

Ημέρες Παθολογίας 2023

"Διλήμματα στην Κλινική Παθολογία"



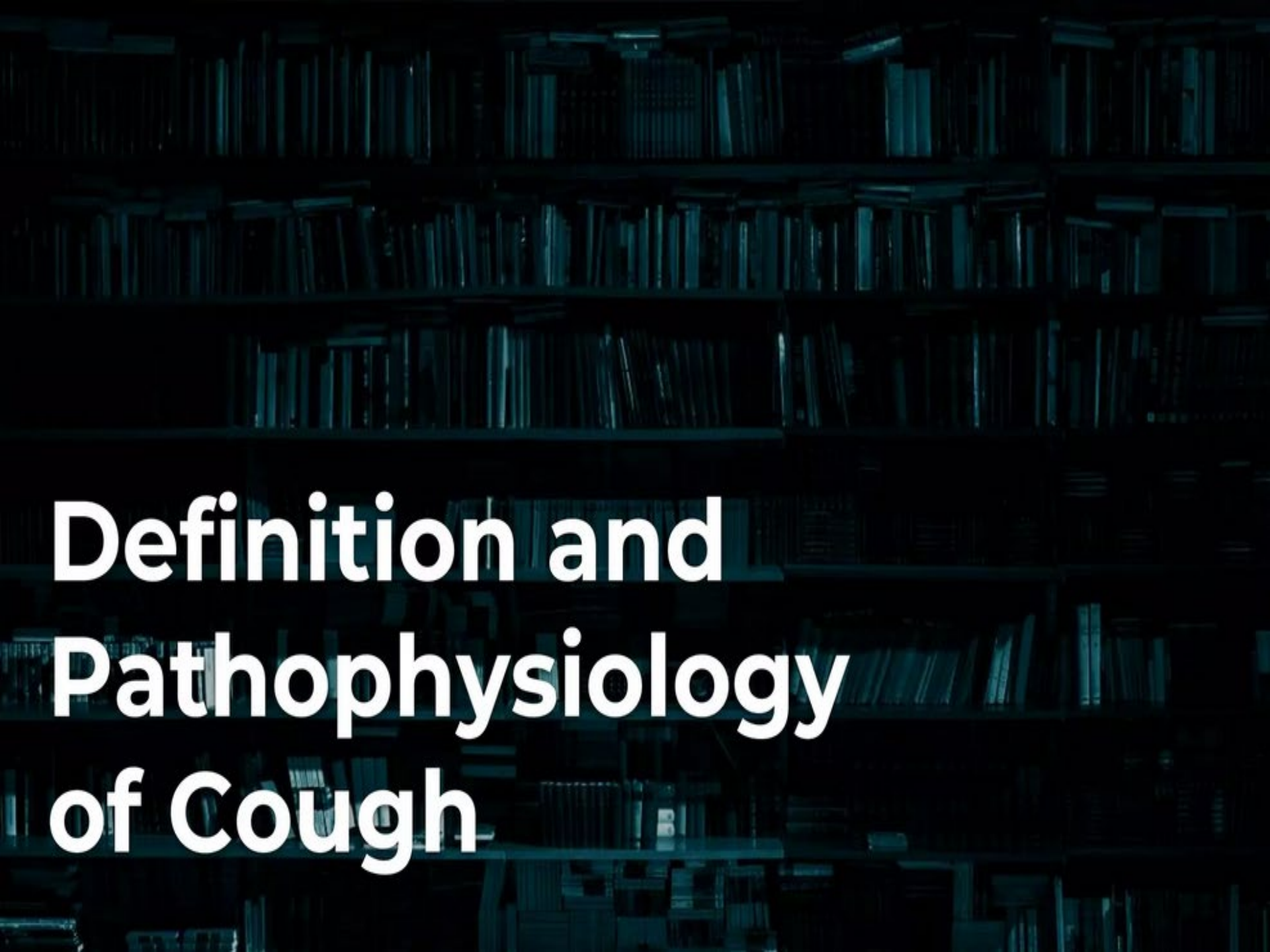
30 Μαρτίου έως
01 Απριλίου
2023

Διερεύνηση και αντιμετώπιση χρόνιου βήχα

Μαρκοζάννες Ε.
Επιμ.Α' - Πνευμονολόγος
ΝΝΘΑ ΣΩΤΗΡΙΑ

Δομή παρουσίασης

- Ορισμοί & Παθοφυσιολογία
- Επιδημιολογία & αίτια
- Διαγνωστική προσέγγιση
- Φαινότυποι χρόνιου βήχα
- Θεραπευτική προσέγγιση

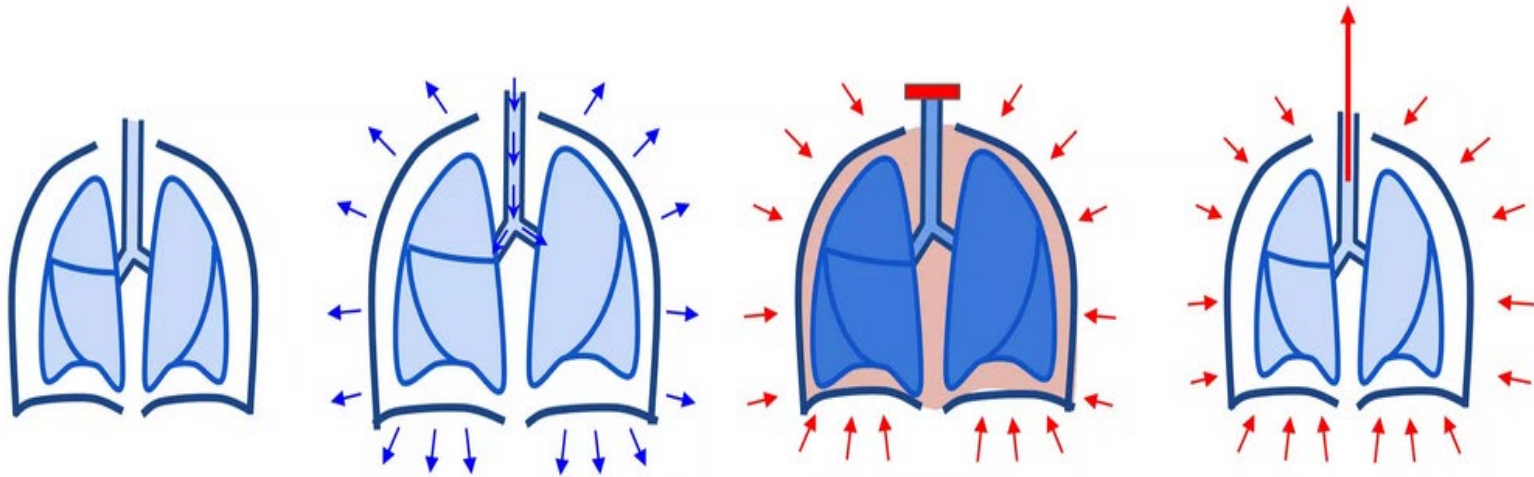


Definition and Pathophysiology of Cough

Definition: What is Cough?

- **Physiologic** temporary reconfiguration in breathing pattern to:
 - protect the lung from inhalation of noxious agents
 - clear excessive secretion
- Defined as a **triphasic event**:
 - inspiratory phase
 - compressive phase
 - expulsive phase
- Distinguish from other protective reflexes such as an “**expiratory reflex**”:
expulsive effort without a preceding inspiration

Pathogenesis: Mechanism of Cough



Irritation phase

- Neural activation from solitary nucleus
- Can be cortically suppressed

Inspiratory phase

- Brief inspiration:
- Glottis opens
 - Diaphragms contract
 - Thoracic cage expands

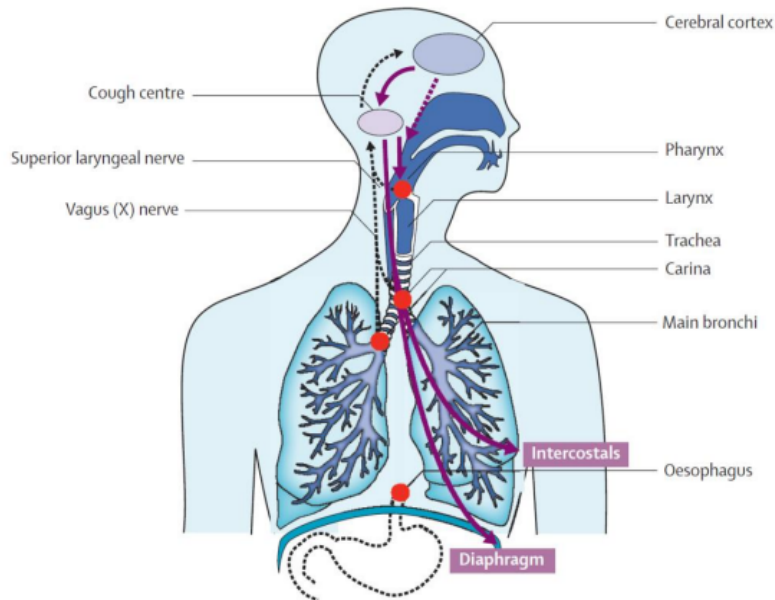
Compressive phase

- Abdominal and thoracic muscles compress air against a closed glottis

Expulsive phase

- Abrupt glottis opens
- Rapid exhalation
- High velocity and shear force allow airway clearance

