Clinical Approach of Upper Airway Cough Syndrome and Laryngopharyngeal Reflux

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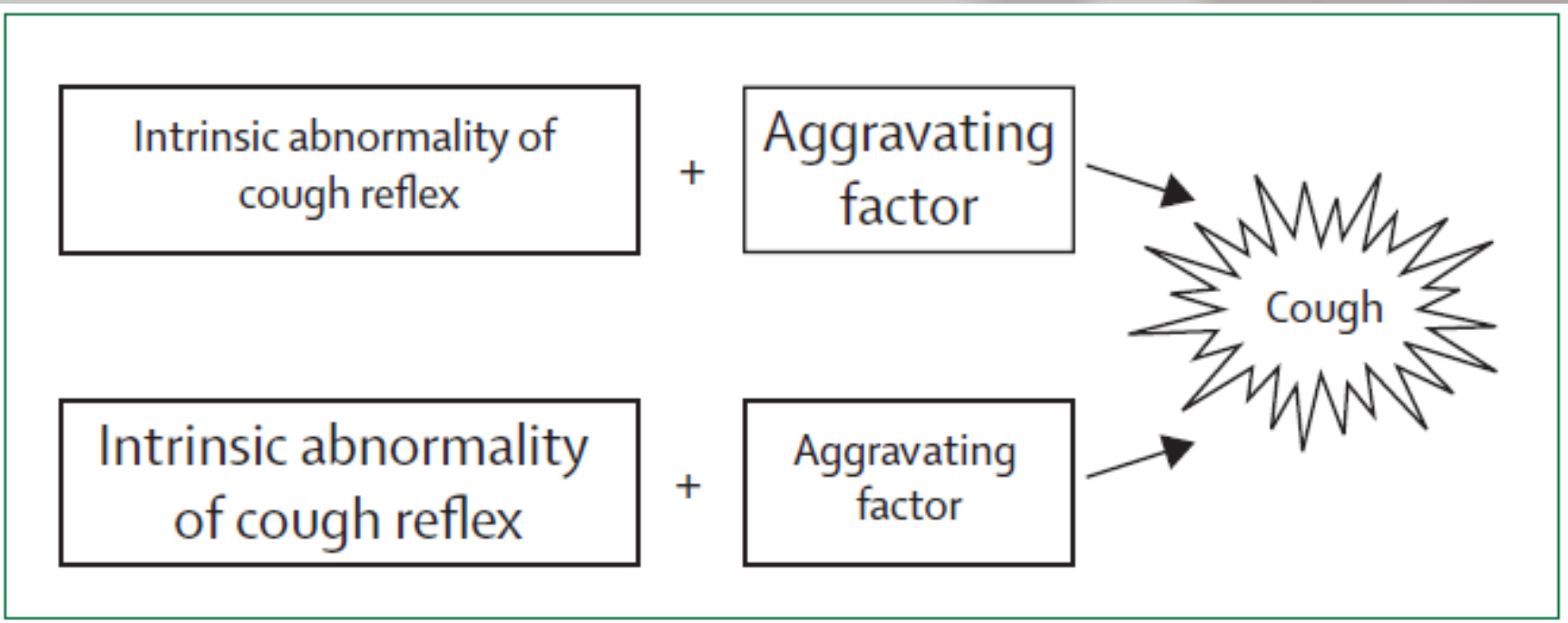
Differences between the Two Major Types of Chronic Cough

	Eosinophlilic 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

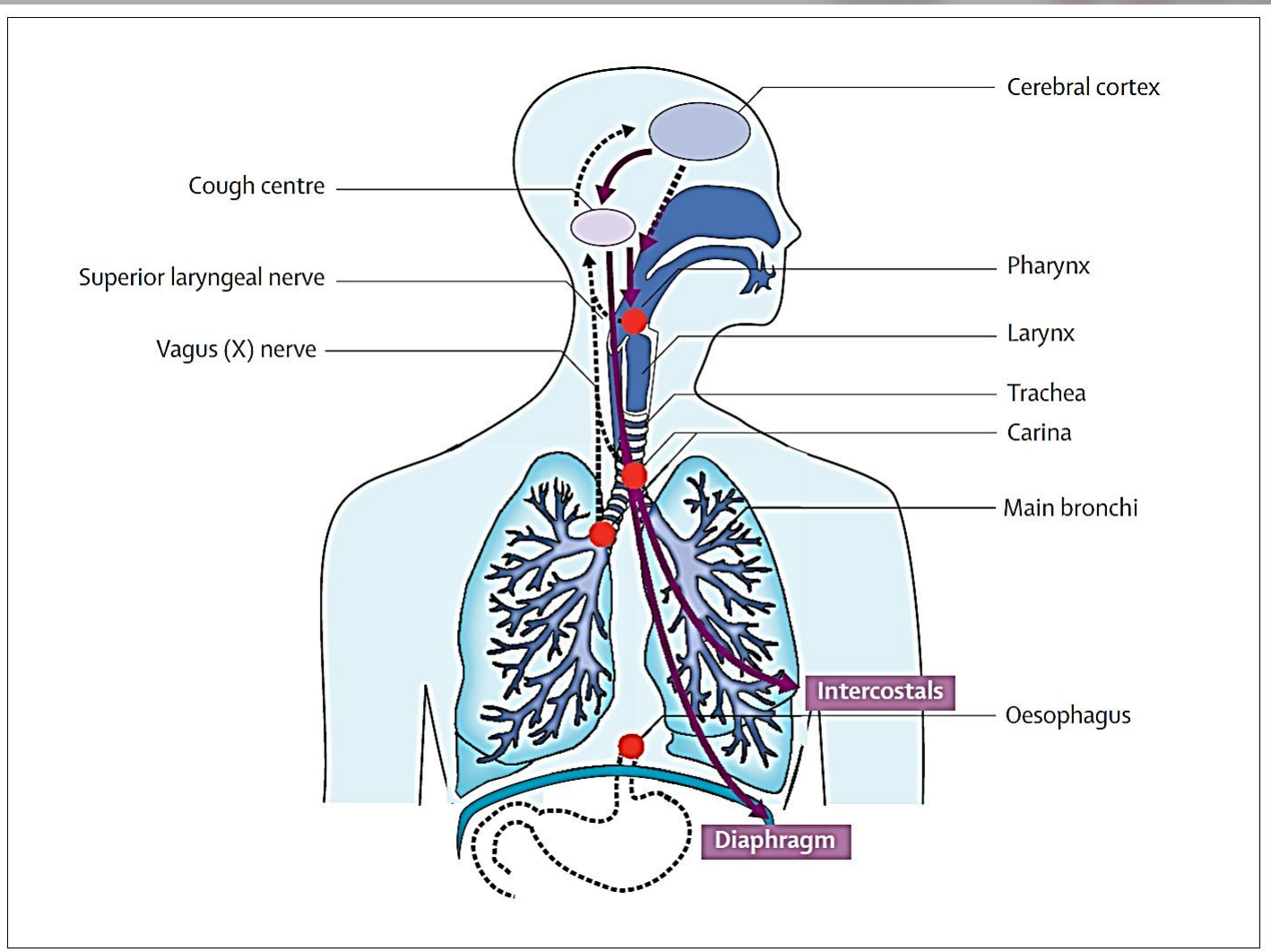
Pavord ID et al. Lancet. 2008;371:1375-84

