Clinical Diagnosis and Differential Diagnosis

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What is asthma?: No single gold-standard test

- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation

- Defined by the history of respiratory symptoms such as **wheeze, shortness of breath, chest tightness and cough** that **vary over time and in intensity**

  ➔History of characteristic symptom pattern

- With **variable expiratory airflow limitation**

  ➔Evidence of variable expiratory airflow limitation

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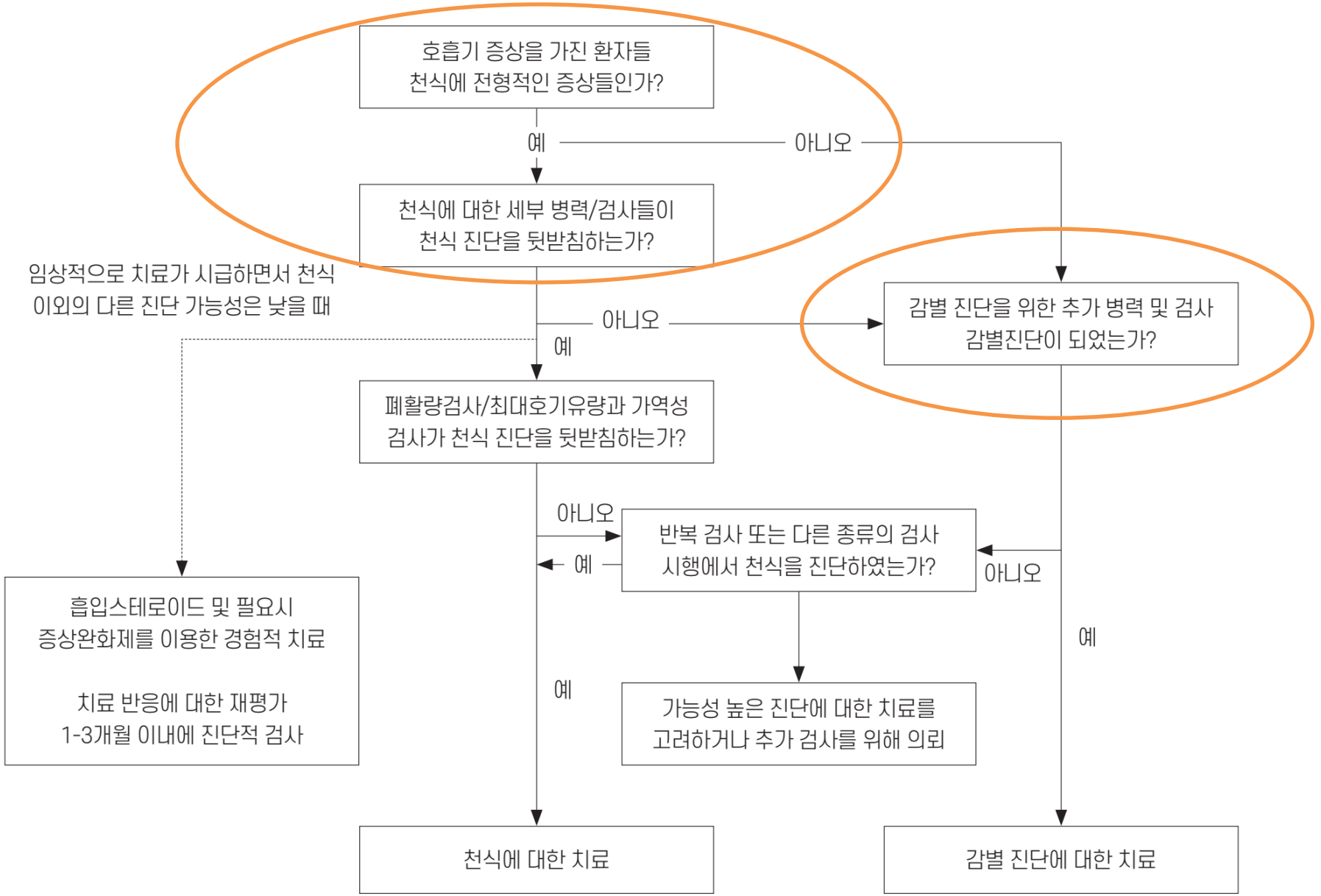
Diagnostic flowchart



KATRD 2020.

Clnical features that increase the probability of asthma

- **Wheeze, shortness of breath, cough and/or chest tightness**
  - ✓ Generally more than one type of respiratory symtoms
  - ✓ Symptoms occur variably over time and vary in intensity
  - ✓ Symptoms are often worse at night or in the early morning
  - ✓ Symptoms are often triggered by viral infections (colds), exercise, allergen exposure, changes in weather, laughter, or irritants (fumes, smoke, or strong smells)

British Thoracic Society. Thorax 2014;69 Suppl 1:1-192.

Clnical features that increase the probability of asthma

- Personal history of atopic disorder
- Family history of atopic disorder and/or asthma
- Widespread wheeze heard on auscultation
- History of improvement in symptoms or lung function in response to adequate therapy

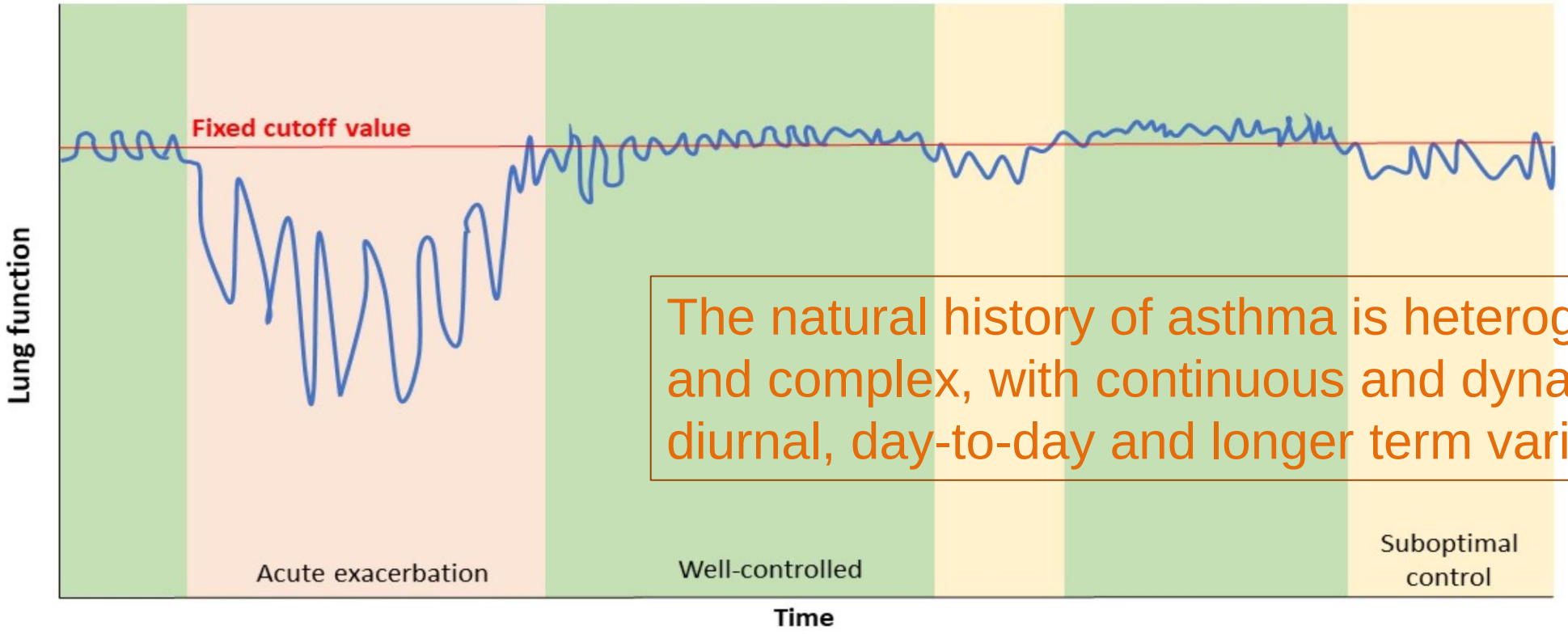
British Thoracic Society. Thorax 2014;69 Suppl 1:1-192.