Βήχας - Υποδοχείς



Μηχανικοί –Χημικοί - Τάσεως

Ρινοφάρυγγα

Λάρυγγα

Τραχεία

Τρόπιδες των μεγάλων αεραγωγών

Περικάρδιο

Οισοφάγο

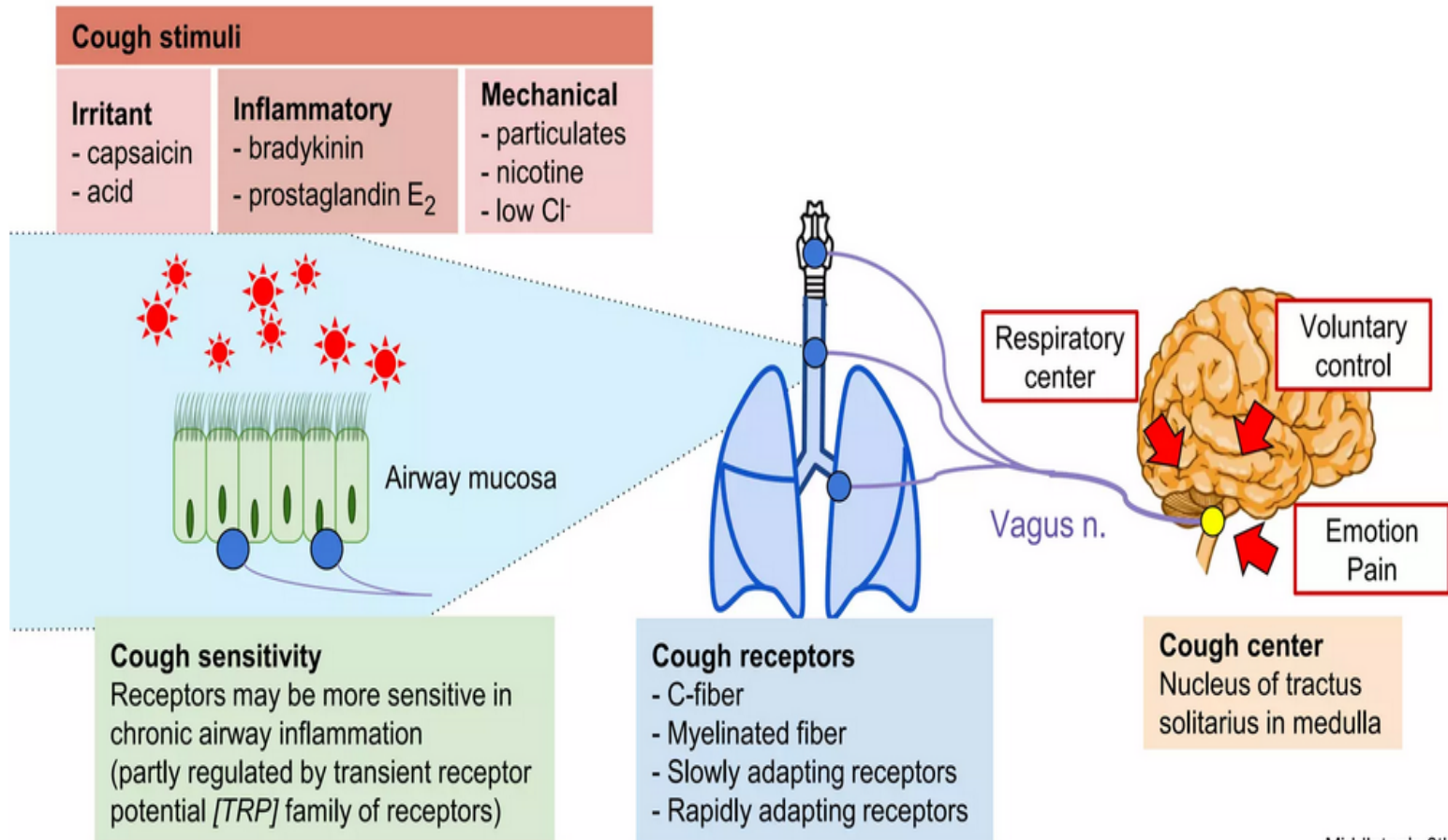
Διάφραγμα

Στομάχι

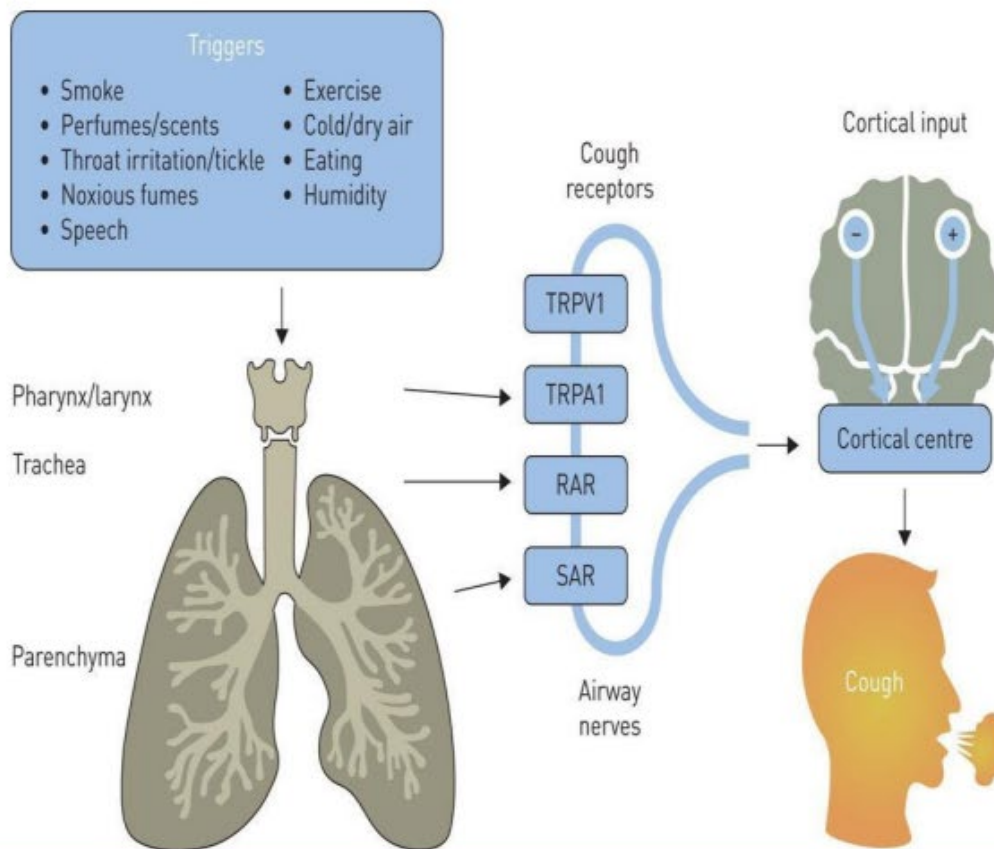
Έξω ακουστικό πόρο

Κέντρο βήχα: Προμήκης μυελός

Pathogenesis: Cough stimulation



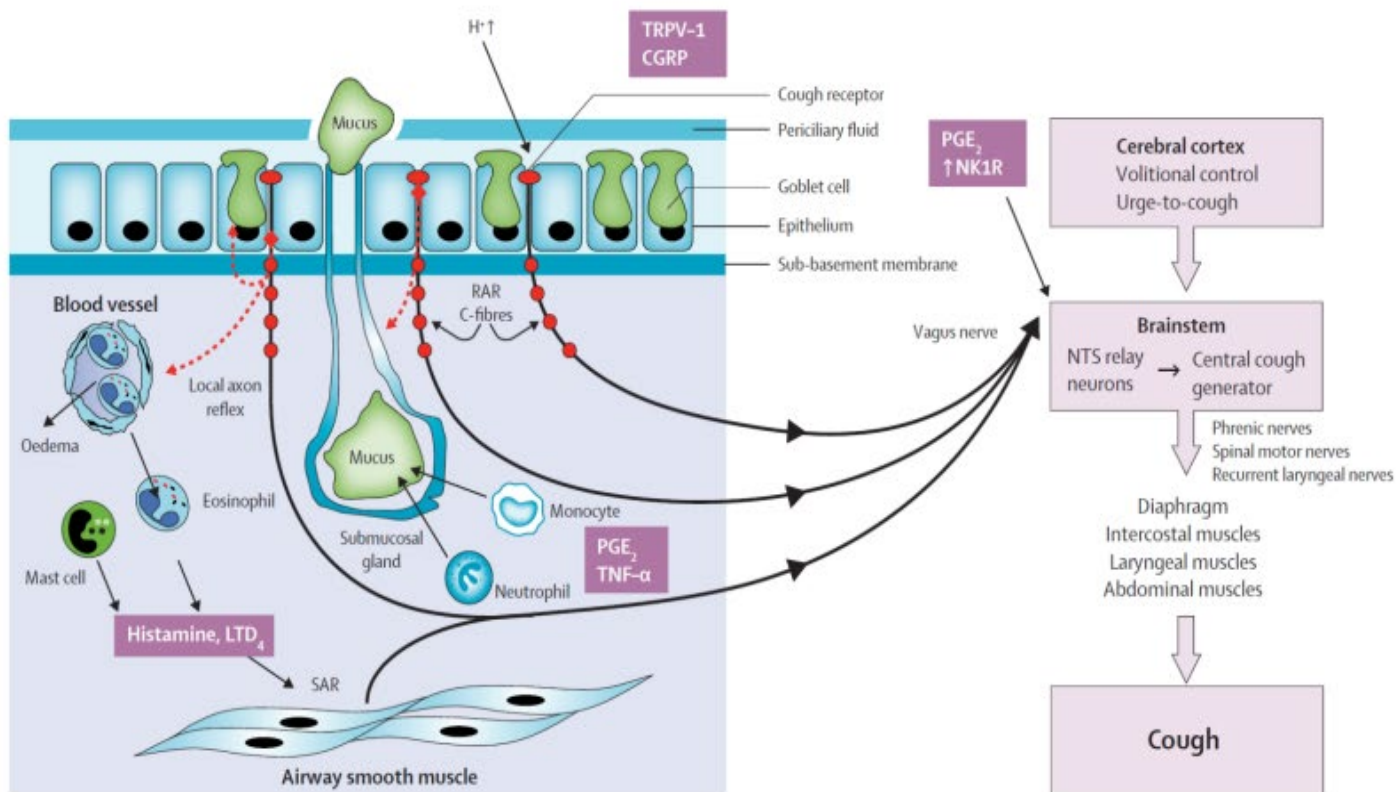
Βήχας – Παθοφυσιολογία



Εκλυτικός παράγοντας - Ερεθισμός των υποδοχέων - Μεταφορά νευρικών ώσεων μέσω του πνευμονογαστρικού, τριδύμου, γλωσσοφαρυγγικού, φρενικού νεύρου προς το ΚΝΣ

