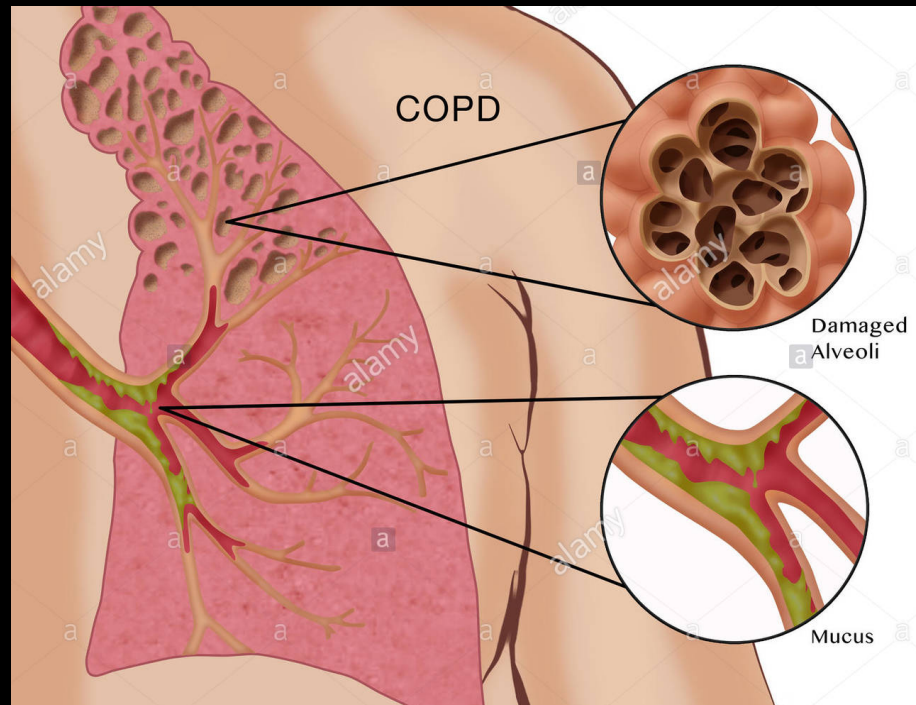


# Husten: häufige (COPD) bis seltene (IPF) Differentialdiagnose

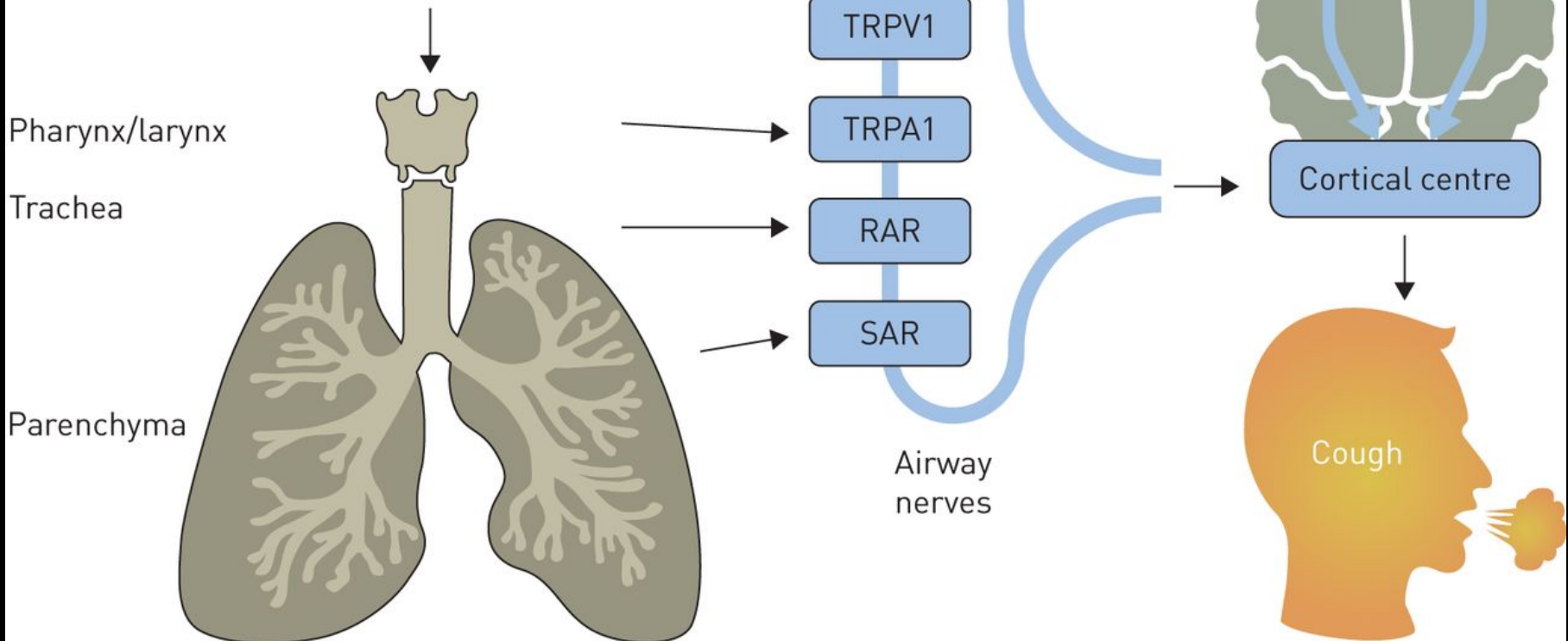


**Univ.-Professor Dr. Mehrdad Baghestanian**  
*Klinische Abteilung für Pulmologie*  
*Univ.-Klinik für Innere Medizin II*

# Pathophysiology of cough.

## Triggers

- Smoke
- Perfumes/scents
- Throat irritation/tickle
- Noxious fumes
- Speech
- Exercise
- Cold/dry air
- Eating
- Humidity



**TRPV1: transient receptor potential vanilloid 1;**

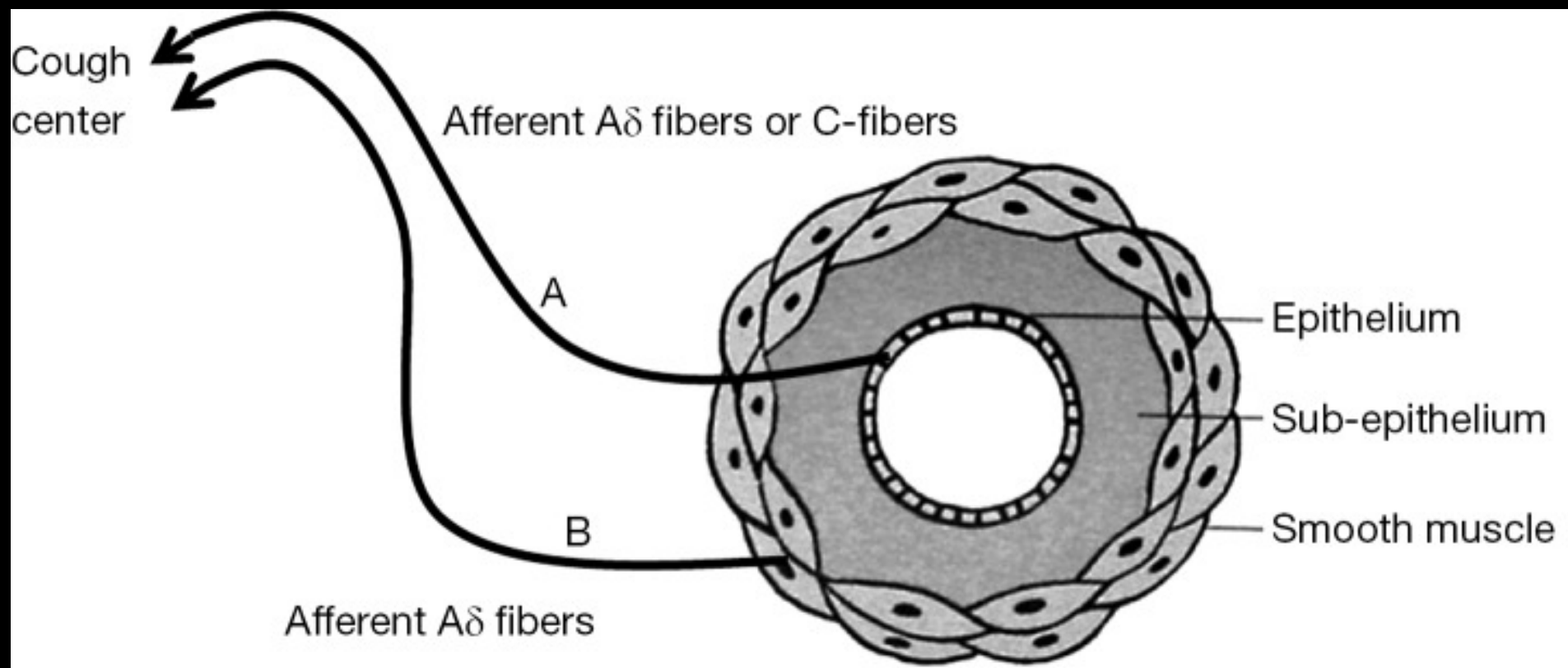
**TRPA1: transient receptor potential ankyrin 1;**

**RAR: rapidly adapting receptor; SAR: slowly adapting receptor**

## Possible peripheral cough response pathway

**A**, hyperstimulation: productive cough, endobronchial foreign body; increased response (cough reflex hypersensitivity): atopic cough, GERD, ACE-I-induced cough;

**B**, hyperstimulation: bronchial asthma; increased response: cough variant asthma.



Because a carefully taken history with detailed questioning of the **character**, **timing**, and **complications of chronic cough** in adults had not been shown to be useful in diagnosing the cause of the cough

Mello CJ, et al. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. *Arch Intern Med*. 1996; 156: 997–1003



The world's first cough guideline developed by the first American College of Chest Physicians (CHEST) Expert Cough Panel suggested in 1998 **that cough be classified according to its duration**

Irwin RS, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest*. **1998**; 114: 133S–181S

Although all coughs are **acute at the outset**, the panel believed that it was the **duration of the cough at the time of patient presentation** to health-care providers that helped narrow the list of possible diagnoses in adults.

