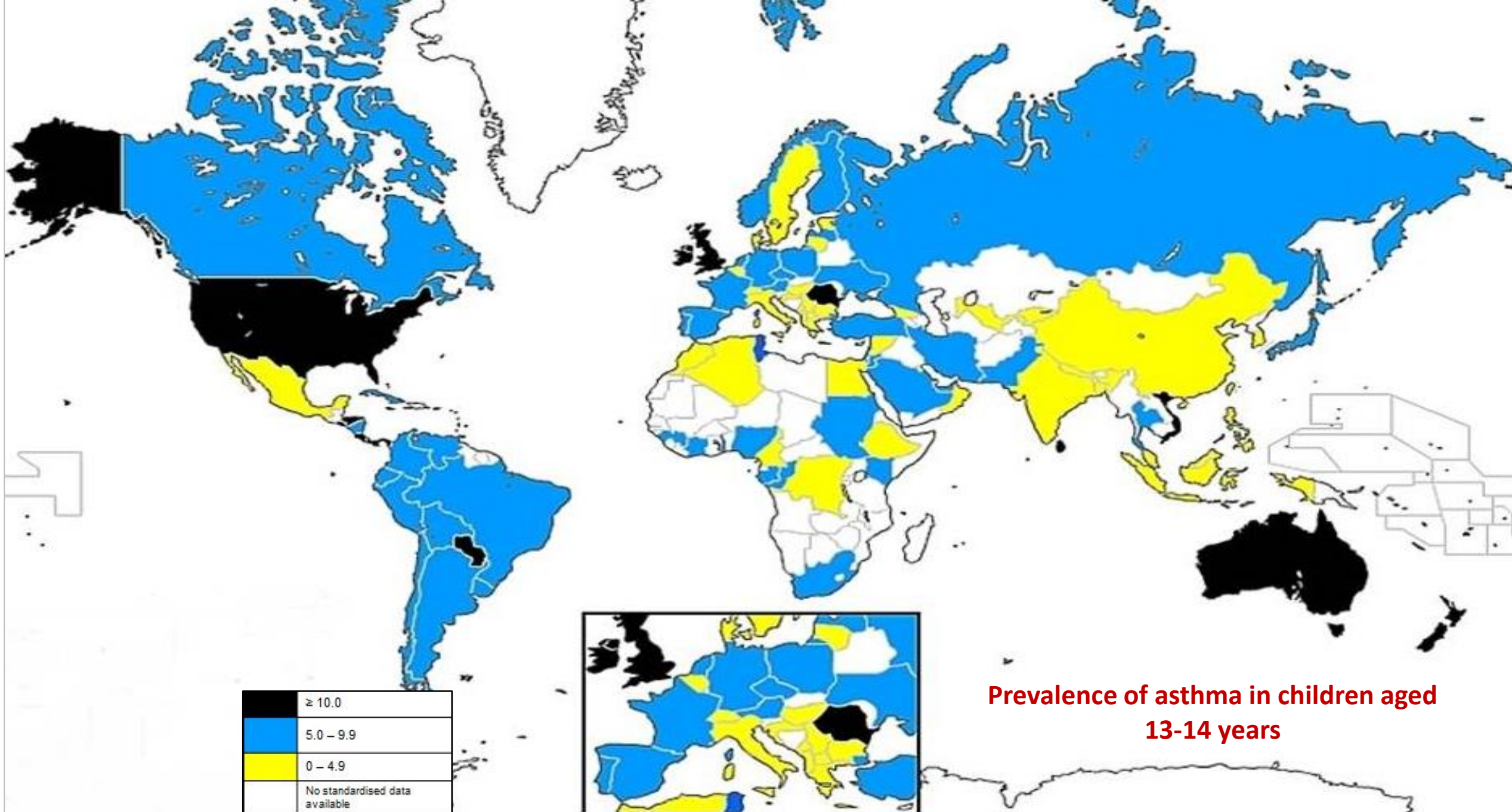


ASTHMA EVALUATION AND DIAGNOSIS

Ali R, Jafarinezhad, MD
pulmonologist

Burden of asthma

- Asthma is one of the most common chronic diseases worldwide with an estimated 300 million affected individuals
- Prevalence is increasing in many countries, especially in children
- Asthma is a major cause of school and work absence
- Health care expenditure on asthma is very high



definition

The Global Initiative for Asthma defines asthma as follows **(GINA)** :

"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation."