Βήχας – Παθοφυσιολογία

The cough reflex: Transient receptor potential vanilloid-1 (TRPV-1) is a capsaicin receptor



Definitions and Common Causes of Cough in Adults and Children

	Acute < 3 weeks	Subacute 3-8 weeks	Chronic > 8 weeks
Adults	<ul style="list-style-type: none"> Common cold Exacerbation of chronic disease Acute environmental exposure Acute cardiopulmonary disease 	<ul style="list-style-type: none"> Postinfectious cough Pertussis Exacerbation of chronic disease 	<ul style="list-style-type: none"> ACEI therapy Smoking Chronic bronchitis Asthma Upper airway cough syndrome (UACS) Non-asthmatic eosinophilic bronchitis (NAEB) GERD Underlying lung disease
Children	<ul style="list-style-type: none"> Common cold Exacerbation of chronic disease Acute cardiopulmonary disease 	<ul style="list-style-type: none"> Asthma Protracted bacterial bronchitis Tracheobronchomalacia Chronic rhinosinusitis Recurrent aspiration GERD Pulmonary infection (e.g., pertussis) Underlying lung disease 	
	Acute < 4 weeks	Chronic > 4 weeks	

Term	Definition
Acute Cough	Cough lasting < 3 weeks. Usually due to a viral infection
Chronic Cough	Cough lasting > 8 weeks
Refractory Chronic Cough (RCC)	Cause identified. Cough persists despite addressing treatable traits. May have symptoms suggestive of cough hypersensitivity.
Refractory Unexplained Chronic Cough (RUCC)	Unexplained; no treatable traits and no symptoms suggestive of cough hypersensitivity.
Cough Hypersensitivity Syndrome	Disorder characterised by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure. Thought to be mediated by sensitisation of the sensory neuronal pathways controlling cough including the vagus nerve and central nervous system.
Laryngeal Hypersensitivity	Neuronal hypersensitivity thought to underlie a range of laryngeal symptoms (including chronic cough, inducible laryngeal obstruction etc). Thought to be mediated by vagal and central nervous system innervation of laryngeal structures.

BTS Clinical statement on chronic cough in adults

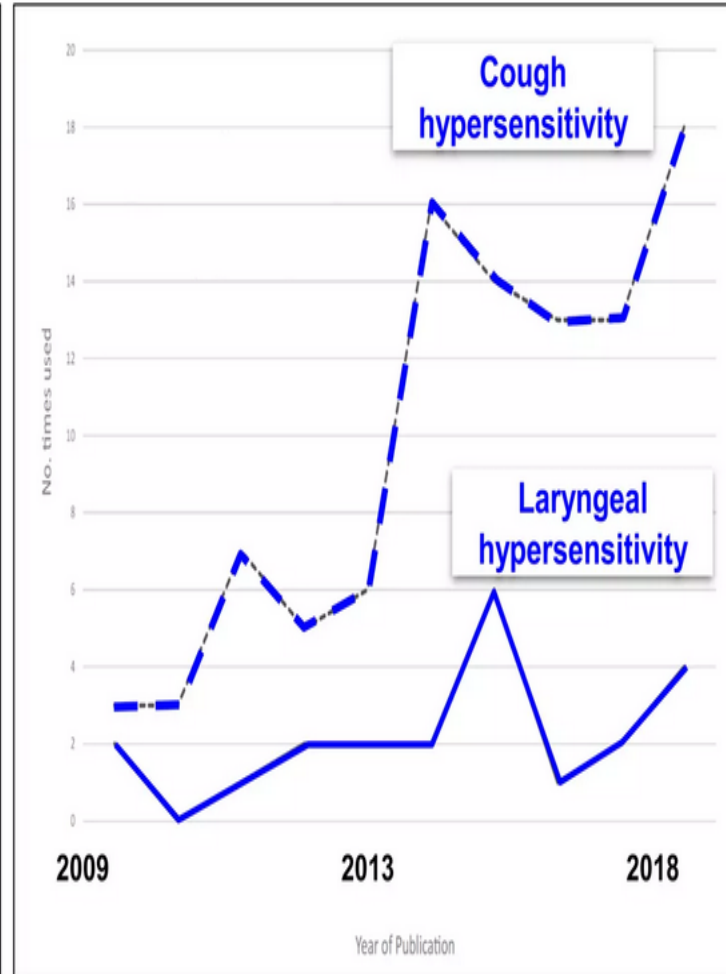
Draft for consultation: 16 November 2022

Clinical Terms

TABLE I. Clinical terms for cough

Term	Frequency of use*
Chronic cough	947
Dry cough	518
Productive cough	463
Persistent cough	236
Acute cough	115
Cough hypersensitivity	74
Refractory cough	32
Unexplained cough	22
Idiopathic cough	17
Subacute	16
Laryngeal hypersensitivity	15
Disease associated: Lung disease-, URTI-, exercise-, pertussis-, reflux-, asthma-, swallow-, pulmonary fibrosis-associated cough	10

■ Characteristic ■ Duration
■ Treatment response ■ Pathophysiology
■ Etiology

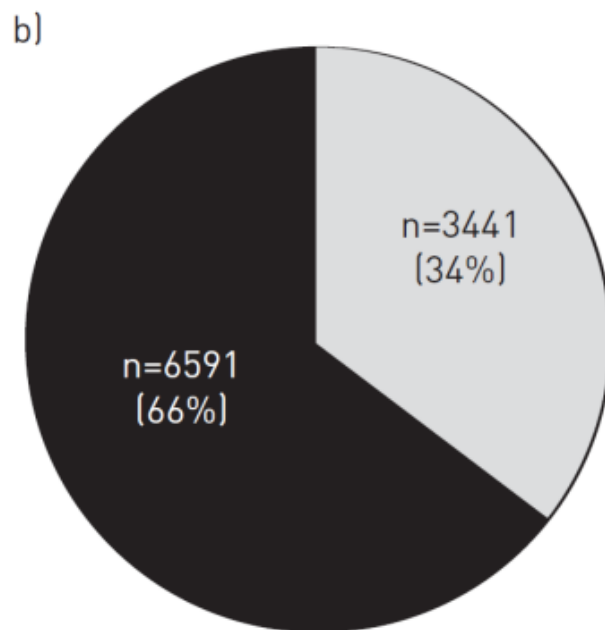
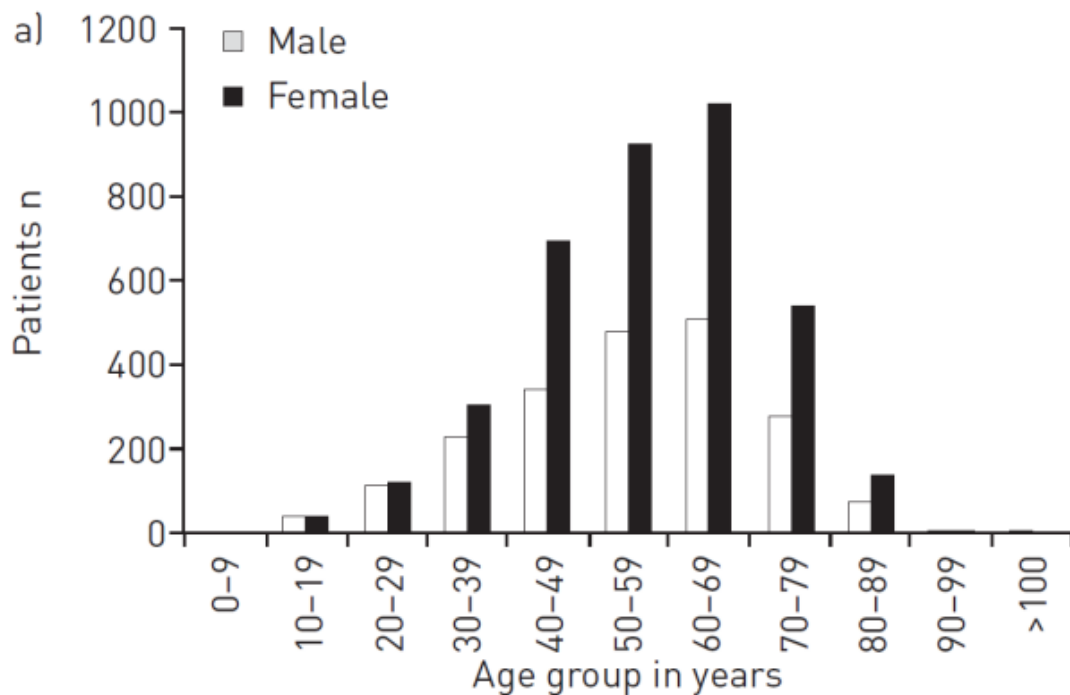




