

Clinical Approach of Upper Airway Cough Syndrome and Laryngopharyngeal Reflux

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Chronic Cough

Duration of Cough and Its Common Causes

- **Acute cough (<3 weeks)**
 - respiratory tract infection, aspiration event, or inhalation of noxious chemicals or smoke.
- **Subacute cough (3–8 weeks duration)**
 - Post-infectious cough
 - residuum from a tracheobronchitis, such as in pertussis or "post-viral tussive syndrome."
- **Chronic cough (>8 weeks)**
 - wide variety of cardiopulmonary diseases including those of inflammatory, infectious, neoplastic, and cardiovascular etiologies
 - **When initial assessment with chest examination and radiograph is normal, cough-variant asthma, gastroesophageal reflux, nasopharyngeal drainage, and medications (angiotensin converting enzyme [ACE] inhibitors) are the most common causes of chronic cough.**

Chronic Cough with A Normal Chest Radiograph

Harrison's Principles of Internal Medicine, 18th ed.

- When initial assessment with chest examination and radiograph is normal, cough-variant asthma, gastroesophageal reflux, nasopharyngeal drainage, and medications (angiotensin converting enzyme [ACE] inhibitors) are the most common causes of chronic cough.

Harrison's Principles of Internal Medicine, 19th ed.

- It is commonly held that (alone or in combination) the use of an ACE inhibitor; postnasal drainage; gastroesophageal reflux; and a normal or noncontributory chest radiograph. However, clinical experience does not support this contention, and strict adherence to this concept discourages the search for alternative explanations by both clinicians and researchers.

Differences between the Two Major Types of Chronic Cough

	Eosinophilic airway diseases	Non-eosinophilic chronic cough
Age	Any	40–60 years
Sex	Equal	Female predominant
Response to corticosteroids	Good	Poor
Pathology	Eosinophilic	Non-eosinophilic
Exhaled nitric oxide	Raised	Low
Variable airflow obstruction	Present in asthma	Absent
Airway hyper-responsiveness	Present in asthma	Absent

Cough Caused by Eosinophilic Airway Diseases

	Asthma	Cough variant asthma	Atopic cough	Eosinophilic bronchitis
Symptoms	Cough, breathlessness, wheeze	Cough only	Cough only	Cough and sputum
Atopy	Common	Common	Common	As in general population
Variable airflow obstruction	+	±	-	-
Airway hyper-responsiveness	+	+	-	-
Capsaicin cough hyper-responsiveness	±	±	-	+
Bronchodilator response	+	+	-	-
Corticosteroid response	+	+	+	+
Response to H ₁ antagonist	±	±	+	NK

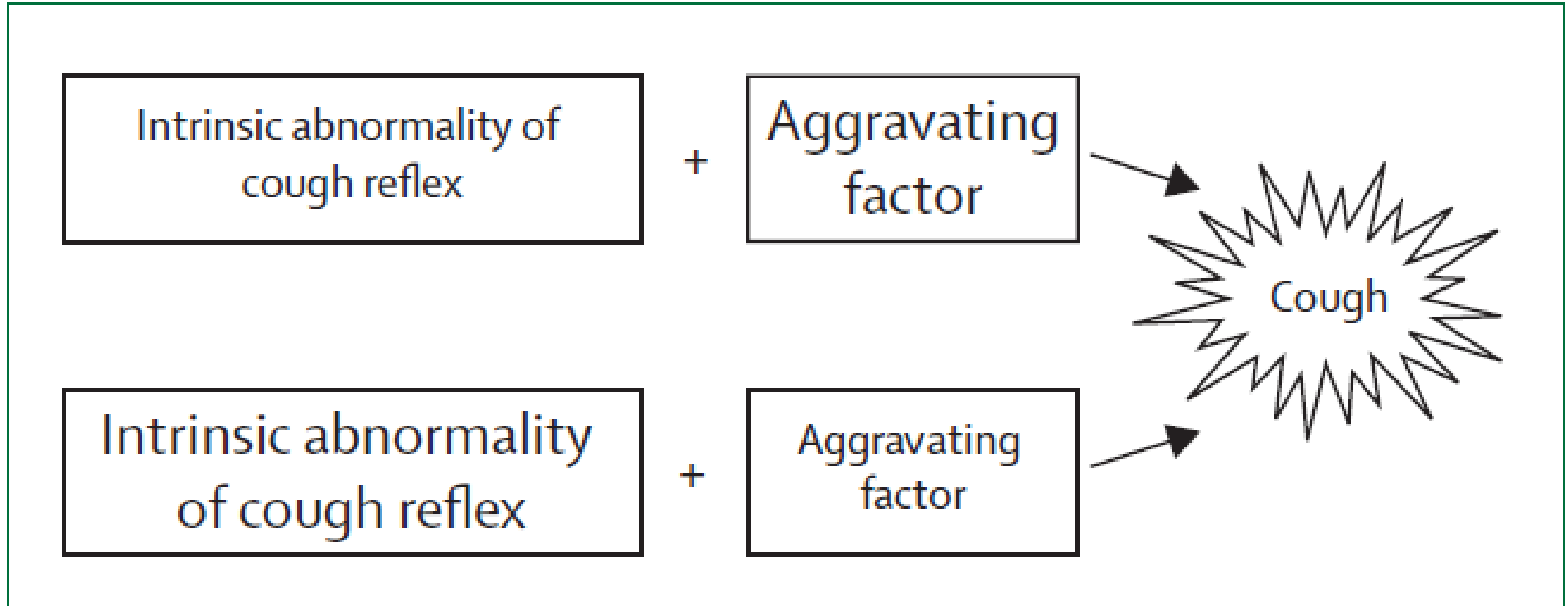
Cough Caused by Eosinophilic Airway Diseases

	Asthma	Cough variant asthma	Atopic cough	Eosinophilic bronchitis
Progression to asthma	n/a	30%	Rare	10%
Sputum eosinophilia (>3%)	Frequent	Frequent	Frequent	Always (by definition)
Submucosal eosinophils	↑	↑	↑	↑
BAL eosinophilia	↑	↑	↓	↑
Mast cells in ASM	↑	↓	NK	↓
Basement membrane thickness	↑	↑	NK	↑