The **first expert cough panel** classified cough duration into  
-**Acute** (ie, lasting < 3 weeks) and  
-**Chronic** (ie, lasting 3-8 weeks) categories

The **second ACCP Expert Cough Panel** suggested in **2006** that cough continue to be classified according to its duration but that there **should be three not two categories**

Irwin RS, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. **2006**;129: 1S–23S

the **second ACCP Expert Cough Panel** suggested in **2006** that cough continue to be classified according to its duration but that there **should be three not two categories**.

Irwin RS, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest*. **2006**;129: 1S–23S

Based on literature that had accumulated between 1998 and 2006, the panel believed that cough should be reclassified into

**Acute** (< 3 weeks),

**Subacute** (3-8 weeks), and

**Chronic** (> 8 weeks) categories

and suggested management algorithms for these categories that suggested the likeliest and most common diagnostic possibilities in each category.

Irwin RS, French CL, et al.; CHEST Expert Cough Panel.  
Chest. 2018 Jan;153(1):196-209

For adult patients seeking medical care **complaining of cough**, we suggest that **estimating the duration of cough is the first step in narrowing the list of potential diagnoses**

For adult patients around the globe **complaining of cough**, we suggest that the **cough be managed using evidence-based guidelines** that are based **upon duration of cough**



# The Causes Of Acute Cough: A Single-Center Study In Japan

Tajiri T, et al. Arerugi. 2018;67:46-52

---

**374 patients** (195 females, mean age 60.3 years) who visited the clinic complaining of cough →

**129 patients (35%)**: 63 females, mean age 61.5 years: suffered from **acute cough**

**All acute cases** were stratified into **two groups** based on the **presence** (n=43) or **absence** (n=86) of **abnormal findings on the chest X-ray**

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129 patients (63 females, mean age 61.5 years) suffered from acute cough

All acute cases were stratified into two groups based on the presence (n=43) or absence (n=86) of abnormal findings on the chest X-ray

The main causes of acute cough with abnormal findings were

Pneumonia (46.5%),

Interstitial pneumonia (18.6%)

Lung cancer (16.3%)

# The Causes Of Acute Cough: A Single-Center Study In Japan

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All acute cases were stratified into two groups based on the presence (n=43) or absence (n=86) of abnormal findings on the chest X-ray

The main causes of acute cough without abnormal findings were

Respiratory tract infection (39.5%),

Post infectious cough (18.6%) and

Bronchial asthma (17.4%).

Acute cough was the primary complaint in 29.5% and 19.6% of all patients diagnosed with bronchial asthma and cough variant asthma, respectively

# The Causes Of Acute Cough: A Single-Center Study In Japan

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129 patients (63 females, mean age 61.5 years) suffered from acute cough

All acute cases were stratified into two groups based on the presence (n=43) or absence (n=86) of abnormal findings on the chest X-ray

Non-infectious diseases including asthma as well as infectious diseases could be the causes in acute cough without abnormal findings on the chest X-ray

# One hundred coughs Family practice case series.

Worrall GJ. Can Fam Physician 2008;54:236-7.e1-3

---

To record the presentation, diagnosis, management, and outcome of acute coughs presenting in family practice.

A case series of consecutive patients with **acute cough as their main symptom**

**One hundred** consecutive patients with cough, ages 1 to 90

# One hundred coughs Family practice case series.

Worrall GJ. Can Fam Physician 2008;54:236-7.e1-3

---

**73** patients had **viral respiratory tract infections**;

**15** had **asthma**;

**6** had influenza;

**4** had pneumonia;

**2** had croup

---

**81** patients **needed no prescription** medication;

**13** were prescribed **steroids** or **bronchodilators** for  
asthma

**6** were prescribed **antibiotics**

No prescriptions for cough suppressants or decongestants were  
written

---

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Worrall GJ. Can Fam Physician 2008;54:236-7.e1-3

---

To record the presentation, diagnosis, management, and outcome of acute coughs presenting in family practice.

A case series of consecutive patients with acute cough as their main symptom

One hundred consecutive patients with cough, ages 1 to 90. MAIN

## CONCLUSION







Most patients with cough **require reassurance** rather than medications, as their **cough is selflimiting**.

Of the minority that requires medication, **twice as many will benefit from adjustment of asthma medication** as from **antibiotics**

# Representative Punum ladders to assess (A) **cough severity** or (B) **overall quality of life**







A

Please check the rung on the ladder that best describes the **severity of your cough taking timing, intensity, distress, and quality into account** over the past week.

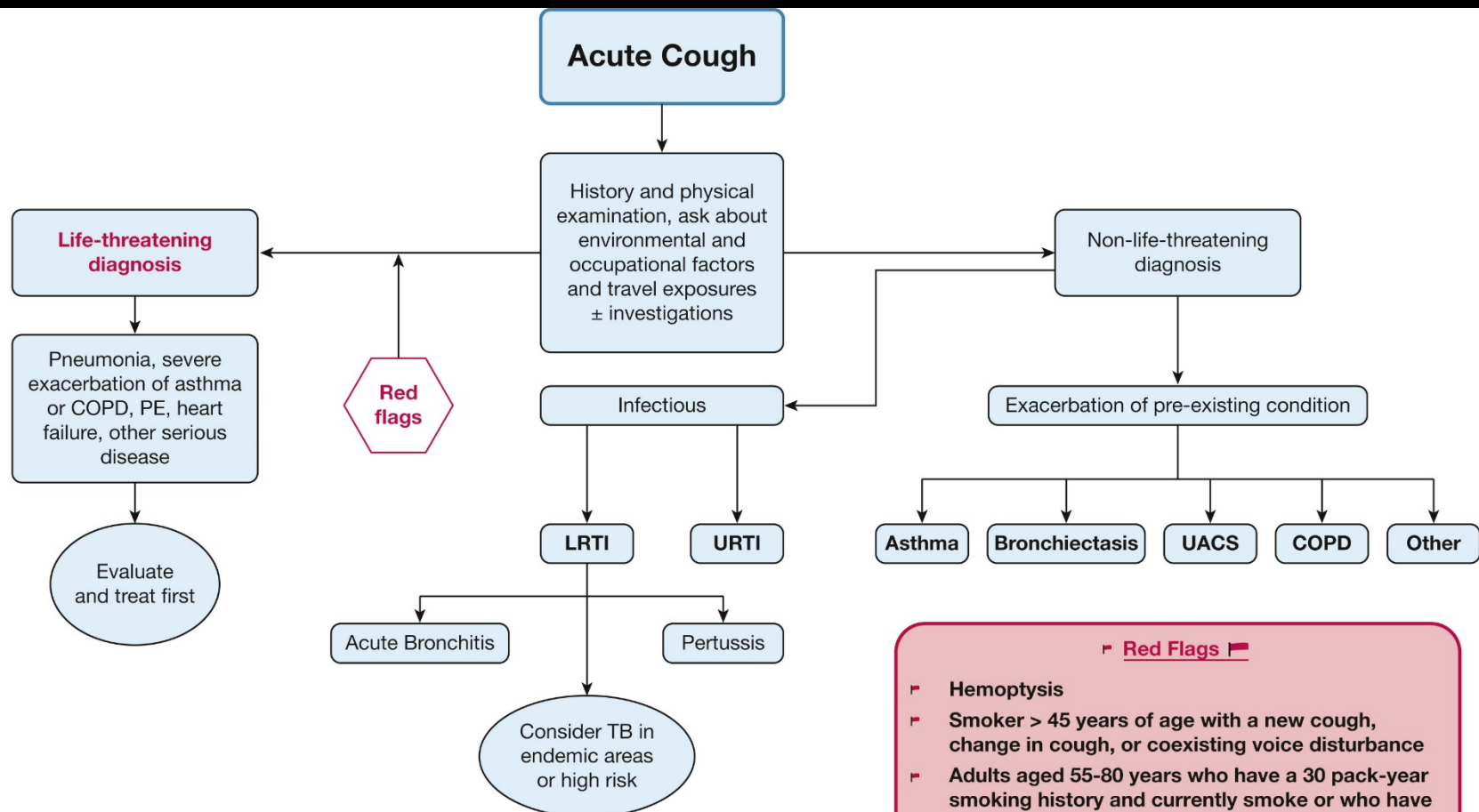
	10	→	<b>WORST POSSIBLE COUGH</b>	→	<input type="checkbox"/>	10
					<input type="checkbox"/>	9
	8	→	<b>VERY SEVERE COUGH</b>	→	<input type="checkbox"/>	8
					<input type="checkbox"/>	7
	6	→	<b>SEVERE COUGH</b>	→	<input type="checkbox"/>	6
					<input type="checkbox"/>	5
	4	→	<b>MODERATE COUGH</b>	→	<input type="checkbox"/>	4
					<input type="checkbox"/>	3
	2	→	<b>MILD COUGH</b>	→	<input type="checkbox"/>	2
					<input type="checkbox"/>	1
	0	→	<b>NO COUGH</b>	→	<input type="checkbox"/>	0

B

Please check the box on the rung of the ladder that best describes your overall quality of life (satisfaction or happiness with life) related to your cough over the past week.