CInical features that decrease the probability of asthma

- Isolated cough with no other respiratory symptoms
- Chronic production of sputum
- Prominent dizziness, light-headedness, peripheral tingling
- Chest pain
- Voice disturbance
- Exercise-induced dyspnea with noisy inspiration

British Thoracic Society. Thorax 2014;69 Suppl 1:1-192.

Variability of asthma with time



The natural history of asthma is heterogeneous and complex, with continuous and dynamic diurnal, day-to-day and longer term variability.

- **Well-controlled period:** characterized by better lung function and less diurnal variability. However, diurnal variation may straddle diagnostic cut offs in some patients.
- **Period of suboptimal control:** may be predictable in individual patients based on the triggers, such as cold weather or during pollen seasons.
- **Acute exacerbation:** characterized by marked deterioration in lung function and exaggerated diurnal variability.

Wang R, et al. Thorax 2021;76:624-31.

Diurnal variations of asthma symptoms

- Diurnal rhythmicity, typically worsening symptoms overnight or early in the morning
- Noctural symptoms → 74% asthma patients leading to night awakening ≥1/wk
- Excessive diurnal variations in symptoms and airflow obstruction
  - ✓ Associated with disease severity and risk of death

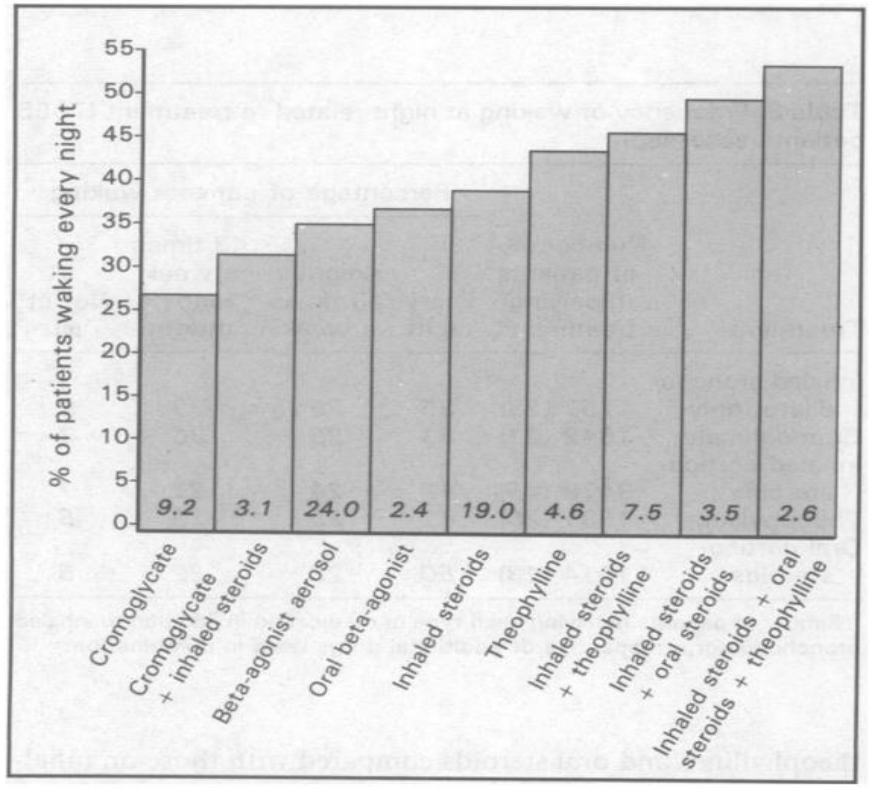


TABLE IV—*Clinical features of 9 patients who sustained respiratory crises with ventilatory arrest*

	General ward	High dependency unit
Number of episodes	9*	1
Occurrence between midnight and 0600	7	1
Pulse rate >120/min on admission	0	1
Pulsus paradoxus >20 mm Hg on admission	1	0
Peak expiratory flow rate <100 l/min on admission	4	0
Diurnal variation in peak expiratory flow rate >50%	8†	1
[illegible]	[illegible]	[illegible]
Blood gas analysis on admission	2	1
Failed resuscitation	3	0

*One patient suffered two episodes on two separate admissions.
†Remaining one patient had severe nocturnal symptoms but no peak flow chart recovered.