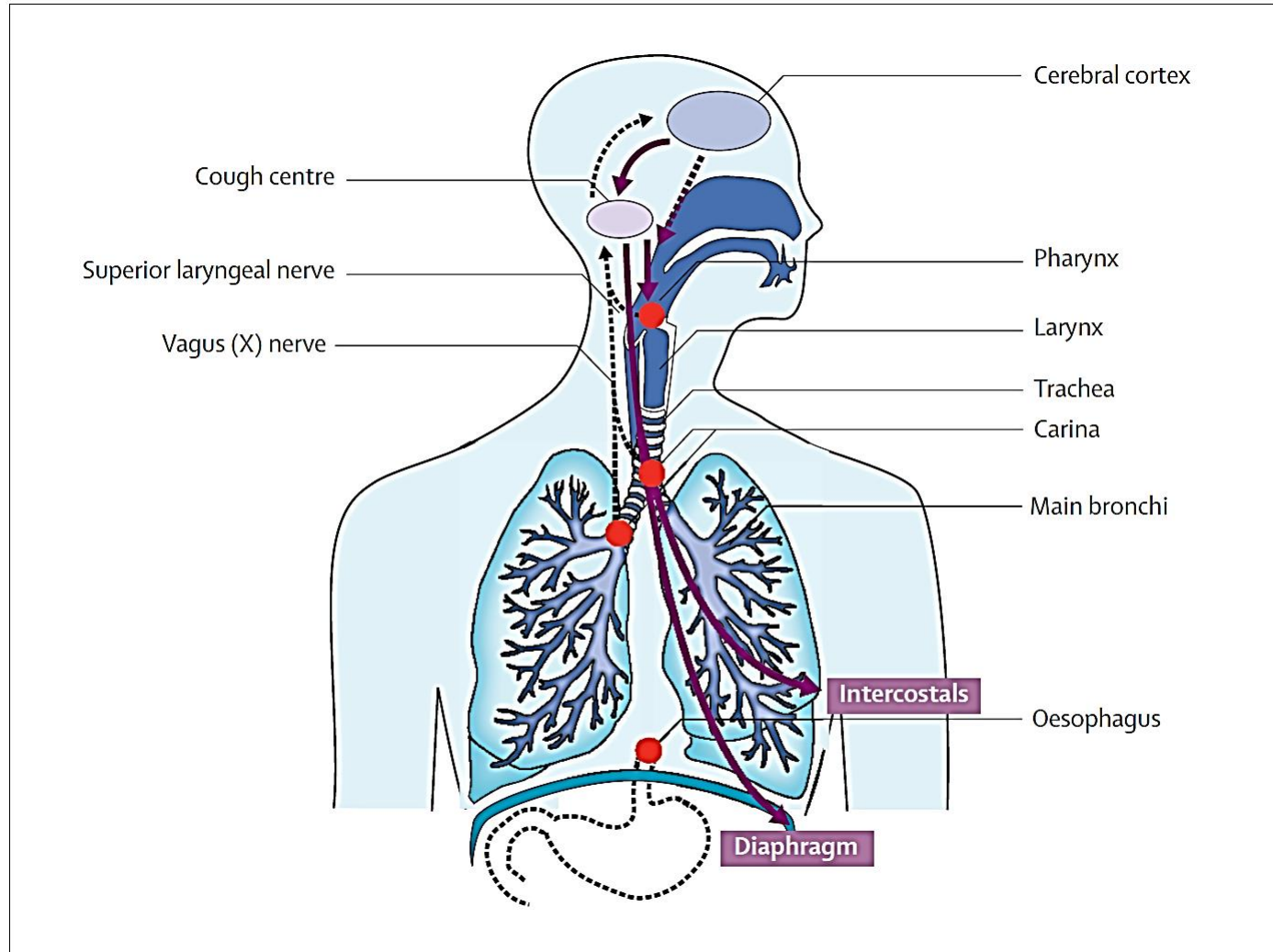
ASM=airway smooth muscle. BAL=bronchoalveolar lavage. n/a=not applicable. NK=not known. ±=sometimes present. --=not present. +=often present. ↑=increased. ↓=not increased.

Table 3: Cough caused by eosinophilic airway diseases

Model for Pathogenesis of Non-asthmatic Chronic Cough



Anatomy of Cough Pathways



Location of Cough Receptors and Associated Sensory Nerve

Region	Afferent nerve
Paranasal	Trigeminal (V)
Pharynx	Glossopharyngeal (IX)
Larynx/tracheobronchial tree*	Vagus (X)
External auditory canal/ tympanic membrane	Vagus (X)
Esophagus, stomach, pleura	Vagus (X)
Diaphragm, pericardium	Phrenic

*Greatest concentration of cough receptors.



Clinical Approach of Upper Airway Cough Syndrome (UACS)

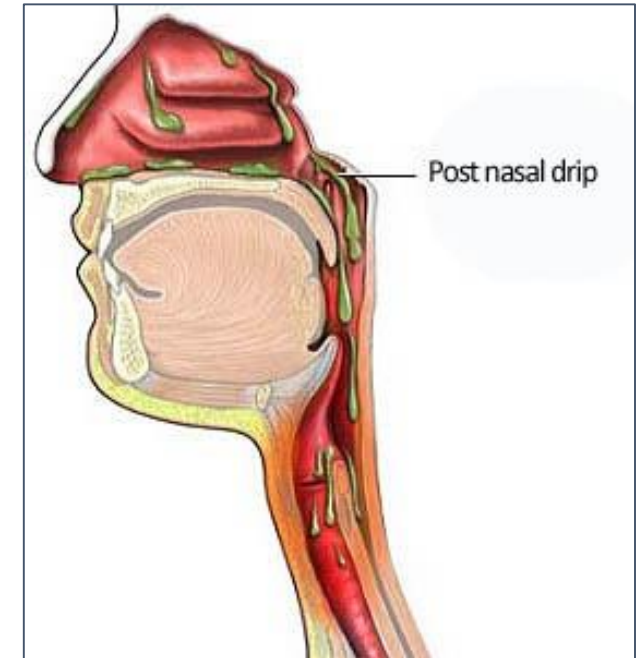
Postnasal drip vs. UACS

- **Postnasal drip (PND)**

- Drainage of secretions from the nose or paranasal sinuses into the pharynx

- **Upper airway cough syndrome (UACS)**

- (+) irritation or inflammation of upper airway structures that directly stimulate cough receptors

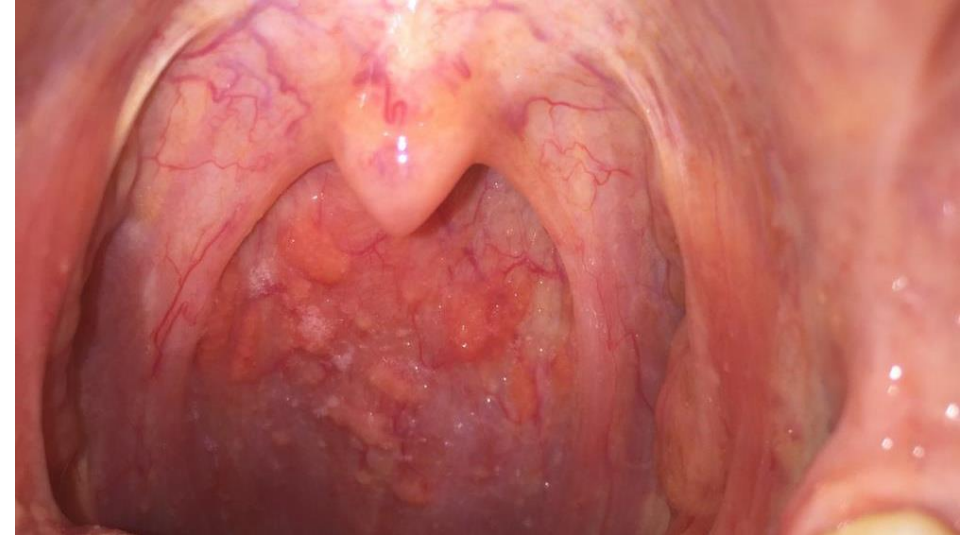


Symptoms of UACS

- **Symptoms**
 - Cough
 - **Sensation of something draining into the throat**
 - **Need to clear the throat**
 - Tickle in the throat
 - **Nasal congestion and/or a nasal discharge**
 - Hoarseness
 - Silent

Physical Examination of UACS

- **Physical examination**
 - Drainage in posterior pharynx
 - Throat clearing
 - Nasal discharge
 - **Cobblestone appearance of the oropharyngeal mucosa**
 - **Mucus in the oropharynx**



PREVALENCES OF UPPER RESPIRATORY SYMPTOMS AND SIGNS*

Variables	Diagnostic Groups				
	PNDS (n = 36)	Asthma (n = 11)	GER (n = 14)	Chronic Bronchitis (n = 3)	Bronchiectasis (n = 5)
Symptoms					
PND	61	64	57	33	60
TC	72	64	79	33	80
ND	36	36	29	67	20
PND or TC	81	73	93	33	80
PND + TC	53	55	42	33	60
PND, TC, ND	25	27	0	33	0
PND, TC, or ND	92	73	93	67	100
Signs					
Cob	67	64	64	0	40
Muc	56	46	50	67	80
Cob + Muc	31	36	29	100	40
Cob or Muc	92	73	86	67	80
Symptoms and signs					
PND, TC, Cob, or Muc	100	82	100	67	80
PND, TC, ND, Cob, or Muc	100	82	100	100	100

Definition of abbreviations: PNDS = postnasal drip syndrome; GER = gastroesophageal reflux; PND = postnasal drip; TC = throat-clearing; ND = nasal discharge; Cob = cobblestone appearance; Muc = mucus.

* Only patients with one of five major causes of cough have been tabulated.