Epidemiology and Etiologies of Chronic Cough

Χρόνιος βήχας: η ηλικία και το φύλο αποτελούν ισχυρούς παράγοντες κινδύνου

A worldwide survey of 11 cough clinics (10,000 patients)



Etiologies: intrathoracic

Lungs and Airways

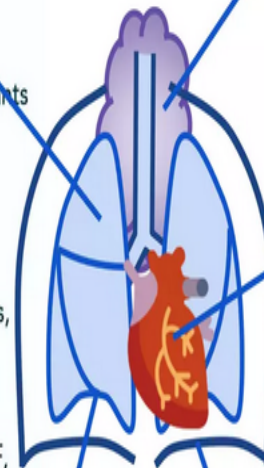
1
 Asthma
 Nonasthmatic eosinophilic bronchitis
 Chronic bronchitis
 Bronchiectasis
 ACEIs
 Inhaled medications
 Chronic exposure to environmental and occupational irritants
 Bronchogenic and metastatic carcinoma
 Bronchial carcinoid
 Foreign body or endobronchial suture
 Bronchiolith
 Infectious and noninfectious bronchiolitis
 Chronic infectious pneumonias (e.g., bacterial, tuberculous, fungal, parasitic)
 Chronic infectious tracheobronchitis (as in tuberculosis or aspergillosis)
 Chronic interstitial lung disease (e.g., sarcoidosis, HSP, IPF, asbestosis)
 Pulmonary vasculitis (as in granulomatosis with polyangiitis)
 Sjögren syndrome with xerotrachea
 Relapsing polychondritis

Pleura

2
Chronic effusion

Diaphragm

3
Transvenous pacemaker stimulation



Mediastinum

5
 Neural tumors
 Thymoma
 Teratoma
 Lymphoma
 Metastatic lymphadenopathy
 Intrathoracic goiter
 Bronchogenic cyst

Cardiovascular

4
 Mitral stenosis
 Left ventricular failure
 Pulmonary thromboembolism
 Enlarged left atrium
 Vascular ring
 Aberrant innominate artery
 Aortic aneurysm
 Pericardial stimulation by transvenous pacemaker

Etiologies: extrathoracic

Head and Neck

Rhinitis and sinusitis
Nasal polyps
Rhinolith
Oropharyngeal dysphagia
Laryngeal disorders (e.g., vocal fold dysfunction, laryngomalacia)
Postviral vagal neuropathy
Recurrent aspiration
Elongated uvula
Chronically infected tonsils
Neurilemmoma of vagus nerve
Neuroma of internal laryngeal nerve
Ascending palatine artery aneurysm
Osteophytes of cervical spine
Mammomanogamus (Syngamus) laryngeus infection
Thyroiditis



Central Nervous System



Psychogenic or habit cough
Tic disorders
Gilles de la Tourette syndrome

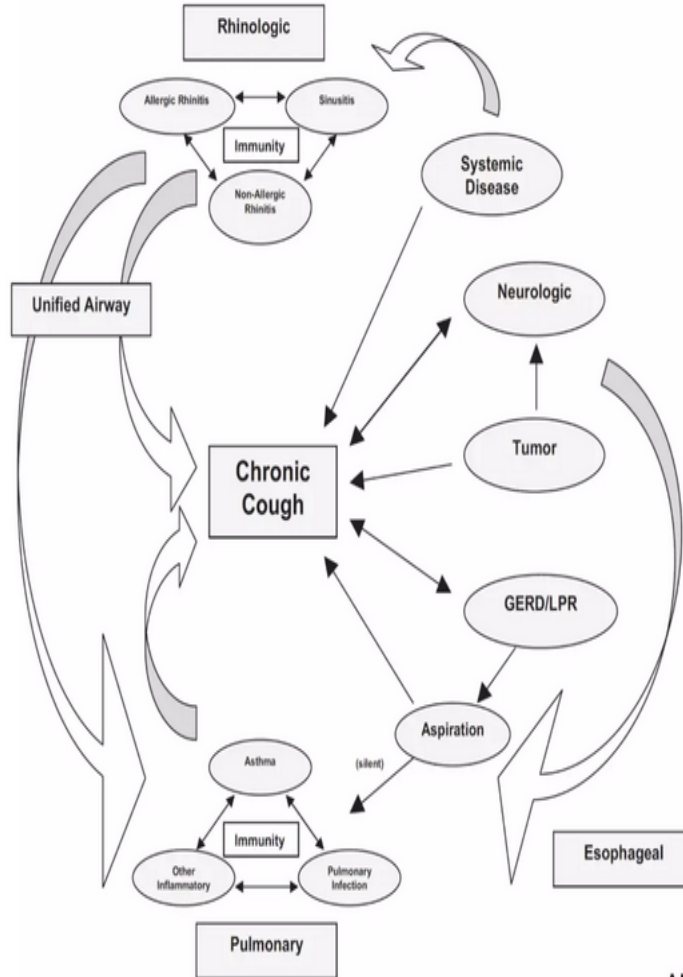
Upper Gastrointestinal



Gastroesophageal reflux disease
Esophageal cyst or diverticulum
Tracheoesophageal fistula

Head & Neck

The interrelatedness of factors contributing to cough



GERD, Gastroesophageal reflux disease
LPR, laryngopharyngeal reflux.

Thorax

ALTMAN et al. J Allergy Clin Immunol Pract. 2019 May 8.

Επιπλοκές χρόνιου βήχα

- Συγκοπτικά επεισόδια
- Ακράτεια
- Ανησυχία περιβάλλοντος για μεταδοτικά νοσήματα
- Προβλήματα σχέσεων
- Κοινωνική απομόνωση
- Σημαντικές ψυχολογικές συνέπειες
 - 50% των ασθενών σε ιατρεία βήχα έχουν κατάθλιψη
 - Ποιότητα ζωής ανάλογη με εκείνη των ασθενών με ΧΑΠ

Morice AH, *Breathe* 2006

Dicpinigaitis PV, *Chest* 2006

- **Καρδιαγγειακές:** υπόταση, αρρυθμίες, απώλεια αισθήσεων
- **Αναπνευστικές:** πνευμοθώρακα, τραυματισμό λάρρυγγα
- **Γαστρεντερικές:** επεισόδιο ΓΟΠ, κήλες
- **Ουροποιογεννητικές:** ακράτεια ούρων
- **Μυοσκελετικό:** ρήξη μυών, κατάγματα
- **Νευρολογικές:** σπασμούς, πονοκεφάλους, ΑΕΕ
- **Οφθαλμολογικές:** ενδοφθάλμια αιμορραγία
- **Δερματολογικές:** πετέχιες, ρήξη τραυμάτων
- **Συστηματικές:** ακατάσχετη εφίδρωση, ανορεξία, εξάντληση



Approach to Chronic Cough in Adults

Αλγόριθμος

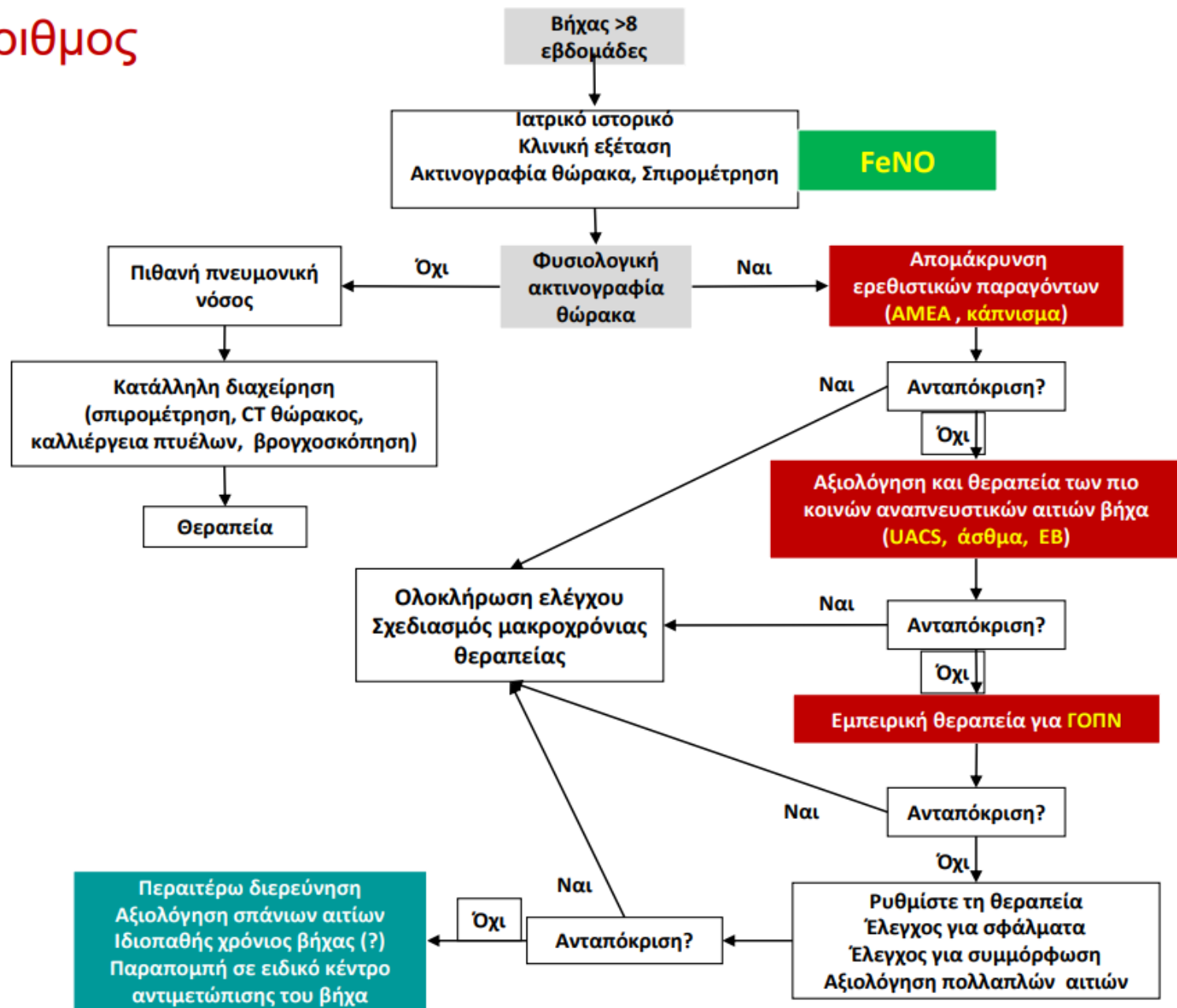


Table 1 Comparison of guideline recommendation in different chronic cough guidelines