Model for pathogenesis of non-asthmatic chronic cough



Pavord ID et al. Lancet. 2008;371:1375-844

Anatomy of Cough Pathways



Pavord ID et al. Lancet. 2008;371:1375-84

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

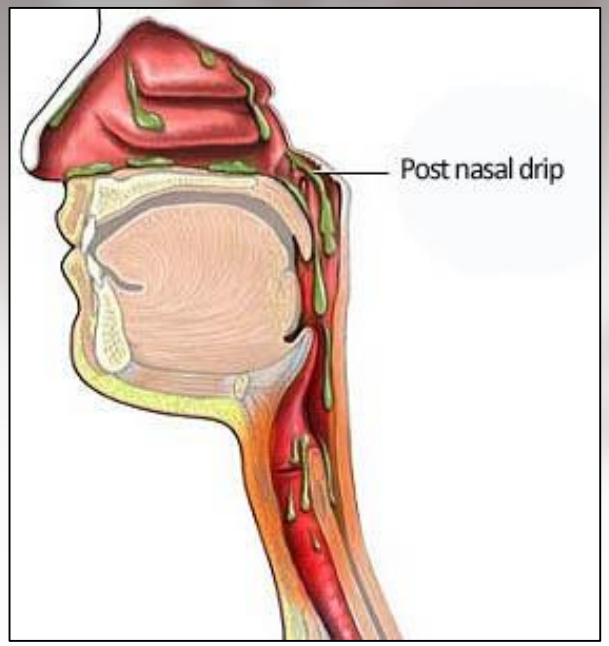
*Greatest concentration of cough receptors.

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

- **<u>Upper airway cough syndrome (UACS)</u>**
  - (+) irritation or inflammation of upper airway structures that directly stimulate cough receptors



Irwin et al. Chest 2006;129:1S-23S.

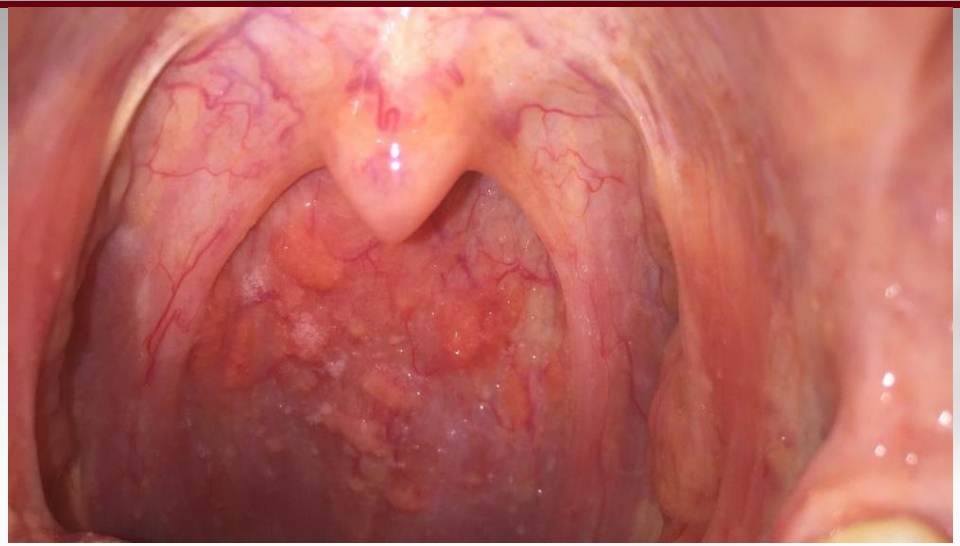
Symptoms of UACS

- **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

Pratter MR. Chest 2006;129(1 Suppl):63S-71S.

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.

Irwin RS et al. Am Rev Respir Dis. 1990;141(3):640-7.

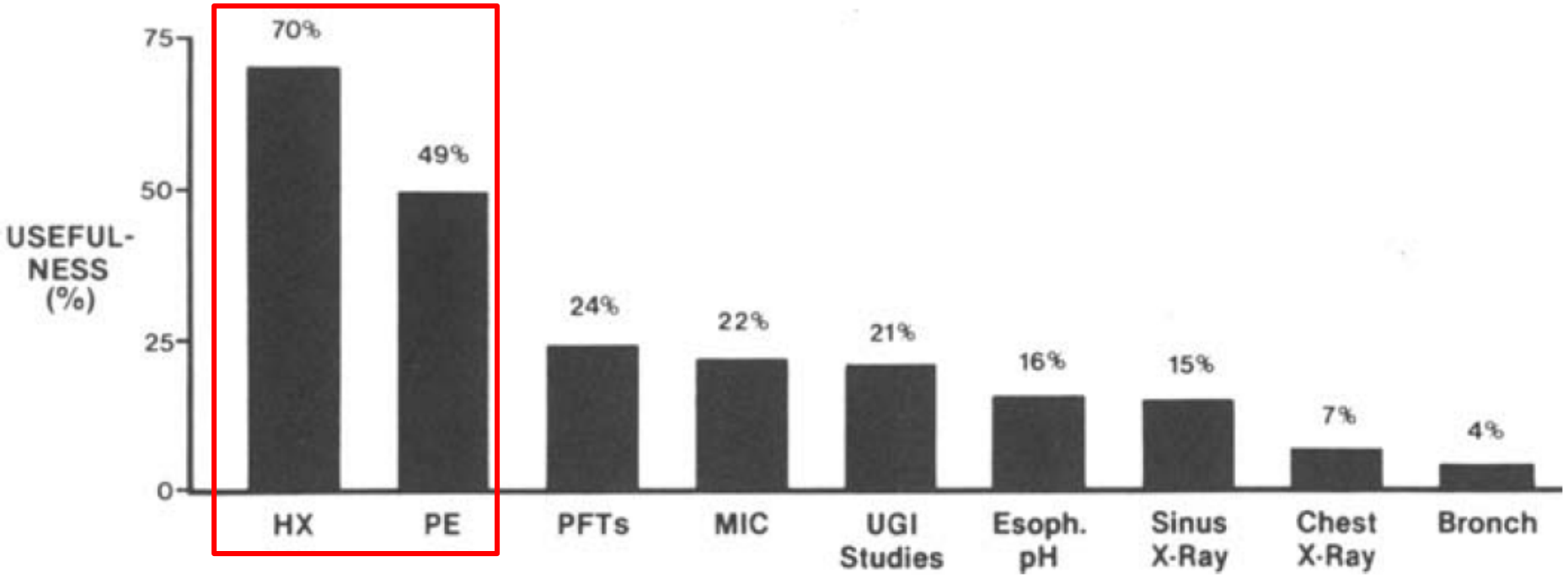


Fig. 2. The relative usefulness (true positive result) of each component of the diagnostic protocol in determining the 131 causes of cough (HX = history; PE = physical examination; PFTs = pulmonary function tests; MIC = methacholine inhalational challenge; UGI = upper gastrointestinal; esoph. pH = prolonged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

Irwin RS et al. Am Rev Respir Dis. 1990;141(3):640-7.