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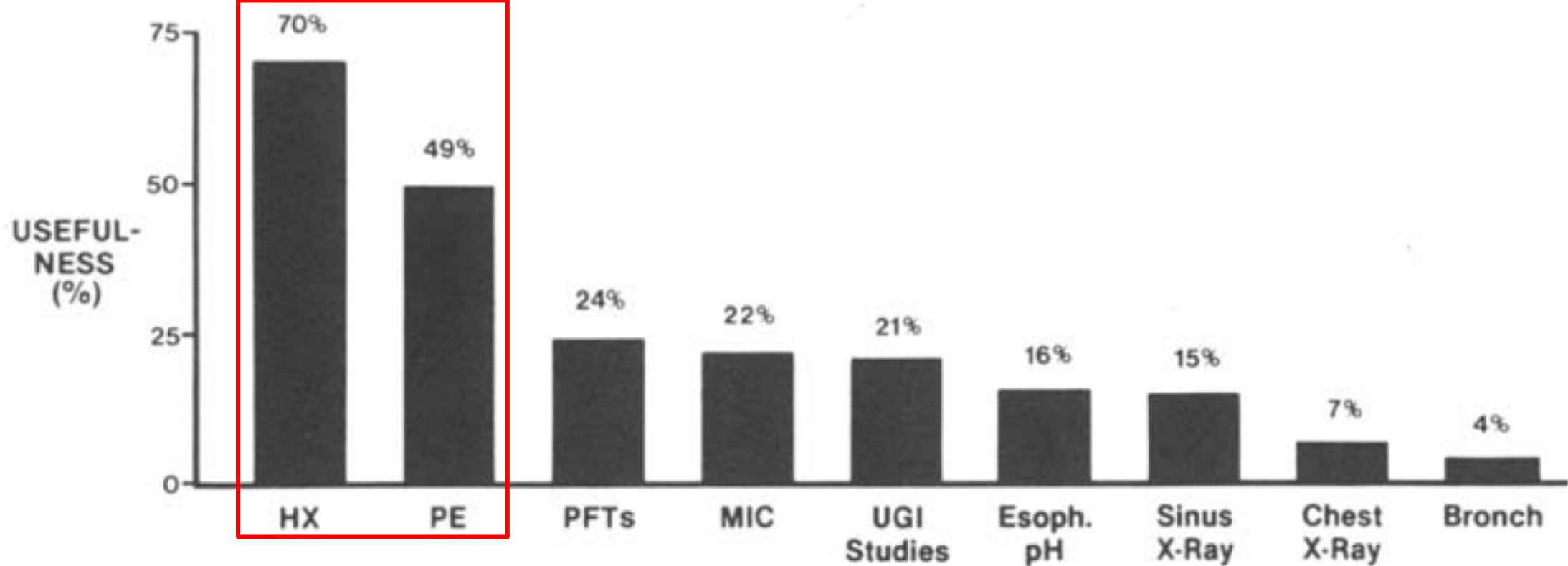


Fig. 2. The relative usefulness (true positive result) of each component of the diagnostic protocol in determining the 131 causes of cough (HX = history; PE = physical examination; PFTs = pulmonary function tests; MIC = methacholine inhalational challenge; UGI = upper gastrointestinal; esoph. pH = prolonged esophageal pH monitoring; bronch = flexible fiberoptic bronchoscopy).

Diagnosis of UACS

- **Diagnosis**

- The symptoms and signs of UACS are **nonspecific**, and a **definitive diagnosis cannot be made from the medical history and physical examination alone.**

Medical History and Physical Examination

+

Treatment Response

(Diagnostic and Therapeutic trial)

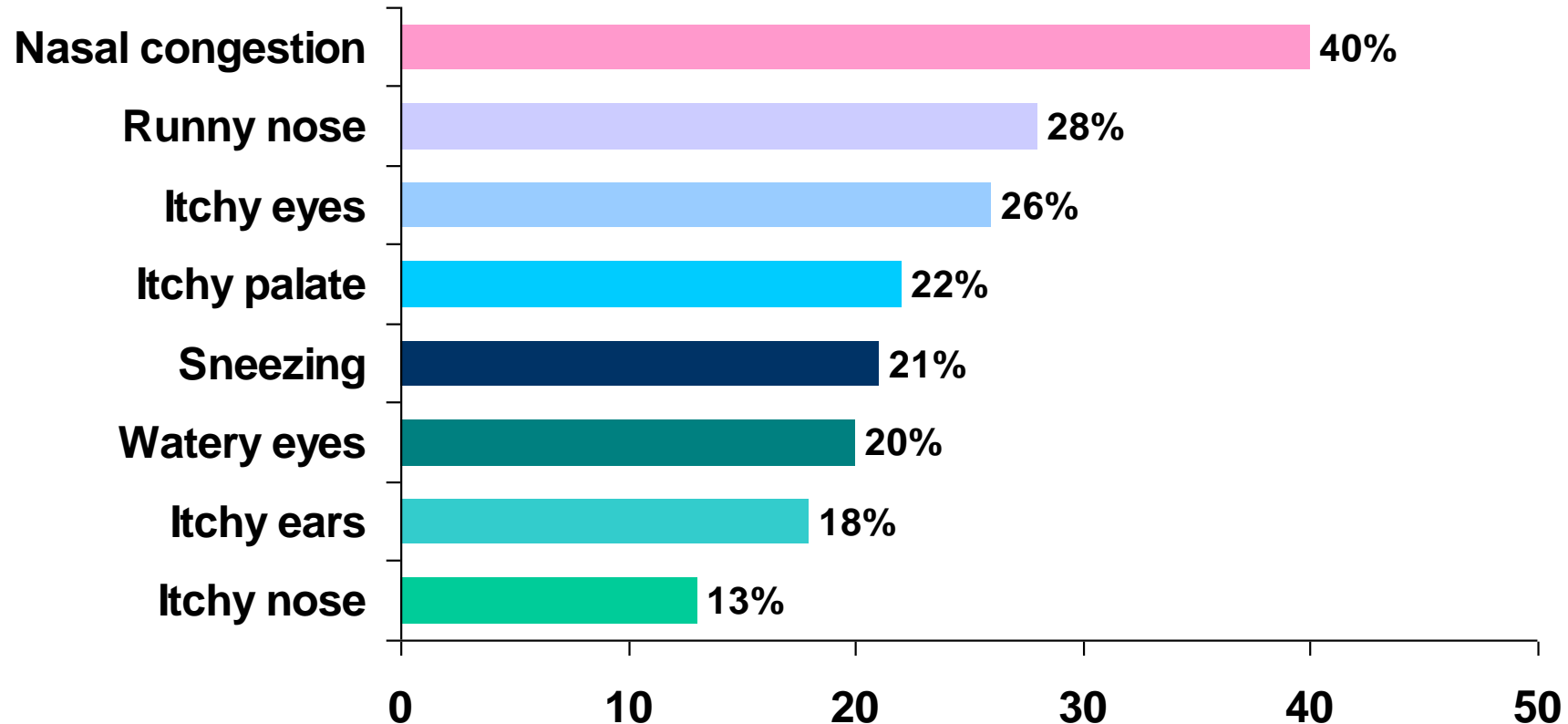
(± Laboratory results)

Differential Diagnosis of UACS

- **Differential diagnosis**
 1. **Allergic rhinitis (seasonal, perennial)**
 2. **Perennial non-allergic rhinitis (vasomotor, NARES)**
 3. **Post-infectious UACS**
 4. **Bacterial sinusitis**
 5. **Allergic fungal sinusitis**
 6. **Rhinitis due to anatomic abnormalities**
 7. **Rhinitis due to physical or chemical irritants**
 8. **Occupational rhinitis**
 9. **Rhinitis medicamentosa**
 10. **Rhinitis of pregnancy**

