

# TOSSE CRONICA

Aspetti clinici

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# INTERNATIONAL GUIDELINES

**ERS – ERJ** [2007](#); 29: 1256 e **ERJ** [2019](#); DOI:10.1183/13993003,0136-2019

**ACCP – CHEST** [2006](#); 129: 1S-292S; CHEST [2016](#); 149: 27-44.

**BRITISH THORACIC SOCIETY – THORAX** [2006](#); 61: (Suppl.) i1-i24.

**AUSTRALIAN COUGH GUIDELINES – MJA** [2010](#); 192: 265-271.

**GERMAN RESPIRATORY SOCIETY – Pneumologie** [2010](#); 64: 701-711.

# DEFINIZIONE TOSSE

**TOSSE ACUTA:** durata < 3 settimane in genere per infezioni alte vie aeree.

**TOSSE SUBACUTA:** tosse >3 <8 settimane

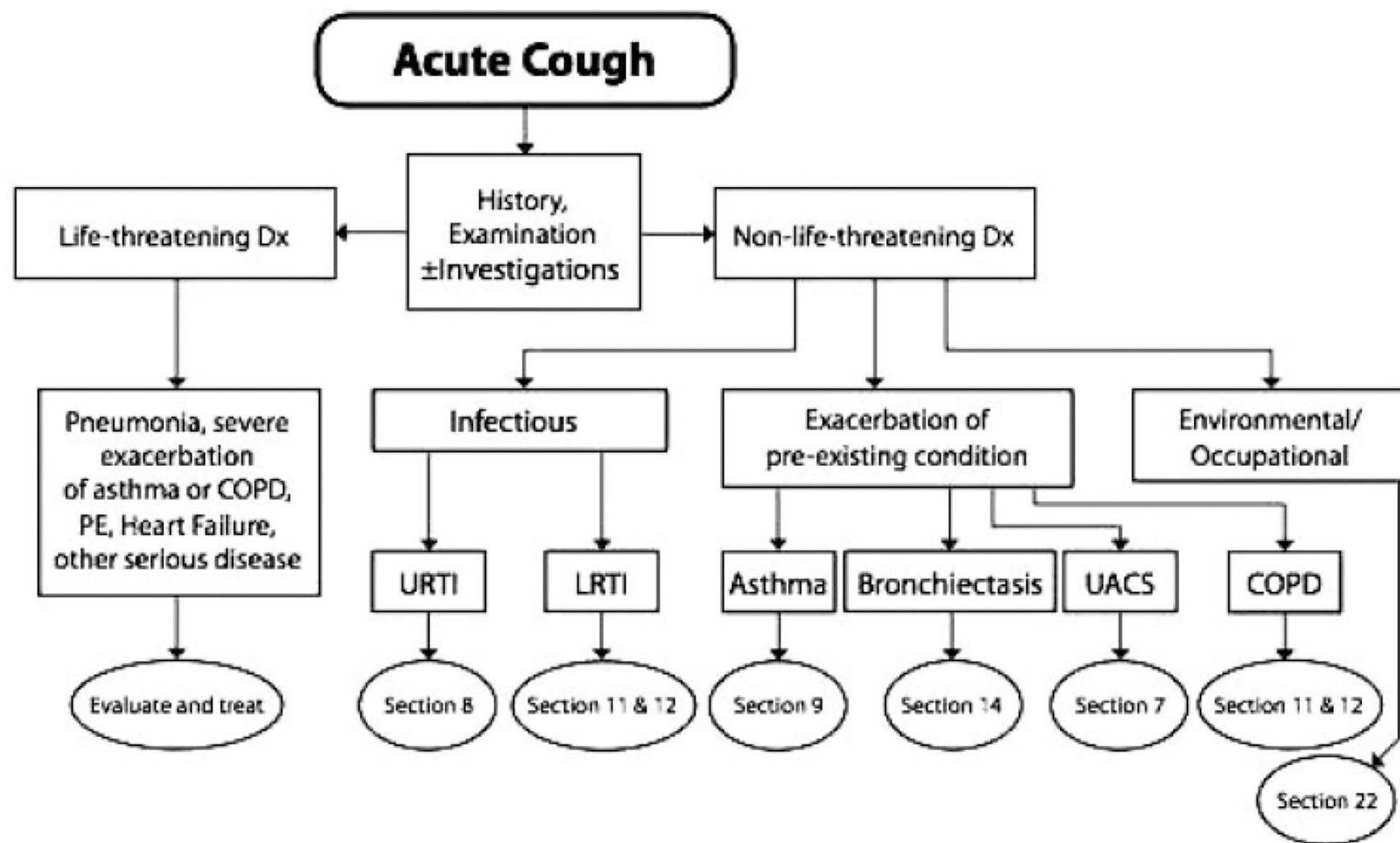
**TOSSE CRONICA:** durata > 8 settimane.

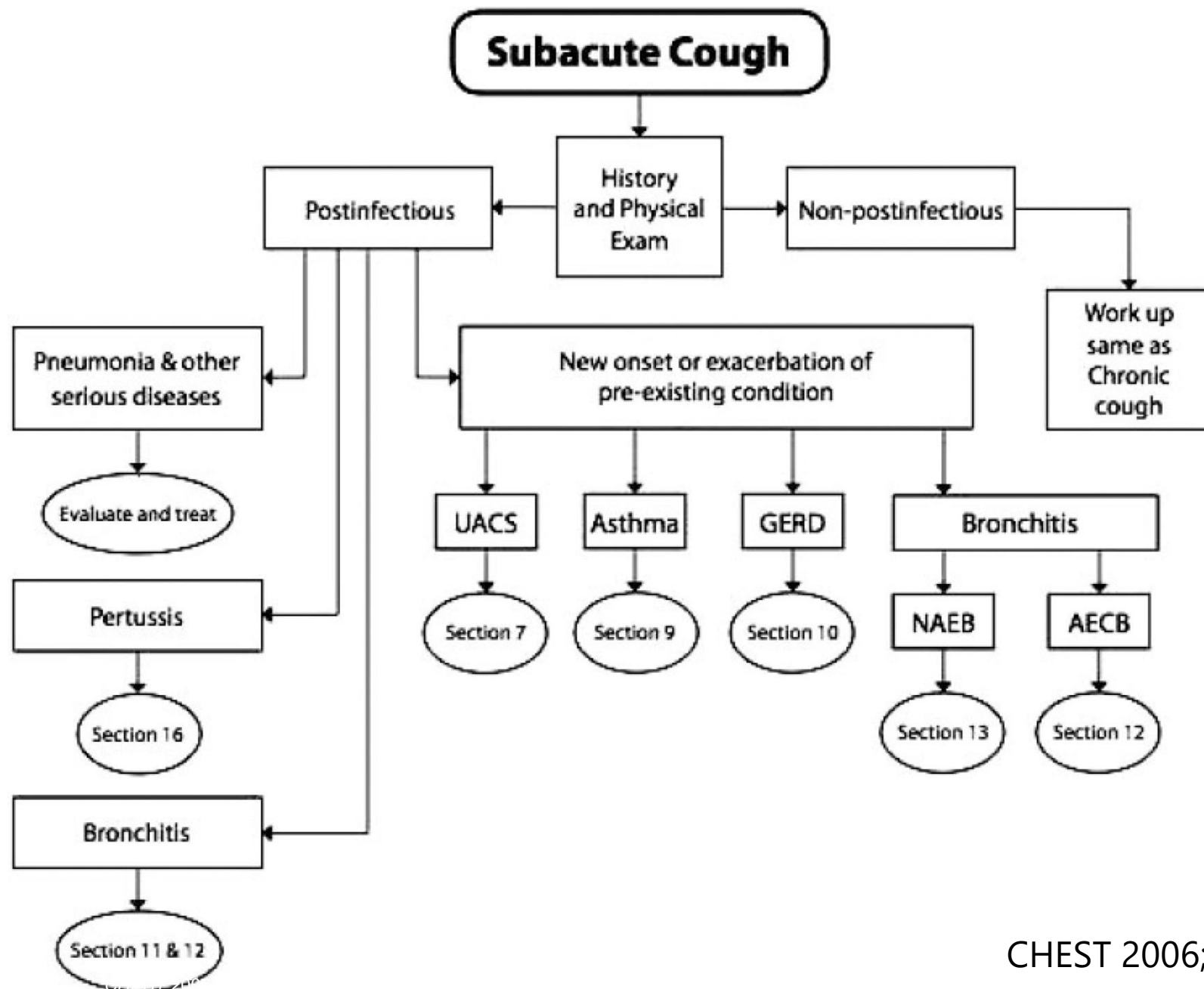
ERJ **2007**; 29: 1256 e **2019**; DOI:10.1183/13993003,0136-2019