Reactive airways disease

Transient symptoms of cough and wheeze when confirmation of a diagnosis of asthma is lacking(very young children)

Reactive airways dysfunction syndrome (RADS)

Refers to an airway disorder resulting from an intense exposure to an inhaled chemical irritant or noxious gas(asthma-like features)

CLINICAL FEATURES

- **Asthma is diagnosed before the age of seven years in approximately 75 percent of cases (allergies)**

Personal or family history of atopy – A strong family history of asthma and allergies or a personal history of atopic diseases (eg, atopic dermatitis, seasonal allergic rhinitis and conjunctivitis)

- **Occupational asthma** (10 percent of cases of new-onset asthma)
- **Aspirin-sensitive asthma** (aspirin-exacerbated respiratory disease)
- **Obesity**
- **pregnancy**
- **Exercise-triggered symptoms** typically develop 5 to 15 minutes after a brief (eg, five minutes) period of exertion or about 15 minutes into prolonged exercise and resolve with rest over approximately 30 to 60 minutes

Aspirin-exacerbated respiratory disease (AERD) (also called NSAID-exacerbated respiratory disease or NERD)

- Describes patients with asthma and chronic rhinosinusitis (CRS) with nasal polyposis, who experience acute upper and lower respiratory tract symptoms following the ingestion of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs)
- AERD affects 5 to 20 percent of all patients with asthma. Reactions to NSAIDs typically begin 30 minutes to 3 hours after ingestion and present as a sudden worsening of asthma and nasal congestion, sometimes accompanied by other symptoms
- Patients with AERD require guideline-based therapy for asthma and medical and surgical management of CRS with nasal polyposis

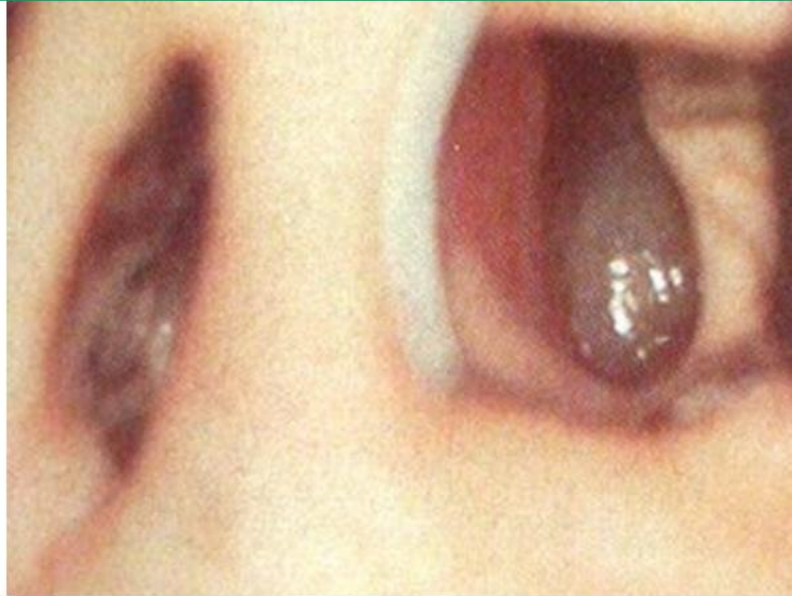
For patients with AERD and moderate-to-severe asthma, we recommend adding a leukotriene-modifying agent (LTMA) to their other asthma therapy

Aspirin desensitization:

- Nasal polyposis that is worsening or recurring despite intranasal glucocorticoids, surgery, and other appropriate therapies
- Inflammatory conditions requiring daily NSAID therapy that cannot be treated with selective COX-2 inhibitors
- Atherosclerotic heart/vascular disease requiring the antiplatelet effects of aspirin
- Recurrent headaches or other conditions requiring intermittent use of NSAIDs

Nasal polyps in nostril

Nasal polyps in nostril



Nasal polyps appear as glistening, gray or white, mucoid masses in the nasal cavities.

Courtesy of Glenis Scadding, MD and Peter Andrews, BSc, FRCS.

Pregnancy

1/3 improved , 1/3 unchanged , 1/3 deteriorate

SABA , ICS , theophylline shown to be safe

there is less safe about LABA , antileukotrienes

NO CONTRAINDICATION TO BREAST FEEDING FOR THESE DRUG

TABLE 309-1 RISK FACTORS AND TRIGGERS INVOLVED IN ASTHMA

Endogenous Factors	Environmental Factors
Genetic predisposition	Indoor allergens
Atopy	Outdoor allergens
Airway hyperresponsiveness	Occupational sensitizers
Gender	Passive smoking
Ethnicity	Respiratory infections
Obesity	Diet
Early viral infections	Acetaminophen (paracetamol)
Triggers	
Allergens	
Upper respiratory tract viral infections	
Exercise and hyperventilation	
Cold air	
Sulfur dioxide and irritant gases	
Drugs (β blockers, aspirin)	
Stress	
Irritants (household sprays, paint fumes)	

Questions to help identify asthma triggers*

Questions to help identify asthma triggers*

Allergen exposures
Do you have asthma symptoms year-round or only certain times of year?
Do you have pets? Or birds? Are they indoors or outdoors most of the time?
Have you seen cockroaches at home/school/work in the past month? How about rodents?
Is there moisture, dampness, moldy odor, or visible mold in your home?¶
For patients who live in dry climates, do you use an evaporative cooler (also known as a swamp cooler)? These coolers are associated with increased humidity and increased mold/dust mites.
Do your asthma symptoms get worse during pollen seasons (eg, tree pollen in early spring in New England) or more humid times of year (suggests molds and dust mites)?
Have you ever had allergy skin or IgE testing? If so, do you have the results?