Differential Diagnosis of UACS: Allergic Rhinitis

- Allergic rhinitis
 - Symptoms

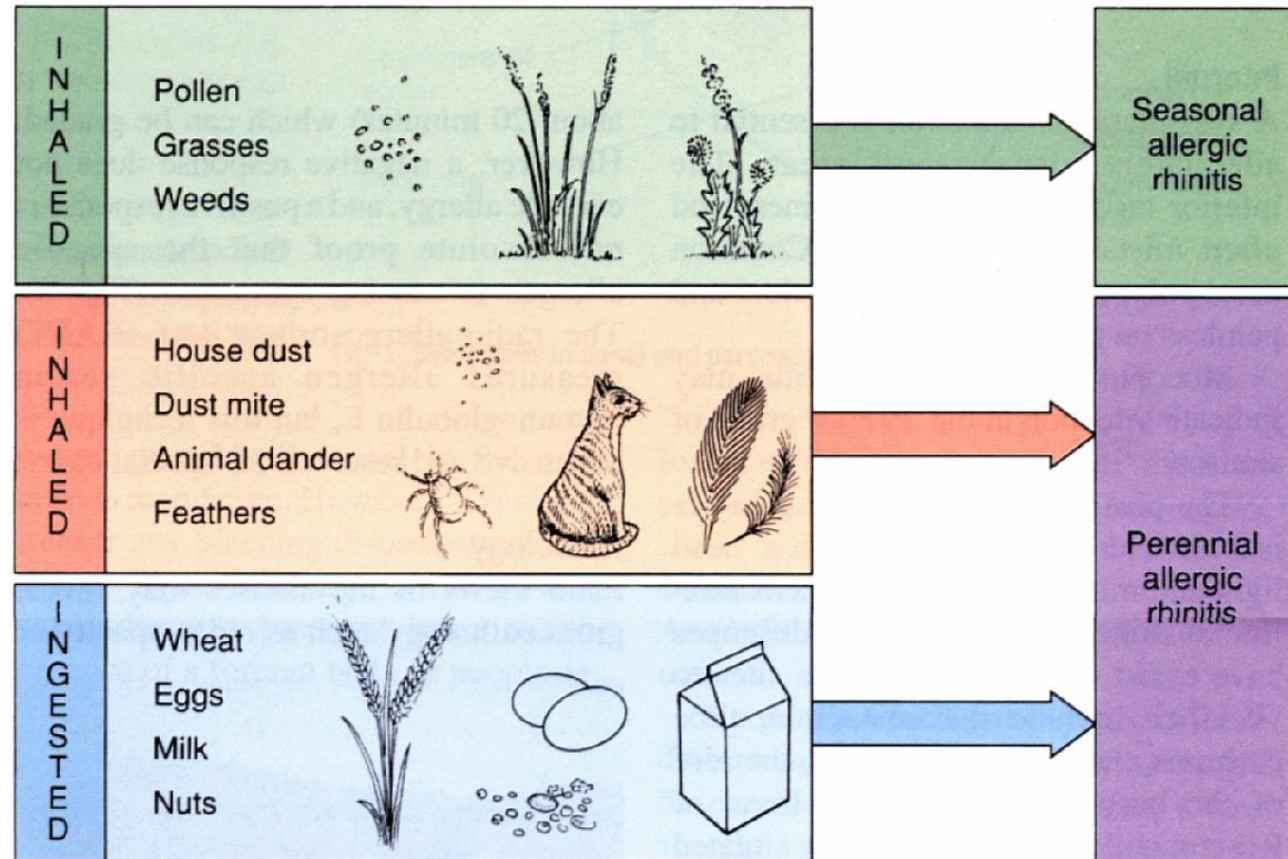


Differential Diagnosis of UACS: Allergic Rhinitis

- Allergic rhinitis

- **Seasonal**: outdoor antigens such as grass and tree pollens
- **Perennial**: indoor antigens such as dust mite and cockroach

- Specific allergen test



Differential Diagnosis of UACS: Perennial Non-allergic Rhinitis

- **Perennial non-allergic rhinitis**

- **Vasomotor:**

- Sudden unexpected onset of profound rhinorrhea, or nasal congestion with or without the sensation of postnasal drip
- Stimuli such as odors, changes in temperature or humidity, eating (called gustatory rhinitis), or alcohol ingestion
- Allergy test: negative
- Diagnosis of exclusion

- **Nonallergic rhinitis with eosinophilia (NARES)**

- Similar nasal symptoms to those of vasomotor
- Pruritus of nasal and ocular mucosa as well as excessive lacrimation
- Clinical symptoms with presence of eosinophils in nasal secretions
- Diagnosis of exclusion

Differential Diagnosis of UACS: Sinusitis

- **Bacterial sinusitis & Allergic fungal sinusitis**

Major symptoms	% of patients	Minor symptoms	% of patients
Nasal discharge	82	Headache	83
Nasal obstruction	94	Ear pain pressure	68
Facial congestion	85	Halitosis	53
Facial pain- pressure-fullness	83	Dental pain	50
Loss of smell	68	Cough	65
		Fever	33
		Fatigue	84

Differential Diagnosis of UACS: Sinusitis

- **Bacterial sinusitis & Allergic fungal sinusitis**

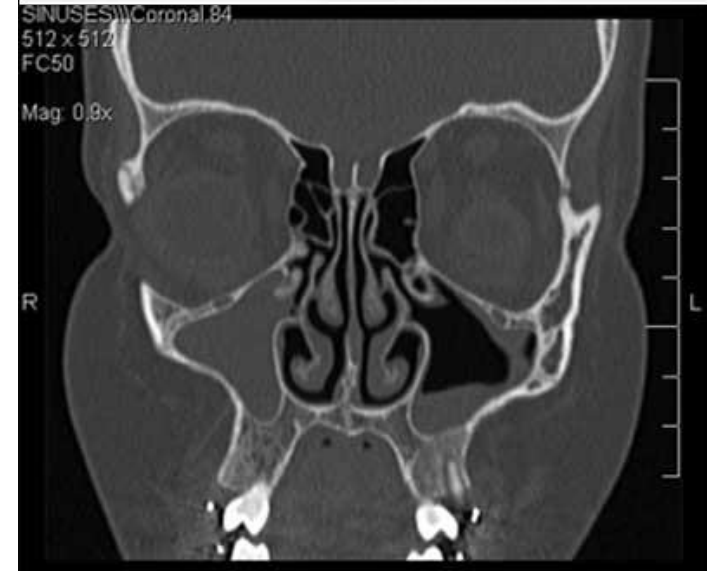
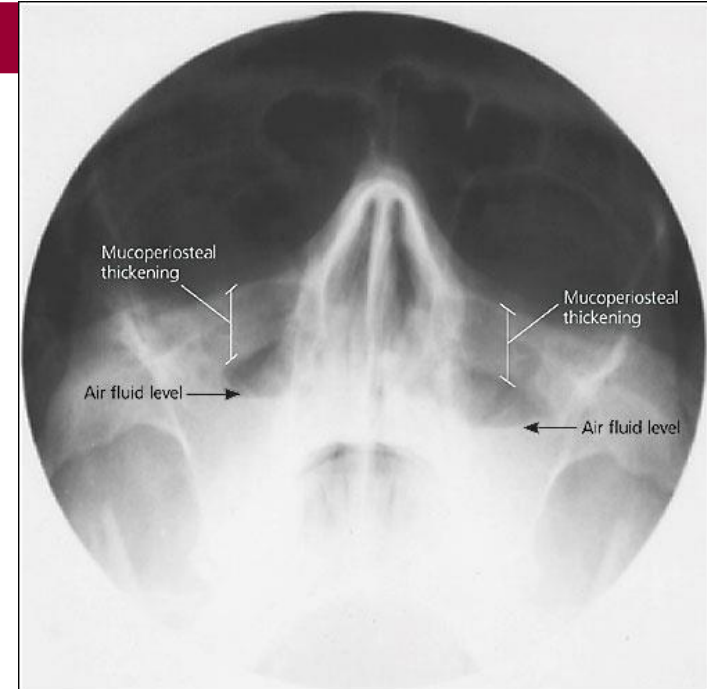
- **Radiologic evaluation**

- Sensitivity 84%, Specificity 77%
- Sinus mucosal thickening
- Opacification
- Air-fluid levels

- **Histopathological evaluation**

- **Nasal lavage evaluation**

- **Serologic evaluation**



Differential Diagnosis of UACS: Post-infectious cough, etc.