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.**

Diagnosis of UACS

- **Diagnosis**

  – **Medical History and Physical Examination**

  +

  Treatment Response

  (Diagnostic and Therapeutic trial)

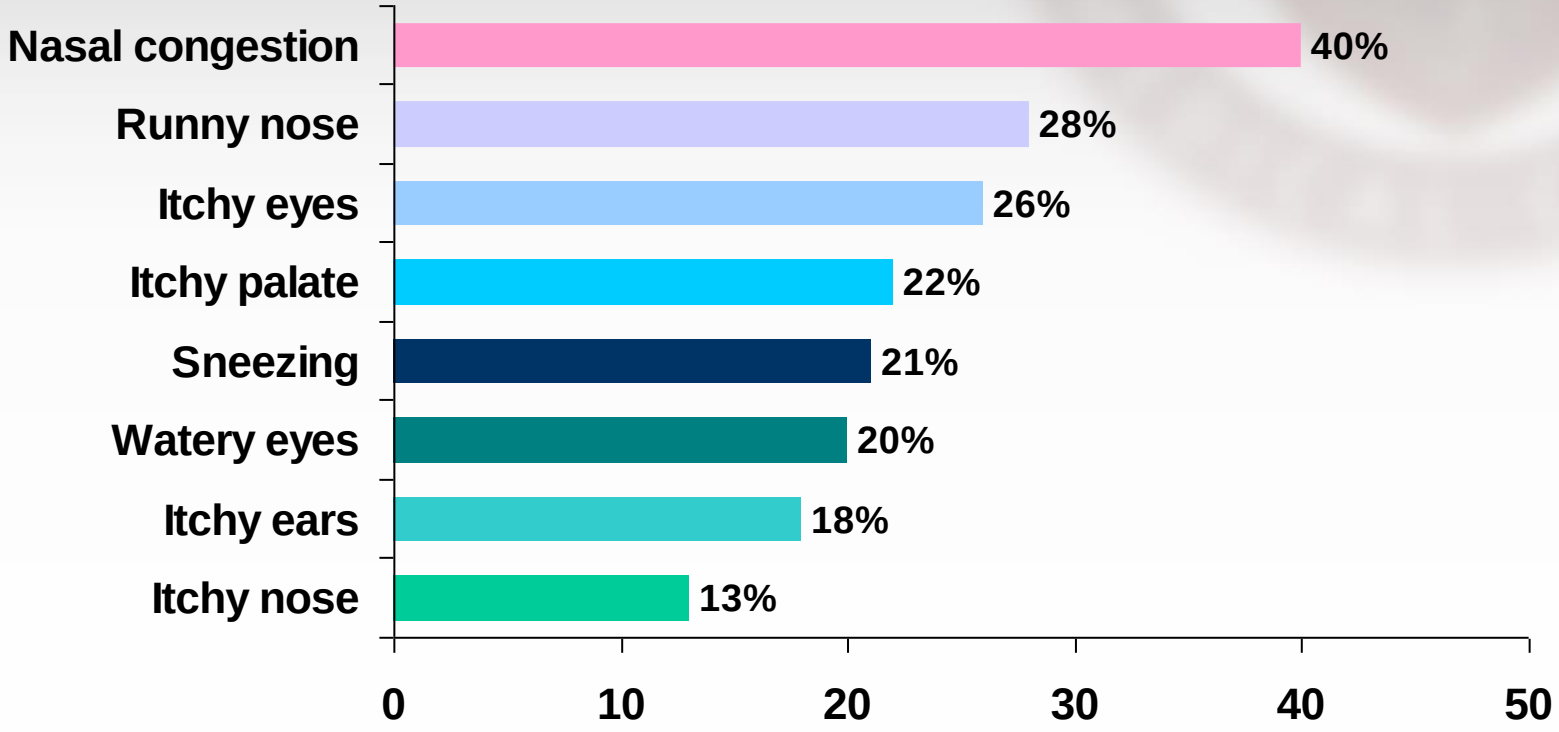
  (± Laboratory results)

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**

DDx. Of UACS: Allergic Rhinitis

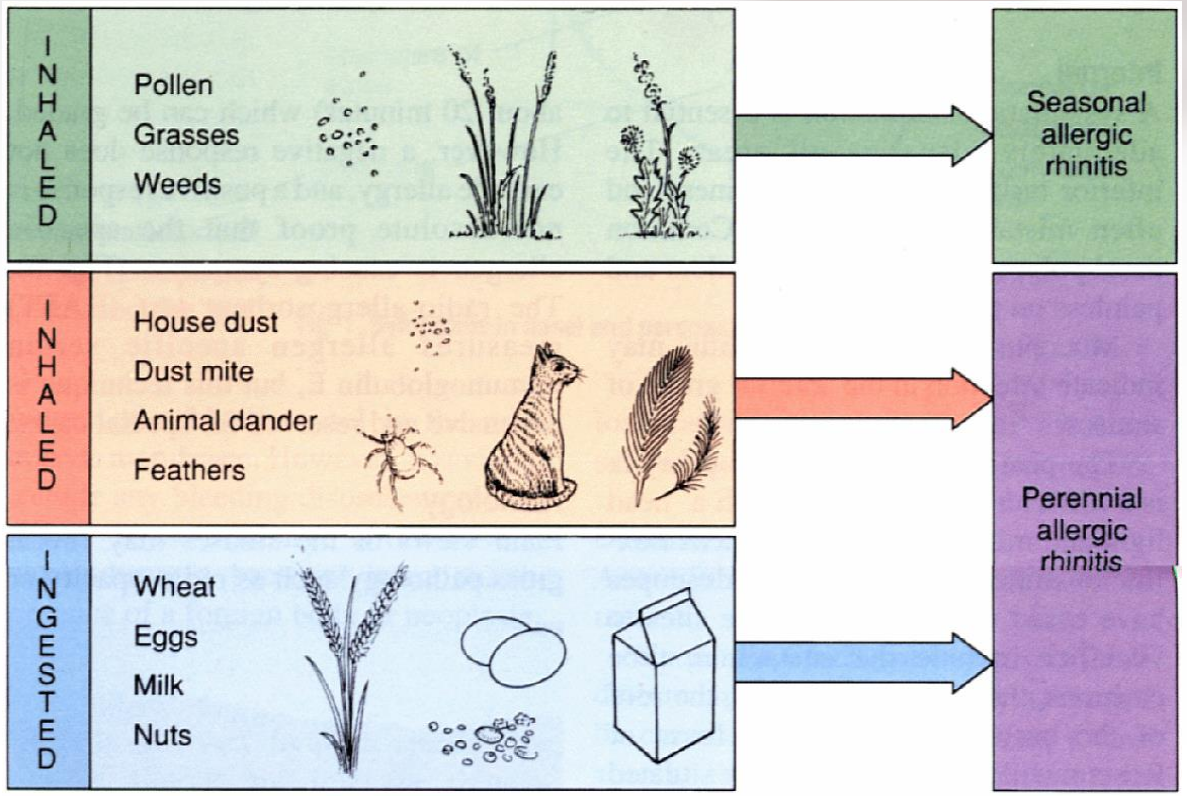
- **Allergic rhinitis**
  - **Symptoms**