Irritant exposures

Do you smoke cigarettes? If so, how many/day and how long have you smoked?

Does anyone at home/work/daycare smoke?

Do you smoke cannabis (marijuana), use electronic cigarettes, or vape?

Do you use a wood-burning stove or fireplace at home?

Do you have any unvented/open fire stoves or heaters at home?

Are you exposed regularly to smells or fumes from perfumes, cleaning agents, or sprays?

Work and school

Do you cough, wheeze or need your inhaler more during the week at work/school than on weekends or times away from work/school?

Do your eyes or nose itch or feel irritated at work/school?

Do coworkers or other students have similar symptoms?

Are you exposed to fumes, dusts, or vapors at work? If so, what?

Nasal problems

Do you have seasonal or persistent nasal congestion, runny nose, postnasal drip, or decreased sense of smell?

Are your nasal symptoms worse at home/school/work?

Gastroesophageal reflux

Do you have heartburn (burning sensation in the chest); does food come back up into your mouth; or do you sense/taste sour stomach acid coming up into your throat?

Medications that can worsen asthma
Do you use eye drops? If so, which? Do your asthma symptoms worsen after taking them?
Do you use any medications that contain beta-blockers or ACE inhibitors? Has your asthma worsened since you started taking this medication?
Do you take aspirin or other NSAIDs? Do your asthma symptoms flare when you take them?
Possible sulfite sensitivity ^Δ
Do you have wheezing, coughing, or shortness of breath after eating shrimp, dried fruit, or processed potatoes or after drinking beer or wine?

IgE: immunoglobulin E; ACE: angiotensin-converting enzyme; NSAID: nonsteroidal anti-inflammatory drug.

* These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.

¶ Higher humidity makes mold and mite exposure more likely. Visible mold suggests significant mold exposure.

Δ Rare issue in children.

Adapted from: National Heart, Blood, and Lung Institute Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma. NIH Publication no. 08-4051, 2007.

pathophysiology

Airway inflammation

inflammation in the Respiratory mucosa From trachea to terminal bronchioles

The common pattern is eosinophilic infiltration

The some patients with severe asthma show a neutrophilic pattern

Mast Cells

Activated by allergens through an IgE- dependent mechanism

Macrophages and dendritic cells

dendritic cells are the major antigen-presenting cells

Eosinophils

Blocking antibodies to IL-5 is not associated with reduced AHR or asthma symptoms ,although in selected patients with steroid-resistant air way reduction exacerbation

Neutrophils

pathophysiology

T lymphocytes

Release cytokines ,resulting in the recruitment and survival of eosinophils and mast cells in air ways

TH2 (CD4) cells predominate

[IL5 (eosinophils) IL -4 ,IL-13 (increased IgE)]