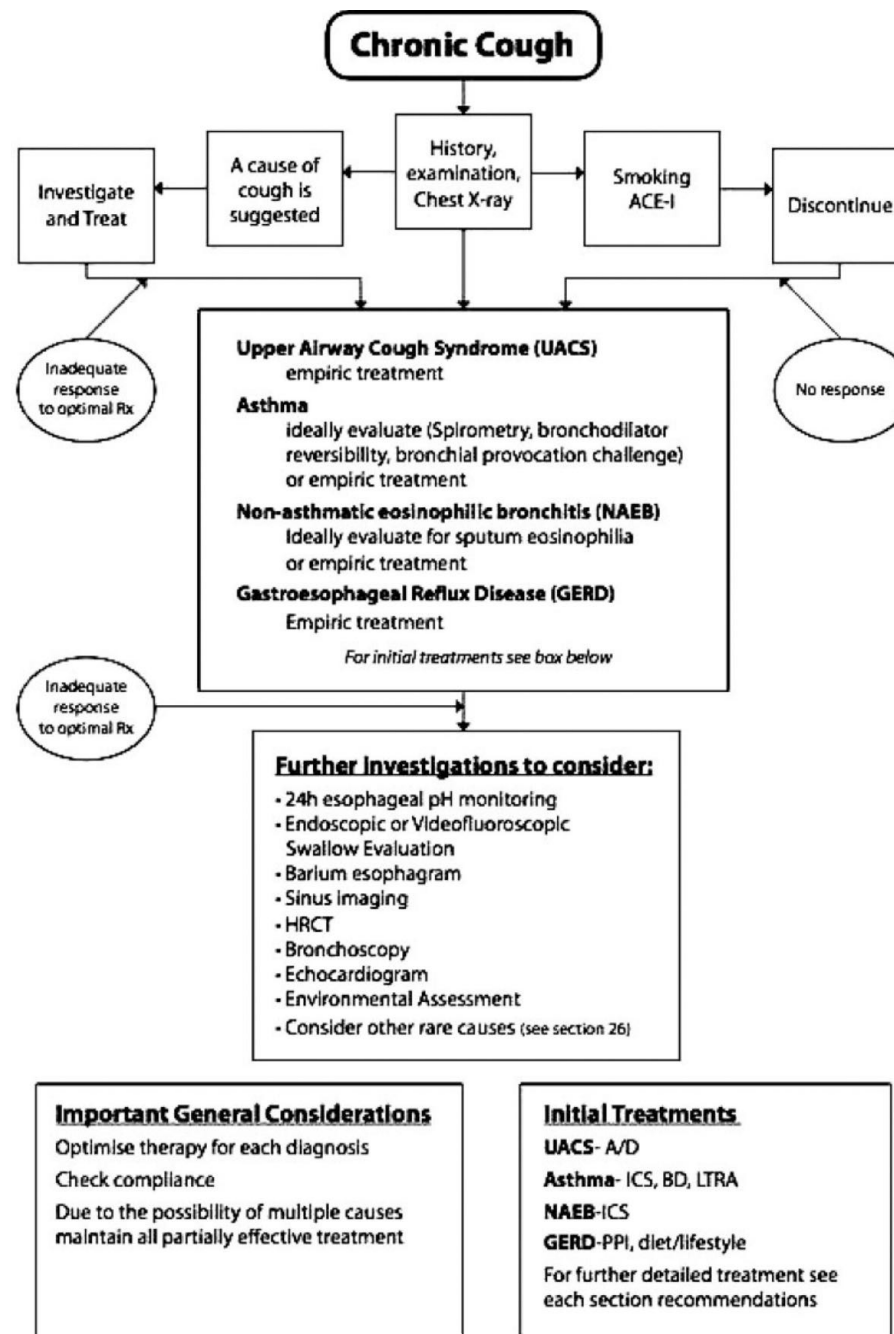
Med J Aust 2010; 192: 265

CHEST 2006; 129: 1S e successivo aggiornamento  
<https://doi.org/10,1016/j.chest.2017.10.016>)

Chin Med J 2011; 124: 3207







# TOSSE CRONICA

Anni '60: sintomo di patologia respiratoria cronica infettiva o di bronchite (Ann Intern Med 1956; 45: 216);

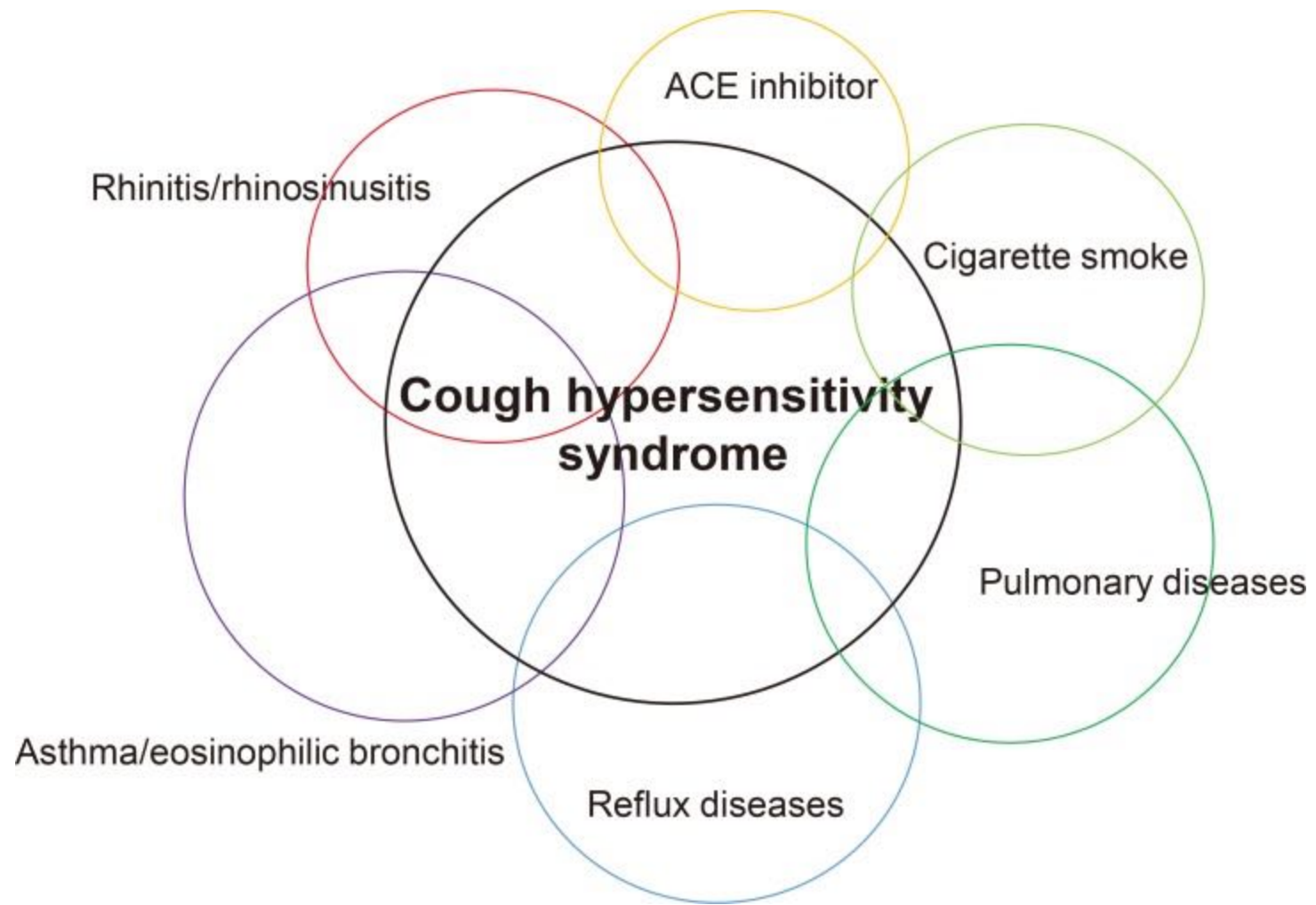
1977: Sintomo della TRIADE:

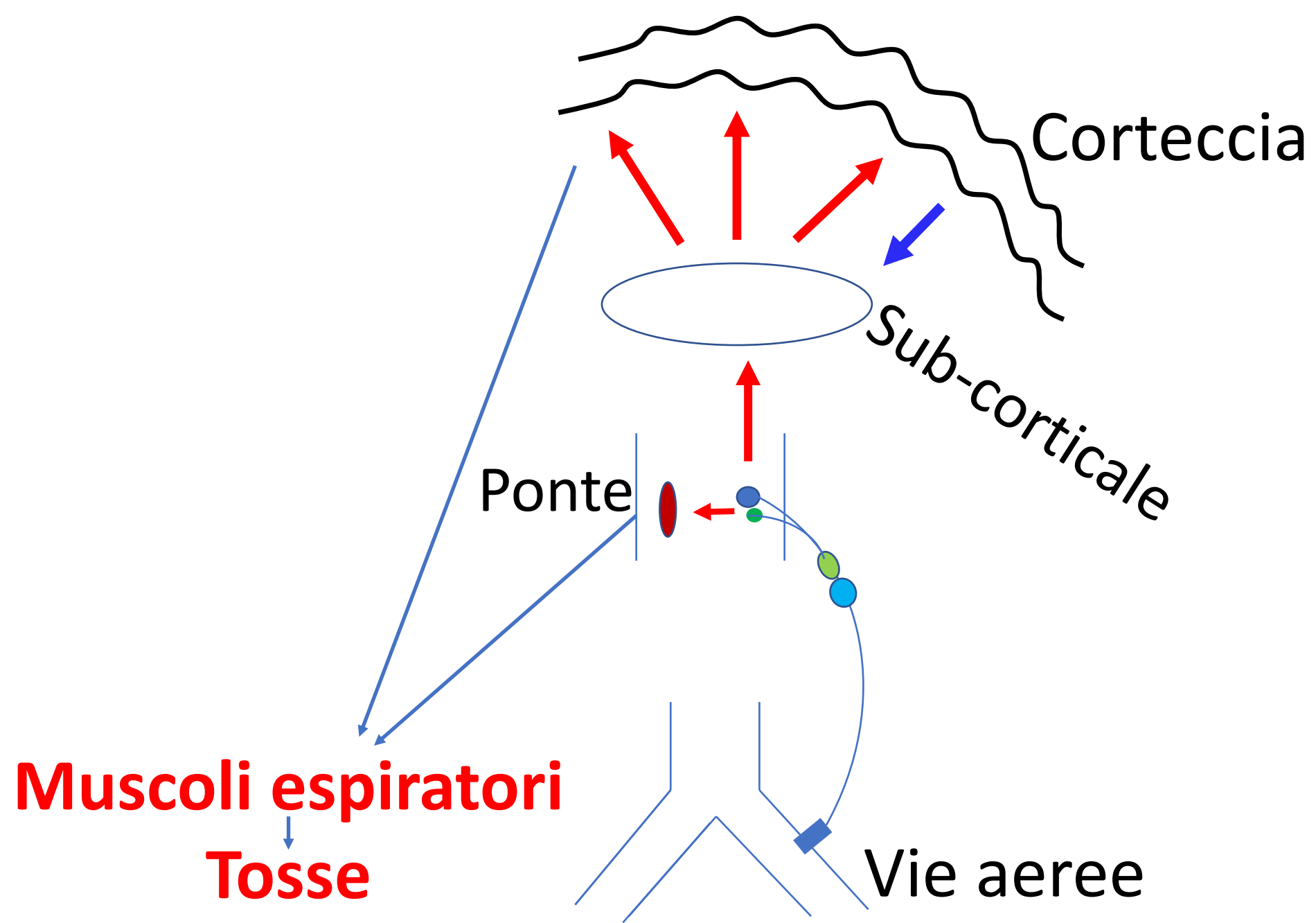
1. RINITE (*postnasal drip*/sindrome della tosse delle alte vie aeree);
2. INFIAMMAZIONE EOSINOFILA DELLE VIE AEREE (asma e bronchite eosinofila);
3. MALATTIA DA REFLUSSO GASTROESOFAGEO (GERD) (Arch Intern Med 1977; 137: 1186).