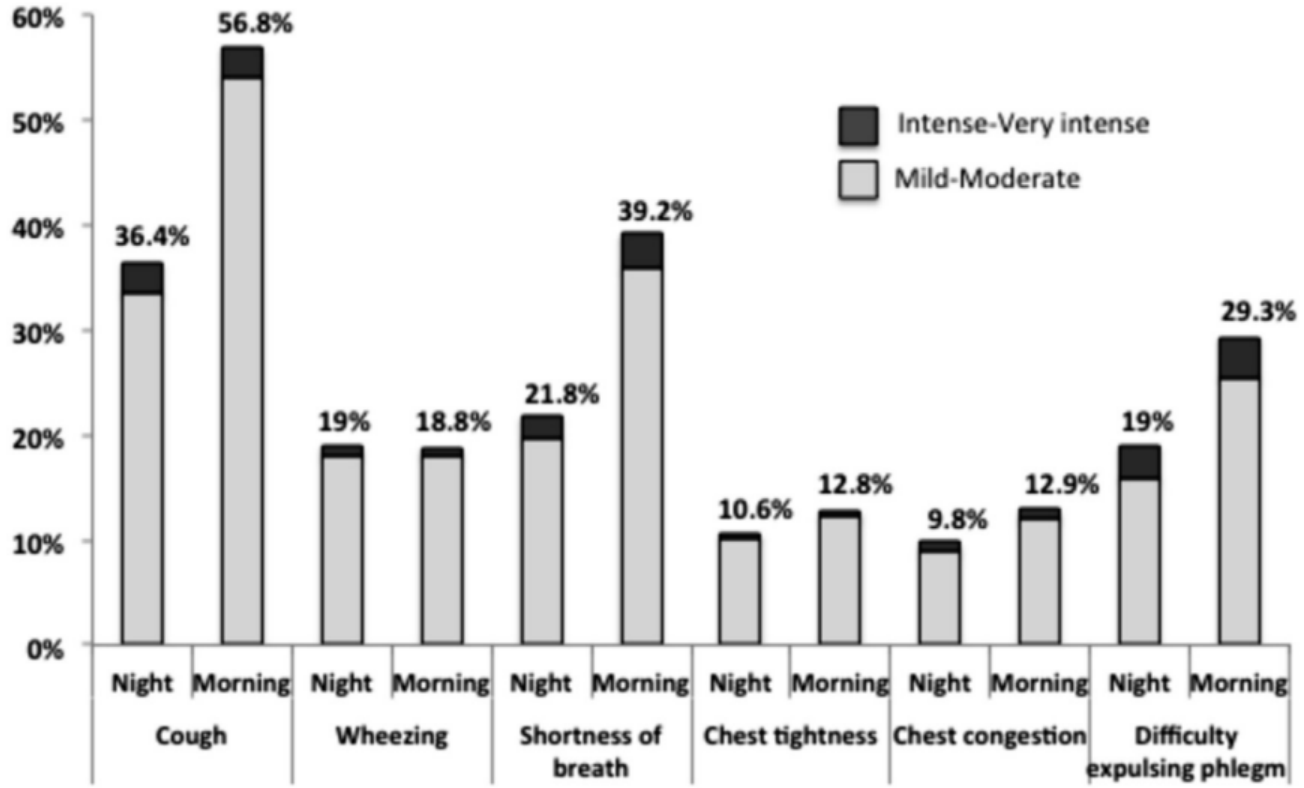
Turner-Warwick . J R Coll Gen Prac 1989;39(323):239-43.

Hetzel MR, etl al. Br Med J 1977;1(6064):808-11.

Pitfall of diurnal variation

- Low sensitivity and specficity of self-reported diurnal symptoms
- Difficult to differentiate asthma from other small airway disease

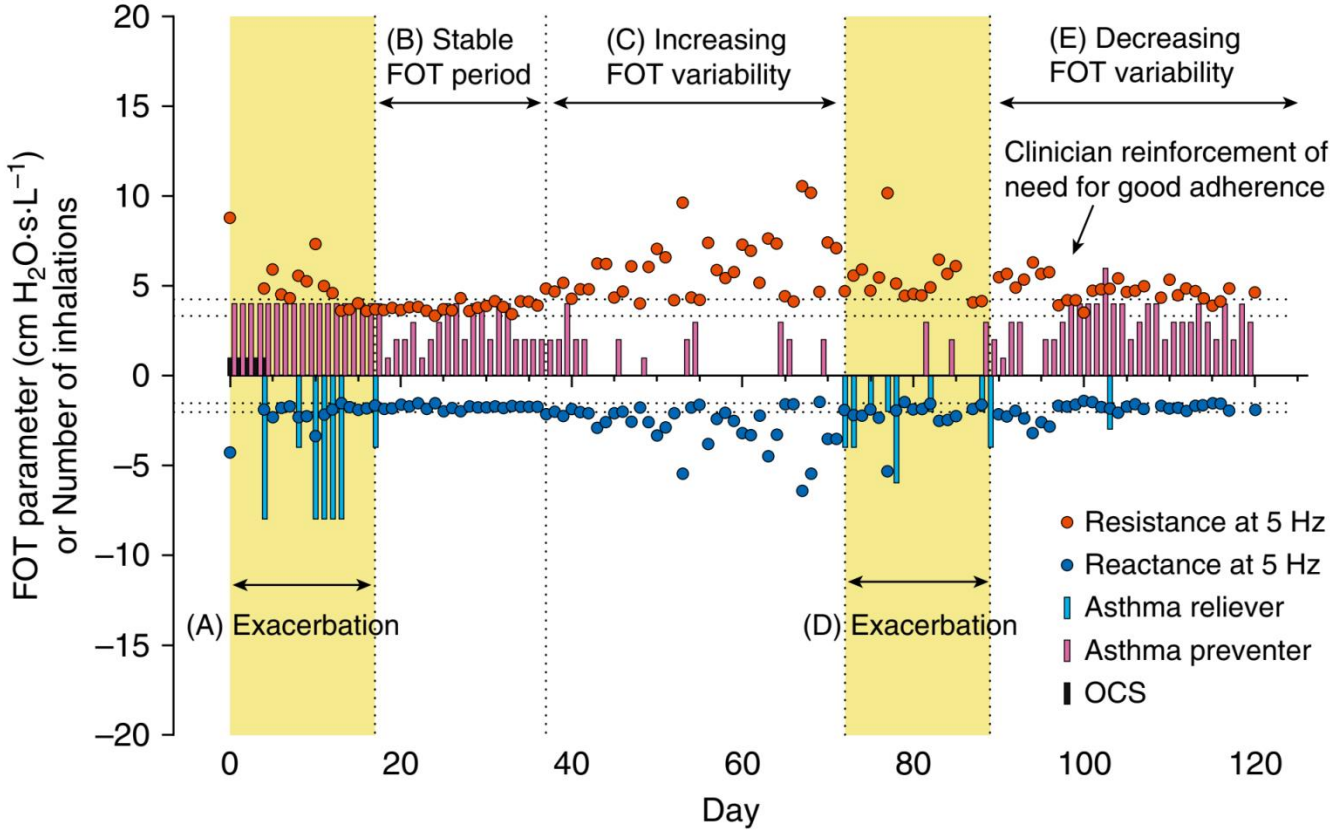
- Example of COPD patients
  - ✓ Self-report night-time or early morning: 80%
  - ✓ Variability in symptoms over a week: 90%



Miravitlles M, et al. Respir Med 2017;129:165-72.