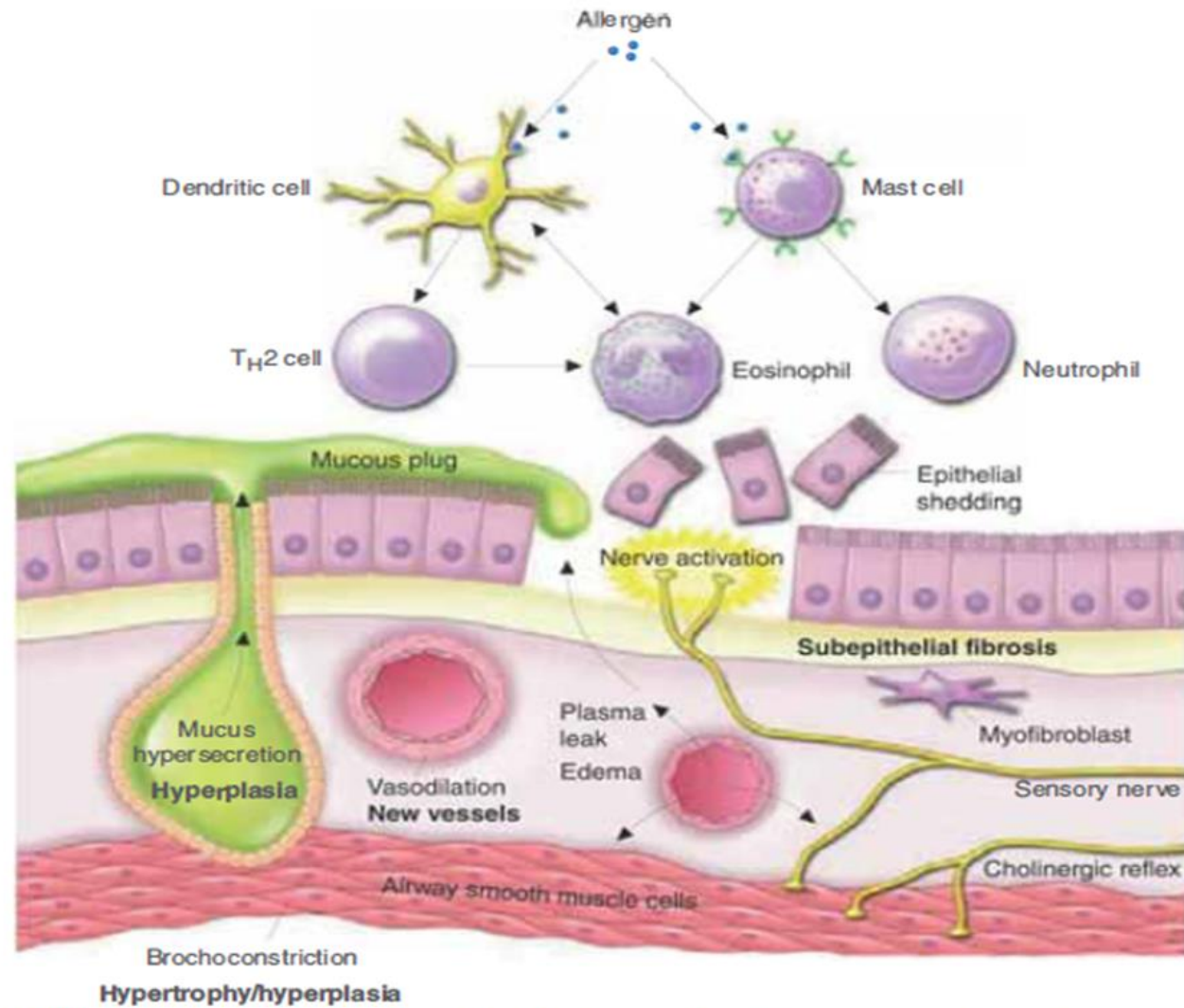


FIGURE 309-3 The pathophysiology of asthma is complex with participation of several interacting inflammatory cells, which result in acute and chronic inflammatory effects on the airway.

EVALUATION

Spirometry:

The results of spirometry can be used to determine the following:

- Determine whether baseline airflow limitation (obstruction) is present (reduced FEV1/FVC ratio)
- Assess the reversibility of the obstructive abnormality by repeating spirometry after administration of a bronchodilator
- Characterize the severity of airflow limitation (based on the FEV1 as a percentage of the normal predicted value)
- For patients with normal airflow (normal FEV1/FVC ratio), identify a restrictive pattern as an alternate explanation for dyspnea (eg, FVC <80 percent predicted)

Bronchodilator response

An increase in FEV1 of 12 percent or more, accompanied by an absolute increase in FEV1 of at least 200 mL, can be attributed to bronchodilator responsiveness with 95 percent certainty

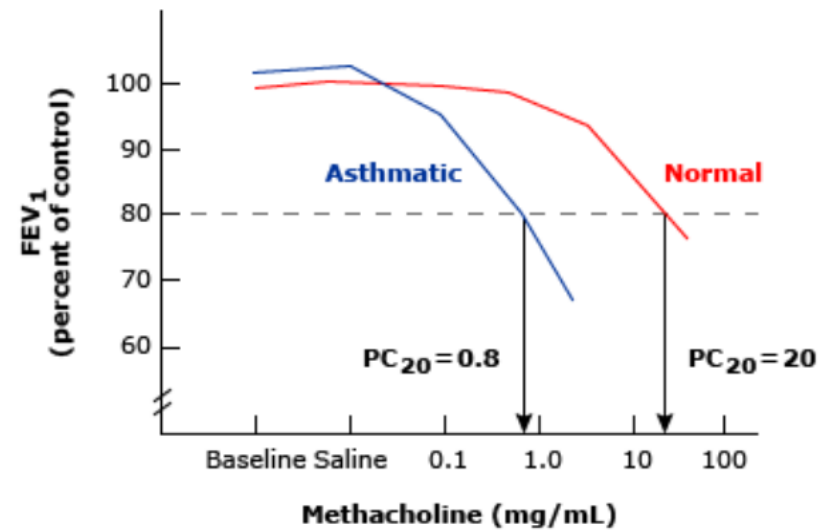


Bronchoprovocation testing

- Bronchoprovocation testing is a useful tool for diagnosing asthma in patients with normal baseline airflow
- Using a **cut point of 8 mg/mL** of methacholine or less to indicate the presence of hyperresponsiveness, as many as 5 percent of the normal population and a greater percentage of non-asthmatic persons with rhinitis will exhibit positive results

Bronchoprovocation testing

Bronchoprovocation testing



The effect of increasing the inhaled dose of methacholine in a healthy subject (red) and an asthmatic patient (blue). The provocative concentration is the amount of inhaled agonist required to drop the FEV₁ by 20 percent from the baseline (PC₂₀ FEV₁) and is much less in the asthmatic than in the normal subject: 0.8 mg/mL versus 20 mg/mL. In general, a PC₂₀ ≤ 8 mg/mL is consistent with asthma; and a PC₂₀ > 16 mg/mL is considered a negative test. Thus, an increase in airway responsiveness is characterized by a decrease in the PC₂₀.