2006: Linee Guida ACCP.

2008: Nuova definizione: **SINDROME DA IPERSENSIBILITA' O IPERREATTIVITA' ALLA TOSSE.**

Motivazione: nel 12-42% dei pazienti la tosse non è spiegata dalla triade (Lung 2008; 186 Suppl 1: S78).





# SENSORI PERIFERICI: FIBRE C e FIBRE A ( $\delta$ e $\beta$ )

**Fibre C:** rispondono a stimolanti chimici (capsaicina, cinnamaldeide, isotiocianati, ozono, fumo di sigaretta, prostaglandine, prodotti di perossidazione, bradichinina), temperatura aria respirata, osmolarità e pH.

**Fibre A $\delta$  (RECETTORI DELLA TOSSE)** rispondono a stimoli meccanici e a basso pH solo in caso per rapida caduta.

Fibre A $\beta$  rispondono a alla distensione del polmone (RAR e SAR).

Interazioni positive tra fibre C e A $\delta$  e A $\beta$ .

# RECETTORI DELLE FIBRE C

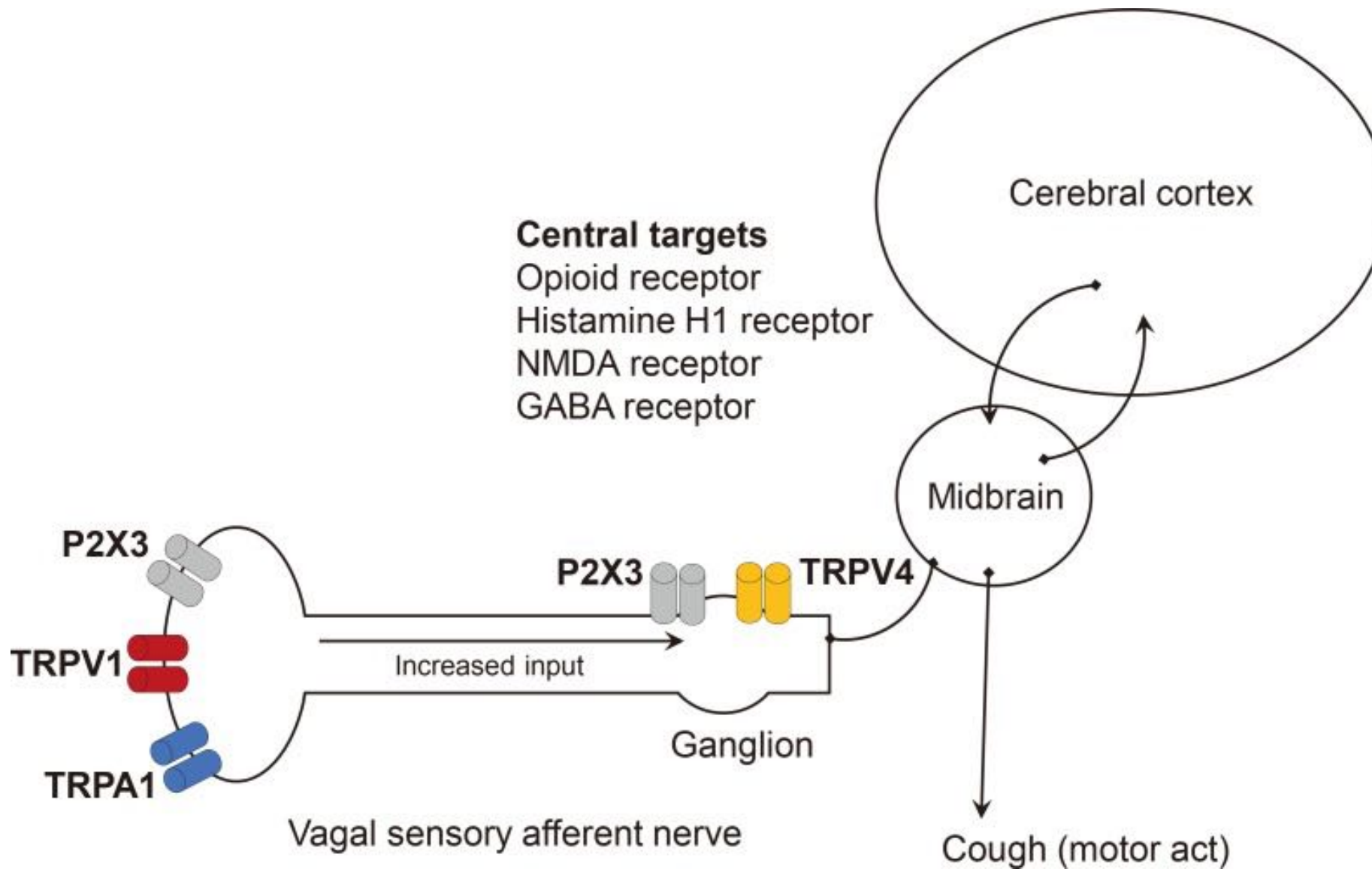
## 1. RECETTORI IONOTROPICI:

- A. RECETTORE DELLA NICOTINA
- B. RECETTORE SEROTONINERGICO PER 5 HT-3
- C. RECETTORI PURINERGICI P2X
- D. TRANSIENT RECEPTOR POTENTIAL:
  - I. TRPV1
  - II. TRPA1
  - III. TRPM8
- E. CANALI ACIDI

## 2.RECETTORI METABOTROPICI

- A. BRADICHININA
- B. ISTAMINA
- C. 5HT
- D. ADENOSINA
- E. RECETTORI ATTIVATI DALLE PROTEASI
- F. EICOSANOIDI

## 3.RECETTORI DEI CANALI DEL Na<sup>+</sup> VOLTAGGIO DIPENDENTI E POTENZIALI D'AZIONE (NaVs)



Recettore NMDA (N-Metil-D-Aspartato)  
 Recettore GABA (Acido Gamma-Amino-Butirrico)

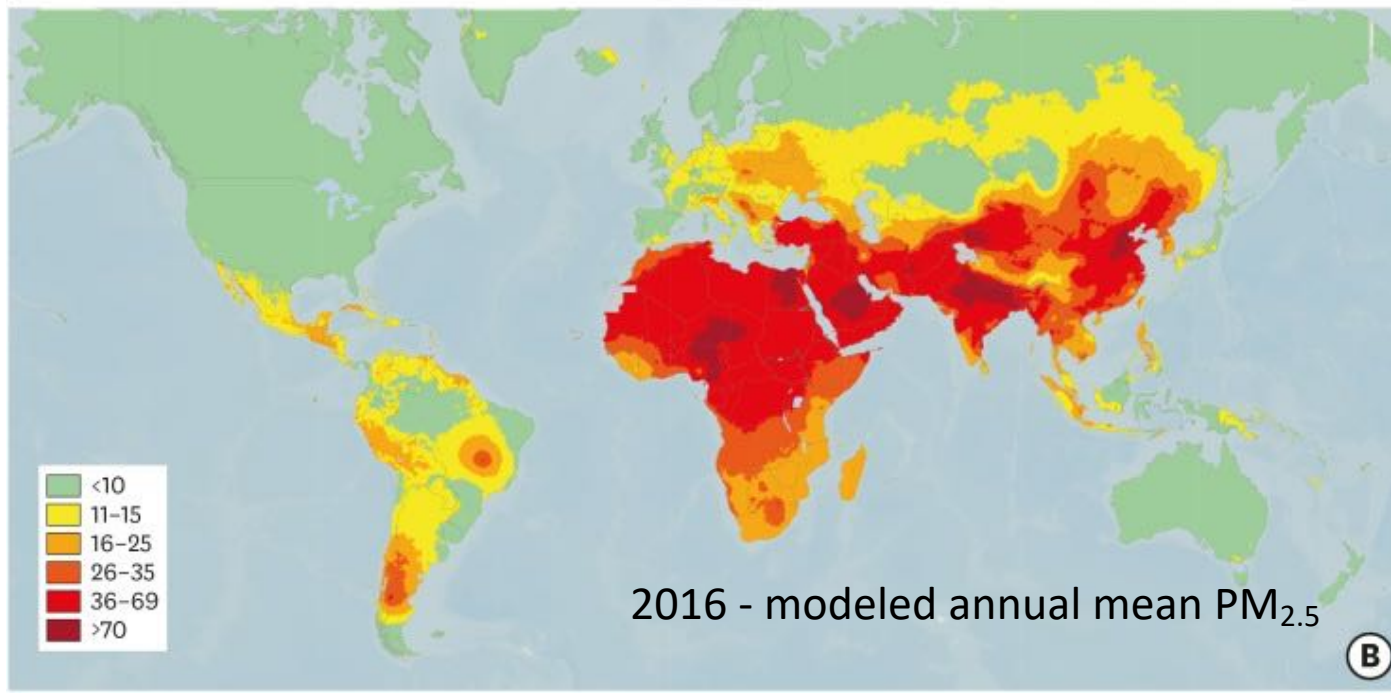
# **The complications of cough appear to stem from physiologic events**

The magnitude of pressures, velocities, and energy that is generated during vigorous coughing allow coughing to be an effective means of clearing the airways of excessive secretions and foreign material, and providing cardiopulmonary resuscitation; however, they can also cause a variety of profound physical and psychosocial complications.