	10	→	<b>WORST POSSIBLE PROBLEM</b>	→	<input type="checkbox"/>	10
					<input type="checkbox"/>	9
	8	→	<b>VERY SEVERE PROBLEM</b>	→	<input type="checkbox"/>	8
					<input type="checkbox"/>	7
	6	→	<b>SEVERE PROBLEM</b>	→	<input type="checkbox"/>	6
					<input type="checkbox"/>	5
	4	→	<b>MODERATE PROBLEM</b>	→	<input type="checkbox"/>	4
					<input type="checkbox"/>	3
	2	→	<b>MILD PROBLEM</b>	→	<input type="checkbox"/>	2
					<input type="checkbox"/>	1
	0	→	<b>NO PROBLEM</b>	→	<input type="checkbox"/>	0





**PE** = pulmonary embolism;  
**UACS** = upper airway cough syndrome  
**LRTI** = lower respiratory tract infection  
**URI** = upper respiratory tract infection

#### Reminders

1. Check for  - see adjacent box
2. Routinely assess cough quality of life or cough severity with validated tool
3. Routinely follow up with patient in 4-6 weeks

#### Red Flags

- Hemoptysis
- Smoker > 45 years of age with a new cough, change in cough, or coexisting voice disturbance
- Adults aged 55-80 years who have a 30 pack-year smoking history and currently smoke or who have quit within the past 15 years
- Prominent dyspnea, especially at rest or at night
- Hoarseness
- Systemic symptoms
  - Fever
  - Weight loss
  - Peripheral Edema with weight gain
- Trouble swallowing when eating or drinking
- Vomiting
- Recurrent pneumonia
- Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough

# Chronic cough

is defined as a cough lasting

**more than 8 weeks** (aged  $\geq 15$  years old)

**more than 4 weeks** in children (aged  $< 15$  years old)

It is a frequent cause of medical consultation and is associated with a large number of pulmonary and extrapulmonary disorders

**Prevalence:** between 11 and 13% of the population

**9.6%** in a recent meta-analysis of 90 studies:

In this study, the prevalence of chronic cough was higher in

**Oceania (18.1%)**

**America (11%)**

**Europe (12.7%)**

**Asia (4.4%) / Africa (2.3%)**

Song WJ, et al. The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. Eur Respir J. 2015;45:1479–1481

Although **chronic cough in adults** can be caused by many etiologies, **four conditions account for most cases:**

---

- Upper airway cough syndrome  
secondary to rhinosinus diseases

---

- Gastroesophageal reflux disease /  
Laryngopharyngeal reflux disease

---

- Asthma

---

- Nonasthmatic eosinophilic bronchitis

---

Chronic Cough: Evaluation and Management

CHARLIE MICHAUDET, et al. *Am Fam Physician*. 2017 Nov 1;96(9):575-580.

# **Non-asthmatic eosinophilic bronchitis** and its relationship with **asthma**. Lai K, et al. Pulmo Pharmacol Ther, 2017; 47:66-71

---

Non-asthmatic eosinophilic bronchitis (NAEB) represents **10%–30% of chronic cough cases**, is an important cause of chronic cough

---

NAEB shares similar **eosinophilic inflammation of airway ( $\geq 3\%$  in induced sputum)** and **response to corticosteroids** with asthma.

However, in contrast to asthma

NAEB subjects have **no airflow obstruction** and **airway hyperresponsiveness**

# **Non-asthmatic eosinophilic bronchitis** and its relationship with **asthma**. Lai K, et al. Pulmo Pharmacol Ther, 2017; 47:66-71

---

On the prognosis of NAEB, long term follow-up study suggested that **NAEB should be a distinct entity** rather than an early stage of asthma or COPD

There is no study on dose and duration of treatment

The **relapse rate is high after treatment**

Assessing sputum eosinophils after treatment is useful to identify those at risk of relapse.

# **Non-asthmatic eosinophilic bronchitis** and its relationship with **asthma**. Lai K, et al. Pulmo Pharmacol Ther, 2017; 47:66-71

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## **Treatment**

**Low / medium doses of inhaled corticosteroid (ICS) for 4–8 weeks are usually efficient but long-term treatment can be necessary**

**In patients with severe cough or refractory to ICS, oral prednisolone (10–30 mg/d) for 3–5 days might be proposed**

**Up to 60% recurrence has been described after treatment cessation, and associated with sputum eosinophilia**

# Cough variant asthma (CVA)

---

**Cough alone** may sometimes be the **sole presenting symptom** of asthma

---

Patients experience cough **without wheeze** or **shortness of breath** and **with normal baseline pulmonary function test results**

---

These patients do, however, **demonstrate bronchial hyperreactivity** +

They also **respond** to specific traditional asthma therapy

---

These patients are considered to have a **specific asthma phenotype: cough variant asthma**

# Cough variant asthma (CVA)

---

In prospective studies of patients with chronic cough, an **average of 25%** have CVA.

---

Patients have

- chronic cough:  
**diurnal variation of symptoms**      **recurrent episodes of symptoms**
- **normal baseline pulmonary function tests,**
- **positive bronchial inhalation challenge results**  
[**Metacholin Test**]
- **response to specific asthma therapy**  
[**response to inhalation of short acting  $\beta_2$  agonist**]



# Cough variant asthma (CVA)

---

CVA was associated with **high FeNO levels** as well, and **high FeNO levels were specific to CVA**

However, these useful characteristics **were not significant** in the patients who **had been prescribed ICS before** visiting our hospital.

**Medical examination** (SABA) and **determination of FeNO levels** are useful for the differential diagnosis of prolonged/chronic cough, before treatment with ICS.

# Cough variant asthma (CVA)

---

## Treatment

All therapies for typical bronchial asthma have been **successful** in controlling cough in patients with CVA

The **overall prognosis of CVA is excellent**, with most patients **requiring chronic inhaled corticosteroid therapy**

# Differential Diagnosis Between Various Diseases With Eosinophilic Inflammation of the Airways Associated With Chronic Cough

	Eosinophilic Bronchitis	Eosinophilic Asthma	Cough Equivalent Asthma
Symptoms	Cough	Dyspnea, cough & wheezing	Cough
Atopy	No	Yes	Yes
Bronchial hyperreactivity	No	Yes	Yes
FEM viability	No	Yes	No
Eosinophils in sputum	Yes	Yes	Yes
Response to bronchodilators	No	Yes	Yes
Response to corticosteroids	Yes	Yes (if eosinophils in sputum)	Yes (if eosinophils in sputum)

**Risk factors for chronic cough among 14,669 individuals from the general population. Çolak Y, et al. Chest. 2017;152(3):563–573**

---

**Smoking is obviously a risk factor for chronic cough**

A recent large study performed on **14,669 subjects** in Copenhagen found a **prevalence of chronic cough** of  
**3% in never smokers,**  
**4% in former smokers**  
**8% in current smokers**

---

The main risk factors of chronic cough could differ depending on smoking status, including

- i) female sex, asthma and GORD in never smokers;**
- ii) obesity, asthma and GORD in ex-smokers**
- iii) airflow limitation in current smokers.**

A smoking history 20 pack-years or a modification of the cough in a smoker 45 years old should lead to further investigation

# Grades of Recommendation/Evidence of Antireflux Treatment in Patients With Chronic Cough

Treatment	Grade of Recommendation	
	Strong Recommendation	Low Quality of Evidence
General and Dietary Measures		
H2 antagonists	Strong recommendation	Low quality of evidence
PPIs	Strong recommendation	Moderate quality of evidence
Prokinetics	Weak recommendation	Very low quality of evidence
Antireflux surgery	Weak recommendation	Low quality of evidence

Sensitivity and Specificity of Signs and Symptoms of Chronic Cough			
Disease	Symptoms and Parameters	Sensitivity (%)	Specificity (%)
Asthma	Wheezing	94	66
	Dyspnea	82	51
	Airway obstruction	35	80
	Bronchial reversibility	11	95
Gastroesophageal reflux	Acid taste in the mouth	50	80
	Retrosternal pyrosis	72	68
Rhinitis	Post-nasal drip	100	67
	Clearing of the throat	100	37

