, chest, and skin.
  - Spirometry to demonstrate obstruction and assess reversibility, including in children 5 years of age or older. Reversibility is determined either by an increase in FEV_1 of ≥12 percent from baseline or by an increase ≥10 percent of predicted FEV_1 after inhalation of a short-acting bronchodilator.
  - Additional studies as necessary to exclude alternate diagnoses.

KEY POINTS: INITIAL ASSESSMENT OF ASTHMA

- Once the diagnosis has been established, information obtained from the diagnostic evaluation, and additional information, if necessary, should be used to characterize the patient's asthma in order to guide decisions for therapy (EPR—2 1997):

  — Identify precipitating factors (e.g., exposure at home, work, daycare, or school to inhalant allergens, or irritants such as tobacco smoke, or viral respiratory infections) (Evidence A)

  — Identify comorbidities that may aggravate asthma (e.g., sinusitis, rhinitis, GERD) (Evidence B)

  — Classify asthma severity, using measures in both the impairment (Evidence B) and risk domains (Evidence C)

- Measures of pulmonary function, using spirometry, are recommended for assessing asthma severity. Low FEV_1 indicates current obstruction (impairment domain) and risk for future exacerbation (risk domain) (Evidence C). For children, FEV_1/FVC appears to be a more sensitive measure of severity in the impairment domain; FEV_1 is a useful measure of risk for exacerbations (Evidence C).

KEY POINTS: OVERVIEW OF MEASURES OF ASTHMA ASSESSMENT AND MONITORING

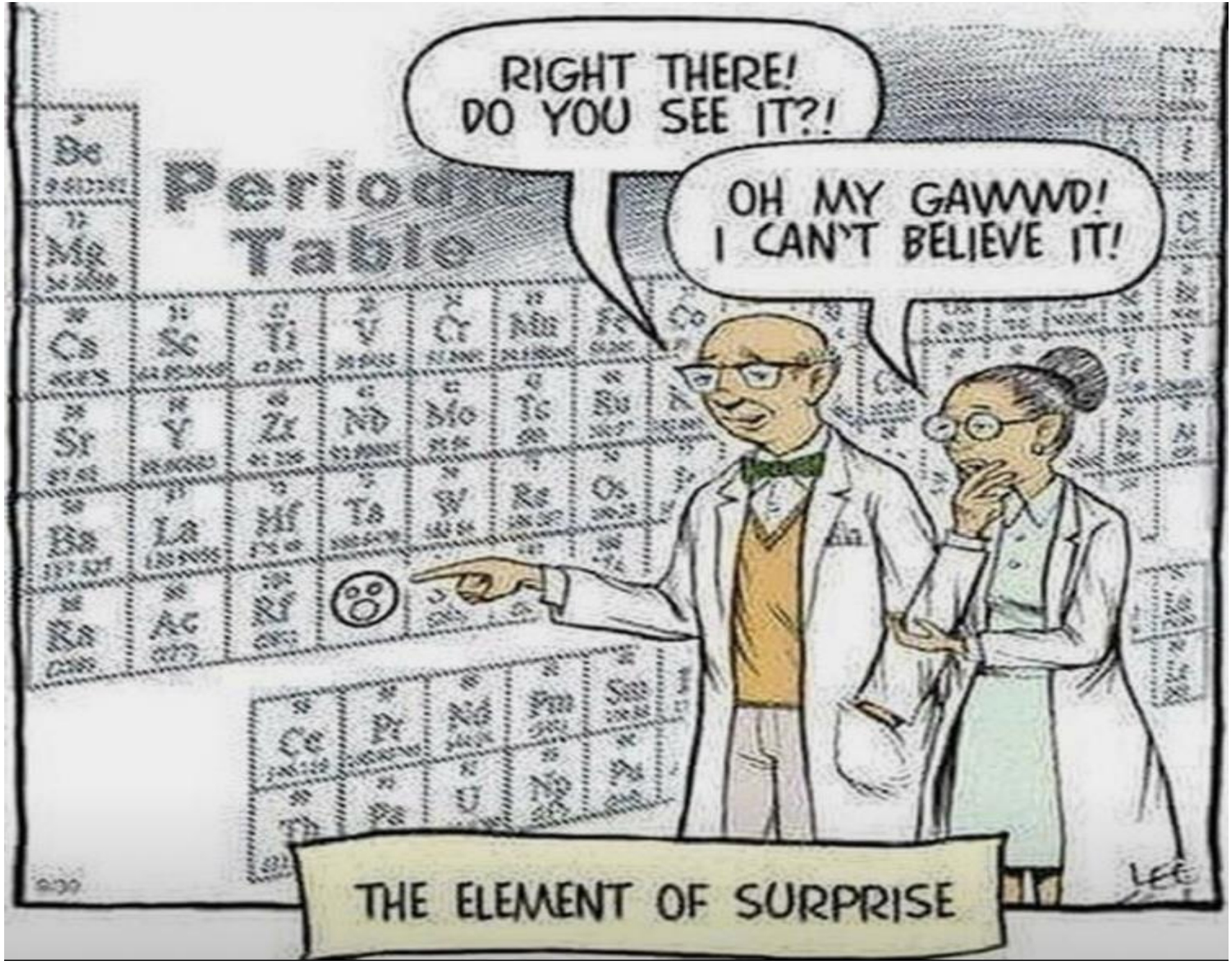
- The functions of assessment and monitoring are closely linked to the concepts of severity, control, and responsiveness to treatment:
  - — Severity: the intrinsic intensity of the disease process. Severity is measured most easily and directly in a patient not receiving long-term-control therapy.
  - — Control: the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met
  - — Responsiveness: the ease with which asthma control is achieved by therapy.
- Both severity and control include the domains of current impairment and future risk:
  - — Impairment: frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced
  - — Risk: the likelihood of either asthma exacerbations, progressive decline in lung function (or, for children, reduced lung growth), or risk of adverse effects from medication

- The concepts of severity and control are used as follows for managing asthma:

  — During a patient's initial presentation, if the patient is not currently taking long-term control medication, asthma severity is assessed to guide clinical decisions on the appropriate medication and other therapeutic interventions.

  — Once therapy is initiated, the emphasis thereafter for clinical management is changed to the assessment of asthma control. The level of asthma control will guide decisions either to maintain or adjust therapy.

  — For population-based evaluations, clinical research, or subsequent characterization of the patient's overall severity, asthma severity can be inferred after optimal therapy is established by correlating levels of severity with the lowest level of treatment required to maintain control. For clinical management, however, the emphasis is on assessing asthma severity for initiating therapy and assessing control for monitoring and adjusting therapy.


RIGHT THERE! DO YOU SEE IT?!
OH MY GAWWD! I CAN'T BELIEVE IT!
Periodic Table
THE ELEMENT OF SURPRISE
LEE