Day-to-day variability

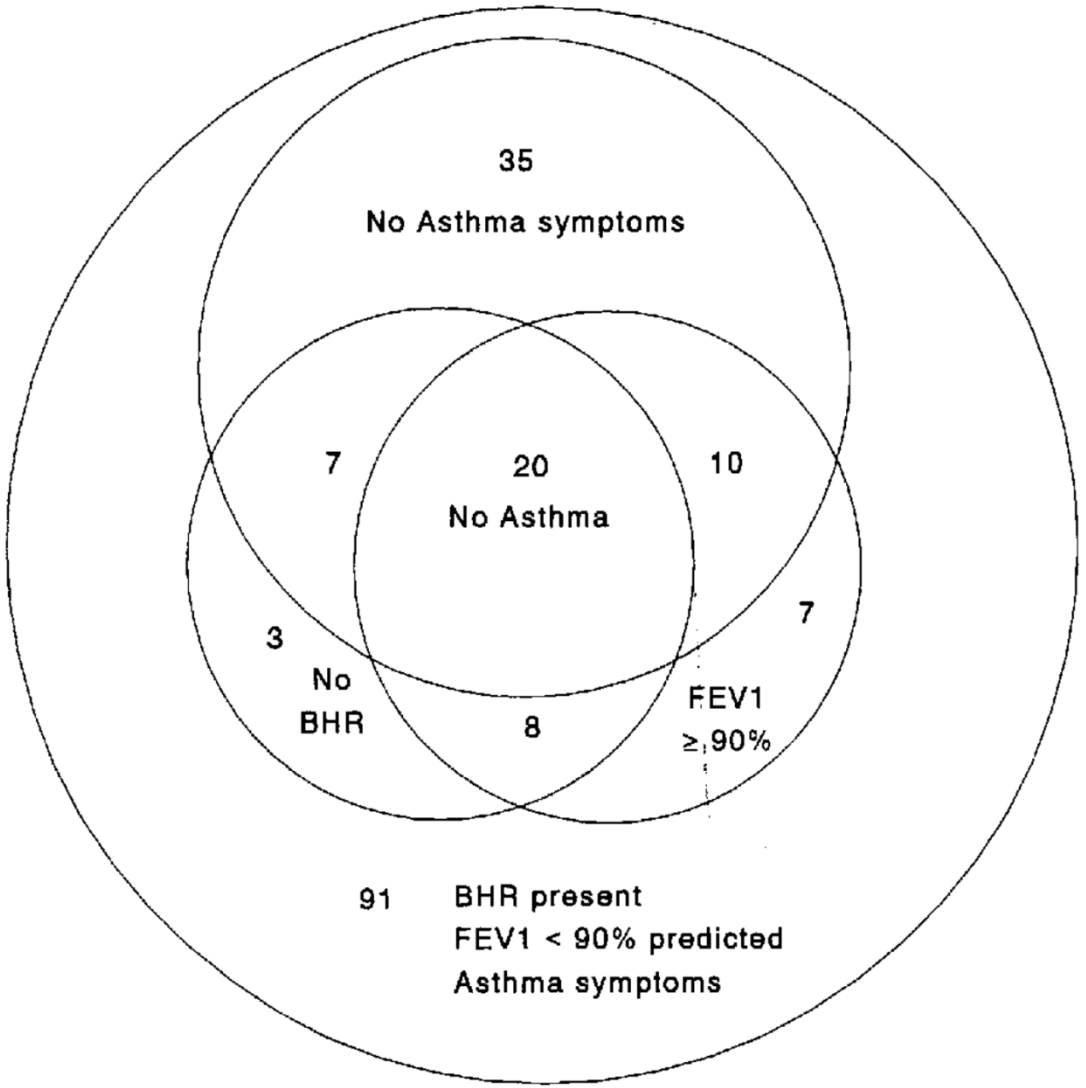
- Increased day-to-day variability, reflecting underlying airway instability
- Related with asthma control, medication adherence, future exacebation risk



Wong A, et al. Am J Respir Crit Care Med 2019;199(9):1156-60.

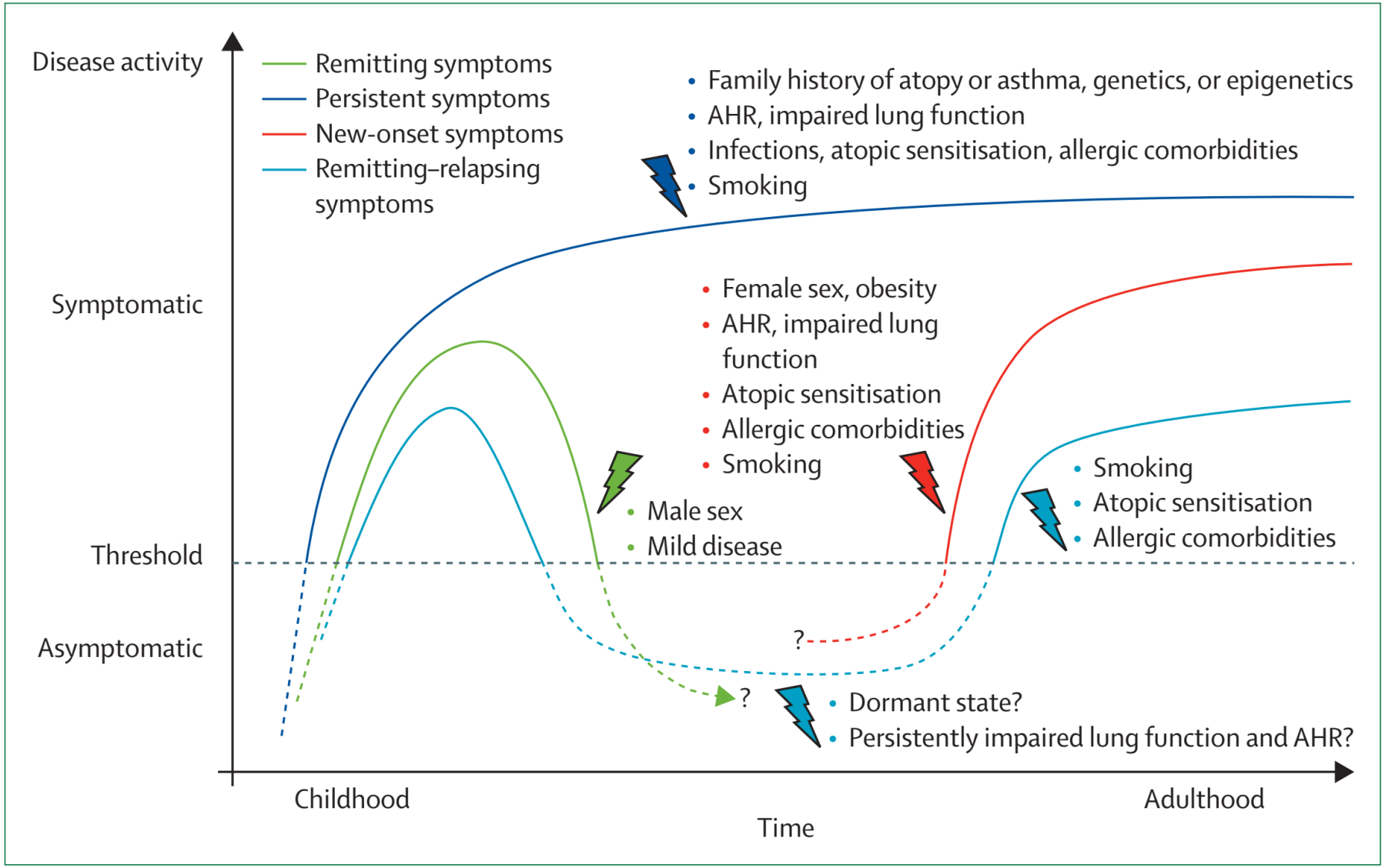
Long-term variability

- Change in asthma phenotypes after 25 years in 181 initially symptomatic asthmatic patients