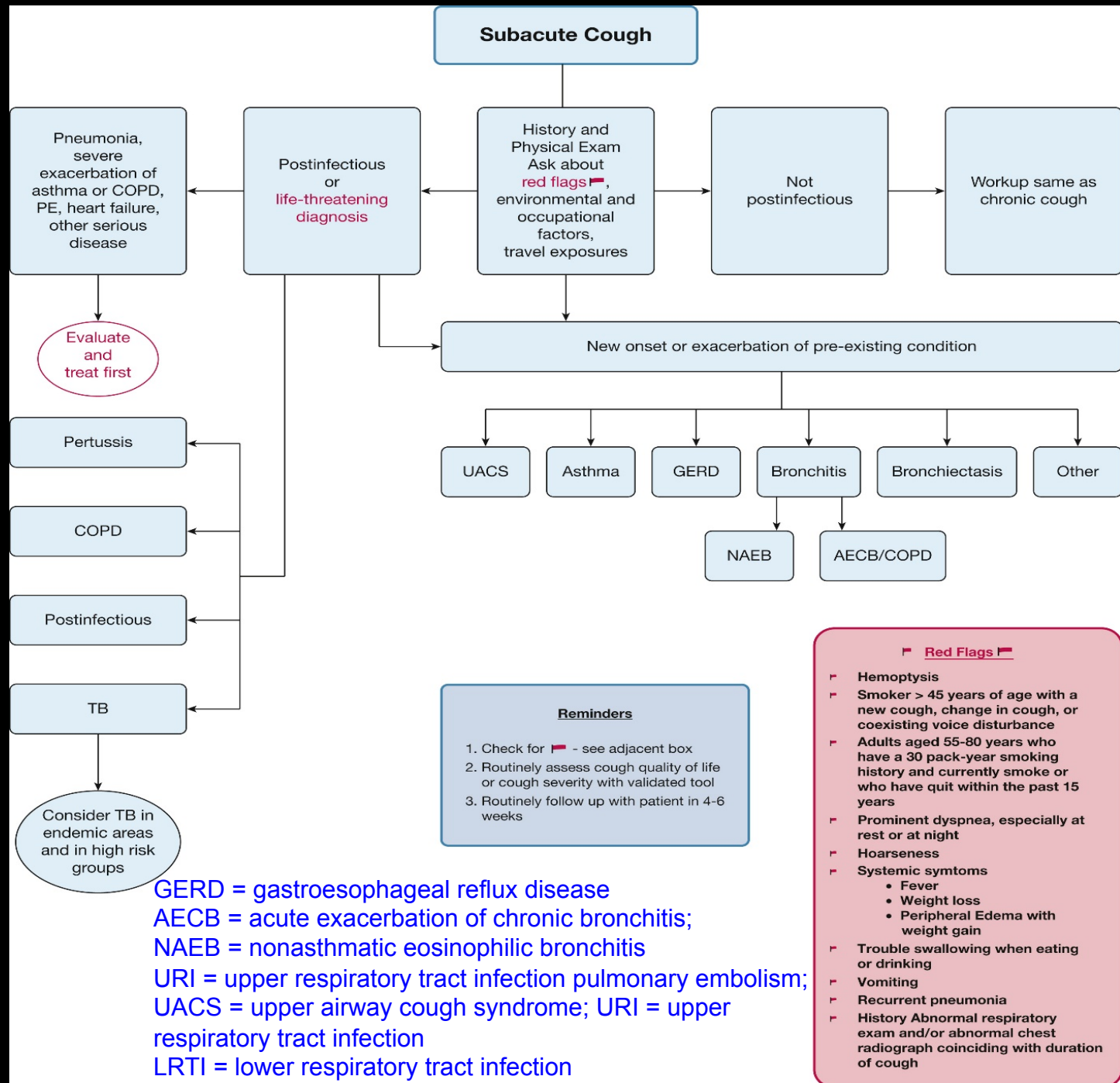
# Causes of chronic cough and warning symptoms.

## Causes of chronic cough

- Acute tracheobronchial infections including pertussis
- Chronic infections: bronchiectasis, tuberculosis, cystic fibrosis
- Airway problems: chronic bronchitis, osteoplastic tracheopathy, asthma, post-nasal drip
- Pulmonary parenchymal diseases: diffuse interstitial fibrosis, emphysema, sarcoidosis
- Tumors: lung cancer, bronchioloalveolar carcinoma, benign airway tumors, mediastinal tumors
- Foreign bodies in the airways
- Irritation of external auditory meatus
- Cardiovascular diseases: left ventricular dysfunction, pulmonary infarction, aortic aneurysm
- Other diseases: gastroesophageal reflux or bronchoesophageal reflux, Zenker's diverticulum, achalasia, recurrent aspiration, endobronchial sutures
- Drugs: angiotensin-converting enzyme inhibitors, coartem

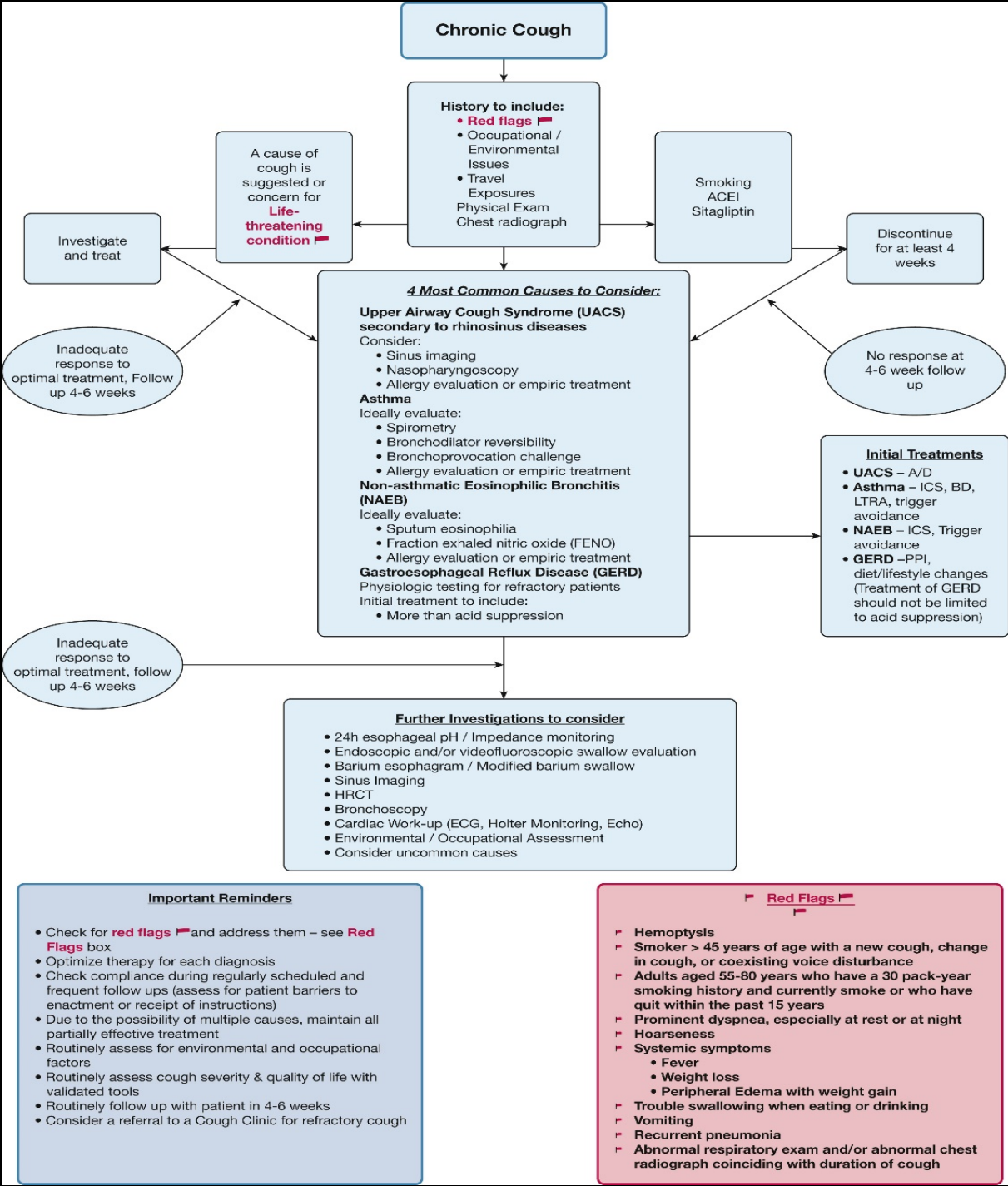
## Warning symptoms

Hemoptysis, snoring, significant production of sputum, systemic symptoms, gastroesophageal reflux complicated with weight loss, anemia, hematemesis, dysphagia, or no response to specific treatment, choking or vomiting, recurrent pneumonia, or abnormal chest X-ray