The adverse occurrences include cardiovascular, constitutional, GI, genitourinary, musculoskeletal, neurologic, ophthalmologic, psychosocial, respiratory, and skin complications, and a decrease in health-related quality of life.

Knowledge of the spectrum of complications should enable clinicians to appreciate (1) the impact of cough on patients, (2) why it is imperative to exhaust all possible diagnostic and therapeutic options to eliminate cough, and (3) why it is inappropriate to minimize a patient's complaint of cough and/or advise him/her to "live with it."

(CHEST 2006; 129:54S–58S)



## **TOSSE CRONICA ED ESPOSIZIONE CONTINUATIVA AD INQUINANTI ATMOSFERICI**

STUDI TRASVERSALI: tosse cronica in soggetti esposti a polveri professionali (Int Arch Occup Environ Health 1990; 62:311) o metalli (Occup Environ Med 2019; 76: 222);

STUDI LONGITUDINALI: bronchite cronica e tosse per aumenti di PM<sub>10</sub> (Environ Health Perspect 2018; 126: 027005); riduzione della tosse con riduzione del PM<sub>10</sub> (AJRCCM 2009; 179: 579).

## **TOSSE CRONICA ED ESPOSIZIONE AD ALTI LIVELLI DI INQUINANTI ATMOSFERICI**

WTC 2001: tosse nei pompieri (29%) con persistenza a distanza di 3-4 anni (22%) (CHEST 2011; 140: 1146);

Terremoto di Taiwan del 2016: tosse nei pompieri (23%) fino a 3 settimane dopo (Occup Environ Med 2018; 75: 639).

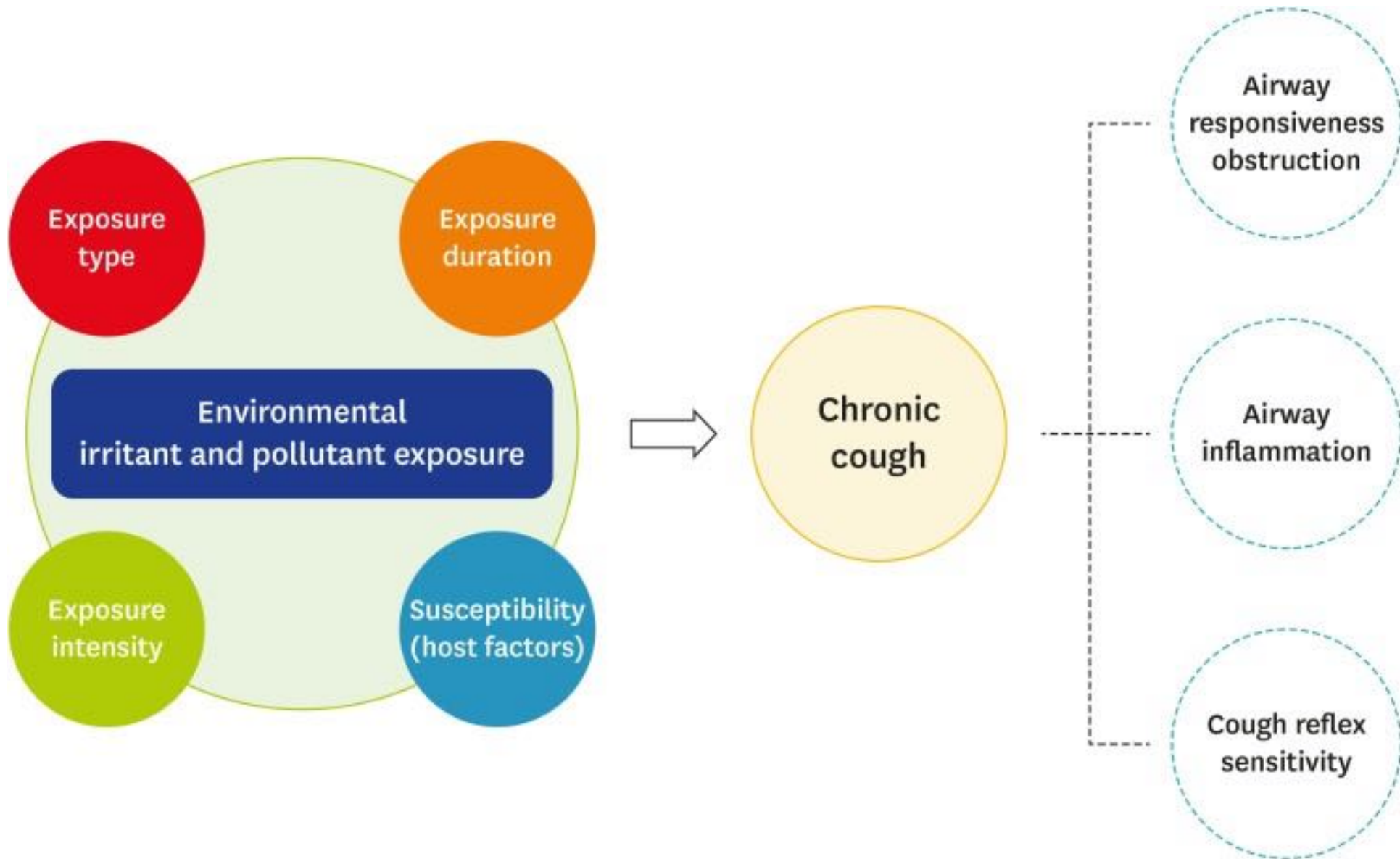
# **ESPOSIZIONE AD INQUINANTI AMBIENTALI E TOSSE CRONICA NELL'INFANZIA**

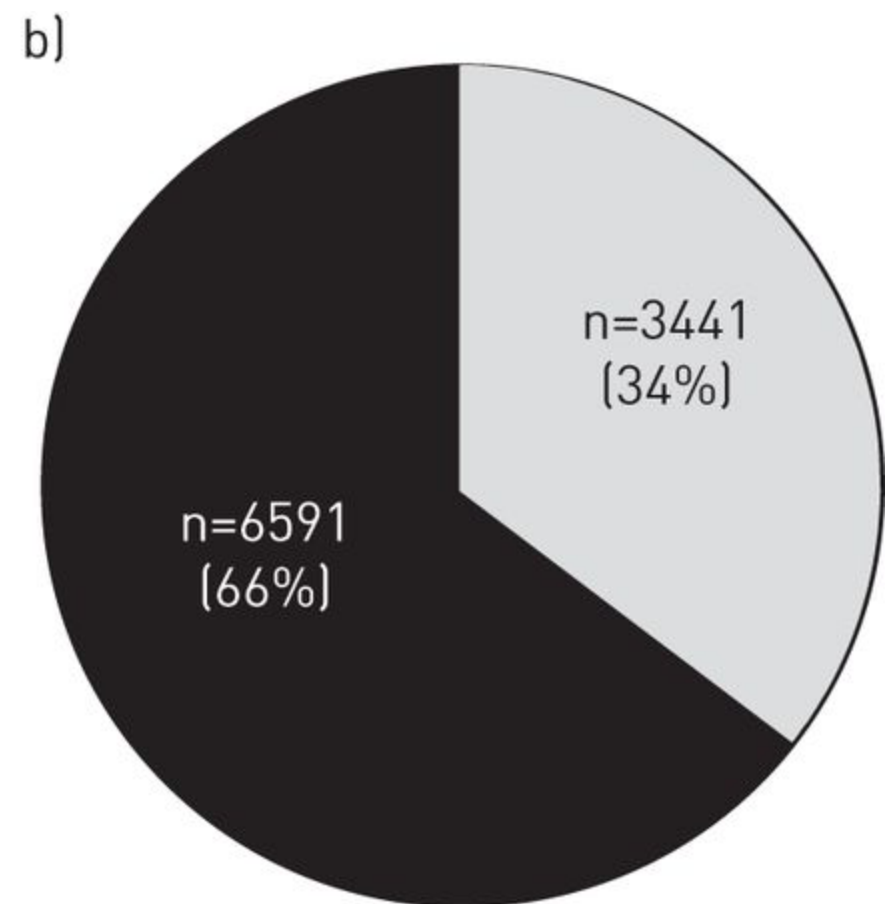
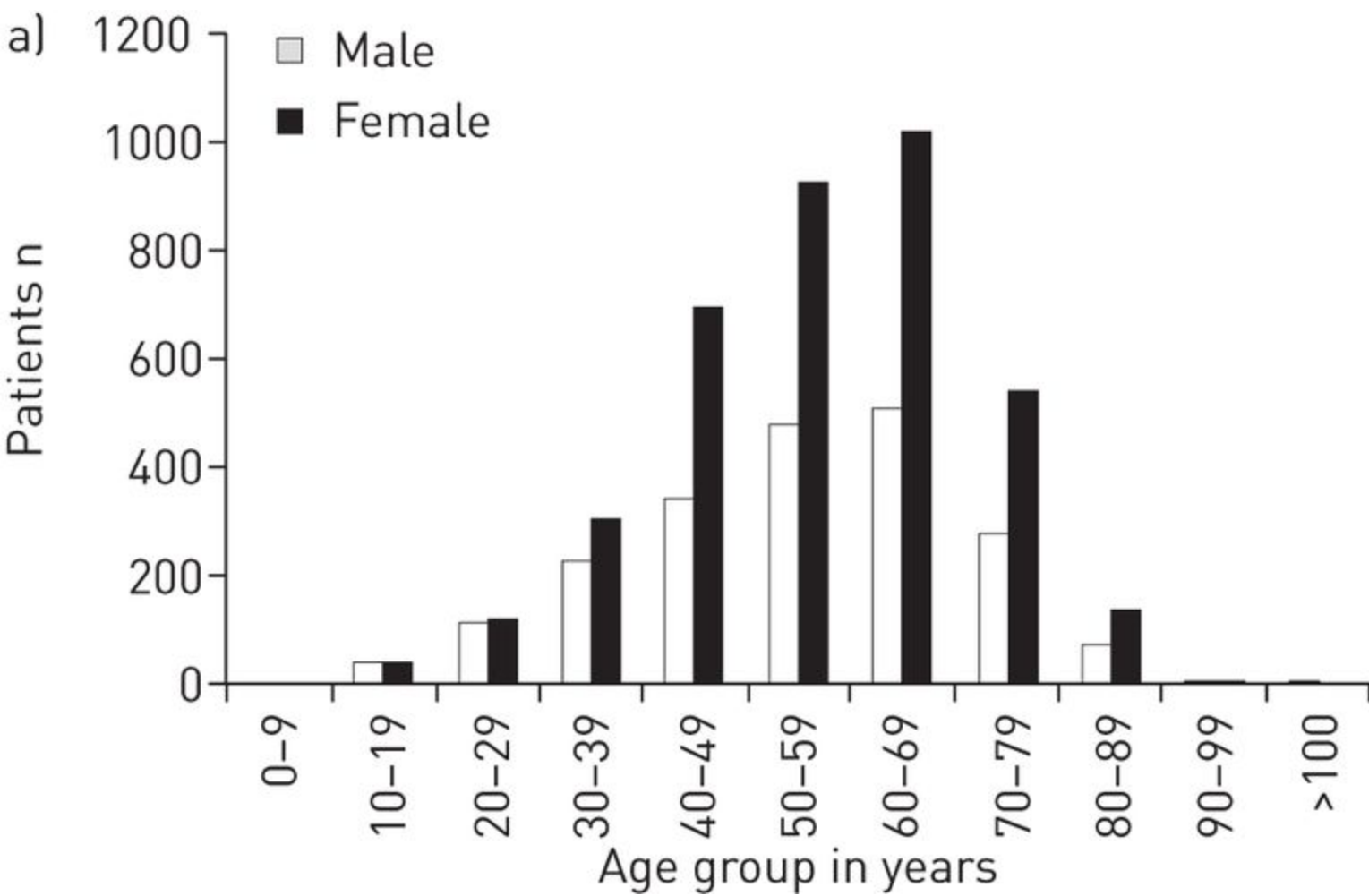
Esposizione ad inquinanti del traffico stradale correlata a tosse cronica all'età di 1 anno di età in 756 bambini tedeschi (ERJ 2002; 19: 690);