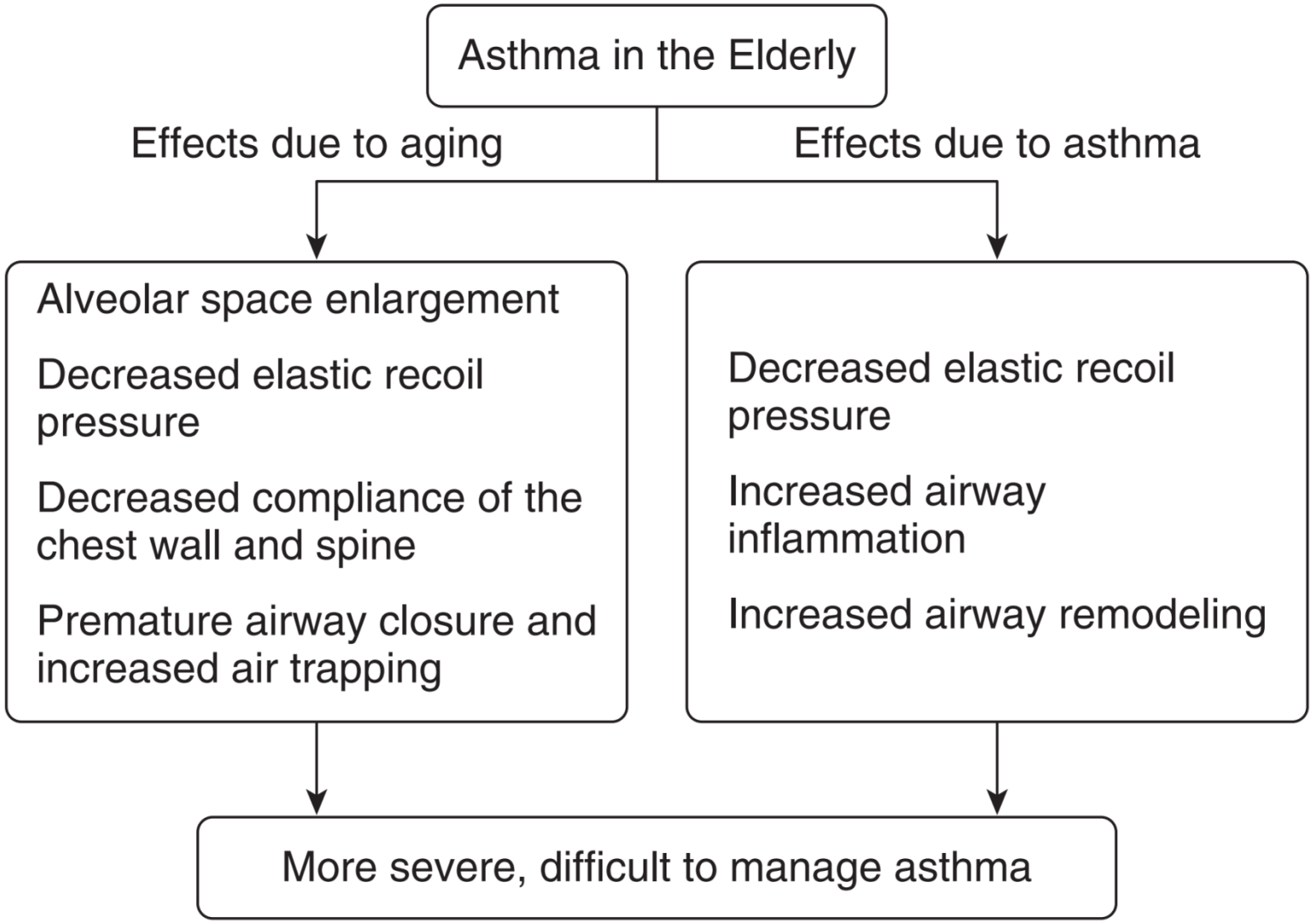
Panhuysen CI, et al Am J Respir Crit Care Med 1997;155(4):1267-72.

Determinants of disease course across asthma transition



Fuchs O, et al. Lancet Respir Med 2017:5(3):224-234.

Synergistic pathologic changes of asthma and elderly



Skloot GS, et al. Ann Am Thorac Soc 2016;13(11):2064-77.

Diagnostic comparison of elderly and younger patients

	Elderly	Young
Spirometry	May be less useful in frail patients; reference standards not widely available	Generally useful tool to assess asthma severity
Bronchodilator responsiveness/FeNO	May be less pronounced May be useful	Variable but generally greater May be useful
Methacholine challenge	Less often used because of more frequent contraindications (e.g., cardiovascular disease, low lung function)	Useful Overall fewer contraindications
Atopy	Less common	Common
Comorbidities	COPD, heart disease more common	Allergic rhinitis more common
Phenotypes	Limited knowledge, but late-onset asthma, long-standing asthma, and ACO described	Multiple phenotypes described
Sputum cellularity	Generally more neutrophilic	Generally more eosinophilic

Skloot GS, et al. Ann Am Thorac Soc 2016;13(11):2064-77.