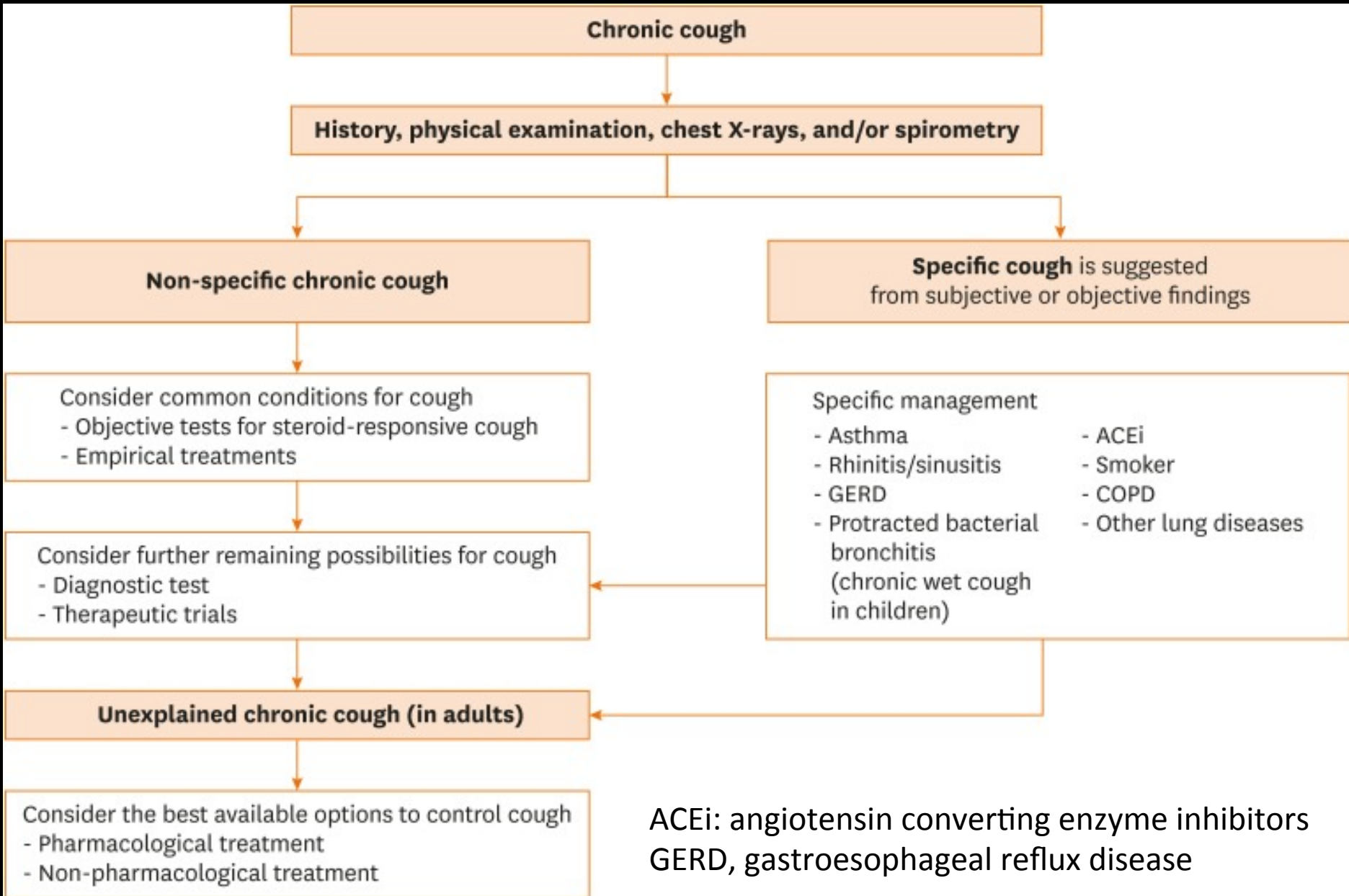


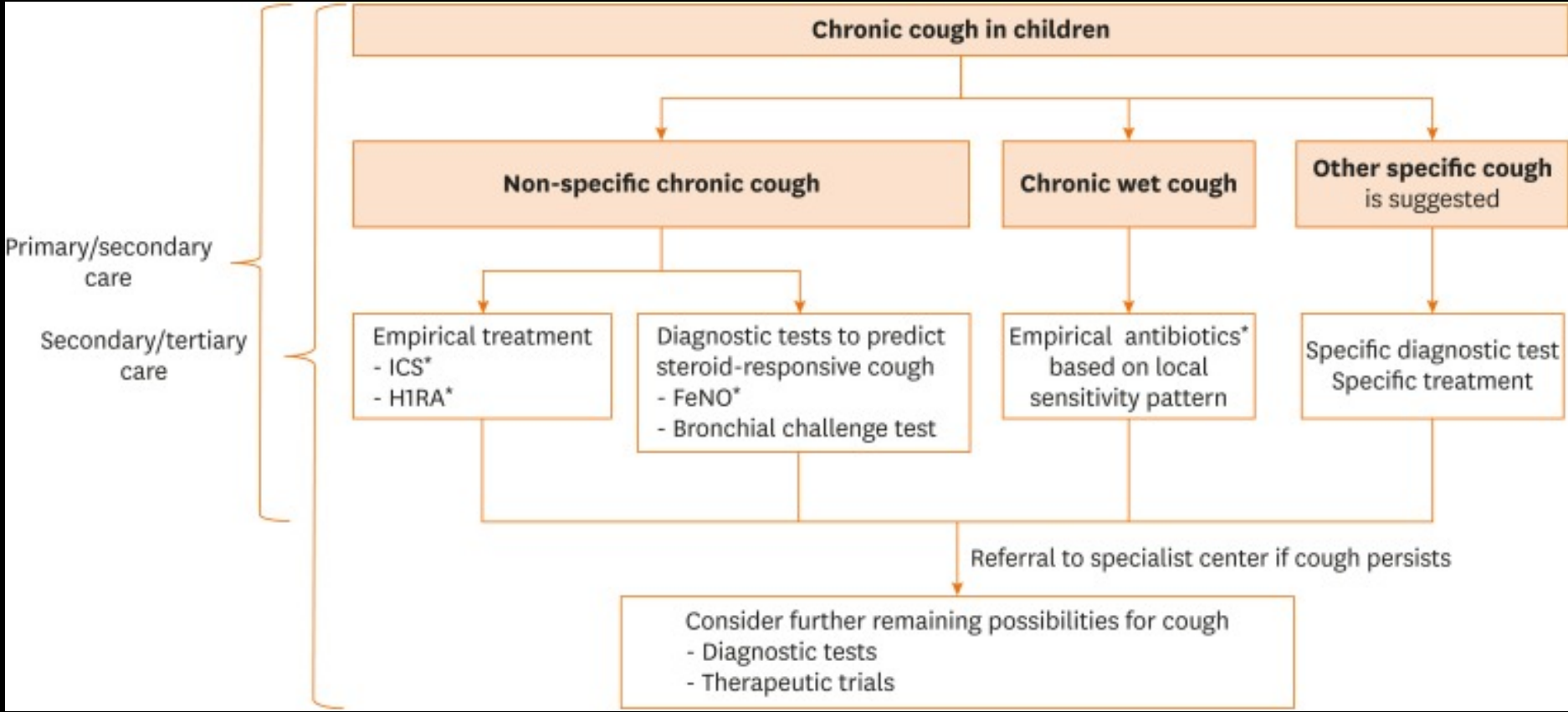


ACEI = angiotensin-converting enzyme inhibitor;  
A/D = antihistamine/decongestant;  
BD = bronchodilator;  
HRCT = high-resolution CT;  
ICS = inhaled corticosteroid;  
LTRA = leukotriene antagonist;  
PPI = proton pump inhibitor.