- **Post-infectious cough**
 - A history of a upper respiratory tract infection is the key to making the diagnosis of post-infectious UACS.
 - Viral, Mycoplasma pneumoniae, Chlamydia pneumoniae, Pertussis
- **Rhinitis due to anatomic abnormalities**
 - A deviated nasal septum, enlarged turbinates, or a dysfunctional nasal valve
- **Rhinitis due to physical or chemical irritants**
- **Occupational rhinitis**
 - Episodic rhinitis that is related to the work environment.
 - either allergic or non-allergic,
 - Either the primary cause or an aggravating factor.
- **Rhinitis medicamentosa:** long-term use of topical α -agonists
- **Rhinitis of Pregnancy**

Treatment of UACS

- **Treatment**

- **First-generation antihistamine/decongestant**

- **Allergic rhinitis**

- Nasal corticosteroids, nasal cromolyn, nasal antihistamines, oral leukotriene inhibitors, oral antihistamines

- **Vasomotor rhinitis**

- Ipratropium bromide nasal spray

- **Sinusitis**

- Acute bacterial sinusitis: antibiotics

- **Rhinitis due to physical or chemical irritants**

- Avoidance of exposure, improved ventilation, filters

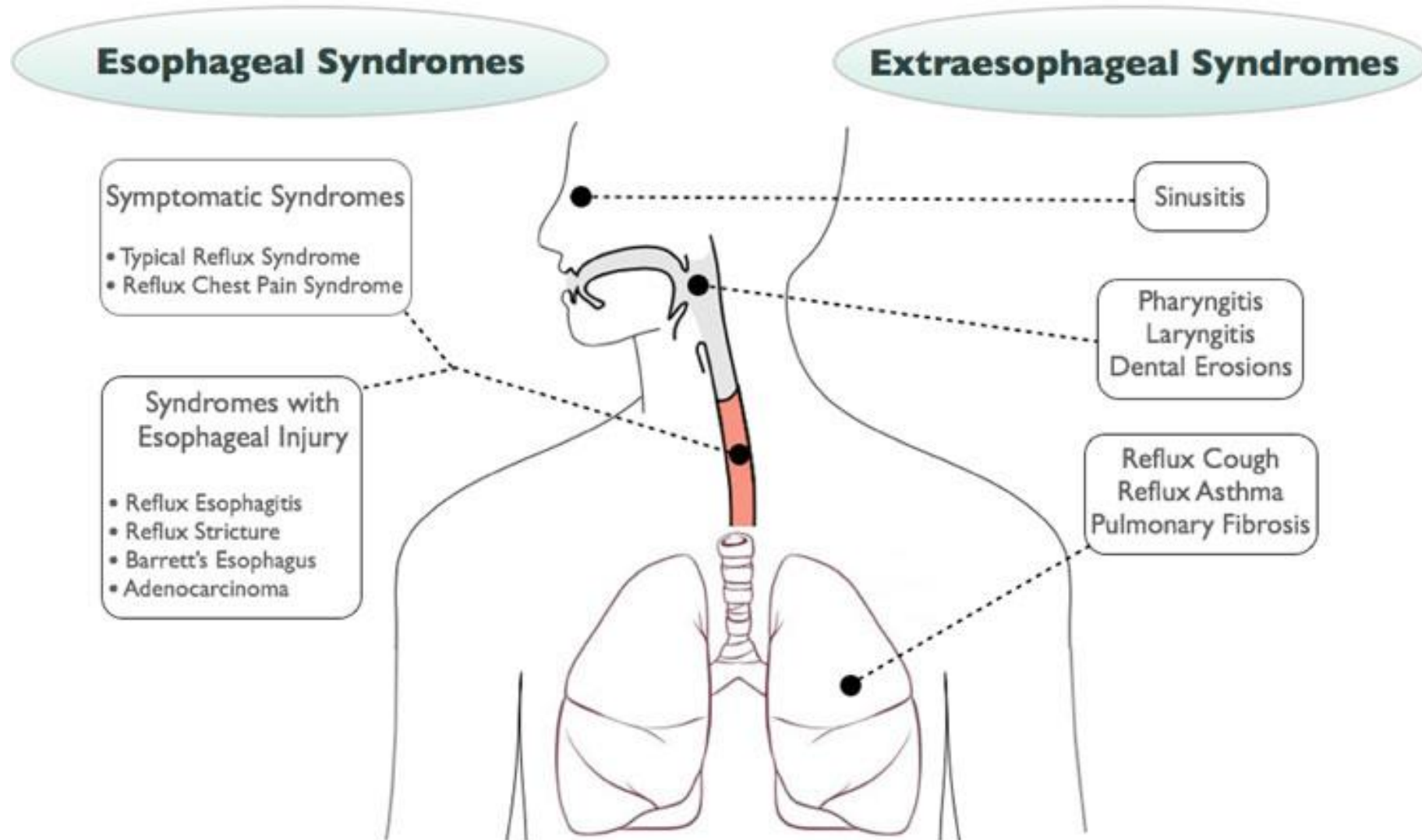
- **Rhinitis medicamentosa**

- stopping or weaning off the offending agent



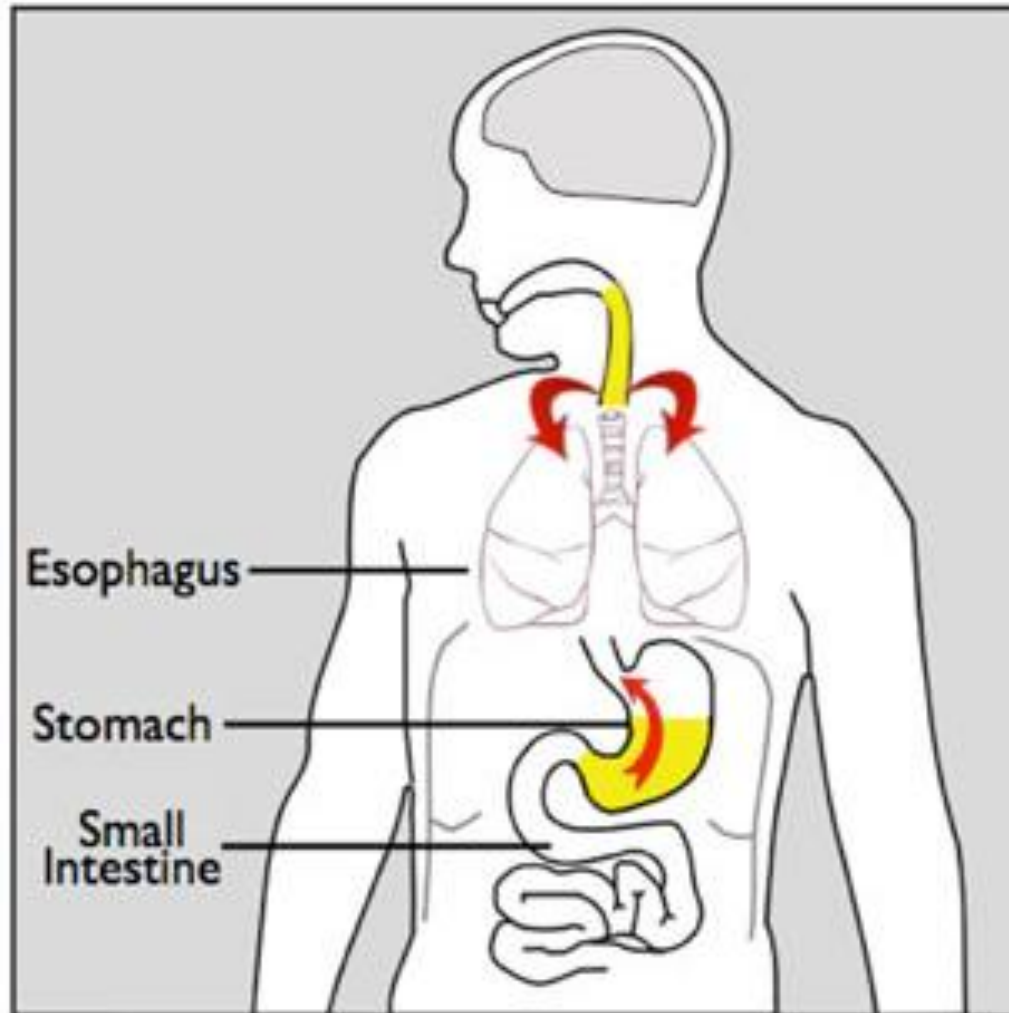
Clinical Approach of Laryngopharyngeal Reflux (LPR)