C.van Drunen et al. Allergy 2005;60:5-19

DDx. 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



DDx. Of UACS: Perennial non-allergic rhinitis

- **Perennial non-allergic rhinitis**
  - **<u>Vasomotor</u>**:
    - 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
  - **<u>Nonallergic rhinitis with eosinophilia (NARES)</u>**
    - 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

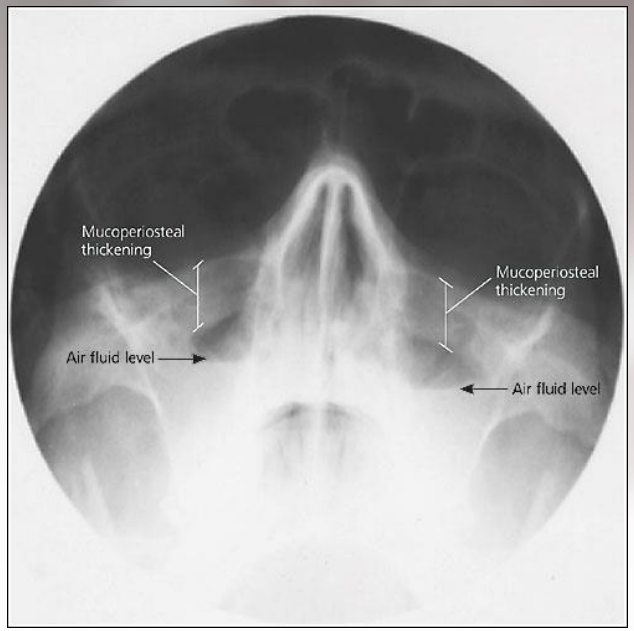
DDx. Of UACS: Sinusitis

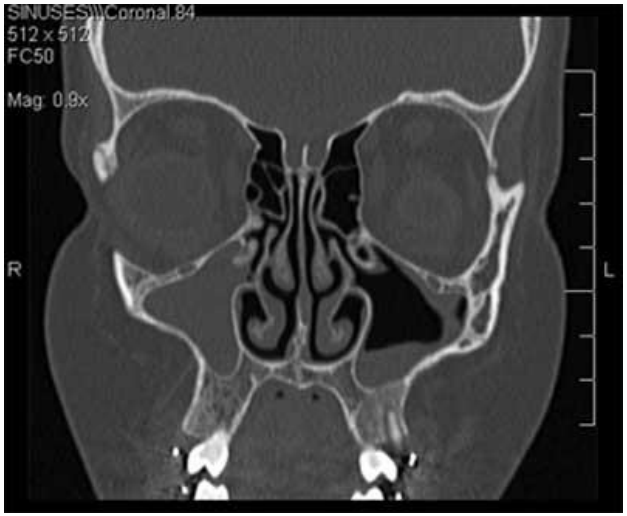
- **Bacterial sinusitis & Allergic fungal sinusitis**

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

DDx. Of UACS: Sinusitis

- **Bacterial sinusitis & Allergic fungal sinusitis**
  - **Radiologic evaluation**
    - **<u>Sensitivity 84%, Specificity 77%</u>**
    - Sinus mucosal thickening
    - Opacification
    - Air-fluid levels
  - **Histopathological evaluation**
  - **Nasal lavage evaluation**
  - **Serologic evaluation**





DDx. 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

‘Unified Airway’ Theory

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Otolaryngol Clin N Am
41 (2008) 257–266

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The Unified Airway—Conceptual Framework

The presence and severity of disease processes within the upper and lower airways are linked closely, and exacerbations of disease in one component of the airway are likely to encourage worsening of airway disease diffusely.[1]

Rhinogenic Laryngitis, Cough, and the Unified Airway

John H. Krouse, MD, PhD[a,*], Kenneth W. Altman, MD, PhD[b]

Krouse JH. Otolaryngol Clin North Am. 2008;41:257-66.
Krouse JH et al. Otolaryngol Clin North Am. 2010;43:111–21.