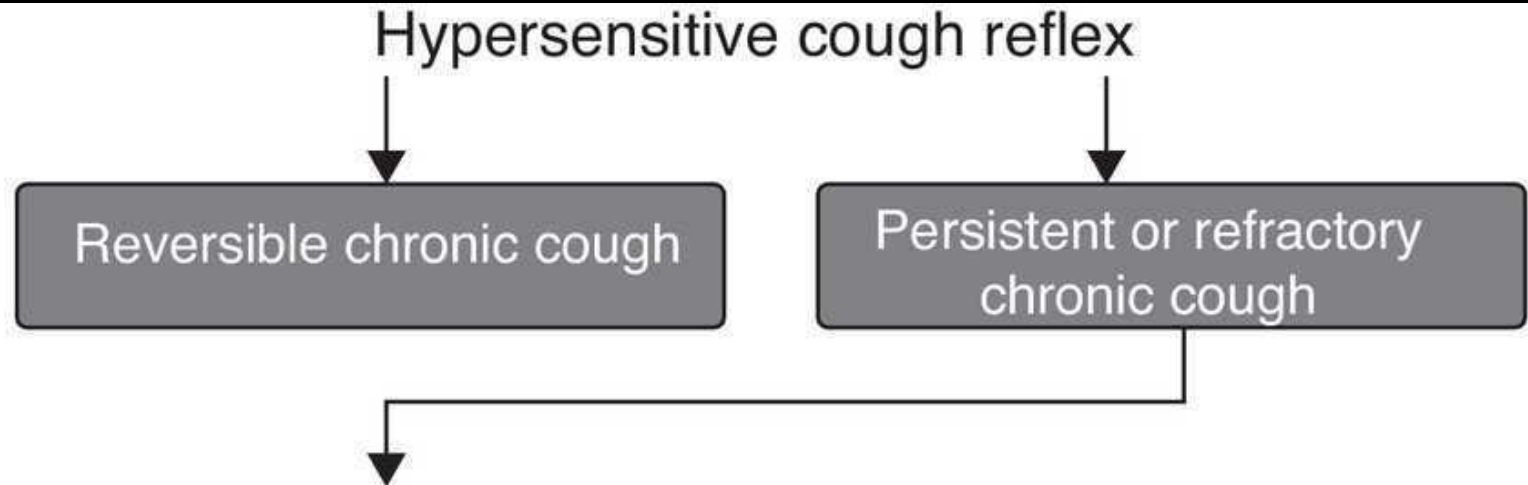


# Overview of clinical approaches for the treatment of chronic cough in Korean patients





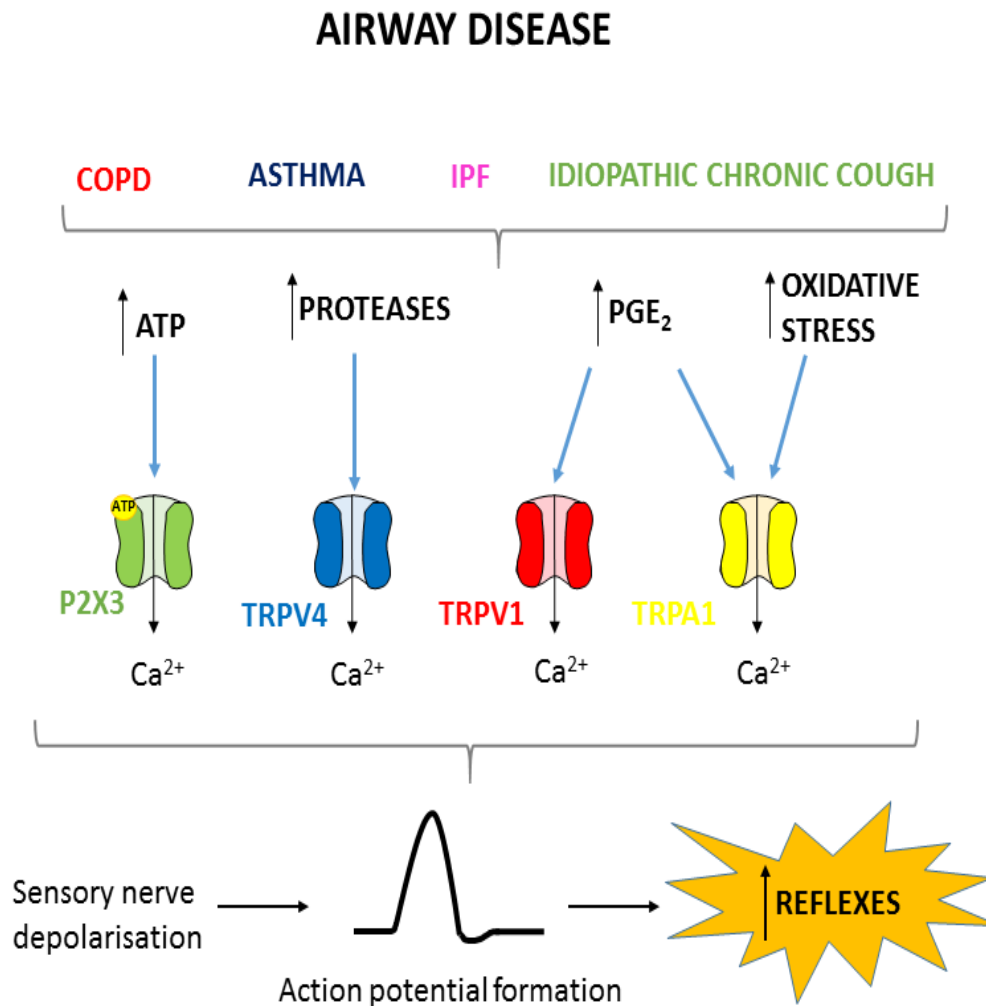
# Algorithm for the management of refractory chronic cough



1. Rhinosinusitis
2. Laryngeal neuropathy or CV dysfunction.
3. GER/laryngopharyngeal reflux
4. Central hypersensitivity
5. Psychogenic

1. Antihistamines. Nasal corticosteroids
2. Speech pathology. Neuromodulators
3. Strict anti-GER measures. Alginates, high-dose PPIs, prokinetics, fundoplication?
4. Neuromodulators
5. Psychiatric evaluation

# Effect of ion channels in cough in airway disease







**Vielen Dank Für Ihre Aufmerksamkeit**

**Eine gute Rede ist eine Ansprache, die das Thema erschöpft, aber keineswegs die Zuhörer**

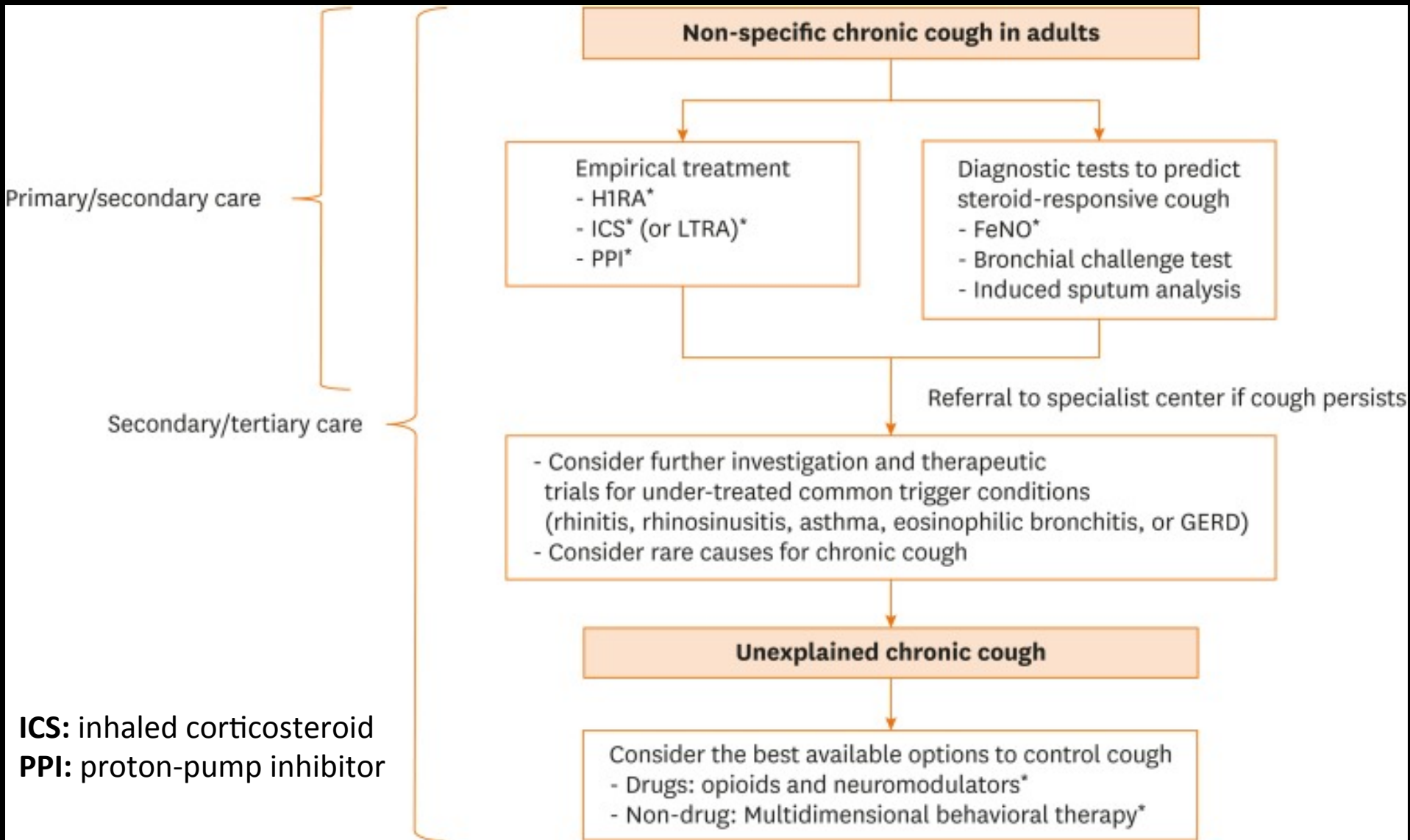
**Winston Churchill**

There are **three phases of cough**:

- An **inhalation phase** which generates enough volume for an effective cough,
- A **compression phase** with pressure against a closed larynx by the contraction of chest wall, diaphragm and abdominal muscles
- An **expiratory phase** when the glottis opens resulting in high air flow