Gastroesophageal Reflux Disease (GERD)



Laryngopharyngeal Reflux (LPR)

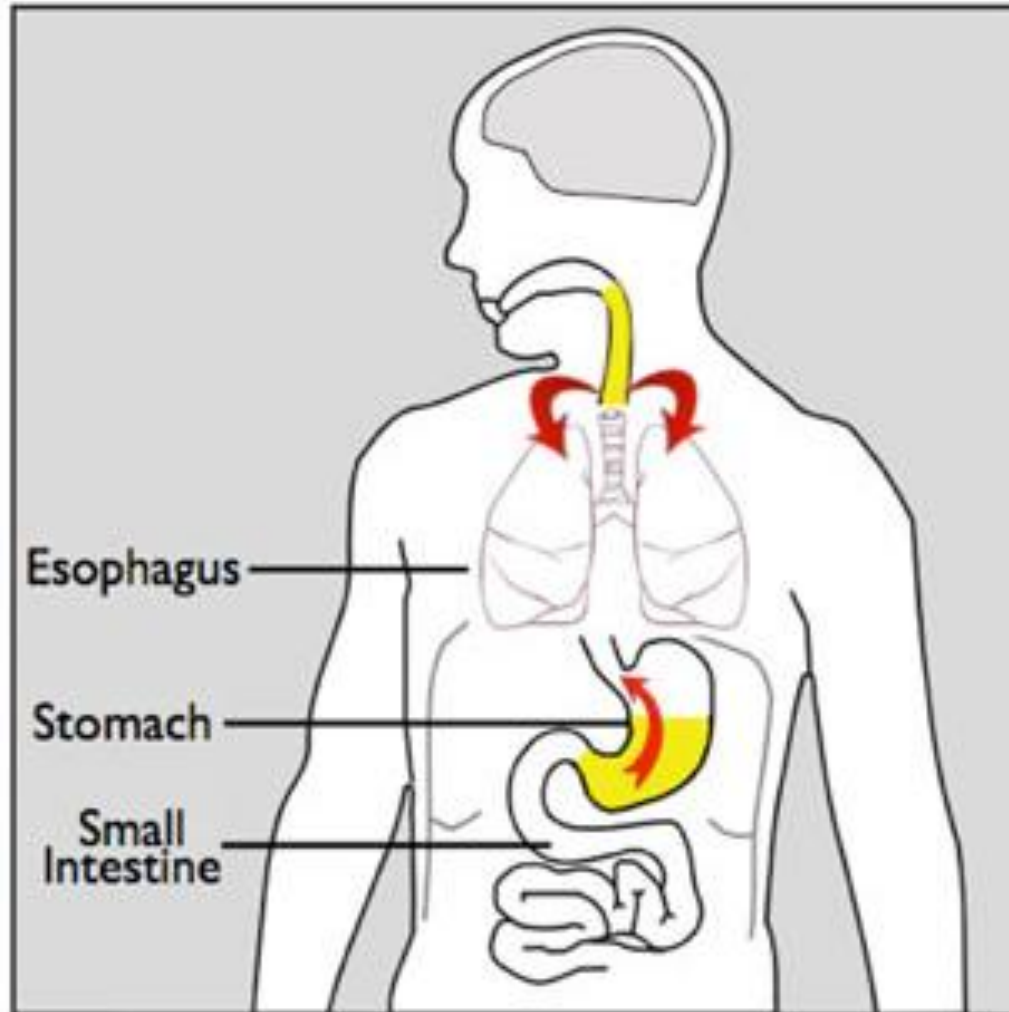
Pathophysiology of Extraesophageal Manifestations



- Reflux thorough esophageal sphincters causing pulmonary, laryngeal, pharyngeal, or extraesophageal symptoms.
- Direct contact of gastric refluxate with bronchial and laryngeal areas

Laryngopharyngeal Reflux (LPR)

Pathophysiology of Extraesophageal Manifestations



- ‘Esophageal-Bronchial cough reflex’
 - Reflux into distal esophagus stimulates vagally-mediated reflex.
- Common embryonic origins between esophagus and bronchial tree.

GERD vs. LPR

	GERD	LPR
Involvement of	LES	UES
Heartburn sensation	All	About 40%
Aggravation	Recumbent position	Upright position during periods of physical exertion
Sign of esophagitis on biopsy	Majority	About 25%

Symptoms of LPR

- **Symptoms**

- Dysphonia or hoarseness (71%)
- Cough (51%)
- Globus (47%)
- Throat clearing (42%)
- Dysphagia (35%)

Normal Laryngoscopy Findings

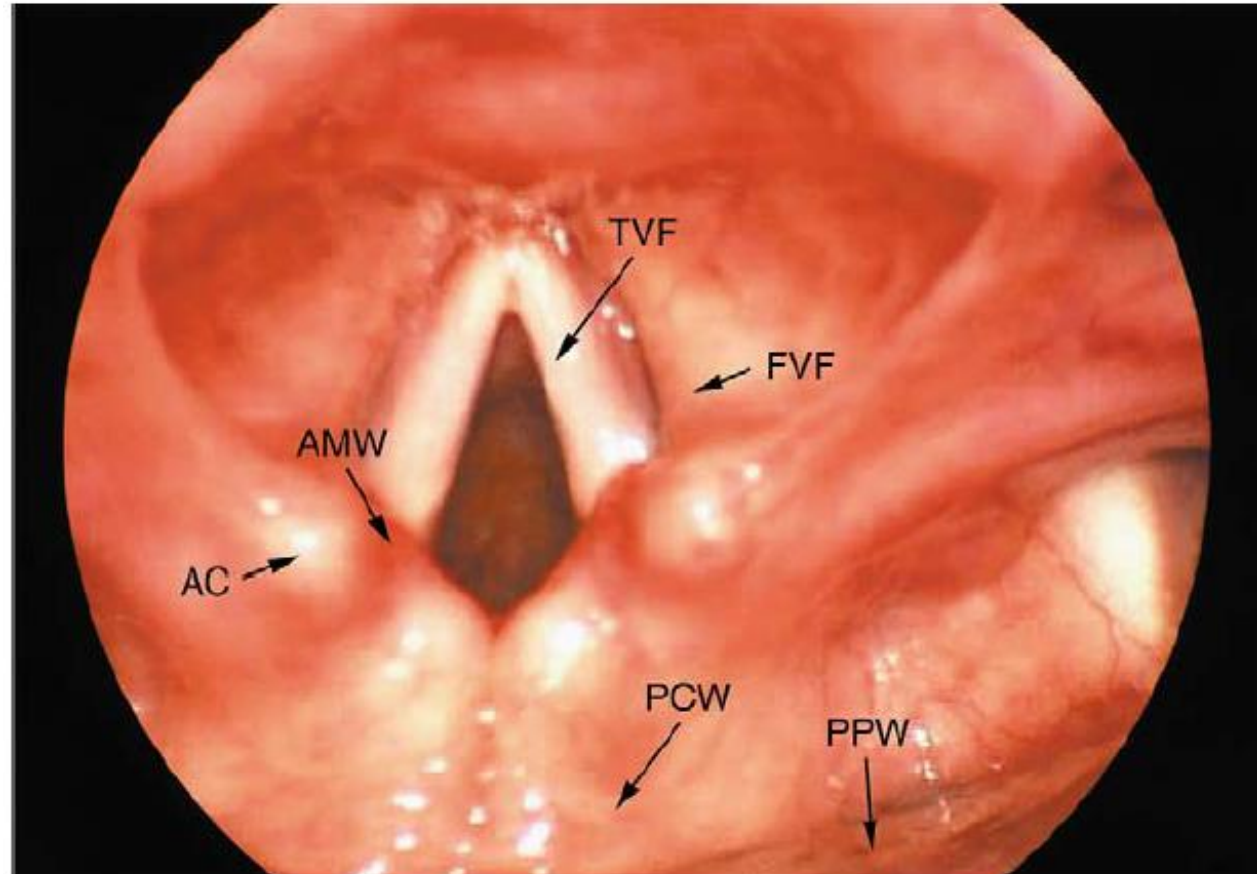


Figure 2. Normal laryngeal tissue. TVF, true vocal fold; FVF, false vocal fold; AMW, arytenoid medial wall; AC, arytenoid complex; PCW, posterior cricoid wall; PPW, posterior pharyngeal wall.