Peak expiratory flow

The range of normal values around the mean is up to 80 to 100 L/min

Technique for peak flow measurement in asthma

Technique for peak flow measurement in asthma

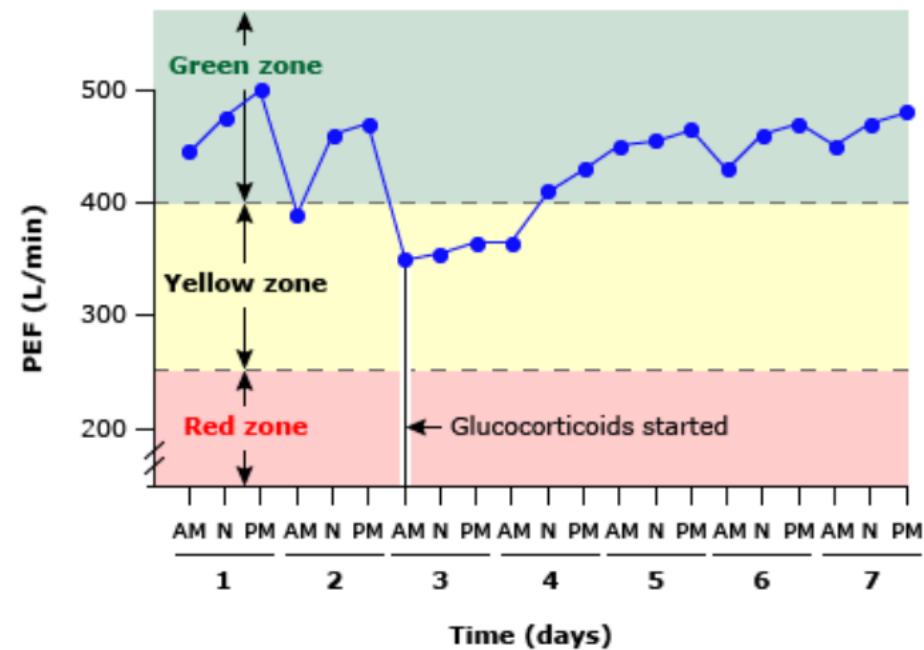
Move peak flow meter indicator to zero.
Sit or stand up straight.
Take in a deep breath, as deep as you can.
Place peak flow meter in your mouth and close your lips around the mouthpiece*.
As soon as your lips are sealed around mouth piece, blow out as hard and fast as you can using your chest and belly muscles¶. This should take no more than 2 seconds.
Write down the result.
Repeat two more times (three total).
Record the highest of the three values.

* Nose clips are not necessary.
¶ Make sure to use all of your breathing muscles, not just your mouth muscles. This needs a lot of force, like blowing out a candle several feet away.



Peak flow diary in asthma

Peak flow diary in asthma



Diary record of peak expiratory flow (PEF) from an asthmatic patient over a one week period. The patient recorded PEF three times a day at waking (AM), noon (N) and upon retiring (PM). The red zone is set at 50 percent of the personal best, whereas the yellow is from 50 to 80 percent and the green zone is >80 percent. Notice the reproducible

Limitations of PEF

Peak flow values often underestimate the severity of airflow obstruction

Reduced peak flow measurements may be seen in both obstructive and restrictive diseases

Peak flow measurements are not sufficient to distinguish upper airway obstruction

Exhaled nitric oxide

Normal level does not exclude asthma.

The test is based on the observation that eosinophilic airway inflammation associated with asthma leads to up-regulation of nitric oxide synthase in the respiratory mucosa, which in turn generates increased amounts of nitric oxide gas in the exhaled breath.

An elevated FENO (≥ 40 to 50 parts per billion) can help “rule in” asthma although potentially confounding respiratory diseases (eg, allergic rhinitis, eosinophilic bronchitis) must be excluded.

The measurement of FENO and its potential role in asthma diagnosis and monitoring are discussed separately

Allergic sensitivity to specific allergens in the environment can be assessed using either of two methods:

Blood tests for allergen-specific IgE {(RAST) radioallergosorbent tests}

aeroallergens (eg, house dust mite antigen, cat and dog danders, cockroach antigen, mouse and rat antigens, pollens, and mold spores) are the types of allergens most commonly implicated in asthma. Orally ingested food allergens rarely cause isolated asthmatic symptoms

- Moderate-to-severe persistent asthma when considering treatment with anti IgE monoclonal antibody (omalizumab)
- Allergic bronchopulmonary aspergillosis
- Very high total IgE levels (>1000 IU/mL)
 - Allergic bronchopulmonary aspergillosis
 - Parasitic infections
 - Sometimes eczema

Allergy skin tests are performed to a panel of indoor and outdoor aeroallergens

Blood tests

No blood tests are available that can determine the presence or absence of asthma or gauge its severity