Particolati totali, SO<sub>2</sub> e NO<sub>2</sub> positivamente associati ad aumento del rischio per tosse secca in 21-28% su una popolazione di bambini cinesi (Respir Med 2010; 104: 1903);

Aumento della tosse del 4.7% per aumento mensile di PM<sub>10</sub> di 10 mcg/m<sup>3</sup> su una popolazione di 9881 adolescenti di Hong Kong (Int Environ Health Res 201; 20: 219);

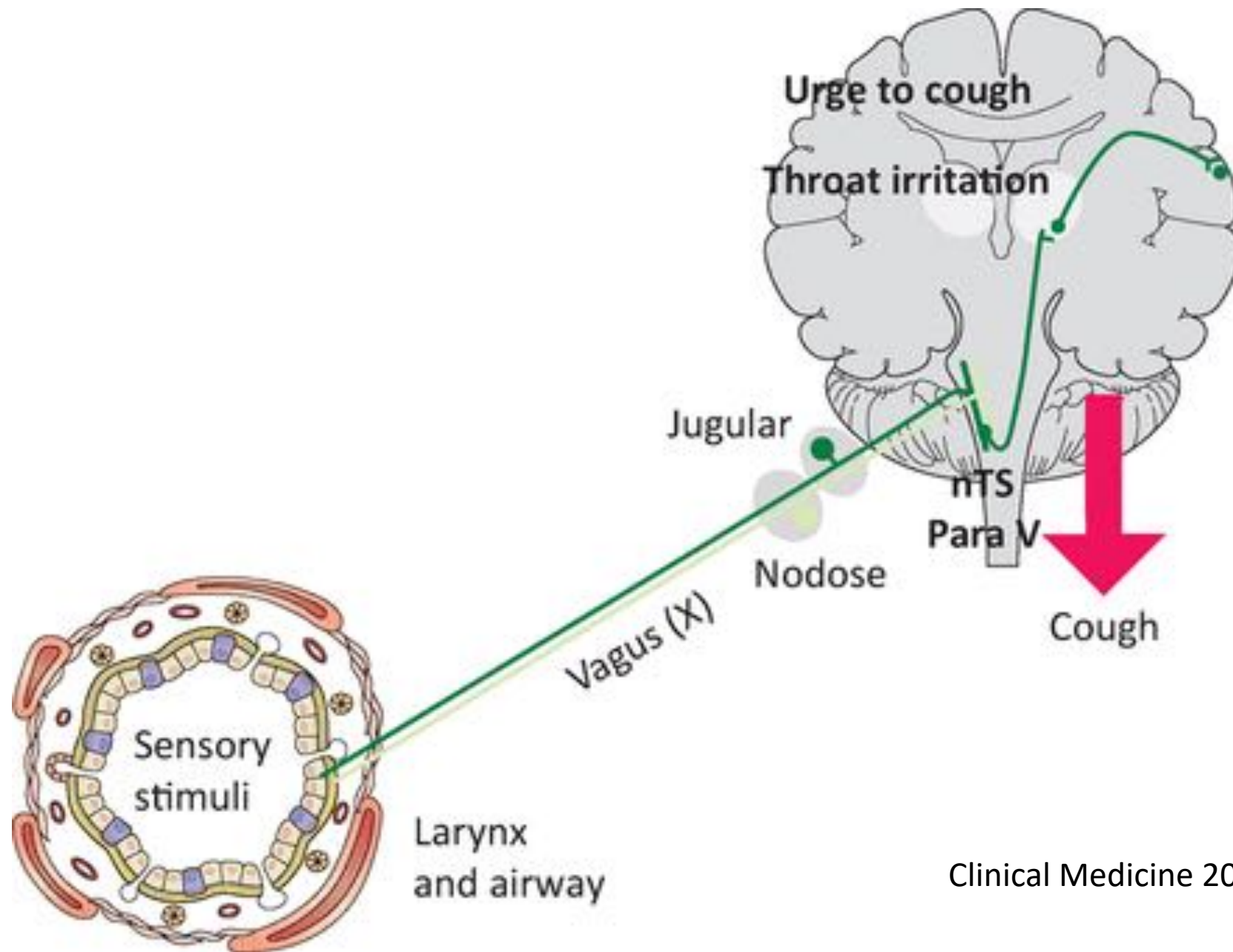
Esposizione a fumo passivo prima dei 18 anni in 35.000 bambini di Singapore associata a tosse cronica (OR 2.1) (Thorax 2005; 60: 1052).