ERJ	ACCP	CTS
Question 1: Should chest CT scan be routinely performed on chronic cough patients with normal chest X-ray and physical examination?		
<p>Recommendation 1: We suggest that clinicians do not routinely perform a chest CT scan in patients with chronic cough who have a normal chest X-ray and physical examination. (conditional recommendation, very low-quality evidence)</p>	<p>In the flowchart, CT, as a further investigation, is recommended for the patients with chronic cough who have inadequate response to optimal treatment after 4–6 weeks follow up (1)</p>	<p>Chest radiographs are routinely recommended for chronic cough (Grade 2D). If an obvious abnormality is observed on plain films, additional investigation is selected based on the characteristics of the lesion. High-resolution CT is helpful for the early diagnosis of interstitial pulmonary diseases and atypical bronchiectasis</p>

Ιστορικό

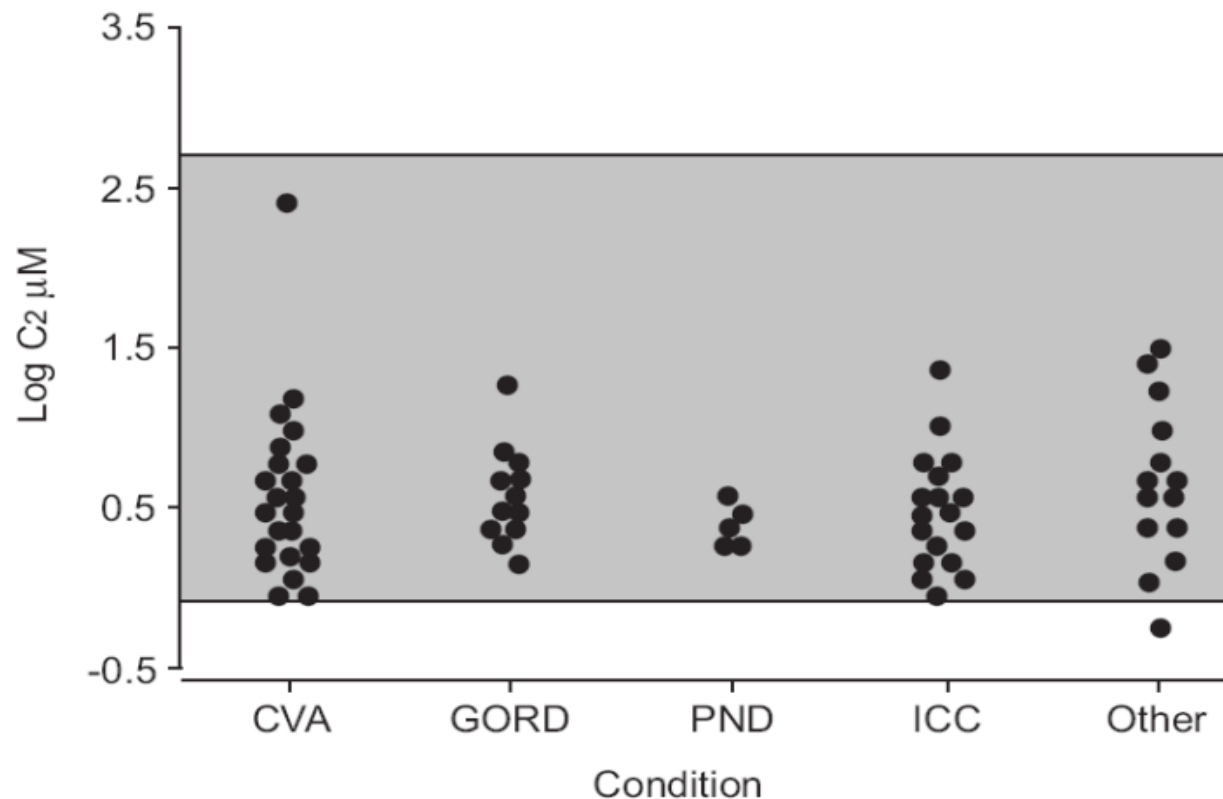
- Έναρξη βήχα
- Φάρμακα (ΑΜΕΑ)
- Κάπνισμα
- Εποχιακή κατανομή
- Ώρα επιδείνωσης στο 24ωρο
- Ατοπία
- Συσχέτιση με γεύματα
- Συνυπάρχουσες παθήσεις



Ερωτηματολόγια

- Cough-specific Quality of life Questionnaire
- Leicester Cough Questionnaire
- Burden of Cough Questionnaire

Δοκιμασία πρόκλησης με καψαΐσίνη



- Καταγράφονται οι συγκεντρώσεις που προκαλούν δύο (C2) και πέντε (C5) επεισόδια βήχα
- Σημαντική μεταβλητότητα σε διαδοχικές μετρήσεις στον ίδιο ασθενή, σημαντική επικάλυψη μεταξύ υγιών και ασθενών με χρόνια βήχα και μεταξύ ασθενών με βήχα διαφορετικής αιτιολογίας
- Περιορισμένος ρόλος στη ΔΔ

Morice AH, *ERJ* 2007; 29: 1256–1276. (ERS Task Force)

Approach in Adults

1 Identify obvious causes

- Diagnosis based on Hx, PE, CXR → **specific treatment**
- Often multiple etiologies
- Consider exacerbation of chronic diseases

Red Flags

- Hemoptysis
- Voice disturbance
- Dysphagia
- Vomiting
- Dyspnea
- Systemic symptoms
 - Fever
 - Weight loss
 - Edema
- Recurrent pneumonia
- Abnormal PE / CXR
- Smoker
 - Age>45 + new symptom
 - Age>55 + smoke>30PY

Smoking

ACEI

4 Most common

- Upper airway cough syndrome
- Asthma
- NonAsthmatic eosinophilic bronchitis
- Gastroesophageal reflux disease

- Allergy Asthma Immunol Res. 2018 Nov;10(6):591-613.
 - CHEST Guideline and Expert Panel Report. Chest 2018;153:196-209.
 - ข้อเสนอแนะการปฏิบัติมาตรฐานสุขภาพ การรักษาผู้ป่วยโรคเรื้อรังในผู้ใหญ่ พ.ศ.2559

May not helpful in diagnosis

- character: paroxysmal, loose, productive, dry
- sound quality: barking, honking
- timing: nocturnal

- no obvious cause found
- not fully response after optimal & adequate treatment

2 Investigation +/- empirical treatment for common causes

- negative study
- not fully response after treatment

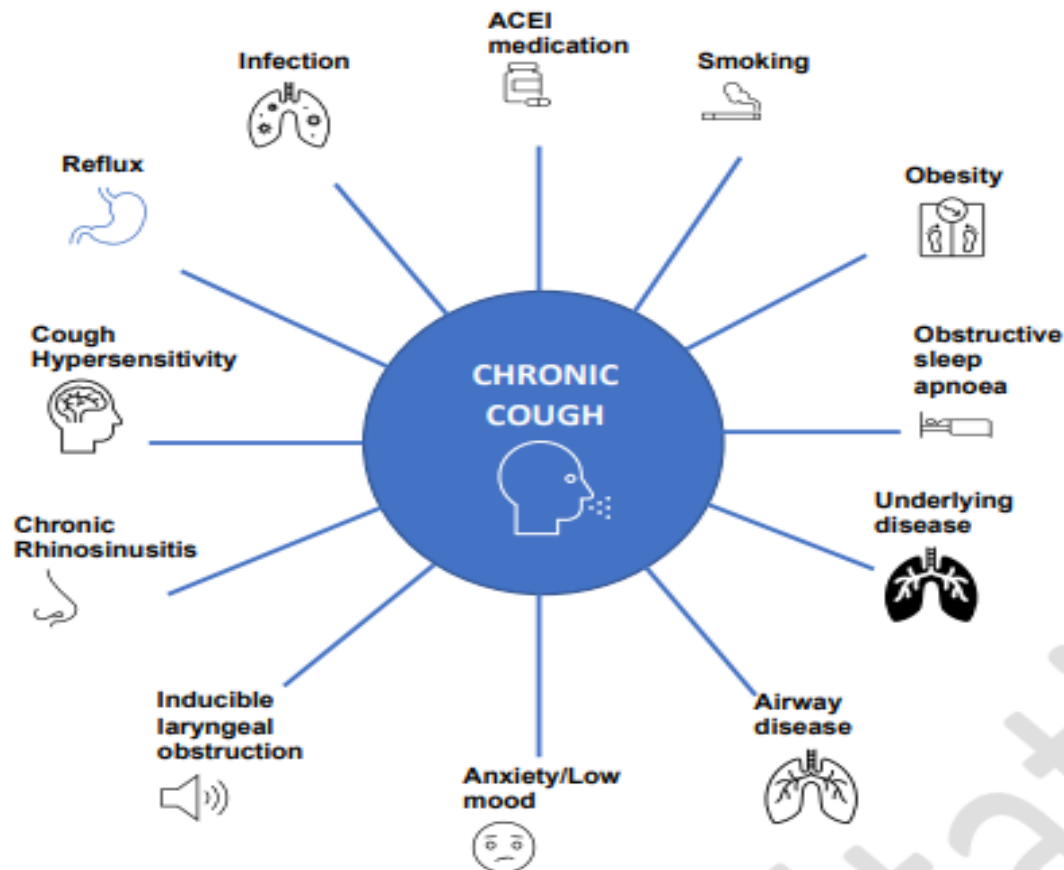
3 Further investigation

- negative study

4 "Unexplained chronic cough"