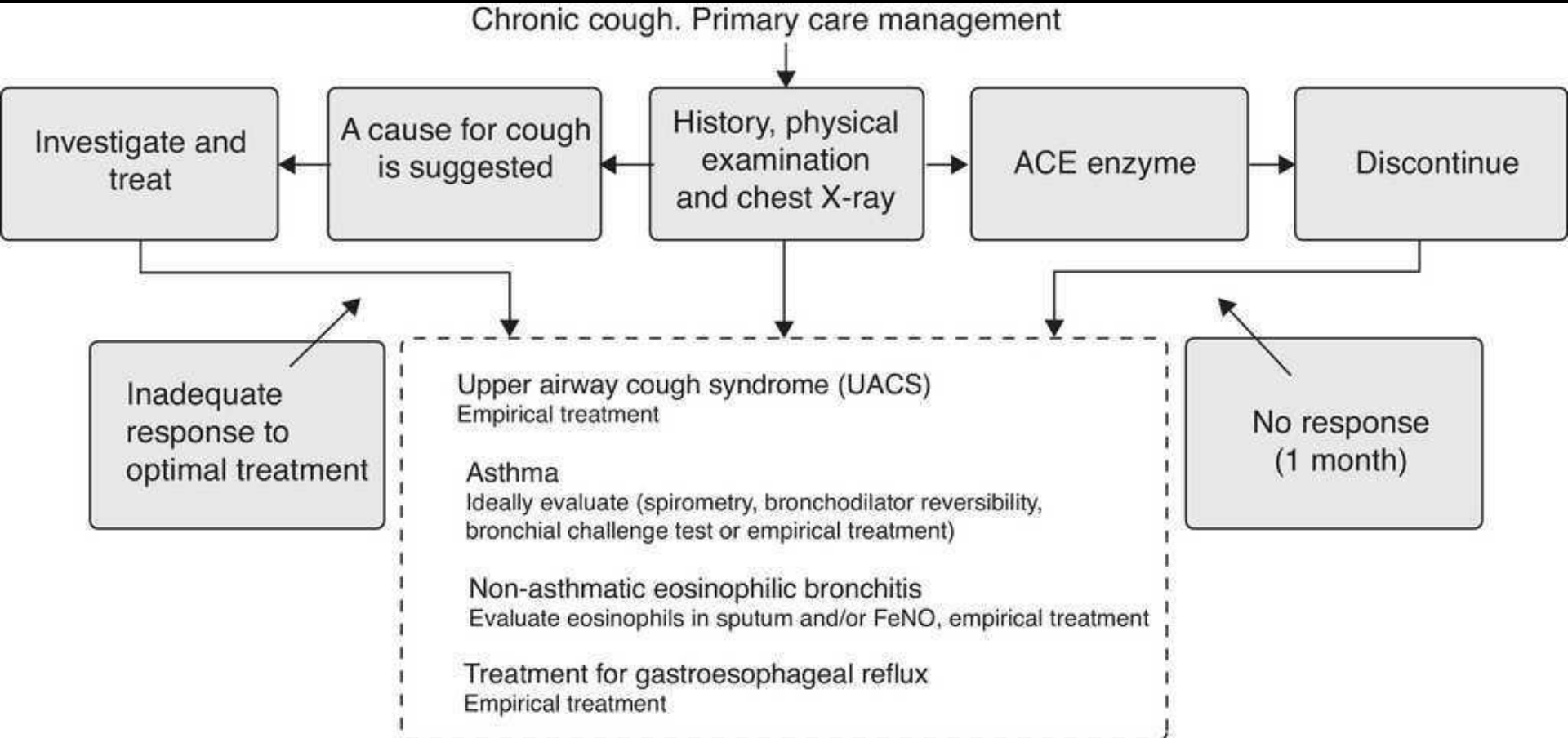


# Approach for non-specific chronic cough in Korean adults (age $\geq 15$ years)

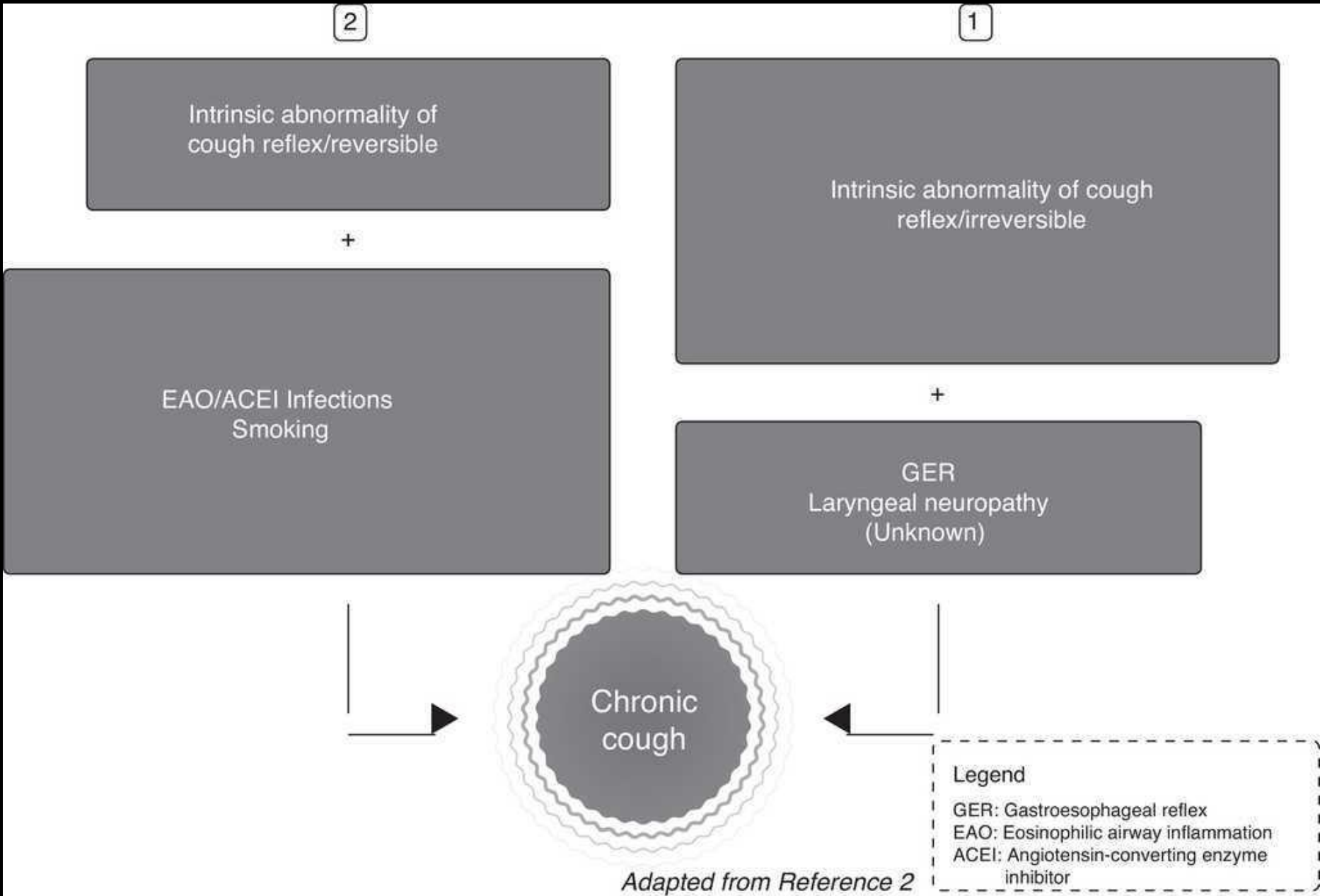


**H1RA:** histamine-1 receptor antagonist

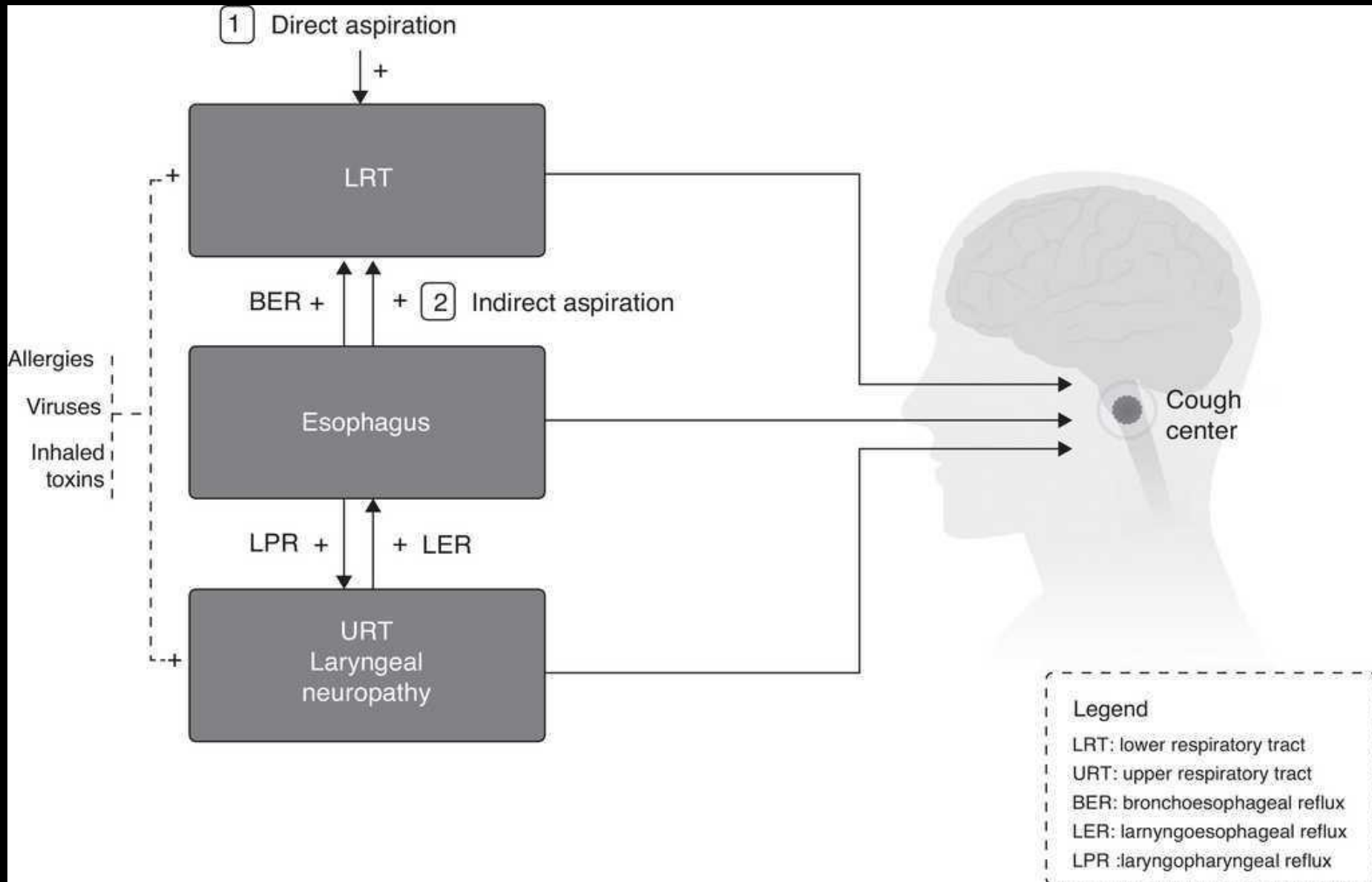
# Algorithm for the management of chronic cough in primary care