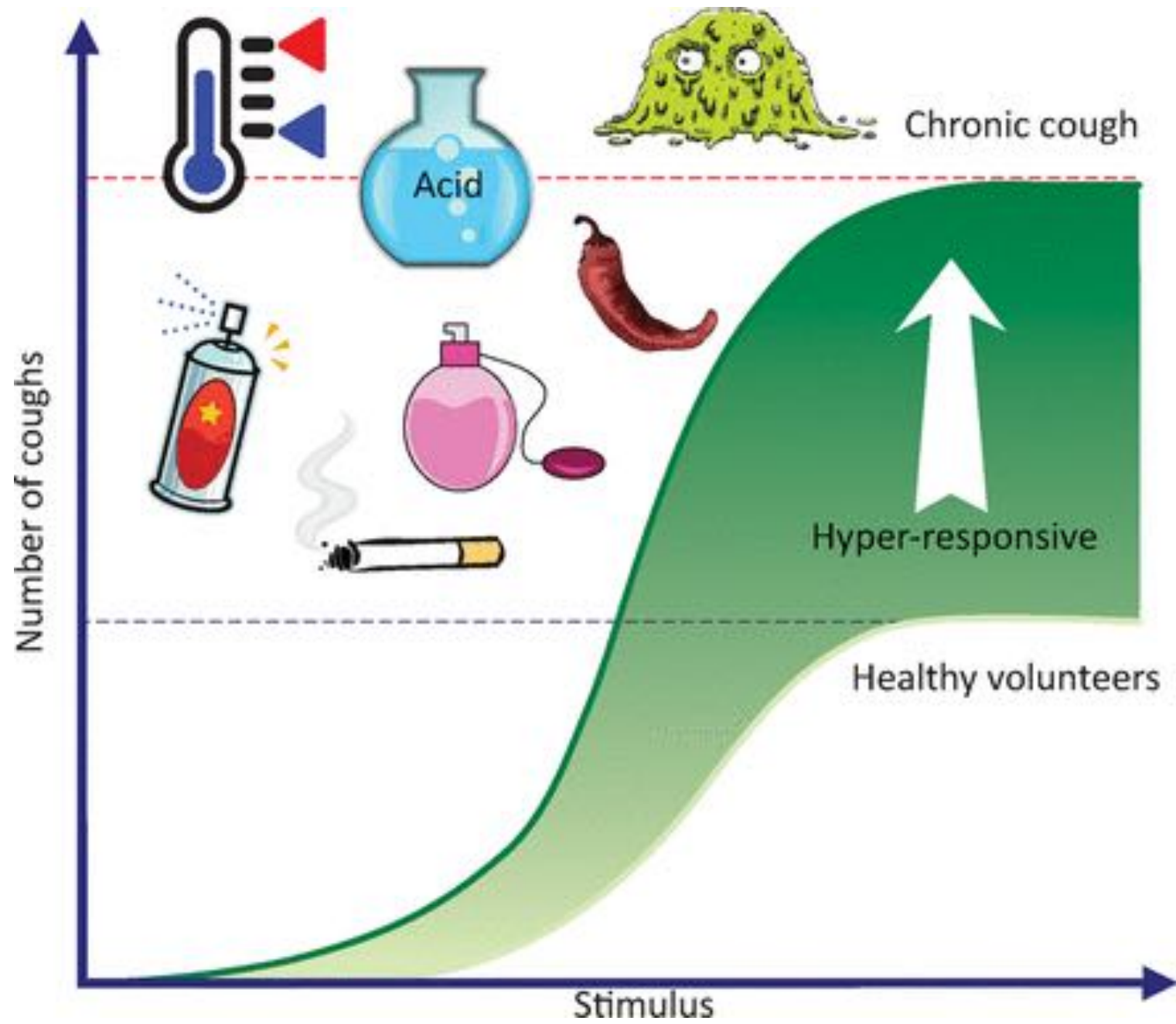


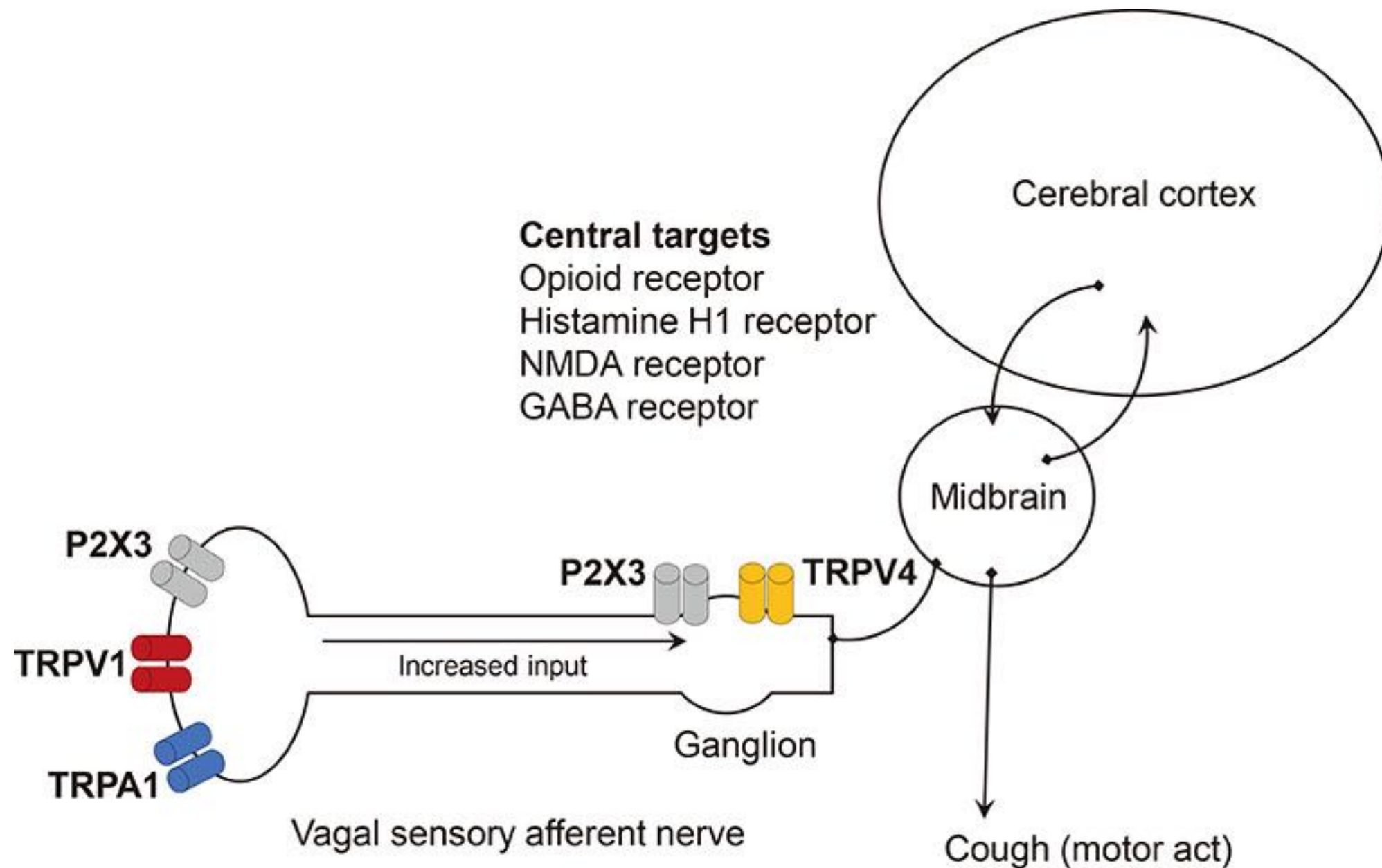


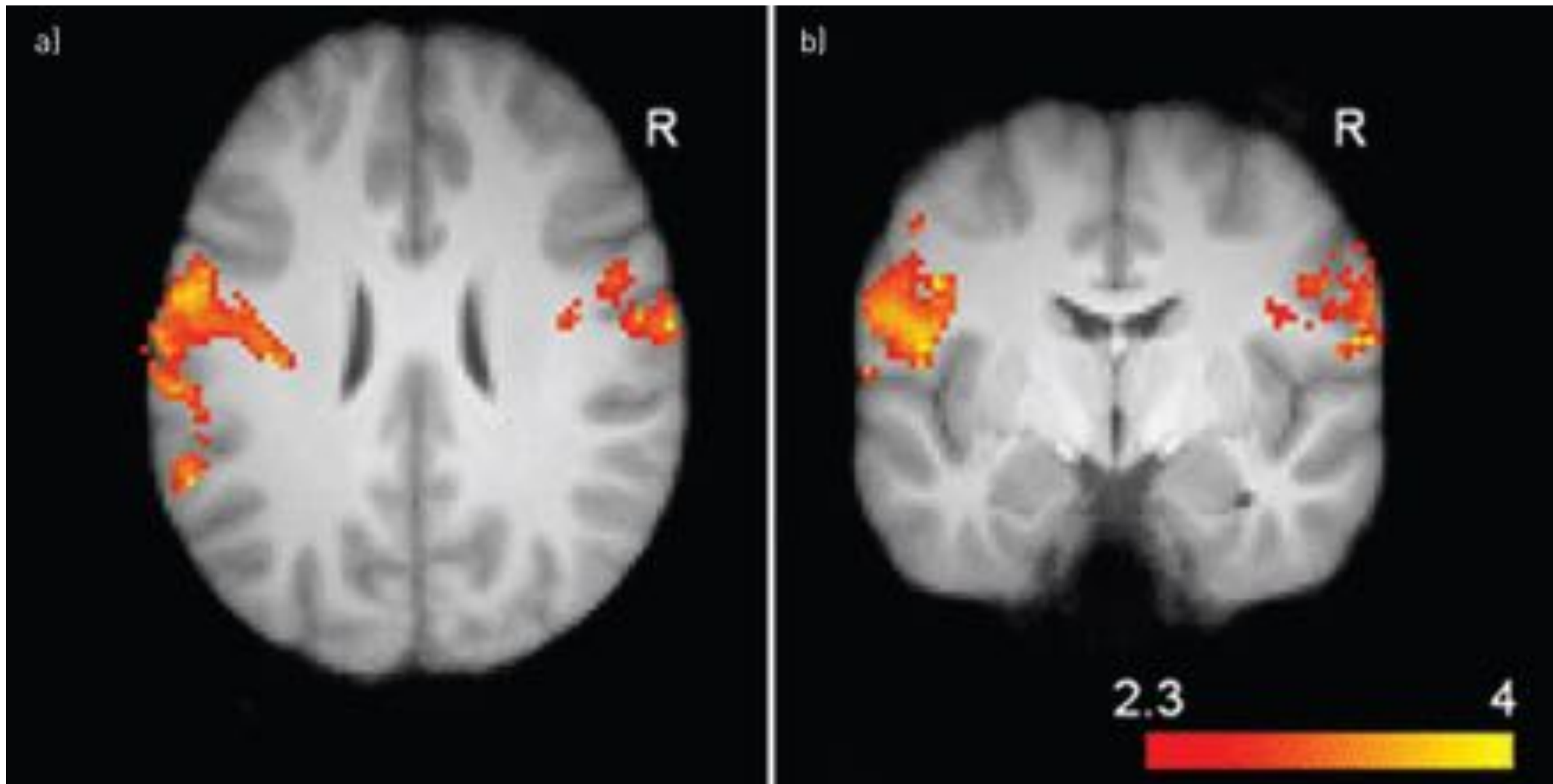
# TOSSE CRONICA: CAUSE

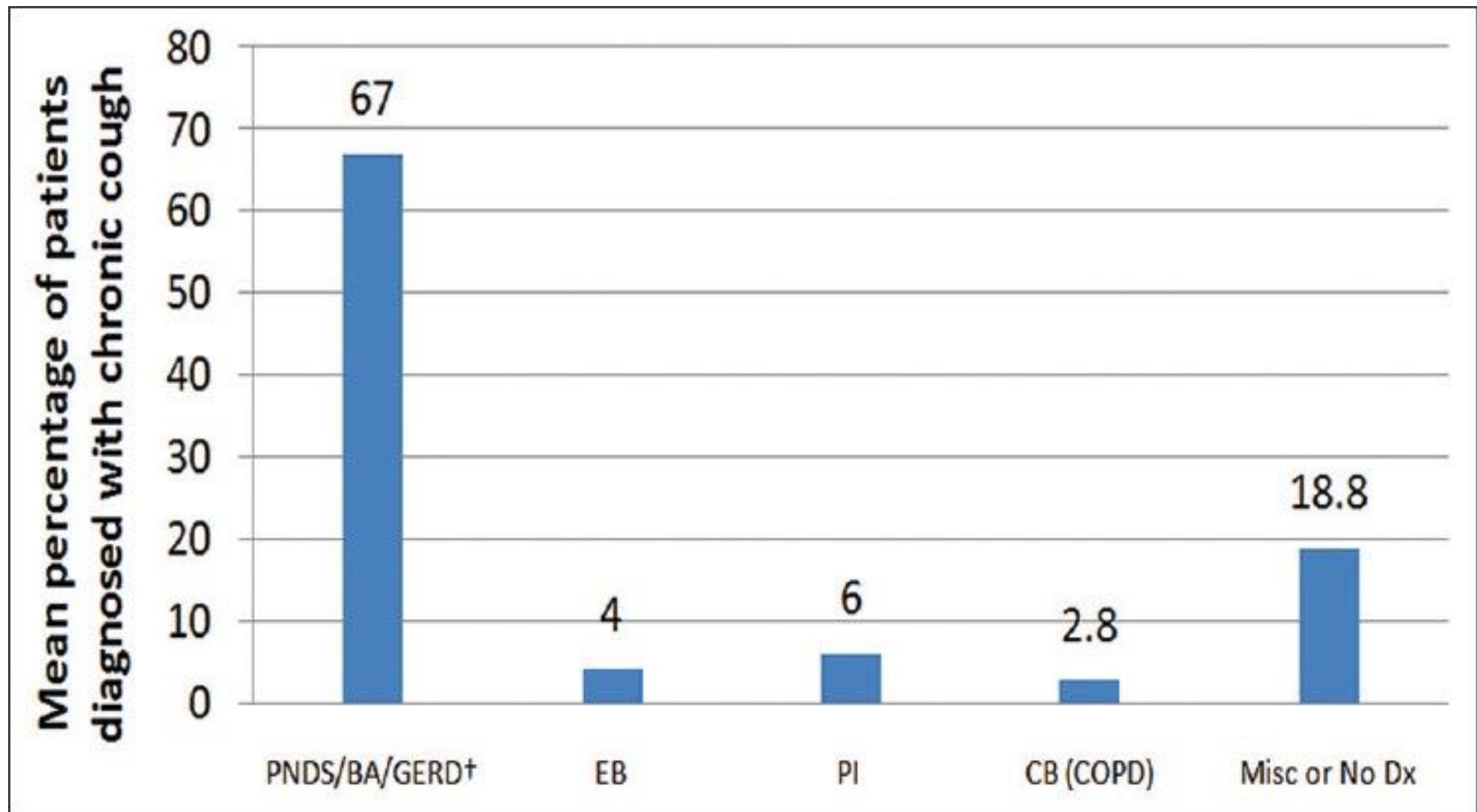
1. FARMACI (ACE-inibitori, betabloccanti, methotrexate)
2. Malattie cardiovascolari (Edema polmonare, TEP)
3. MRGE
4. Aspirazione corpi estranei
5. UPPER AIRWAY COUGH SYNDROME
6. Malattie apparato respiratorio (neoplasie, m. restrittive, m. ostruttive, bronchite eosinofila, m. infettive)
7. Inalazione gas irritanti (Fumo di sigaretta, inquinanti ambientali/professionali, smog)
8. Infezioni
  - a. VIRUS (adenovirus, coronavirus, parainfluenza; virus influenzale A e B; Virus sinciziale)
  - b. BATTERI (bordetella pertussis; mycoplasma, clamidia, legionella streptococco, hemophylus e moraxella, micobatterio, anaerobi, pseudomonas)
  - c. PARASSITI (ascari, anchilostoma e strongyloides per eosinofilie polmonari da parassiti; schistosoma, toxocara)
  - d. PROTOZOI (Leishmania)
  - e. FUNGHI (aspergillus, blastomiceti, criptococco, hystoplasma, paracoccidioides e pneumocystis jiroveci)

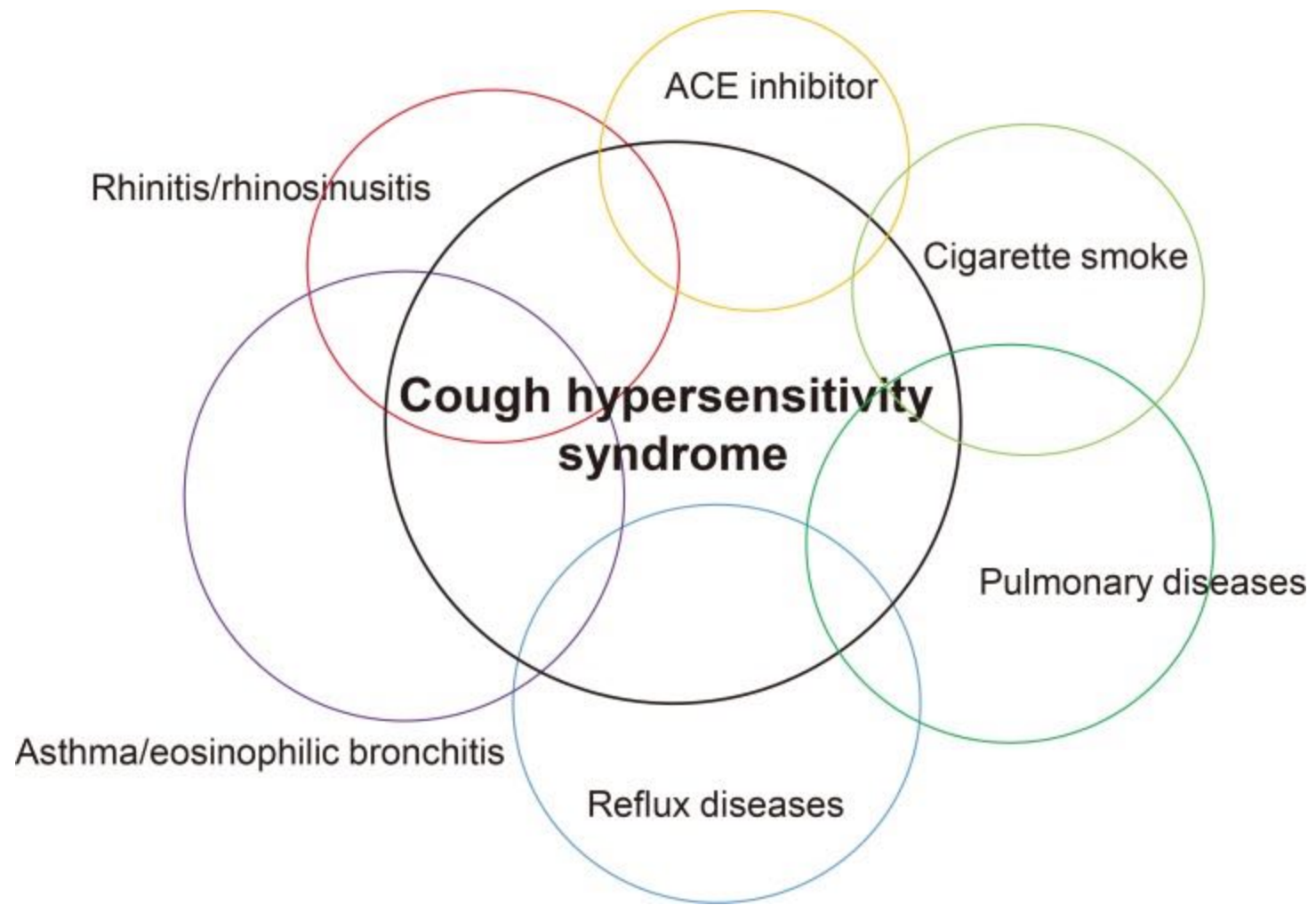