‘Unified Airway’ Theory

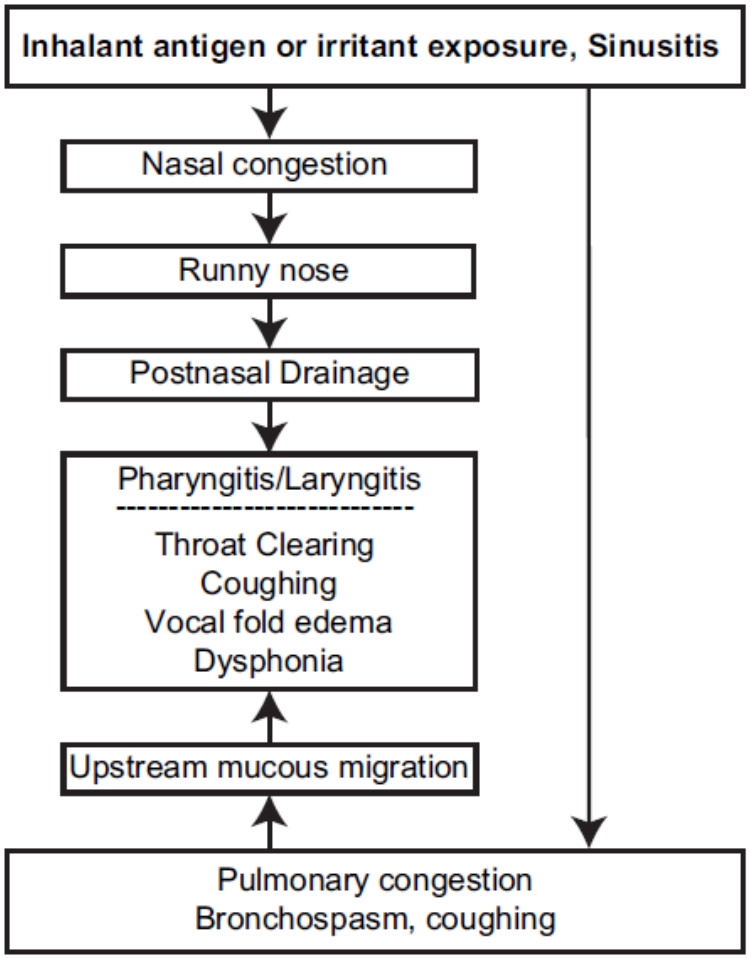
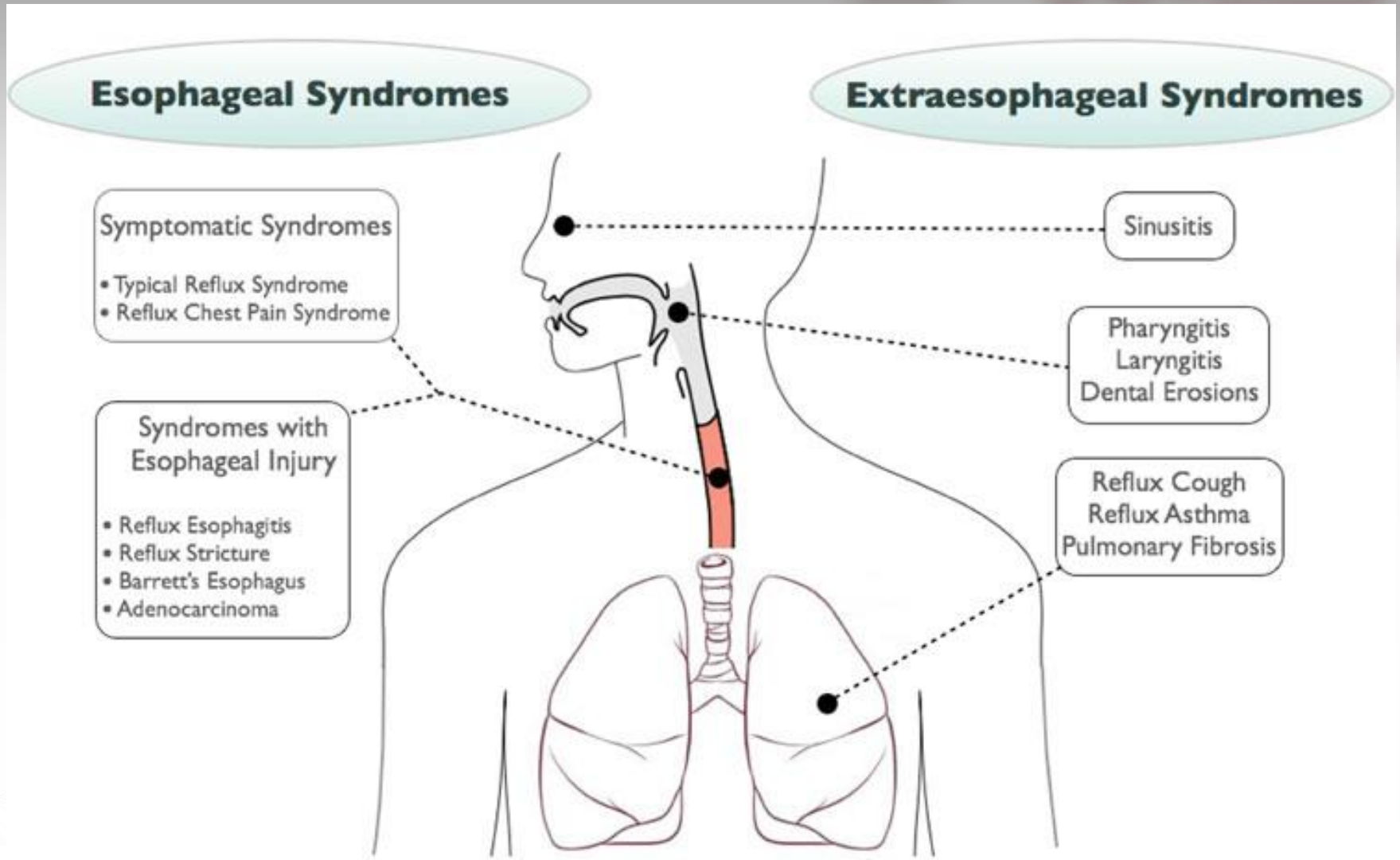


Fig. 3. Flow diagram. Downstream and upstream inflammatory reactions may induce laryngeal changes and symptoms. (*Modified from* Dworkin JP, Stachler RJ. Management of the patient with laryngitis. In: Krouse JH, Derebery MJ, Chadwick SJ, editors. Managing the allergic patient. Philadelphia: Elsevier; 2007. p. 262; with permission.)

Krouse JH et al. Otolaryngol Clin North Am. 2010;43:111–21.

Clinical Approach of Laryngopharyngeal Reflux (LPR)

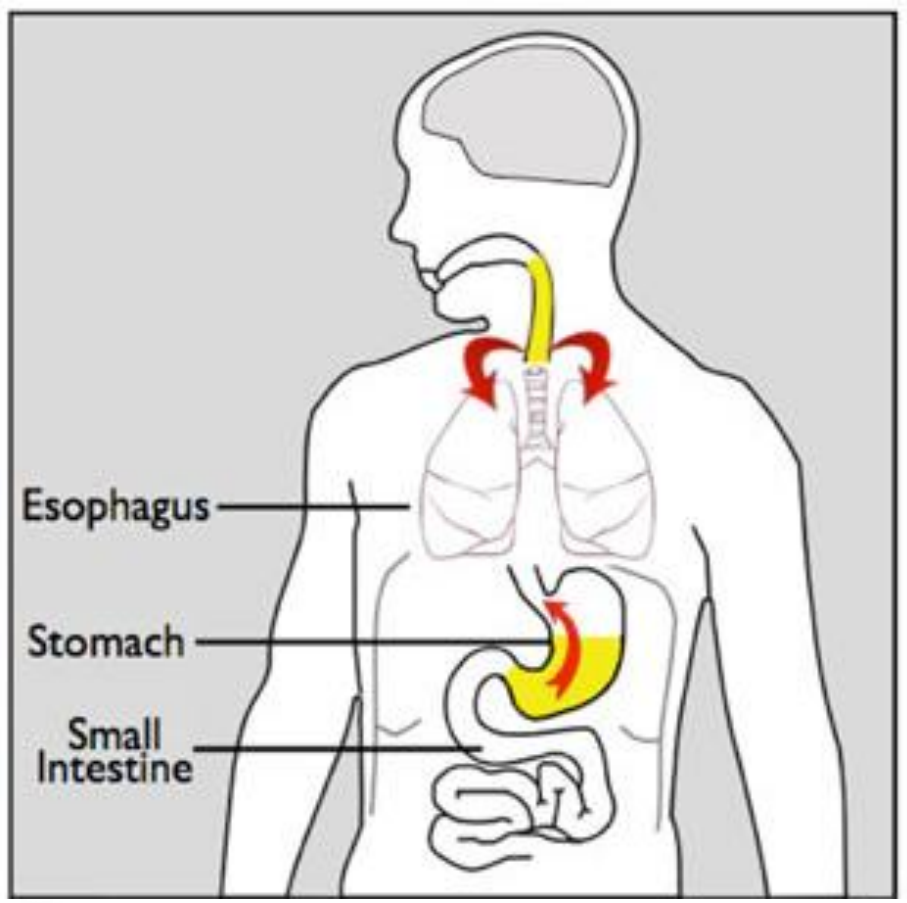
Gastroesophageal Reflux Disease (GERD)