Markedly elevated **eosinophil percentages (>15 percent) or counts (>1500 eosinophils/microL)** may be due to allergic asthma, but should prompt consideration of alternative or additional diagnoses, including:

- ☐ **parasitic infections** (eg, Strongyloides)
- ☐ **drug reactions**
- ☐ **syndromes of pulmonary infiltrates with eosinophilia** including:
 - Allergic bronchopulmonary aspergillosis
 - Eosinophilic granulomatosis with polyangiitis
 - Hypereosinophilic syndrome

Imaging

In the absence of comorbid illness, the chest radiograph is almost always normal in patients with asthma. However, many clinicians, including ourselves, obtain a chest radiograph for new-onset, moderate-to-severe asthma in adults over age 40 to exclude the occasional alternative diagnosis that may mimic asthma (eg, the mediastinal mass with tracheal compression or heart failure)

chest radiography(CXR , CT SCAN) is indicated in patients presenting with features that are atypical for asthma, including any of the following:

- Fever
- Chronic purulent sputum production
- Persistently localized wheezing
- Hemoptysis
- Weight loss
- Clubbing
- Inspiratory crackles
- Significant hypoxemia (eg, pulse oxygen saturation less than approximately 94 percent) in the absence of an acute asthmatic attack
- Moderate or severe airflow obstruction that does not reverse with bronchodilators

DIAGNOSIS

Increased probability that symptoms are due to asthma if:

More than one type of symptom (wheeze, shortness of breath, cough, chest tightness)

Symptoms often worse at night or in the early morning

Symptoms vary over time and in intensity

Symptoms are triggered by viral infections, exercise, allergen exposure, changes in weather, laughter, irritants such as car exhaust fumes, smoke, or strong smells

Decreased probability that symptoms are due to asthma if:

Lack of improvement following anti-asthmatic medications

Onset of symptoms after age 50

Isolated cough with no other respiratory symptoms

Chronic production of sputum

Shortness of breath associated with dizziness, light-headedness or peripheral tingling

Chest pain

Exercise-induced dyspnea with noisy inspiration (stridor)

DIAGNOSIS

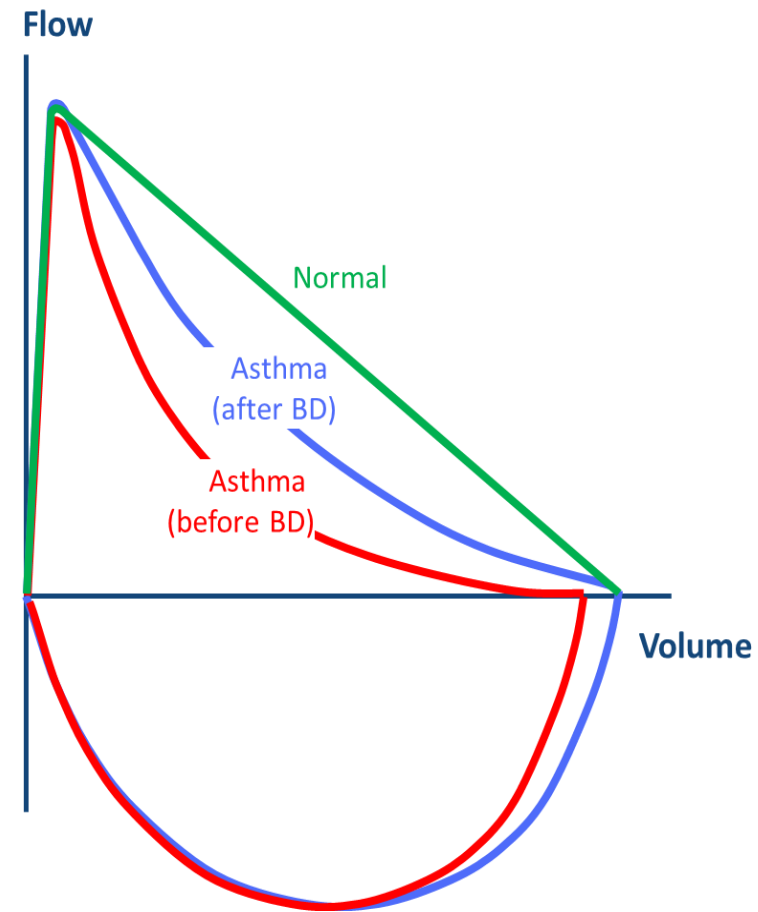
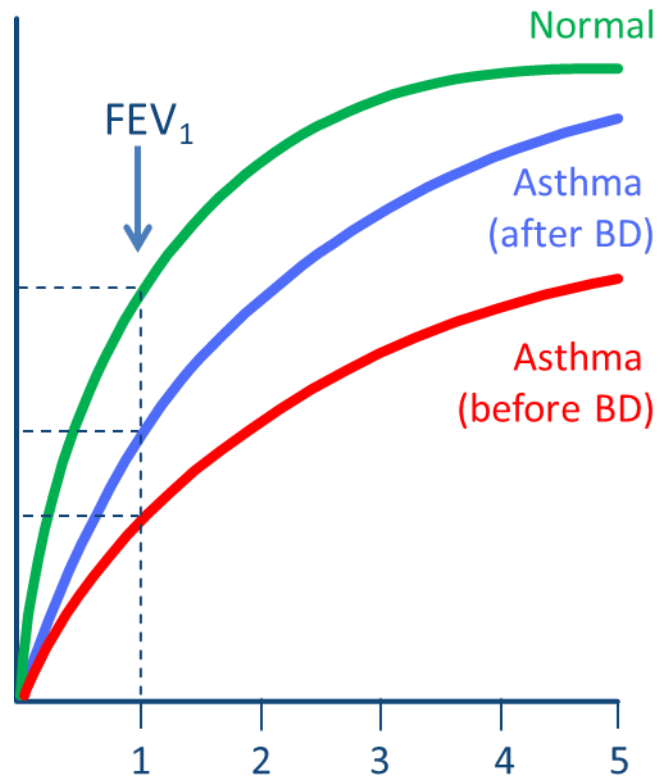
- **The demonstration of variable expiratory airflow limitation, preferably by spirometry**