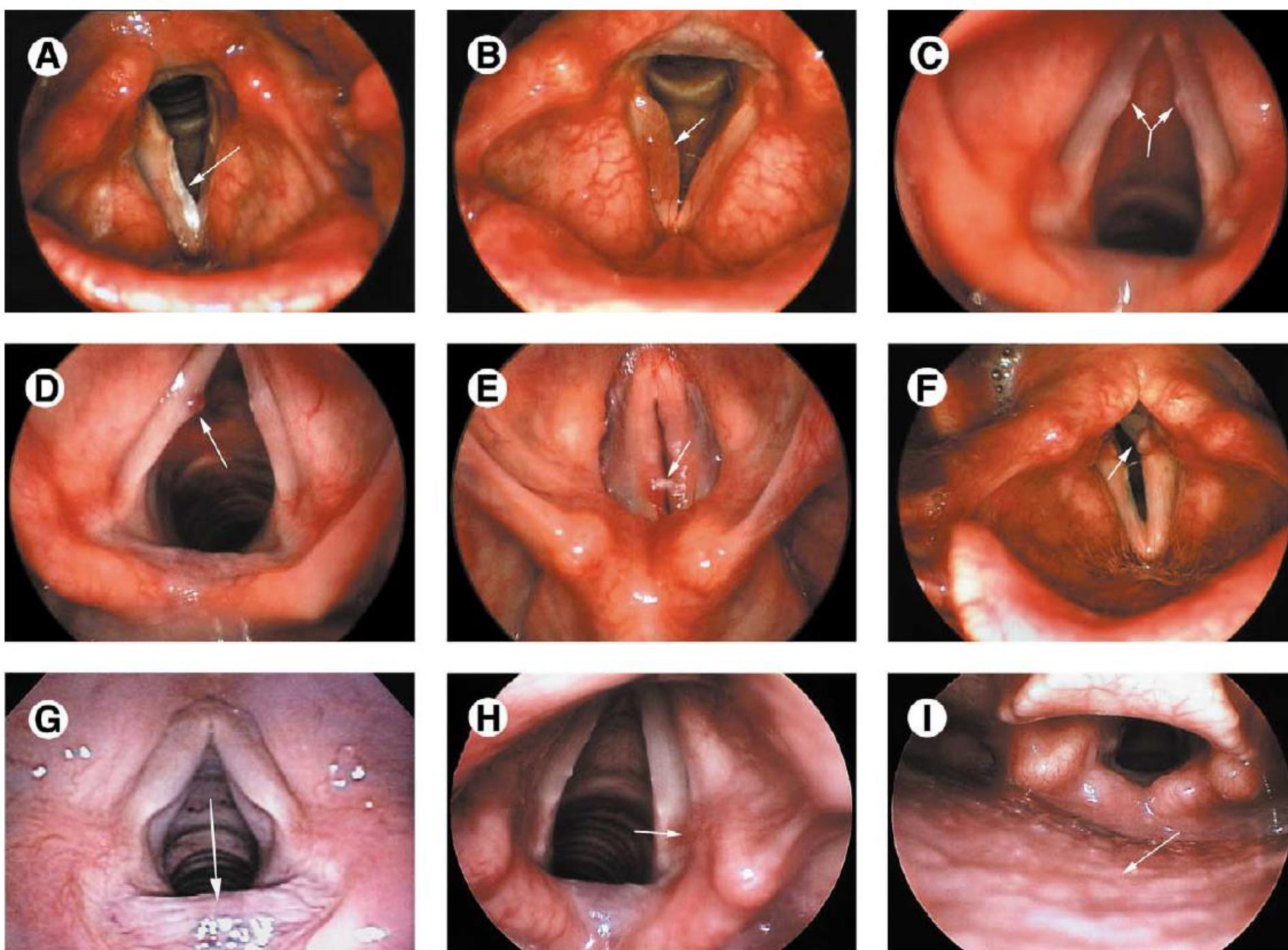


Figure 3. Abnormal larynx. (A) Leukoplakia; (B) Reinke's edema; (C) bilateral true vocal fold nodules; (D) true vocal fold hemorrhagic polyp; (E) true vocal fold erythema; (F) vocal fold granuloma; (G) interarytenoid bar; (H) arytenoid medial wall erythema; (I) posterior pharyngeal wall cobblestoning. *patol.* 2003;1(5):333-44.

Abnormal Findings in Normal Subjects

Table 3. Laryngoscopic Findings in Healthy Subjects

Common findings	
Interarytenoid bar	75/105 (71%)
Arytenoid medial wall erythema	31/105 (30%)
Posterior pharyngeal wall cobble stoning	22/105 (21%)
Interarytenoid bar erythema	16/105 (15%)
Arytenoid medial wall granularity	15/105 (14%)
Rare findings	
Posterior cricoid wall erythema	0/105 (0%)
Posterior pharyngeal wall erythema	0/105 (0%)
True/false vocal cord erythema/edema	2/105 (2%)
Posterior commissure erythema	0/105 (0%)

Table 4. More Specific Laryngeal Signs of GERD

ENT signs	Normals (n = 105) ^a	GERD (n = 34)	<i>P</i>
Posterior cricoid wall erythema	0%	76%	<0.001
Posterior pharyngeal wall cobble stoning	21%	15%	0.8
Interarytenoid bar	71%	76%	0.4
True/false vocal cord erythema/edema	2%	70%	<0.001
Arytenoid medial wall erythema/edema	30%	82%	<0.001

The Reliability of the Assessment of Endoscopic Laryngeal Findings Associated With Laryngopharyngeal Reflux Disease

Ryan C. Branski, MA; Neil Bhattacharyya, MD; Jo Shapiro, MD

coefficients ranging from -0.121 to 0.837 . Conclusions: Accurate clinical assessment of laryngeal involvement with LPRD is likely to be difficult because laryngeal physical findings cannot be reliably determined from clinician to clinician. Such variability makes the precise laryngoscopic diagnosis of LPRD highly subjective. *Key Words:* Gastroesophageal reflux disease, chronic laryngitis, reliability.

Laryngoscope, 112:1019–1024, 2002

TABLE I.
Reflux Finding Score (RFS).

Subglottic edema	0 = absent 2 = present
Ventricular	2 = partial 4 = complete
Erythema/hyperemia	2 = arytenoids only 4 = diffuse
Vocal fold edema	1 = mild 2 = moderate 3 = severe 4 = polypoid
Diffuse laryngeal edema	1 = mild 2 = moderate 3 = severe 4 = obstructing
Posterior commissure hypertrophy	1 = mild 2 = moderate 3 = severe 4 = obstructing
Granuloma/granulation tissue	0 = absent 2 = present
Thick endolaryngeal mucus	0 = absent 2 = present

Diagnostic Tools for LPR

Method	Advantages	Disadvantages
Laryngoscopy	<ul style="list-style-type: none"> No sedation required Direct visualization of the larynx and laryngeal pathology 	<ul style="list-style-type: none"> No specific laryngeal signs for reflux Over-diagnoses reflux as the etiology for patients' symptoms
Endoscopy	<ul style="list-style-type: none"> Easy visualization of mucosal damage/erosions 	<ul style="list-style-type: none"> Poor sensitivity/specificity/PPV Requires sedation High cost
pH monitoring	<ul style="list-style-type: none"> Easy to perform Relatively non-invasive Prolonged monitoring Ambulatory 	<ul style="list-style-type: none"> Many are catheter-based May have up to 30 % false negative rate No pH predictors of treatment response for extraesophageal reflux
Impedance monitoring	<ul style="list-style-type: none"> + Measures acidic and non-acidic gas and liquid reflux (combined with pH) 	<ul style="list-style-type: none"> Catheter based False negative rate unknown but Most likely similar to catheter-based pH monitoring Unknown clinical relevance when abnormal on PPI therapy Unknown importance in extraesophageal reflux

Treatment of GERD(LPR)



표 4. 위식도역류성 기침을 의심할 수 있는 임상적 상황

1. 만성기침
2. 기침을 유발할 만한 자극제 (담배연기, 공해물질, 독성물질 등)에 노출력이 없다.
3. 현재 흡연자가 아니다.
4. 흉부 방사선이 정상이거나 이전과 변함이 없다.
5. 천식이 배제되었다 (천식 치료에도 기침 호전이 없거나, 기관지유발검사가 음성이다).
6. 상기도기침증후군이 배제되었다 (1세대 항히스타민제에 기침 호전이 없고 무증상 비부비동염이 배제되었다).
7. 호산구성기관지염이 배제되었다 (적절하게 시행한 유도객담 검사가 음성이거나 흡입 혹은 전신스테로이드에 기침 호전이 없다).