Hom C, Vaezi MF. Drug 2013;73:1281-1295

Laryngopharyngeal Reflux (LPR)

Pathophysiology of Extraesophageal Manifestations

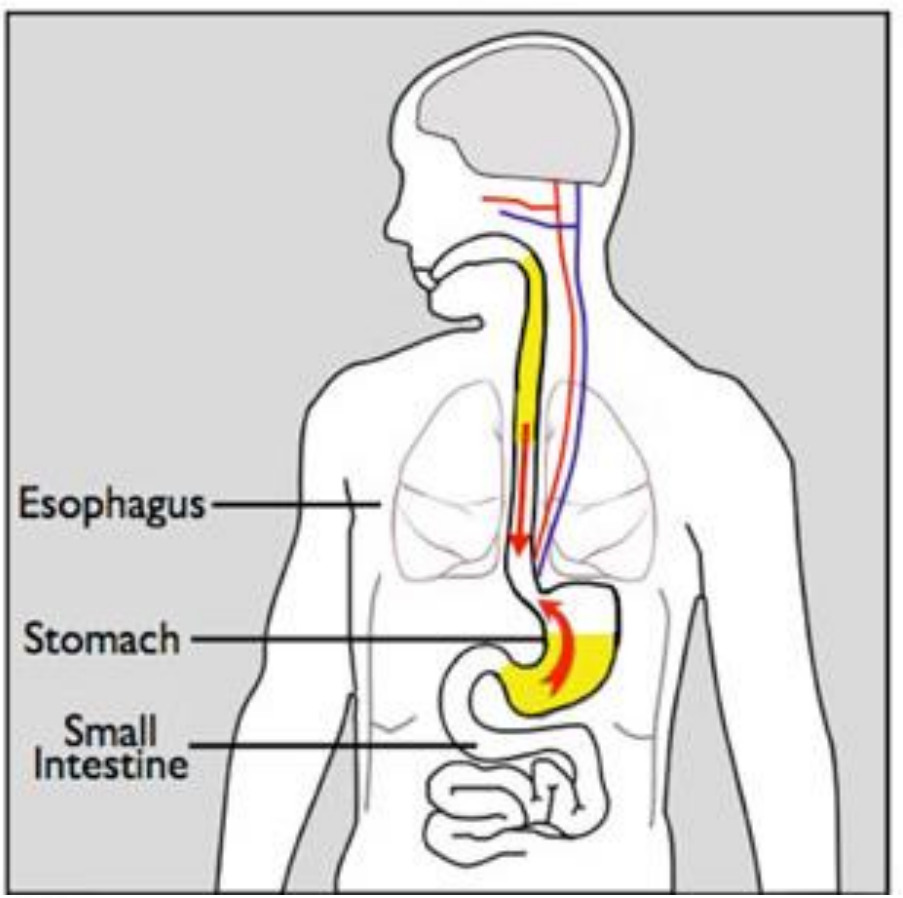


- Reflux thorough esophageal sphincters causing pulmonary, laryngeal, pharyngeal, or extraesophageal symptoms.
- **Direct contact of gastric refluxate with bronchial and laryngeal areas**

Hom C, Vaezi MF. Drug 2013;73:1281-1295

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.

Hom C, Vaezi MF. Drug 2013;73:1281-1295

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 of LPR**
  - Dysphonia or hoarseness (71 %)
  - Cough (51 %)
  - Globus (47 %)
  - Throat clearing (42 %)
  - Dysphagia (35 %)
  - Sore or burning throat
  - Apnea
  - Laryngospasm
  - Postnasal drip
  - Neoplasm

Vaezi MF et al. Clin Gastroenterol Hepatol. 2003;1(5):333-44.