Moving beyond the anatomical diagnostic protocol

Treatable traits of chronic cough



BTS Clinical statement on chronic cough in adults

Draft for consultation: 16 November 2022

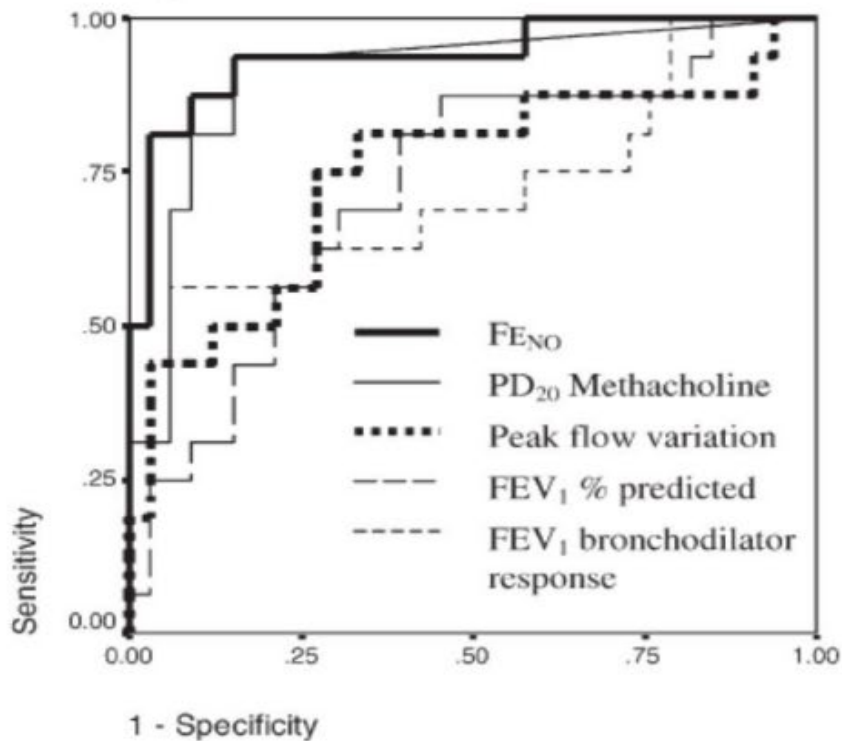
Phenotypes of chronic cough



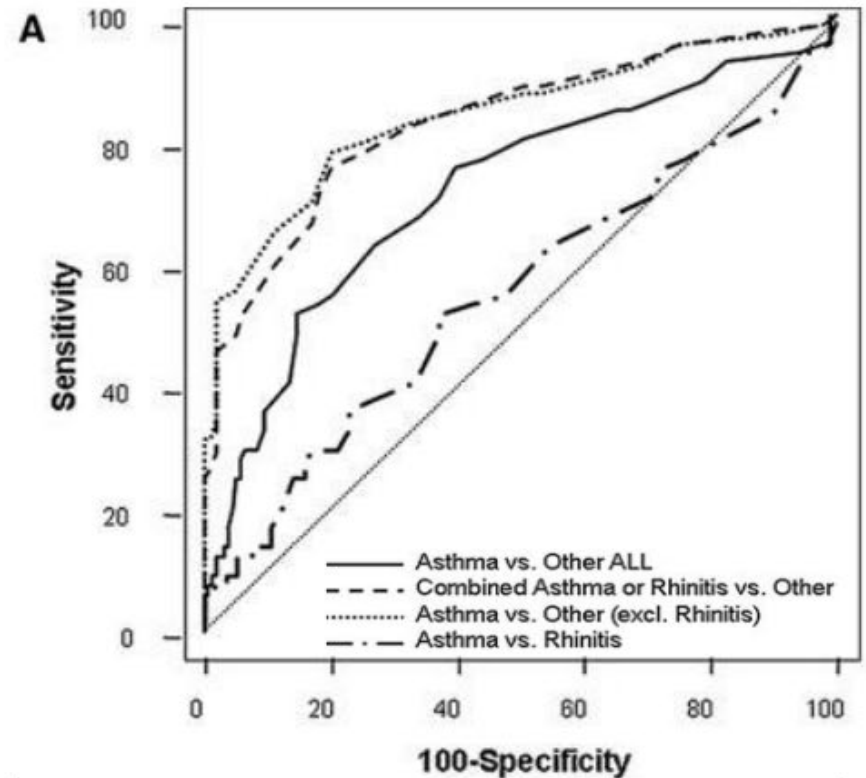
Asthmatic cough/eosinophilic bronchitis

- Asthma
- Cough Variant Asthma (CVA)
- Eosinophilic Bronchitis
- Atopic Cough (AC)
- Σπυρομέτρηση προ & μετά βρογχοδιαστολής
- Δοκιμασίες πρόκλησης (μεταχολίνη)
- Ηωσινόφιλα πτυέλων
- FeNO
- BEC
- SPT

Χρόνιος βήχας και FeNO: πρόβλεψη ηωσινοφιλικής φλεγμονής και απάντησης σε ICS



FeNO >47 ppb "best predictor" of steroid response



FeNO >30 ppb specificity >90% for asthma diagnosis (\pm AR)

Table 1 Comparison of guideline recommendation in different chronic cough guidelines

ERJ	ACCP	CTS
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Question 2: Should FeNO/blood eosinophils be used to predict treatment response to corticosteroids/anti-leukotrienes in chronic cough?

Research recommendation

In adult and adolescent patients with chronic cough due to asthma, we **suggest** that non-invasive measurement of airway inflammation has clinical utility, and the presence of eosinophilic airway inflammation is likely to be associated with a more favorable response to corticosteroids (Grade 2B) (2).

FENO measurement:

In the flowchart, FENO, as an ideal evaluation, is recommended for the patients with suspected non-asthmatic eosinophilic bronchitis (NAEB) who have inadequate response to optimal treatment after 4–6 weeks follow up (1).

Recommendation on blood eosinophils: N/A

(I) Recommendation on FeNO measurement:

(i) An increase in FeNO (>32 ppb) suggests eosinophilic inflammation or corticoid-sensitive cough. However, the sensitivity is not high when FeNO measurement is used for screening of eosinophilic inflammation. Approximately 40% of patients with increased numbers of eosinophils have normal FeNO (Grade 2C).

(ii) The measurement of FeNO is recommended as to supplement of the induced sputum test (Grade 2C).

(iii) **The sensitivity of FeNO is not high for diagnosis of EB, but FeNO of >32 ppb suggests eosinophil-related chronic cough (e.g., EB or CVA) (Grade 2C)**

(II) Recommendation on blood eosinophils: N/A

Reflux cough

ACID REFLUX

NON ACID REFLUX

- Micro-aspiration
- Oesophageal dysmotility
- Other types (weakly acid, non-acid, gaseous, laryngo-pharyngeal)

- Βήχας μετά από γεύμα, κατά την ομιλία, μετά την αφύπνιση
- Καθάρισμα λαιμού, βράγχος, αίσθημα ξένου σώματος
- Καύσος, αναγωγή
- 75% κανένα σύμπτωμα από ΓΕΣ
- Χρονική συσχέτιση παλινδρόμησης/βήχα δεν είναι σταθερή

- Επίδραση οξέος στον οισοφάγο που διεγείρει μέσω πνευμονογαστρικού το οισοφαγο-τραχειοβρογχικό αντανακλαστικό βήχα
- Μικροεισροφήσεις στο λαρυγγοφάρυγγα και στο τραχειοβρογχικό δένδρο

Λαρυγγοφαρυγγικό ανατανακλαστικό (LPR) ή εξωοισοφαγικό GERD

- 24-h pH monitoring
- Οισοφαγογραφία με βάριο
- HR oesophageal manometry

Έμμεσα

- Λαρυγγοσκόπηση : λαρυγγίτιδα, διόγκωση, ερυθρότητα, οίδημα οπίσθιου λάρυγγα
- Οισοφαγοσκόπηση : οισοφαγίτιδα, οισοφαγικό έλκος, στένωση

ERJ

ACCP

CTS

Question 4: Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?

Recommendation 4: We suggest that clinicians do not routinely use anti-acid drugs in adult patients with chronic cough. (conditional recommendation, low quality evidence)

(I) In adult patients with chronic cough suspected to be due to reflux-cough syndrome, we recommend that treatment include: (i) diet modification to promote weight loss in overweight or obese patients; (ii) head of bed elevation and avoiding meals within 3 hours of bedtime; and (iii) in patients who report heartburn and regurgitation, proton pump inhibitors, H₂- receptor antagonists, alginate, or antacid therapy sufficient to control these symptoms (Grade 1C) (4).