- **PPI**

- ✓ 1차 약물
- ✓ 하루 한번 vs. 하루 두 번
- ✓ 4개월 > 2개월

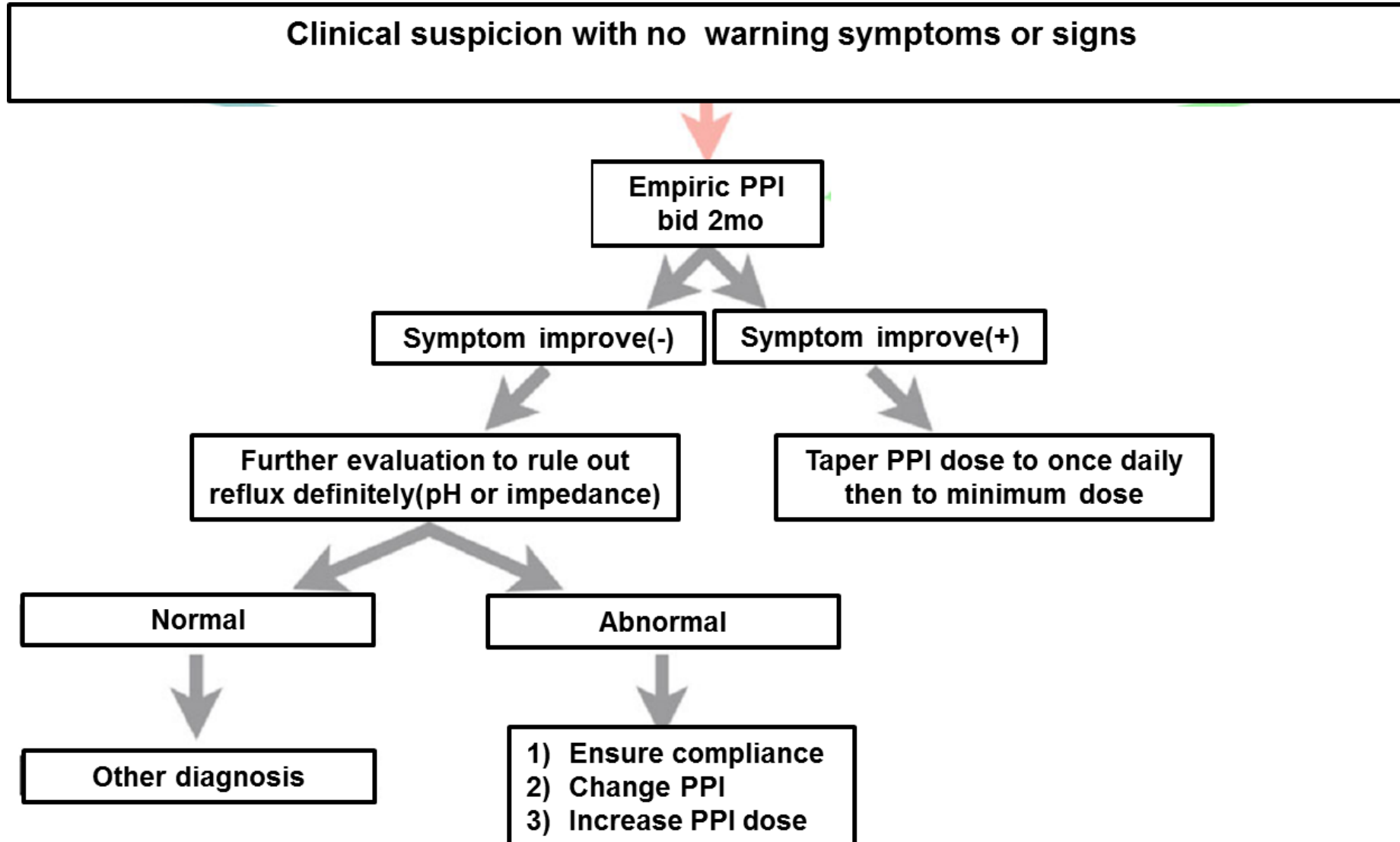
- **H2RA**

- ✓ Nocturnal gastric acid breakthrough

- **Prokinetics, Surgery**

- ✓ Data 부족

Treatment of LPR



Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease

Philip O. Katz, MD¹, Lauren B. Gerson, MD, MSc² and Marcelo F. Vela, MD, MSCR³

Am J Gastroenterol 2013; 108:308–328; doi:10.1038/ajg.2012.444; published online 19 February 2013



EXTRAESOPHAGEAL PRESENTATIONS OF GERD: ASTHMA, CHRONIC COUGH, AND LARYNGITIS

Recommendations

1. GERD can be considered as a potential co-factor in patients with asthma, chronic cough, or laryngitis. Careful evaluation for non-GERD causes should be undertaken in all of these patients. (Strong recommendation, moderate level of evidence).
2. A diagnosis of reflux laryngitis should not be made based solely upon laryngoscopy findings (Strong recommendation, moderate level of evidence).
3. A PPI trial is recommended to treat extraesophageal symptoms in patients who also have typical symptoms of GERD. (Strong recommendation, low level of evidence)
4. Upper endoscopy is not recommended as a means to establish a diagnosis of GERD-related asthma, chronic cough, or laryngitis. (Strong recommendation, low level of evidence)
5. Reflux monitoring should be considered before a PPI trial in patients with extraesophageal symptoms who do not have typical symptoms of GERD. (Conditional recommendation, low level of evidence).
6. Non-responders to a PPI trial should be considered for further diagnostic testing, and are addressed in the refractory GERD section below. (Conditional recommendation, low level of evidence)
7. Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI. (Strong recommendation, moderate level of evidence)

Chronic Cough Due to Gastroesophageal Reflux in Adults

CHEST Guideline and Expert Panel Report



- In adult patients with chronic cough suspected to be due to reflux-cough syndrome, we recommend that treatment include (1) diet modification to promote weight loss in overweight or obese patients; (2) head of bed elevation and avoiding meals within 3 hours of bedtime; and (3) in patients who report heartburn and regurgitation, proton pump inhibitors (PPIs), H₂-receptor antagonists, alginate, or antacid therapy sufficient to control these symptoms (Grade 1C).
- In adult patients with suspected chronic cough due to reflux-cough syndrome, but without heartburn or regurgitation, we recommend against using PPI therapy alone because it is unlikely to be effective in resolving the cough (Grade 1C).
- In adult patients with chronic cough potentially due to reflux-cough syndrome who are refractory to a 3-month trial of medical antireflux therapy and are being evaluated for surgical management (antireflux or bariatric), or in whom there is strong clinical suspicion warranting diagnostic testing for gastroesophageal reflux, we suggest that they undergo esophageal manometry and pH-metry with conventional methodology (Grade 2C).
- In adult patients with chronic cough and a major motility disorder (eg, absent peristalsis, achalasia, distal esophageal spasm, hypercontractility) and/or normal acid exposure time in the distal esophagus, we suggest not advising antireflux surgery (Grade 2C).
- In adult patients with chronic cough, adequate peristalsis, and abnormal esophageal acid exposure determined by pH-metry in whom medical therapy has failed we suggest antireflux (or bariatric when appropriate) surgery for presumed reflux-cough syndrome (Grade 2C).

Thank You for Your Attention