Normal Laryngoscopy Findings

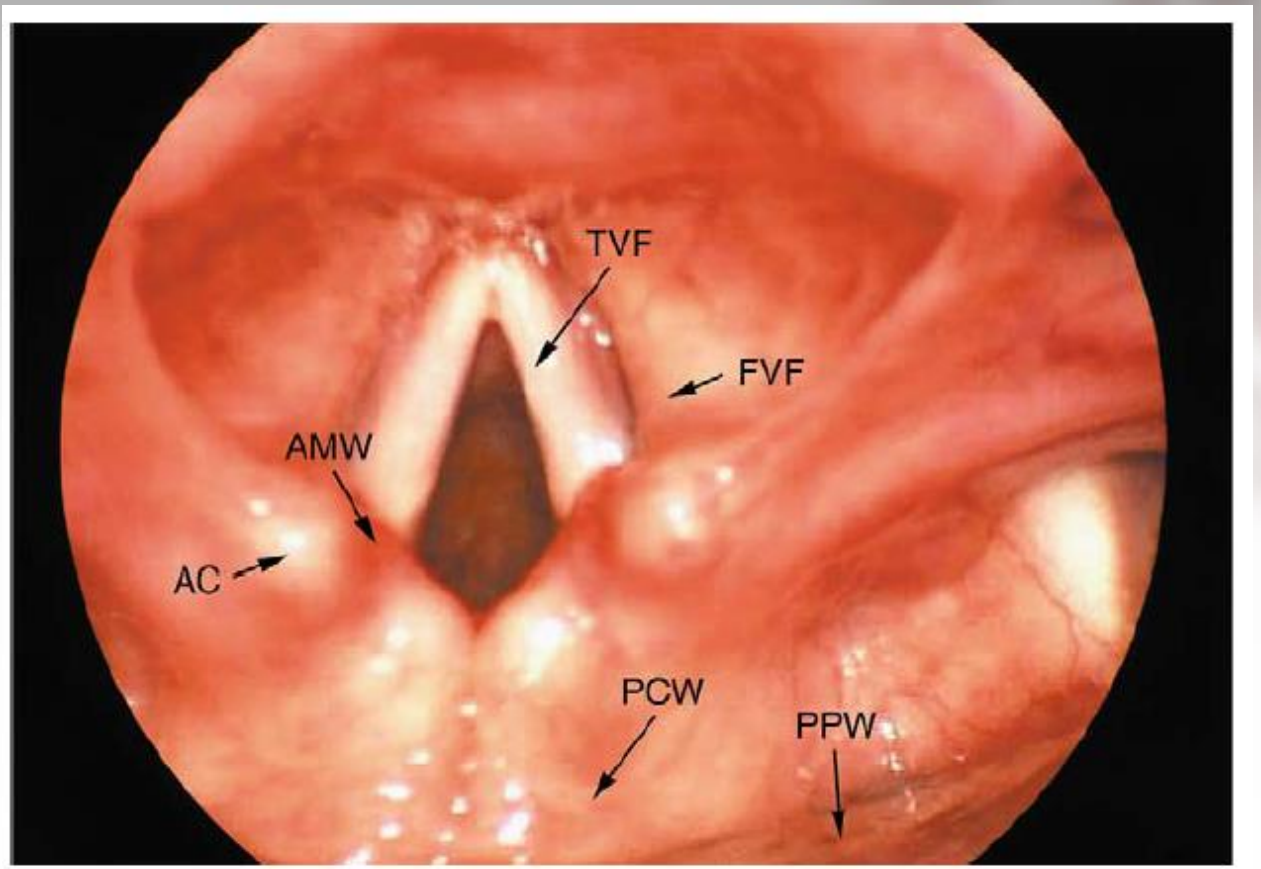


Figure 2. Normal laryngeal tissue. TVF, true vocal fold; FVF, false vocal fold; AMW, arytenoid medial wall; AC, arytenoid complex; PCW, posterior cricoid wall; PPW, posterior pharyngeal wall.

Vaezi MF et al. Clin Gastroenterol Hepatol. 2003;1(5):333-44.

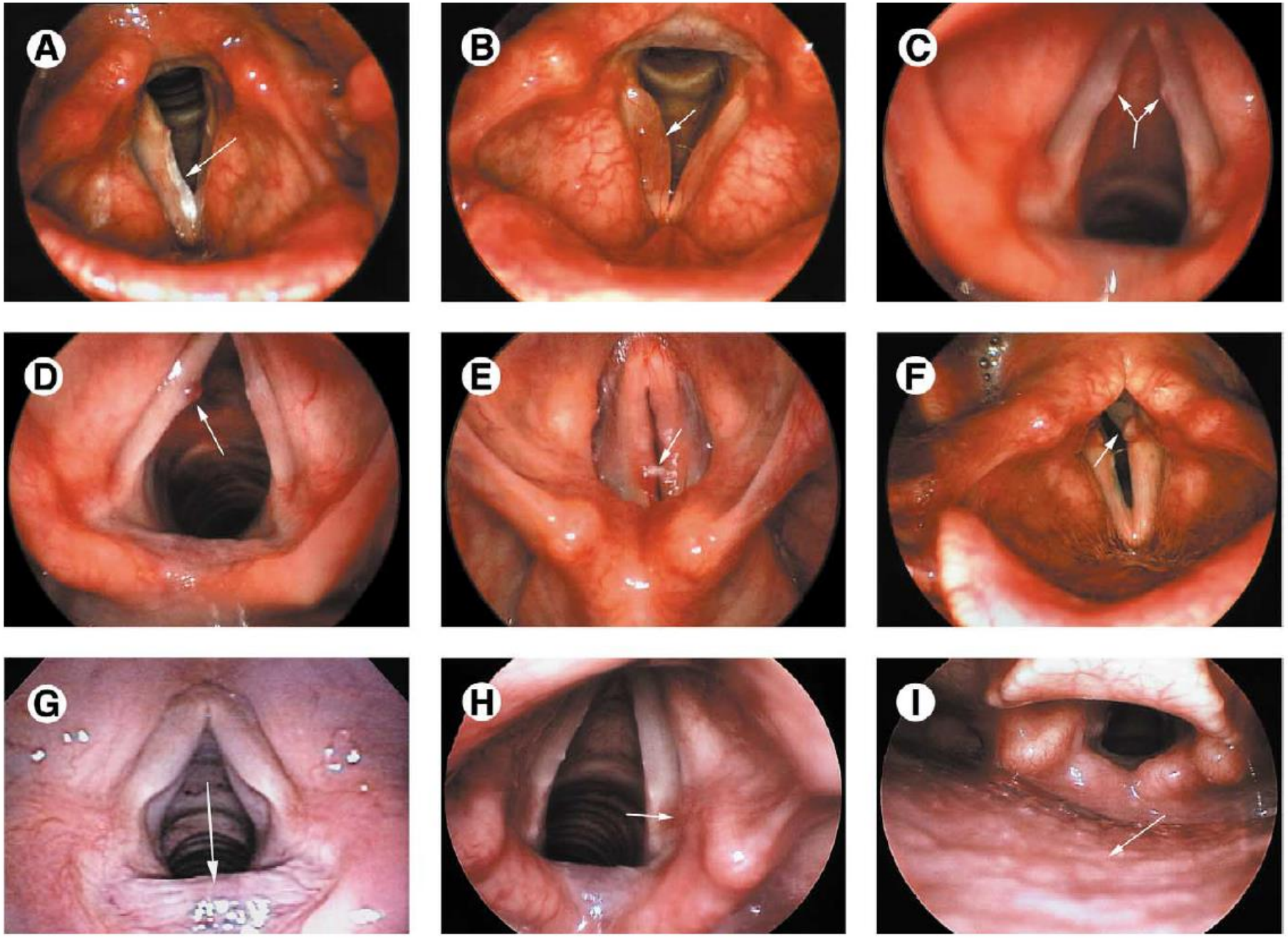


Figure 3. Abnormal larynx. (*A*) Leukoplakia; (*B*) Reinke's edema; (*C*) bilateral true vocal fold nodules; (*D*) true vocal fold hemorrhagic polyp; (*E*) true vocal fold erythema; (*F*) vocal fold granuloma; (*G*) interarytenoid bar; (*H*) arytenoid medial wall erythema; (*I*) posterior pharyngeal wall cobble stoning.

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 commisure erythema	0/105 (0%)

Table 4. More Specific Laryngeal Signs of GERD

ENT signs	Normals (n = 105)[a]	GERD (n = 34)	*P*
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

Vaezi MF et al. Clin Gastroenterol Hepatol. 2003;1(5):333-44.

Flexible vs. Rigid Laryngoscopy

TABLE II.
Comparison of Flexible and Rigid Laryngoscopy (156 Observations).