# DATI ANAMNESTICI

- ✓ STORIA DI FUMO DI SIGARETTE, ABITAZIONE, PROFESSIONE, ETA', SESSO, BMI;
- ✓ PREGRESSE MALATTIE (GERD, ASMA, COPD, RINOSINUSITE CRONICA);
- ✓ ANAMNESI FARMACOLOGICA;
- ✓ SINTOMI: TEMPO DI INSORGENZA E SINCRONIA CON ALTRE PATOLOGIE o FARMACI; SUCCESSIVO ANDAMENTO CLINICO; STAGIONALITA' DEL SINTOMO; DISTRIBUZIONE DEL SINTOMO NELLA ARCO DELLE 24 ORE; **IPERTUSSIA; ALLOTUSSIA** PER ELOQUIO, ODORI/PROFUMI, VARIAZIONI DI TEMPERATURA DELL'ARIA RESPIRATA; BOLO FARINGEO; RAPPORTI CON I PASTI E CON LA POSTURA SUPINA; SINTOMI RESPIRATORI ASSOCIATI (DISPNEA, CATARRO, FEBBRE, EMOFTOE, VOCE RAUCA, DISFONIA, POLMONITI RICORRENTI).

# **SCELTA DELLE INDAGINI DIAGNOSTICHE**

1. APPARATO RESPIRATORIO: IMAGING (RX. TORACE/TAC TORACE), TEST DI FUNZIONALITA' RESPIRATORIA COMPLETI (MANOVRE INSPIRATORIE ED ESPIRATORIE FORZATE)+DLCO, TEST ALLA METACOLINA/BETA2, TEST ALLERGOLOGICI, TEST EMATICI PER IPEREOSINOFILIA (>300/ml)/IgE totali, FENO; QUANTIFERON, BRONCOSCOPIA, POLISONNOGRAFIA, ALTRI.
2. APPARATO ORL: LARINGOSCOPIA A FIBRE OTTICHE/TAC MASSICCIO FACCIALE.
3. APPARATO GASTROENTERICO: GASTROSCOPIA/Ph-IMPEDENZIOMETRIA
4. CONSULENZA PSICHIATRICA.