(II) In adult patients with suspected chronic cough due to reflux-cough syndrome, but without heartburn or regurgitation, we recommend against using proton pump inhibitor therapy alone because it is unlikely to be effective in resolving the cough (Grade 1C) (4).

(III) In adult patients with unexplained chronic cough and a negative workup for acid gastroesophageal reflux disease, we suggest that proton pump inhibitor therapy not be prescribed (2C) (3)

Proton pump inhibitor (PPI) is recommended for patients suspected to be due to GERC (Grade 2C).

Antacids: acid suppression is recommended as the standard treatment for GERC (Grade 1A).

When the treatment with the standard dose of PPI is not effective, increasing the dose of PPI may be helpful (Grade 2A).

If treatment with one kind of PPI fails, switching to another PPI may be effective (Grade 2C).

Combining H₂ receptor antagonist with PPI may ameliorate cough symptoms due to refractory gastroesophageal reflux or nighttime acid reflux (Grade 2C)

ERJ

ACCP

CTS

Question 5: Should drugs with **pro-motility activity (reflux inhibitors, prokinetics and macrolides with pro-motility activity)** be used to treat patients with chronic cough?

Recommendation 5: There is currently **insufficient evidence** to recommend the routine use of macrolide therapy in chronic cough. A one-month trial of macrolides can be considered in the cough of chronic bronchitis refractory to other therapy, taking into account local guidelines on antimicrobial stewardship. (conditional recommendation, low quality evidence)

Remarks:
In the **updated 2016 guideline**, it showed that with respect to the treatment arms, they were all placebo controlled with respect to the primary intervention (PPIs in 11 of 14 cases), but most of the trials made no mention of concomitant dietary modifications, lifestyle modifications, or use of prokinetic drugs (4). Due to **lack of sufficient evidence**, the use of prokinetic drugs could not be concluded as a recommendation to treat patients with chronic cough. However, in the 2006 guideline, the prokinetic therapy was recommended in treating some patients with cough due to GERD. The detailed recommendation in the **2006 guideline** was showed as below. In some patients, cough due to GERD will favorably respond to acid suppression therapy alone; proton pump inhibition may be effective when H2-antagonism has been ineffective; **prokinetic therapy and diet, when added to proton pump inhibition**, may be effective when proton pump inhibition alone has been ineffective (Level of evidence, low; benefit, substantial; grade of recommendation, B) (5)

Recommendation on prokinetic agents:
Most patients with GERC have esophageal motility dysfunction, therefore the addition of prokinetic agents (domperidone and mosapride) is **recommended** (Grade 1D)

Upper airways cough syndrome (UACS)

- Post Nasal Drip (PND)
- Nasal disease/Rhinosinusitis
- Inducible laryngeal obstruction
- Ρινοσκόπηση
- Λαρυγγοσκόπηση
- CT σπλαγχνικού κρανίου

Σύνδρομο βήχα ανώτερων αεραγωγών

“Σαν κάτι να στάζει στο λαιμό” ή ανάγκη να καθαριστεί ο λαιμός ή ρινική συμφόρηση/καταρροή

Θεραπευτικά :

- Αντιισταμινικά άγευστά/αποσυμφορητικά
- Ρινικά κορτικοστεροειδή 2-8 εβδομάδες
- Ρινικό spray βρωμιούχο ιπρατρόπιο

iatrogenic cough

- ACE inhibitors
- Bisphosphonates / Calcium channel antagonists (reflux disease)
- Prostanoid eye drops

ACE inhibitors

- 2-33% των ασθενών που έλαβαν ΑΜΕΑ – ξηρό βήχα
- Εμφάνιση : ώρες- μήνες μετά τη λήψη
- Βελτίωση 1-4 εβδομάδες μετά τη διακοπή
- **Μηχανισμός:** αναστολή αποδόμησης βραδυκινίνης και προσταγλανδινών στους αεραγωγούς και άμεσο ερεθισμό των υποδοχέων του βήχα

Other treatable traits

- Smoking / Vaping
- Occupational exposure
- Obesity
- OSAS
- Anxiety / low mood



Expert opinion on the cough hypersensitivity syndrome in respiratory medicine

Alyn H. Morice¹, Eva Millqvist², Maria G. Belvisi³, Kristina Bieksiene⁴, Surinder S. Birring⁵, Kian Fan Chung⁶, Roberto W. Dal Negro⁷, Peter Dicpinigaitis⁸, Ahmad Kantar⁹, Lorcan P. McGarvey¹⁰, Adalberto Pacheco¹¹, Raimundas Sakalauskas⁴ and Jaclyn A. Smith¹²

Eur Respir J 2014; 44: 1132–1148 | DOI: 10.1183/09031936.00218613

- Νευροπαθητική κατάσταση
- Απορρύθμιση TRP (Transient Receptor Potential) υποδοχέων (TRPV-1, TRPA-1)
- Μιμείται ή συνυπάρχει με πολλά νοσήματα

Chronic Refractory Cough

A Disorder of the Brain and the Respiratory System

Peter S. P. Cho, PhD

Richard D. Turner, PhD

London, England



CHEST OCTOBER 2022



EDITORIAL
COUGH

Chronic cough: a disorder of response inhibition?

Stuart B. Mazzone 

Eur Respir J 2019; 53: 1900254

The significance of the study reported by CHO *et al.* [4] is that it presents new evidence that peripheral sensitisation might not be the full story. In their study, patients with refractory chronic cough not only displayed evidence of cough hypersensitivity to inhaled capsaicin, but they also demonstrated little capacity to voluntarily suppress their cough during capsaicin challenges. This contrasts with the healthy participants in the study who could readily suppress capsaicin-evoked cough on command. Moreover, diminished cough suppression was related to the amount of daytime coughing objectively measured in patients using validated cough counting. Taken together, these data present a strong case suggesting that chronic cough involves both peripheral and central neural mechanisms.

The findings of CHO *et al.* [4] are consistent with the notion that chronic cough can involve an imbalance between the level of peripheral drives that induce cough and the central mechanisms that are engaged to suppress cough. However, many questions remain. From a mechanistic point of view, it will be important to investigate whether loss of central suppression is involved in the development or maintenance (or both) of chronic cough. For example, it may be that the longer cough persists in a patient, the peripheral drivers

controls, compared to more traditional cough sensitivity testing. This observation might pave the way for the development of validated clinical challenge tests that allow for patients with predominately sensitive peripheral nerves to be distinguished from those who show lack of central control. In doing so, this should help guide disease management and therapy choice with respect to whether peripherally or centrally acting antitussive (and/ or behavioural) therapies are warranted. It is noteworthy, however, that voluntary cough suppression is not opioid-dependent [24], and as such new centrally acting antitussives that target and restore these central cough suppression networks will need to be developed. One exciting possibility is the centrally acting alpha-7 nicotinic receptor agonist bradanicline, which is currently in early phase 2 trials in refractory chronic cough patients (ClinicalTrials.gov identifier NCT03622216).

History taking and physical examination on presentation

Cough duration

Cough impact and triggers

Family history

Cough score (using VAS or verbal out of 10)

HARQ

Associated symptoms: throat, chest, gastrointestinal

Risk factors: ACE inhibitor, smoking, sleep apnoea

Physical examination: throat, chest, ear

Routine evaluation

Chest radiography

Pulmonary function test

? F_{eNO}

?Blood count for eosinophils

Additional evaluation where indicated

High-resolution oesophageal manometry

Induced sputum for eosinophils

Sputum AAFB

Laryngoscope

Methacholine challenge

Chest CT

Bronchoscopy

Common Pitfalls in Diagnosis

Failure to recognize that

- Etiologies of chronic cough may be **multifactorial**
- GERD and UACS can also **produce phlegm**
- **Cough can be the only manifestation** of:
 - Cough variant asthma
 - Silent UACS
 - Silent GERD

Therapeutic approach

dreamstime®



Common Pitfalls in Management

- **Premature abortion** of treatment
 - Asthma, UACS: up to 4 weeks
 - GERD: up to 6 months
- Fail to recognize **environmental exposure & co-morbids**
 - Asthma, UACS, NAEB: Allergen avoidance
 - GERD: OSA, CCB treatment, foods, lifestyle
- **Premature labelling** of
 - Psychogenic cough
 - Idiopathic cough
 - Unexplained cough

Aggravants?

ACEI→Stop

Smoking→Smoking cessation

Infection→Reassurance, Self care, Antibiotics if appropriate*

Consider Pertussis

Underlying disease

(e.g. asthma/COPD)→Treat

Consider secondary care referral

Treatable Traits

Airway disease→ Optimise treatment.

Trial ICS for 1 month if indicated (FENO>25ppb, BEC ≥0.3)

Reflux →Trial PPI only if symptoms (heartburn)

Rhinosinusitis→Trial nasal steroid/douching

Anxiety/depression→Reassurance /explanation. Psychological +/- pharmacological therapy.

Only treat if objective evidence or symptoms of traits. Avoid empirical treatment.

Refer to secondary care if...

Continue to cough despite treatment

Any red flags

Diagnosis unclear

Suspected bronchiectasis, ILD, TB, heart failure, cancer.