Sign	Flexible Scope n (%)	Rigid Scope n (%)	Odds Ratio (95% Confidence Interval)	Chi-Square *P* Value
Arytenoid complex	119 (76.3)	83 (53.2)	2.83 (1.65–4.84)	<.01
Apex erythema	22 (14.1)	4 (2.6)	6.24 (2.2–17.68)	<.01
Apex edema	5 (3.2)	2 (1.3)	2.55 (0.58–11.24)	.45
Medial wall erythema	113 (72.4)	80 (51.3)	2.5 (1.44–4.31)	<.01
Medial wall erosion	0 (0)	4 (2.6)		*
Medial wall granularity	0 (0)	0 (0)		*
Post Commisure bar	83 (53.2)	81 (51.9)	1.05 (0.72–1.54)	.82
Present	66 (42.3)	60 (38.5)	1.17 (0.78–1.75)	.49
Erythema	31 (19.9)	23 (14.7)	1.43 (0.88–2.34)	.23
Blanched	5 (3.2)	4 (2.6)		*
Irregular	3 (1.9)	2 (1.3)		*
Pseudsulcus	58 (37.2)	12 (7.7)	7.1 (2.76–18.24)	<.01
Interarytenoid mucosa	26 (16.7)	10 (6.4)	2.92 (1.47–5.8)	<.01
Posterior cricoid wall	17 (10.9)	16 (10.3)	1.07 (0.58–1.97)	.85
Posterior pharyngeal wall	17 (10.9)	1 (0.64)	18.96 (3.38–106.48)	<.01
Ventricular obliteration	15 (9.6)	0 (0)		<.01
True Vocal folds	9 (5.8)	5 (3.2)	1.85 (0.54–6.33)	.27
False Vocal folds	5 (3.2)	1 (0.64)	5.13 (0.54–48.44)	*
Epiglottis	4 (2.6)	0 (0)		*
Anterior commissure	2 (1.3)	0 (0)		*
Aryepiglottic folds	0 (0)	0 (0)		*

*Statistical analysis not performed because of low prevalence of findings.

Milstein CF, Charbel S, Hicks DM, et al. Laryngoscope. 2005;115:2256–61

The Laryngoscope
Lippincott Williams & Wilkins, Inc., Philadelphia

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.**

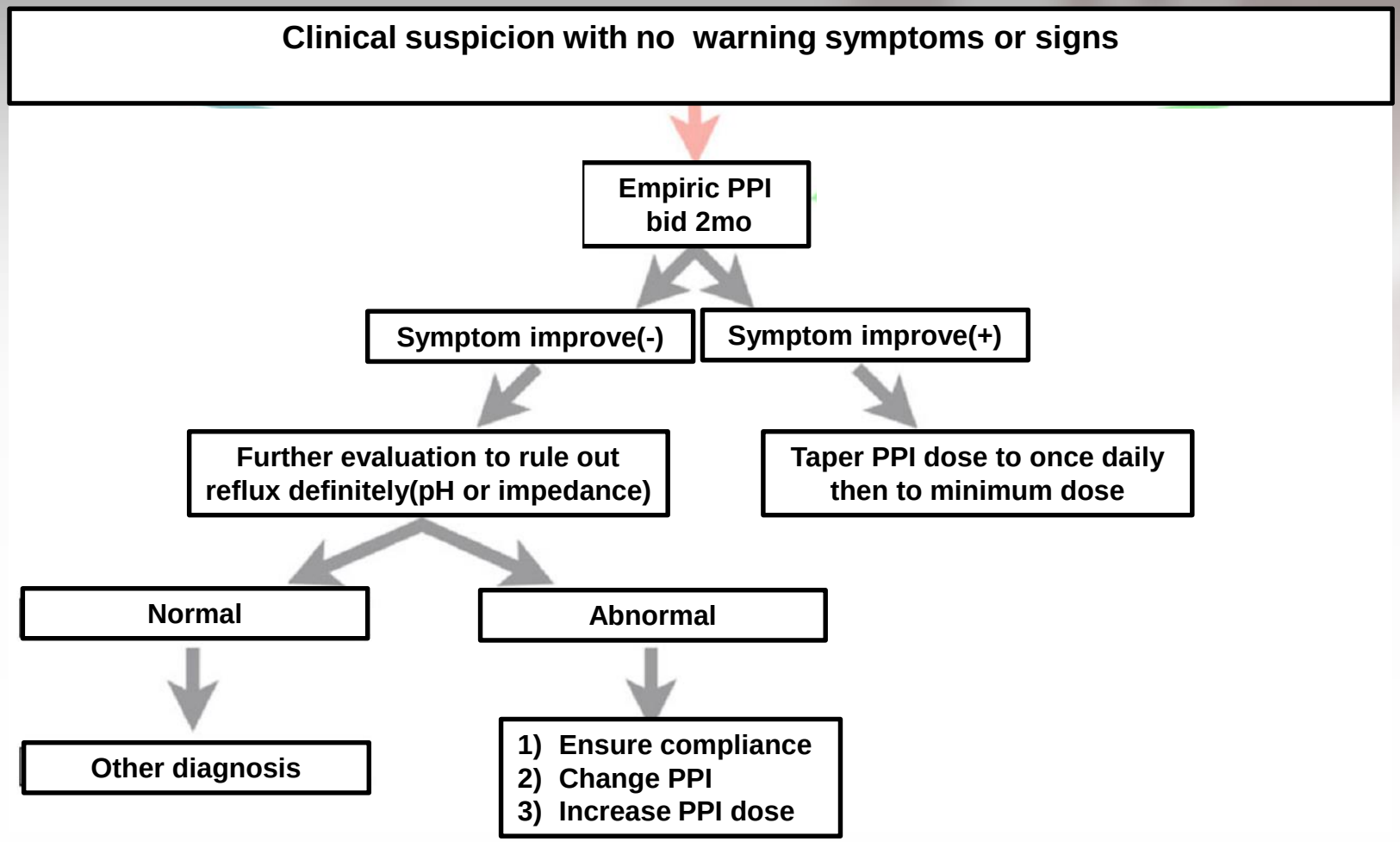
***Laryngoscope*, 112:1019–1024, 2002**

Diagnostic Tools for LPR

Method	Advantages	Disadvantages
Laryngoscopy	• No sedation required • Direct visualization of the larynx and laryngeal pathology	• No specific laryngeal signs for reflux • Over-diagnoses reflux as the etiology for patients' symptoms
Endoscopy	• Easy visualization of mucosal damage/erosions	• Poor sensitivity/specificity/PPV • Requires sedation • High cost
pH monitoring	• Easy to perform • Relatively non-invasive • Prolonged monitoring • Ambulatory	• Many are catheter-based • May have up to 30 % false negative rate • No pH predictors of treatment response for extraesophageal reflux
Impedance monitoring	• + Measures acidic and non-acidic gas and liquid reflux (combined with pH)	• Catheter based • False negative rate unknown but • Most likely similar to catheter-based pH monotoring • Unknown clinical relevance when abnormal on PPI therapy • Unknown importance in extraesophageal reflux

Milstein CF, Charbel S, Hicks DM, et al. Laryngoscope. 2005;115:2256–61; Richter JE. Gastroenterol Clin North Am. 1996;25:75–102

Laryngopharyngeal Reflux (LPR)



Hom C, Vaezi MF. Drug 2013;73:1281-1295

Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease

Philip O. Katz, MD[1], Lauren B. Gerson, MD, MSc[2] and Marcelo F. Vela, MD, MSCR[3]

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)