Occupational asthma

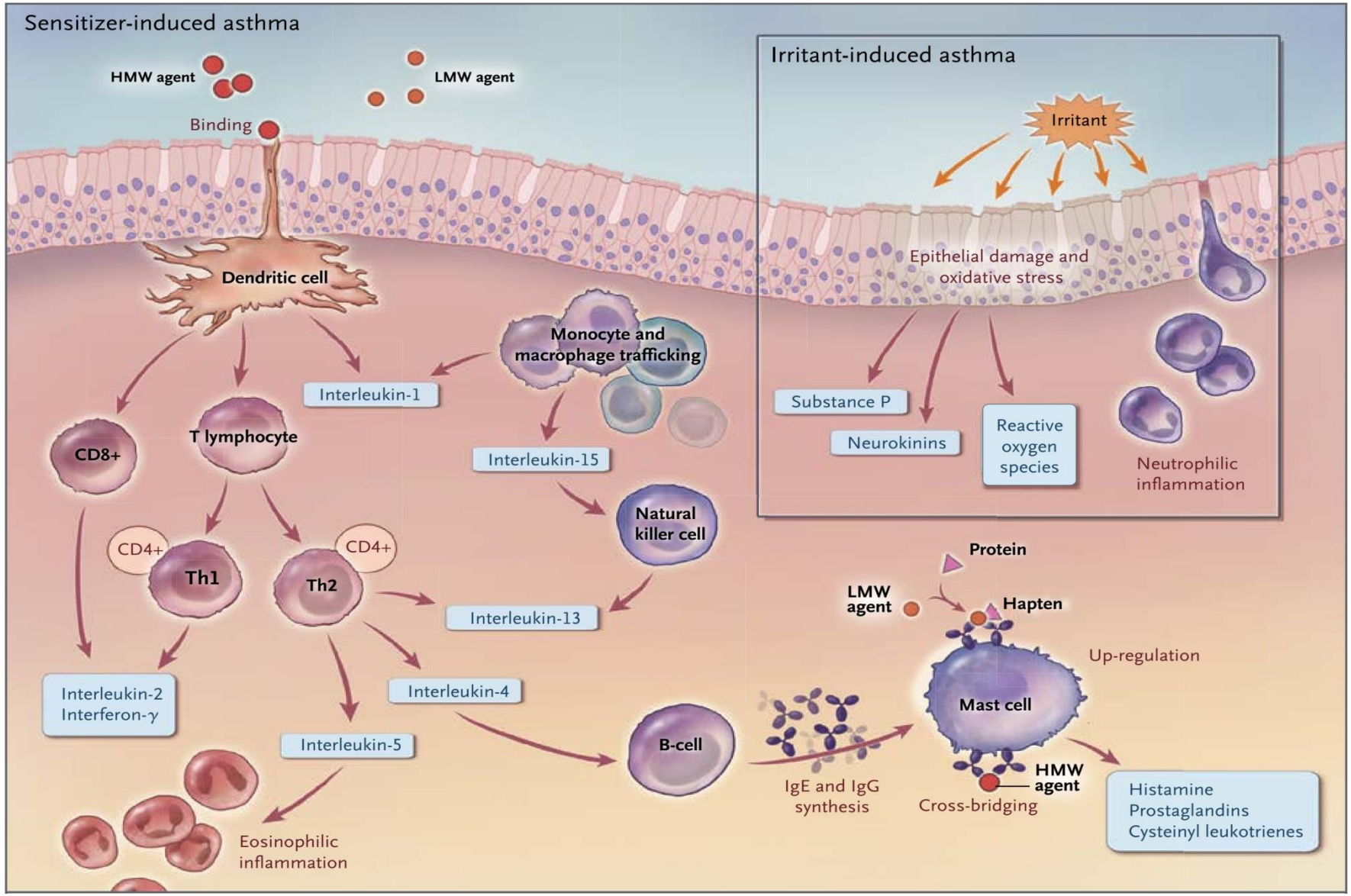
- 5~20% of patients diagnosed as asthma in adulthood
  → suspicion in every adult with new-onset asthma

- **Sensitizer-induced occupational asthma**
  - ✓ High-molecular-weight agents: animal allergens, plants, cereals/grains, milk/egg powder, fungis, enzymes, insects, fish, vegetable gums
  - ✓ Low-molecular-weight agents: Diisocyanates, acid anhydrides, acrylic monomers, wood dusts, metal salts, biocides, drugs

- **Irritant-induced occupational asthma**
  - ✓ From exposure to agents considered to be airway irritants, in the absence of sensitization
  - ✓ Cleaners (domestic and industrial cleaners), nurses, textile workers, hog farmers, poultry workers, aluminum potroom workers

Tarlo SM, et al. N Engl J Med 2014;370:640-9.

Mechanism of occupational asthma



Tarlo SM, et al. N Engl J Med 2014;370:640-9.

Diagnosis of sensitizer-induced asthma

- Asthma-like symptoms begin variably at the beginning of the work shift, toward its end, or even in the evening after working hours
  → Remission or improvement occurs during weekends and holidays

- Rhinitis often accompanies or precedes lower respiratory symptoms

- Serial monitoring of PEF, with or without methacholine challenge, with or without sputum eosinophil counts at work and away from work

- Specific inhalation challenge in the laboratory or at work

- Objective evidence of asthma plus a positive skin test for specific IgE antibodies to the suspected agent

Tarlo SM, et al. N Engl J Med 2014;370:640-9.

Diagnosis of irritant-induced asthma

Criteria for RADS*	Modifications to Criteria for RADS†
History of new-onset asthma	History of new-onset asthma or recurrence of childhood asthma
Symptom onset related to a single high-level exposure (usually accidental)	Symptom onset related to one or more high-level exposures
Onset of symptoms ≤24 hr after exposure	Symptoms can begin >24 hr (in some reports, up to several days) after exposure
Exposure to a very high concentration of gas, fume, or spray with known irritant properties	List of exposures includes highly irritating dust (e.g., after the World Trade Center collapse)
Airway hyperresponsiveness or reversible airflow obstruction	
Symptoms persistent for ≥ 3 months	
No previous lower respiratory tract symptoms	Previous airway disease associated with smoking or atopy may be difficult to rule out

*RADS (reactive airways dysfunction syndrom) criteria from Brooks et al.

†Patients were considered to have irritant-induced asthma in some studies with one or more of these modified criteria

Brooks SM, et al. Chest 1985;88:376-84.
Tarlo SM, et al. N Engl J Med 2014;370:640-9.

Physical examination

- **Often normal**
  - ✓ Wheezing on auscultation, especially on forced expiration
  - ✓ Increased expiratory time
  - ✓ Hyperinflation

- **Wheezing in other conditions**
  - ✓ Respiratory infections
  - ✓ COPD
  - ✓ Upper airway dysfunction
  - ✓ Endobronchial obstruction
  - ✓ Inhaled foreign body

- Wheezing may be absent during severe asthma exacerbations (‘silent chest’)
  - ✓ With or without other physical signs of respiratory failure

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Differential diagnosis

12-39 years	40+ years	All ages
Chronic upper airway cough syndrome	COPD	TB
Inducible laryngeal obstruction	Inducible laryngeal obstruction	
Hyperventilation, dysfunctional breathing	Hyperventilation, dysfunctional breathing	
Cystic fibrosis	Bronchiectasis	
Congenital heart disease	Medication-related cough (ACE inhibitor)	
Alpha1-antitripsin deficiency	Parenchymal lung disease	
Inhaled foreign body	Pulmonary embolism	
	Central airway obstruction	