- Initial spirometry is normal**

- Repeat spirometry at subsequent office visits when the patient is symptomatic
- Patient-recorded serial measurements of PEF over time One useful strategy for diagnosing asthma in patients with normal lung function on initial spirometry is to ask the patient to use a portable hand-held device to measure FEV1 or PEF and record readings obtained twice a day for two weeks or with and without symptoms. The diagnosis of asthma is confirmed by a reliable series of recordings that document more than 20 percent variability in FEV1 or PEF over time
- Bronchoprovocation testing, such as methacholine, mannitol, or exercise challenge

- **Exclusion of alternative diagnoses**

Typical spirometric tracings



Box 1-2. Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years

1. HISTORY OF VARIABLE RESPIRATORY SYMPTOMS	
<i>Feature</i>	<i>Features that support the diagnosis</i>
Wheeze, shortness of breath, chest tightness and cough (Descriptors may vary between cultures and by age)	• Generally more than one type of respiratory symptom (in adults, isolated cough is seldom due to asthma) • Symptoms occur variably over time and vary in intensity • Symptoms are often worse at night or on waking • Symptoms are often triggered by exercise, laughter, allergens, cold air • Symptoms often appear or worsen with viral infections
2. CONFIRMED VARIABLE EXPIRATORY AIRFLOW LIMITATION	
<i>Feature</i>	<i>Considerations, definitions, criteria</i>
2.1 Documented expiratory airflow limitation	At a time when FEV ₁ is reduced, confirm that FEV ₁ /FVC is reduced (it is usually >0.75–0.80 in adults, >0.90 in children ¹³)
AND	
2.2 Documented excessive variability in lung function* (one or more of the following):	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis. If initially negative, tests can be repeated during symptoms or in the early morning.
• Positive bronchodilator (BD) reversibility test	<i>Adults:</i> increase in FEV ₁ of >12% and >200 mL (greater confidence if increase is >15% and >400 mL). <i>Children:</i> increase in FEV ₁ of >12% predicted. Change measured 10–15 minutes after 200–400 mcg salbutamol (albuterol) or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: SABA ≥4 hours, twice-daily LABA 24 hours, once-daily LABA 36 hours
• Excessive variability in twice-daily PEF over 2 weeks	<i>Adults:</i> average daily diurnal PEF variability >10%* <i>Children:</i> average daily diurnal PEF variability >13%*
• Significant increase in lung function after 4 weeks of anti-inflammatory treatment	<i>Adults:</i> increase in FEV ₁ by >12% and >200 mL (or PEF [†] by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
• Positive exercise challenge test	<i>Adults:</i> fall in FEV ₁ of >10% and >200 mL from baseline <i>Children:</i> fall in FEV ₁ of >12% predicted, or PEF >15%
• Positive bronchial challenge test (usually only for adults)	Fall in FEV ₁ from baseline of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
• Excessive variation in lung function between visits (good specificity but poor sensitivity)	<i>Adults:</i> variation in FEV ₁ of >12% and >200 mL between visits, outside of respiratory infections <i>Children:</i> variation in FEV ₁ of >12% in FEV ₁ or >15% in PEF [†] between visits (may include respiratory infections)

BD: bronchodilator (SABA or rapid-acting LABA); FEV₁: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting beta₂-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting beta₂-agonist. See Box 1-4 (p.27) for how to confirm the diagnosis in patients already taking controller treatment. *Daily diurnal PEF variability is calculated from twice daily PEF as (day's highest minus day's lowest) divided by (mean of day's highest and lowest), averaged over one week. [†]For PEF, use the same meter each time, as PEF may vary by up to 20% between different meters. BD reversibility may be lost during severe exacerbations or viral infections,¹⁴ and airflow limitation may become persistent over time. If reversibility is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. In a situation of clinical urgency, asthma treatment may be commenced and diagnostic testing arranged within the next few weeks (Box 1-4, p.27), but other conditions that can mimic asthma (Box 1-5) should be considered, and the diagnosis confirmed as soon as possible.