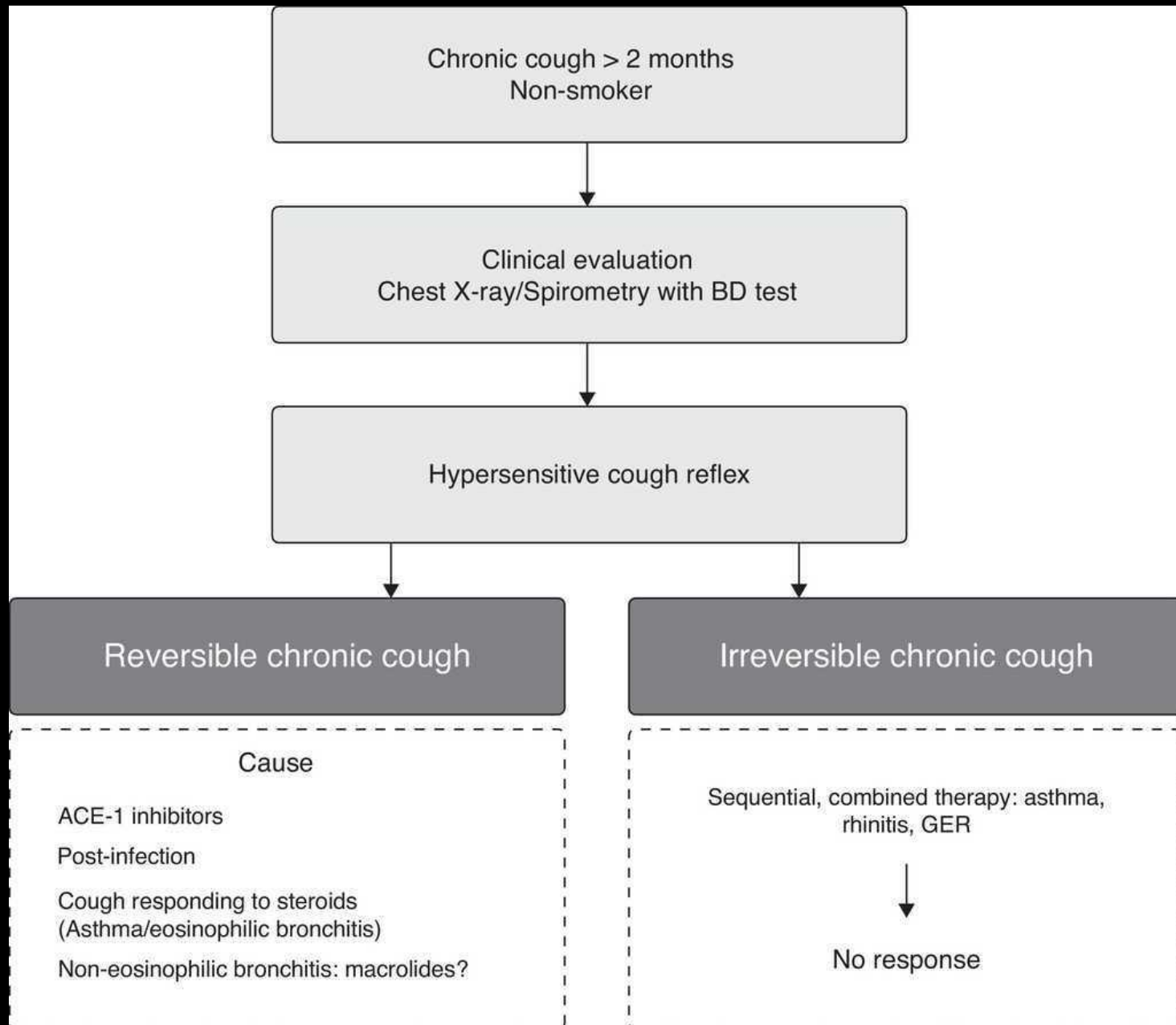
# Two possible access pathways of stimuli of chronic cough



# Interactions among peripheral stimuli of cough reflex



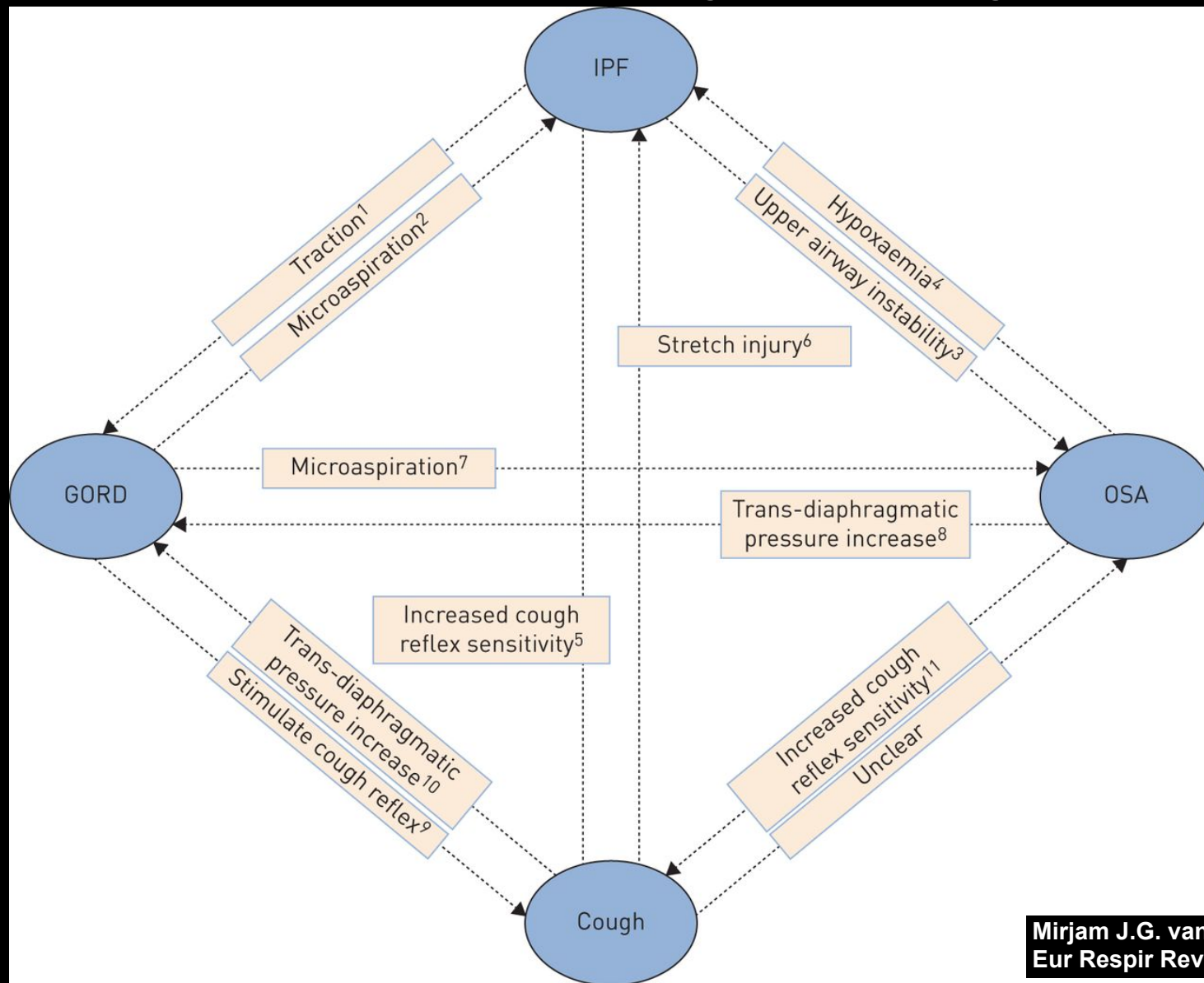
# Practical management of patients with chronic cough



# Interactions between idiopathic pulmonary fibrosis (IPF), gastro-oesophageal reflux disease (GORD), obstructive sleep apnoea (OSA) and cough.

1: traction leading to a weaker lower oesophageal sphincter tonus;

2: microaspiration inducing epithelial damage



# Management of chronic cough in specialized units

## Chronic cough. Specialized Medical Management