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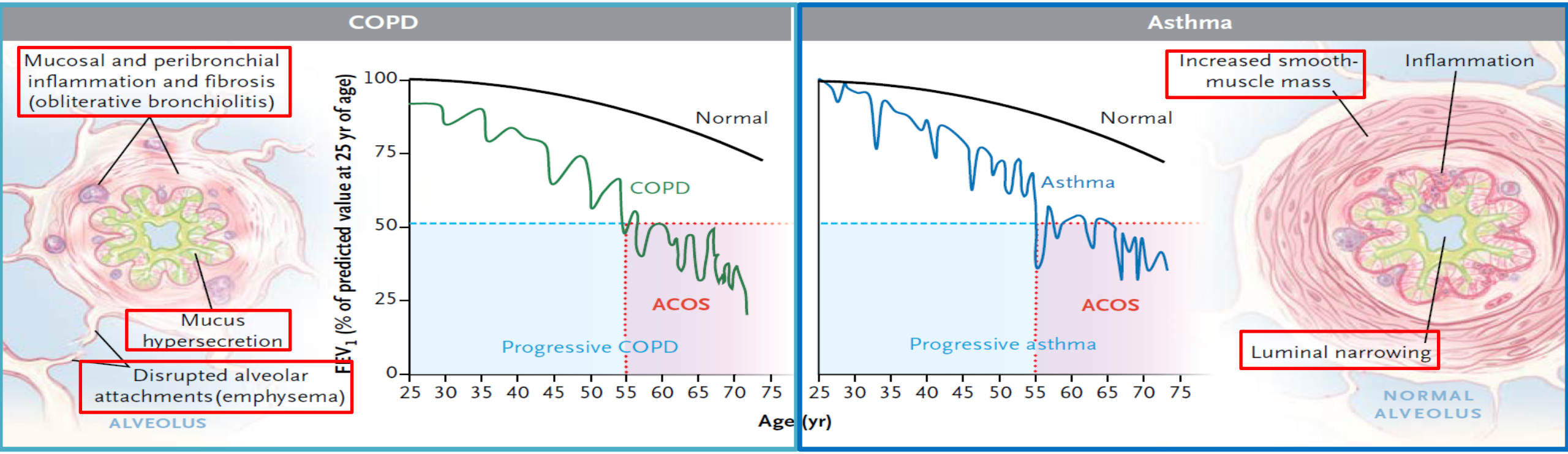
Pathophysiology of ACO



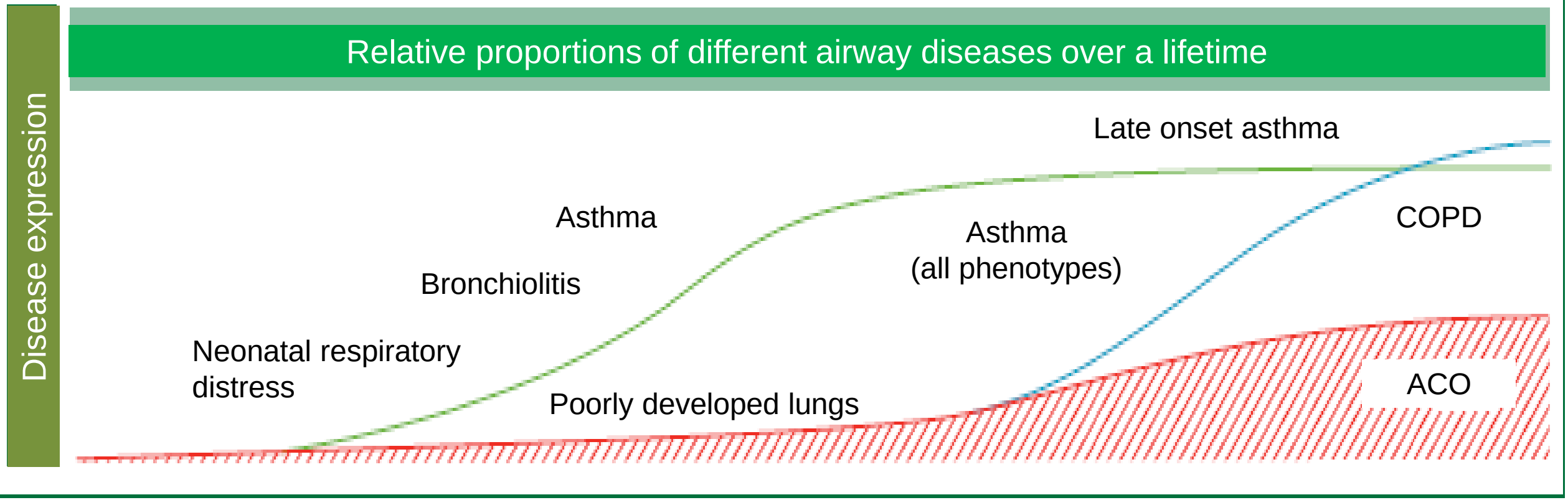
Predominant parenchymal destructive or predominant airflow limitation

Reversible airflow obstruction, airway remodeling and hyperresponsiveness

Postma DS, et al. N Engl J Med 2015;373(13):1241-9.

Chronic airway disease throughout life course

- Interplay of genetic and environmental factors of airway diseases



Bateman ED, et al. Lancet Respir Med 2015;3(9):719-728.

History and clinical assessment of ACO

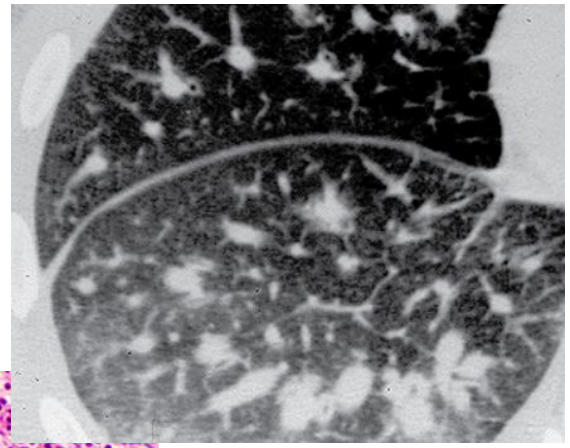
- **Nature and pattern of chronic respiratory symptoms**
  - ✓ Intermittent or episodic
  - ✓ May have started before or after age 40
- **Risk factors for COPD**
  - ✓ History of smoking and/or other toxic exposures
  - ✓ History of low birth weight or respiratory illness (ex: TB)
- **History suggestive of asthma features**
  - ✓ Common triggers (laughter, exercise, allergens, seasonal)
  - ✓ Symptom improvement spontaneously or with bronchodilator or ICS
  - ✓ Asthma diagnosis, current or in childhood

Spirometric measures of ACO

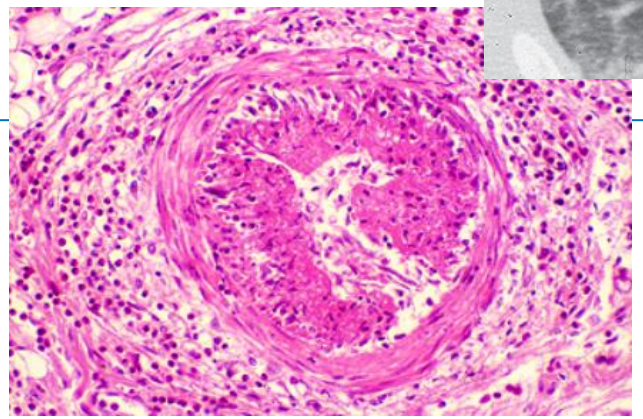
- **Presence of persistent expiratory airflow limitation**
- **Variable expiratory airflow limitation**