Anti-asthmatics

Recommendation 3a: We conditional low suggest a short-term ICS trial (2–4 weeks) in adult patients with chronic cough. (conditional recommendation, low quality evidence)

Recommendation 3b: We suggest a short-term ICS trial (2–4 weeks) in children with chronic dry cough. (conditional recommendation, low quality evidence)

Recommendation 3c: We suggest a short-term anti-leukotriene trial (2–4 weeks) in adults with chronic cough, particularly for those with asthmatic cough. (conditional recommendation, low quality evidence)

Recommendation 3d: We suggest a short-term trial (2–4 weeks) of ICS and long-acting bronchodilator combination in adults with chronic cough and fixed airflow obstruction. (conditional recommendation, moderate quality evidence)

Anti-acid

Recommendation 4: We suggest that clinicians do not routinely use anti-acid drugs in adult patients with chronic cough. (conditional recommendation, low quality evidence)

Pro-motility activity

Recommendation 5: There is currently insufficient evidence to recommend the routine use of macrolide therapy in chronic cough. A one-month trial of macrolides can be considered in the cough of chronic bronchitis refractory to other therapy, taking into account local guidelines on antimicrobial stewardship. (conditional recommendation, low quality evidence)

Neuromodulatory agents

ERS

Recommendation 6a: We recommend a trial of **low dose morphine (5–10 mg bd)** in adult patients with chronic refractory cough. (strong recommendation, moderate quality evidence)

Recommendation 6b: We suggest a trial of **gabapentin or pregabalin** in adult patients with chronic refractory cough. (conditional recommendation, low quality evidence)

ACCP

In adult patients with unexplained chronic cough, we suggest a therapeutic trial of **gabapentin** as long as the potential side effects and the risk-benefit profile are discussed with patients before use of the medication, and there is a reassessment of the risk-benefit profile at 6 months before continuing the drug (Grade 2C) (3)

Chronic cough - guidelines:

Summary of Recommendations and Suggestions

3. In adult patients with unexplained chronic cough, we suggest a therapeutic trial of multimodality speech pathology therapy (Grade 2C).

4. In adult patients with unexplained chronic cough and negative tests for bronchial hyperresponsiveness and eosinophilia (sputum eosinophils, exhaled nitric oxide), we suggest that inhaled corticosteroids not be prescribed (Grade 2B).

5. In adult patients with unexplained chronic cough, we suggest a therapeutic trial of gabapentin as long as the potential side effects and the risk-benefit profile are discussed with patients before use of the medication, and there is a reassessment of the risk-benefit profile at 6 months before continuing the drug (Grade 2C).

6. In adult patients with unexplained chronic cough and a negative workup for acid gastroesophageal reflux disease, we suggest that proton pump inhibitor therapy not be prescribed (Grade 2C).

- Target neuronal pathways:
 - Gabapentin
 - Pregabalin
- Target microbiome and inflammatory pathways:
 - Azithromycin
- Target the cough reflex:
 - AF-219

Unexplained chronic cough – Gabapentin:

- Side effects were more common in the gabapentin group
- 31% adverse effect rate with gabapentin (vs 10% in placebo)
- 1 patient in each arm withdrew due to side effects

	Gabapentin (n=17)	Placebo (n=6)
Blurred vision	1 (6%)	0
Depression	0	1* (17%)
Disorientation, confusion	2 (12%)	0
Dizziness	3 (18%)	1 (17%)
Dry or very dry mouth	2 (12%)	1 (17%)
Fatigue	3 (18%)	1 (17%)
Headache	1 (6%)	0
Memory loss	1 (6%)	0
Nausea, stomach pain	4 (24%)	2 (33%)

Data are number of events (%). n=total number of events associated with study drug. *Possible comorbidity (present before study).

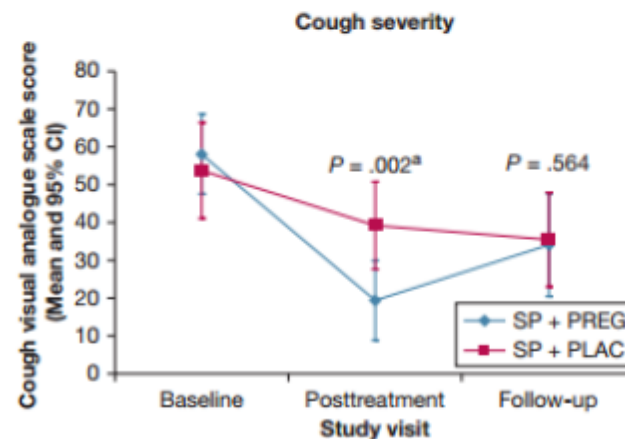
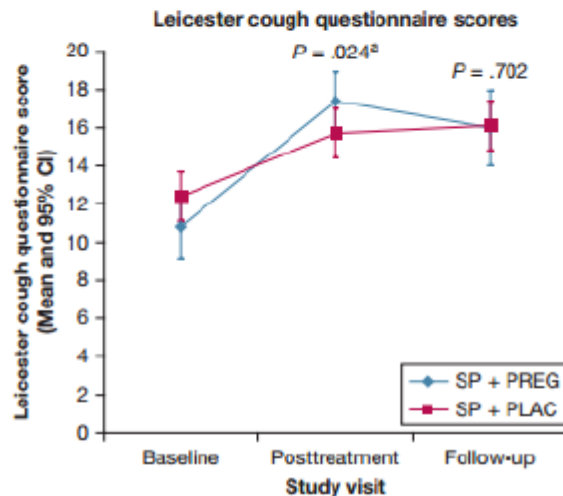
Table 2: Adverse effects

Unexplained chronic cough – Pregabalin:

Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough

A Randomized Controlled Trial

- Random allocation to speech therapy plus pregabalin (up to 300 mg daily) or speech therapy plus placebo for 14 weeks
- Enrolled 40 patients with chronic cough



Unexplained chronic cough – Emerging therapy options:

P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study

Rayid Abdulqawi, Rachel Dockry, Kimberley Holt, Gary Layton, Bruce G McCarthy, Anthony P Ford, Jaclyn A Smith

- P2X3 receptors are expressed by airway vagal afferent nerves
- These receptors contribute to the hypersensitization of sensory neurons.
- Activation could lead to chronic cough.
- AF-219 is an oral P2X3 antagonist

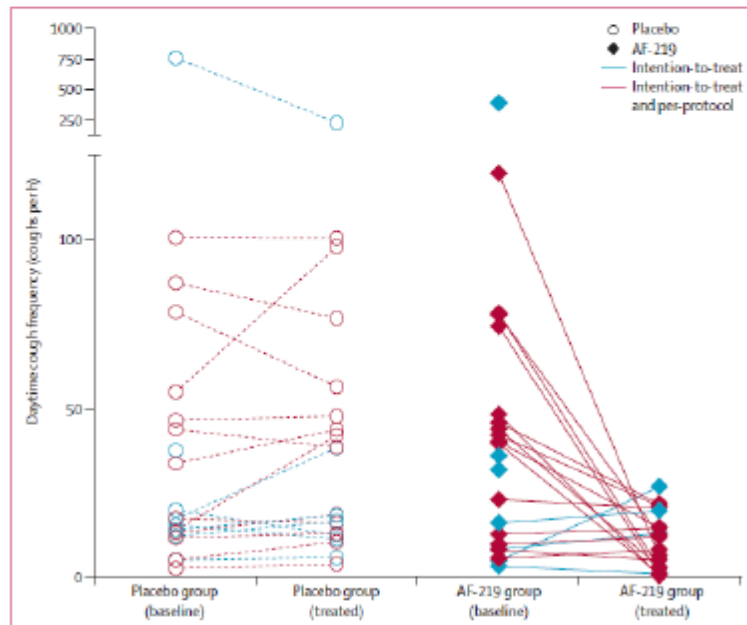


Figure 2: Changes in objective daytime cough frequency from baseline to end of the treatment period. Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

Non-pharmacological therapy






ERS

Recommendation 7: We suggest a trial of cough control therapy in adult patients with chronic cough. (conditional recommendation, moderate quality evidence)

ACCP

In adult patients with unexplained chronic cough, we suggest a therapeutic trial of multimodality speech pathology therapy (Grade 2C) (3)

Cough hypersensitivity and chronic cough

Kian Fan Chung ^{1,2}, Lorcan McGarvey³, Woo-Jung Song ⁴, Anne B. Chang ^{5,6}, Kefang Lai⁷, Brendan J. Canning⁸, Surinder S. Biring⁹, Jaclyn A. Smith¹⁰ and Stuart B. Mazzone ¹¹ 

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Box 4 | **Speech and language therapy management of chronic cough**

The approach to cough-specific speech and language therapy involves four steps.

- **Education.** Patients are provided education on the biology of coughing, chronic cough and cough hypersensitivity, and the negative effects of repeated coughing and throat clearing are explained.
- **Vocal hygiene.** Vocal and laryngeal hygiene and hydration are advised with a reduction in caffeine and alcohol intake. Nasal breathing with nasal douching may be recommended with nasal steam inhalation.
- **Cough control/suppression training.** Following identification of patient cough triggers, patients are taught a range of suppression strategies including forced/dry swallow, sipping water, chewing gum or sucking non-medicated sweets. Breathing pattern re-education is used to promote relaxed abdominal breathing while inhaling through the nose.
- **Psycho-educational counselling.** Behaviour modification is used to reduce over-awareness of the need to cough and facilitate an individual's internalization of control over their cough and to help manage stress and anxiety.

In search for the Holy Grail of cough guidelines

Anne B. Chang^{1,2}

do differ in the concept and scope. ERS is characterized by (I) it views chronic cough as a clinical syndrome but not as a symptom of other diseases and that (II) it suggests identifying cough phenotypes or treatable traits rather than causes of cough. While ACCP and CTS interpret the management of chronic cough according to different causes. Due to the lack of diagnostic criteria of the common causes of chronic cough in ERS guideline, the flow charts are different from those in ACCP and Chinese guidelines. In