DIFFERENTIAL DIAGNOSIS

Wheeze

vocal cord dysfunction syndrome

bronchogenic carcinoma or foreign body aspiration

Cough

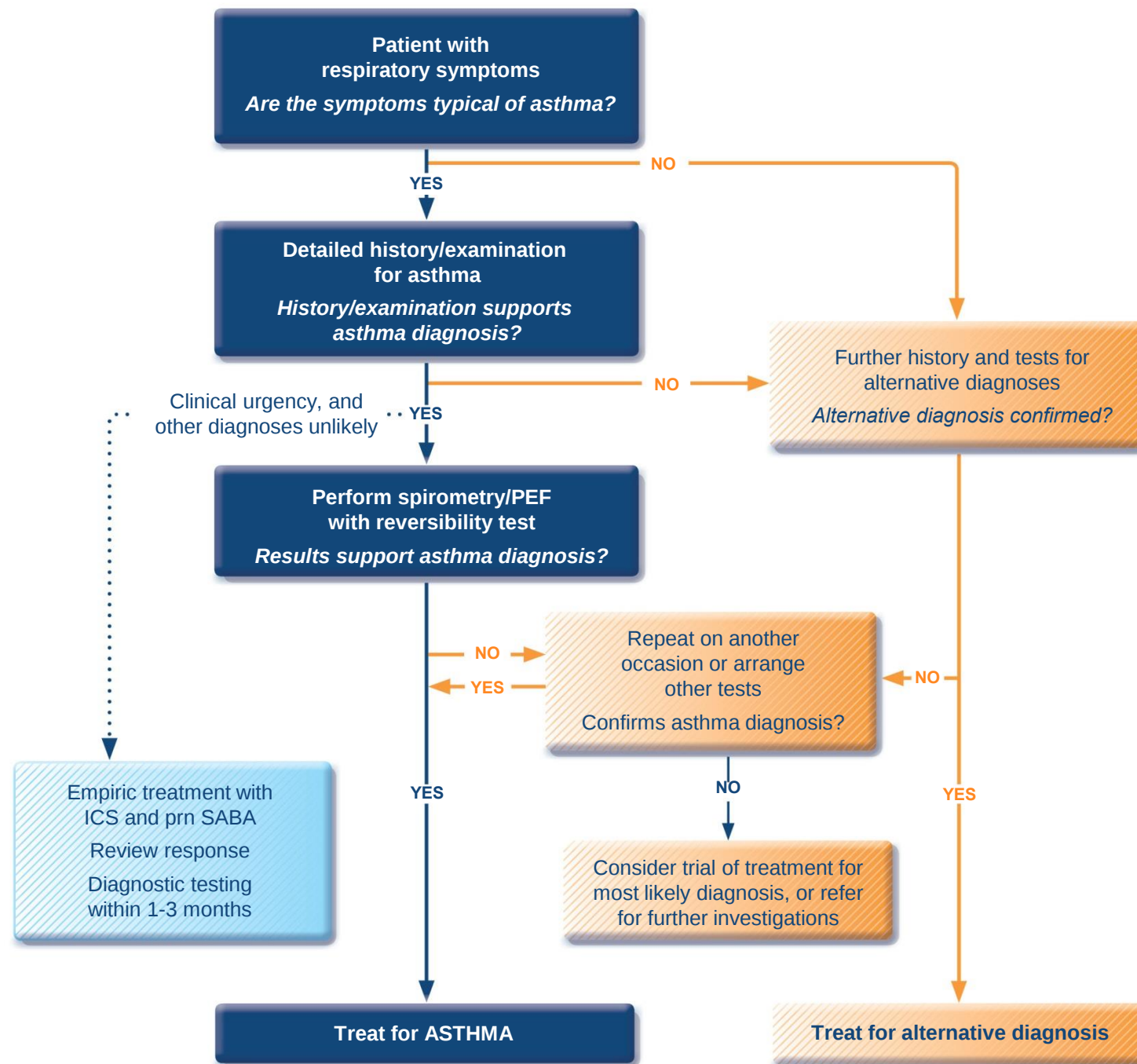
- Rhinitis
- Rhinosinusitis
- gastroesophageal reflux disease (GERD)
- post-viral tussive syndrome
- eosinophilic bronchitis
- angiotensin converting enzyme inhibitors
- Infection with *Bordetella pertussis* ("whooping cough")

Dyspnea

COPD, heart failure, pulmonary embolism, and sarcoidosis

Coexistent conditions

- Allergic rhinitis is present in most patients with allergic asthma and in at least 50 percent of those with non-allergic asthma
- Both obesity and GERD can mimic asthma and can worsen pre-existent asthma
- Patients with obesity and mild asthma may perceive more severe dyspnea than would be anticipated on the basis of spirometry



با تشکر از شما