Spirometric variables	Asthma+COPD
Normal FEV1/FVC pre- or post-BD	Not compatible
Post-BD FEV1/FVC <0.7	Required for diagnosis of asthma+COPD
Post-BD FEV ≥ 80% predicted	Compatible with mild persistent airflow limitation if post-BD FEV1/FVC <0.7
Post-BD FEV < 80% predicted	As for COPD and asthma
Post-BD increase in FEV1 ≥12% and 200mL from baseline (Reversible airflow limitation)	Common and more likely when FEV1 is low
Post-BD increase in FEV1 ≥12% and 400mL from baseline (Marked reversible airflow limitation)	Compatible with asthma+COPD

Churg-Strauss syndrome



- Eosinophilic granulomatosis with polyangiitis (EGPA)
- Systemic vasculitis with multi-organ involvement



- **Diagnostic criteria** (4 or more: positive)
  - ✓ Asthma
  - ✓ Blood eosinophilia (>10%)
  - ✓ Mononeuropathy or polyneuropathy
  - ✓ Migratory or transient pulmonary opacities detected radiographically
  - ✓ Paranasal sinus abnormality
  - ✓ Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas

Masi AT, et al. Arthritis Rheum 1990;33(8):1094-100.

Asthma in EGPA

- 90% in EGPA
- Duration of asthma at EGPA diagnosis, mean 9 years

- **Association with severe asthma**
  → Rule out EGPA in asthma patients who are poorly controlled and require continuous oral corticosteroid administration

◆ Associations between EGPA and asthma drug exposures in the 2-6 months prior to the diagnosis

Drug dispensed prior to Churg–Strauss syndrome diagnosis	Adjusted	
	Multivariate OR	95% CI
Leukotriene modifiers	1.32	0.44–3.96
Asthma drug count†	1.25	0.90–1.72
Inhaled corticosteroids	3.07	1.34–7.03
Oral corticosteroids	5.36	2.51–11.45

Comarmond C, et al. Arthritis Rheum 2013;65(1):270-81.

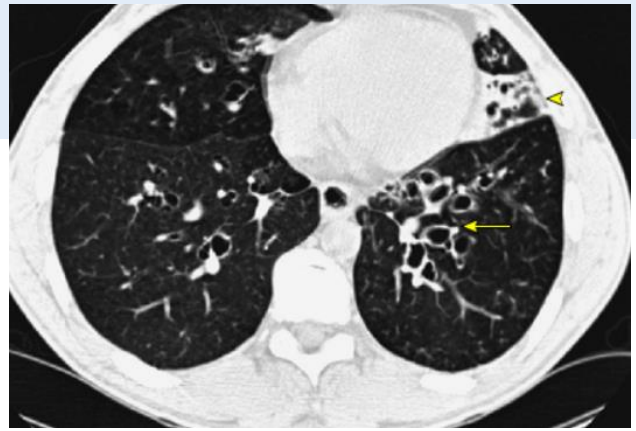
Harrold LR, et al. Pharmacoepidemiol Drug Saf 2007;16(6):620-6.

Bronchiectasis

Clinical and functional similarities between asthma and bronchiectasis	
Asthma	**Bronchiectasis**
Chronic respiratory disease with heterogenous clinical manifestations, such as cough, sptum, dyspnea, obstructive pattern, and wheezing	
Complex pathophysiology	
Chronic airway inflammation	
Mostly eosinophilic	Mostly neutrophilic
Ventilatory disorder	
Obstructive	Mostly obstructive
Mostly reversible	Mostly non-reversible
Exacerbation: marker of disease control	
Infectious (viral?)	Infectious (bacterial, viral mixed, fungal)
Non-infectious (allergens, treatment compliance, pollution)	Non-infectious (?)

Polverino E, et al. Eur Respir J 2018;52(3):1800328.

Bronchiectasis in asthma



- Asthma in 3-8% of bronchiectasis patients
- Bronchiectasis in 25-80% of patient with severe asthma

- Rule out bronchiectasis in patients with severe asthma with frequent exacerbations and patients with non-allergic asthma

TABLE 5 Prevalence of high-resolution computed tomography-diagnosed bronchiectasis in patients with severe asthma

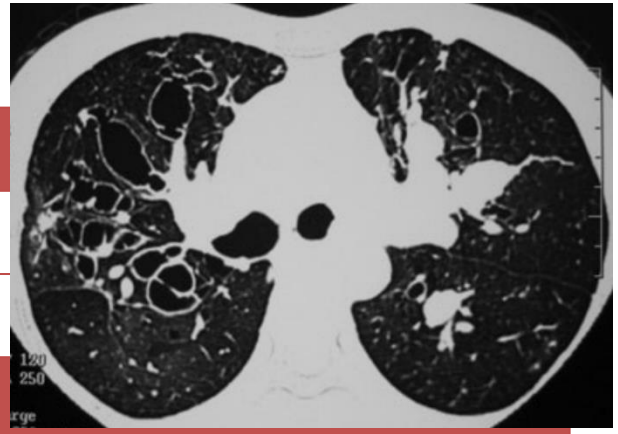
Study	Subjects n	BCH prevalence %	Risk factors associated with BCH
Bisaccioni *et al.*, 2009 [104]	105	24.8	NR
Gupta *et al.*, 2009 [111]	467	40	Disease duration, $FEV_1/FVC < 75\%$
Menzies *et al.*, 2011 [17]	133	35.3	Greater airway obstruction, *Aspergillus fumigatus* sensitisation
Luján *et al.*, 2013 [110]	50 SD *versus* 50 NSD	40 *versus* 12	age and steroid dependence
Dimakou *et al.*, 2017 [18]	40	67.5	Sputum, antibiotic courses, bacterial colonisation

BCH: bronchiectasis; NR: not reported; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SD: steroid-dependent; NSD: non steroid-dependent.

Polverino E, et al. Eur Respir J 2018;52(3):1800328.

Allergic bronchopulmonary aspergiollosis

- Complex hypersensitivity reaction in response to colonization of the airways with *Aspergillus fumigatus*



Predisposing conditions (one must be present):
Asthma
Cystic fibrosis
Obligatory criteria (both must be present):
Serum IgE levels against Aspergillus fumigatus (>0.35 kU/L) or Aspergillus skin test positivity
Elevated total IgE concentration (>1000 IU/mL)
Other criteria (at least two must be present):
Precipitating serum antibodies to A. fumigatus or elevated serum Aspergillus IgG by immunoassay (>27 mg/L)
Radiographic pulmonary opacities consistent with ABPA
Total eosinophil count >500 cells/$\mu\ell$ in glucocorticoid-naïve patients (may be historical)

Agarwal R, et al. Clin Exp Allergy 2013;43(8):850-73.

Thank You for Your Attention