# Cough Measurement tools and related outcomes

Category	Tools and outcomes
Subjective	
Cough-related quality of life	Leicester Cough Questionnaire, Cough-specific Quality-of-Life Questionnaire
Cough severity	Visual analog scale
Objective	
Cough frequency	Leicester Cough Monitor, Hull Automated Cough Counter, VitaloJAK
Cough reflex sensitivity	Tussigen inhalation challenge test (using capsaicin, citric acid, or ATP)/urge-to-cough, C2, C5, maximal cough responses evoked by any tussigen concentration (Emax)

Questionari tosse cronica	Score di base e dopo trattamenti		
	Basale		
	....../.. /.....	....../.. /.....	....../.. /.....
Ipersensibilità alla tosse (Questionario di <b>HULL</b> ) (0-70) *			
Gravità della tosse ( <b>CSI</b> ) (0-40) *			
QoL nella tosse (Questionario di Leicester, <b>LCQ</b> ) (19-133) **			
TOTALE			
1. Dominio fisico			
2. Dominio psicologico			
3. Dominio sociale			
Ipersensibilità laringea ** (Questionario di <b>Newcastle</b> ) (7-98)			
TOTALE			
1. Ostruzione			
2. Irritazione			
3. Allotussia			

\* valori normali bassi; \*\* valori normali alti

Nel corso dell'ultimo mese, quanto disturbo le hanno causato i seguenti problemi ?						
0 = nessun problema e 5 = problema grave/frequente						
Voce rauca o altri problemi alla voce	0	1	2	3	4	5
Bisogno di schiarirsi la voce	0	1	2	3	4	5
Sensazione di qualcosa che scola posteriormente dal naso o sulla parte posteriore della gola	0	1	2	3	4	5
Vomito o conati di vomito durante tosse	0	1	2	3	4	5
Tosse all'atto di sdraiarsi o di piegarsi in avanti	0	1	2	3	4	5
Senso di oppressione toracica o sibili/fischietti respiratori durante tosse	0	1	2	3	4	5
Bruciore o acidità di stomaco, digestione lenta, rigurgito acido dallo stomaco (se assume farmaci per uno di questi problemi segnare 5)	0	1	2	3	4	5
Sensazione di prurito o di nodo in gola	0	1	2	3	4	5
Tosse durante o subito dopo i pasti	0	1	2	3	4	5
Tosse con l'assunzione di certi alimenti	0	1	2	3	4	5
Tosse al momento di alzarsi dal letto al mattino	0	1	2	3	4	5
Tosse scatenata dall'atto di cantare o di parlare (per esempio al telefono)	0	1	2	3	4	5
Tossire di più da svegli che durante il sonno	0	1	2	3	4	5
Sensazione di uno strano sapore in bocca	0	1	2	3	4	5

# Questionario di HULL

Nome e cognome:

Data di nascita:\_\_\_\_\_

DATA DEL TEST:

Fare un cerchietto intorno alla risposta più appropriate

PUNTEGGIO TOTALE\_\_\_\_\_ /70

## **ITER TERAPEUTICO PRATICO:**

TRATTAMENTO DELLA PATOLOGIA DI BASE CAUSA DELLA TOSSE CRONICA.

### **ITER TERAPEUTICO PRATICO PER LA SINDROME DA IPERSENSIBILITA' ALLA TOSSE**

1. INIZIARE CON SEDATIVI DELLA TOSSE (destrometorfano [Bronchenolo sciroppo 1 cucchiaino x 3-4\*]) + ANTIISTAMINICI 1<sup>a</sup> GENERAZIONE (Actifed soluzione 5/10 ml x 3-4);
2. TRATTAMENTO LOGOPEDICO
3. FARMACI NEUROMODULATORI

# Speech pathology treatment for chronic refractory cough (1/2)

## Education

Cough can be triggered by irritation

Cough is not always necessary

Cough has limited physiological benefit in this condition

Cough is under automatic and voluntary control

## Symptom control techniques

Cough suppression swallow

Cough control breathing

Paradoxical vocal fold movement release breathing

Release of laryngeal constriction

# Speech pathology treatment for chronic refractory cough (2/2)

## **Reducing laryngeal irritation**

- Behavioral management of reflux

- Reduce phonotraumatic behaviors

- Hydration

- Minimize exposure to irritating substances

## **Psychoeducational counseling**

- Treatment is hard work

- Setting realistic goals

Eleven RCTs and five systematic reviews were included. The 11 RCTs reported data on 570 participants with chronic cough who received a variety of interventions. Study quality was high in 10 RCTs. The studies used an assortment of descriptors and assessments to identify UCC. Although gabapentin and morphine exhibited positive effects on cough-related quality of life, only **gabapentin** was supported as a treatment recommendation. Studies of inhaled corticosteroids (ICS) were affected by intervention fidelity bias; when this factor was addressed, ICS were found to be ineffective for UCC. Esomeprazole was ineffective for UCC without features of gastroesophageal acid reflux. Studies addressing nonacid gastroesophageal reflux disease were not identified. A **multimodality speech pathology intervention** improved cough severity.

**Question 6: Which cough neuromodulatory agents (pregabalin, gabapentin, tricyclics and opiates) should be used to treat patients with chronic cough?**

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

We suggest a trial of **gabapentin** or **pregabalin** in adults with chronic refractory cough (conditional recommendation, low quality evidence).

### **Amitriptyline**

Amitriptyline is a tricyclic antidepressant and inhibitor of serotonin reuptake that has been successfully used in the treatment of sensory and laryngeal neuropathic cough.

STUDY #1. Primary outcomes were patient self-report percent reduction in cough frequency and severity, and CQLQ. Improved CQLQ scores were associated with amitriptyline (calculated<sup>^</sup> mean (SD) change in score from baseline was 24.5 (5.0) compared to mean (SD) change in score from baseline of 2.9 (3.8) for placebo.

### **Gabapentin**

Gabapentin acts by blocking a subset of central voltage-gated calcium channels and has recently been recommended as a treatment option for refractory CC by the CHEST Guideline and Expert Panel Report

STUDY #1. The primary efficacy outcome was cough quality of life measured by the LCQ. The change in LCQ score from baseline was mean (SD) 2.5 (3.1) for gabapentin and 1.1 (4.1) for placebo,  $p = 0.004$ . Significantly more participants in the gabapentin group who had remained in the study at week 8 had a clinical improvement in LCQ score of greater than 1.3 (the smallest change in score regarded as clinically meaningful) than did those in the placebo group (20 [76.9%] of 26 vs. 12 [46.2%] of 27;  $p = 0.038$ ). After withdrawal of the gabapentin, there was reduced effectiveness further supporting its antitussive effect.

### **Pregabalin**

Pregabalin has a similar structure to gabapentin. It acts on central nervous system calcium channels, leading to decreased release of neurotransmitters such as glutamate, noradrenaline, and substance P.

STUDY #1 The change in LCQ score from baseline for the PREG + SPT group was mean (SD) 6.6 (4.5) compared to the change in LCQ score from baseline for the PLAC + SPT group, mean (SD) 3.3 (2.3),  $p = 0.024$  [meta-analysis]. Importantly there was a sustained effect from the treatment after cessation of the pregabalin.

## ***Morphine***

In a placebo-controlled randomized crossover study, Morice et al. [[88](#)] investigated the treatment of refractory CC with the opiate morphine sulfate compared to placebo. The study demonstrated a favorable benefit of morphine, mean (SD) change in LCQ score from baseline of 3.2 (2.6) over placebo, mean (SD) change in LCQ score from baseline of 1.2 (2.6),  $p = 0.02$ .

## ***Tramadol***

Tramadol is a centrally acting analgesic structurally related to codeine and morphine. Tramadol has two enantiomers, both of which contribute to analgesic activity via different mechanisms. To date, there are no RCTs on the use of tramadol for neurogenic or refractory CC.

### *The TRPV1 receptor antagonist SB-705498*

**STUDY #1.** A significant improvement in C5 values with SB-705498 treatment was reported at 2 h ( $p = 0.005$ ) and borderline significant at 24 h ( $p = 0.026$ ) when compared to placebo treatment. Twenty-four hour objective cough frequency was not improved.

### *The P2X3 receptor antagonist AF-219*

**STUDY 1.** Daytime cough frequency fell from a mean (SD) of 37 (32) coughs/h to 11 (8) coughs/h after AF-219 treatment versus 65 (163) coughs/h to 44 (51) coughs/h after placebo,  $p = 0.0003$ .

**STUDY 2.** MK-7264 at a dose of 50 mg significantly reduced the Awake Cough Frequency outcome Mean  $\log_{10}$  (SD) -0.80 (0.11) compared to placebo Mean  $\log_{10}$  (SD) -0.40 (0.11),  $p = 0.0027$ .

### *The NK1 receptor antagonist Orvepitant*

**STUDY #1.** Statistically significant improvement in daytime cough frequency at Week-4. At the 8-week follow-up, the reduction in daytime cough frequency was sustained; a decrease of 28% from baseline cough frequency suggesting a 'normalizing' effect on the hypersensitized cough reflex.

**STUDY #2:** Orvepitant resulted in a significant, and sustained improvement in objective cough frequency, severity VAS, and QoL; appeared safe (CHEST 2019 Aug 14. pii: S0012-3692(19)31451-5. doi: 10.1016/j.chest.2019.08.001

## Erythromycin and azithromycin

### *Meta-analysis of macrolide antibiotic drugs for refractory CC*

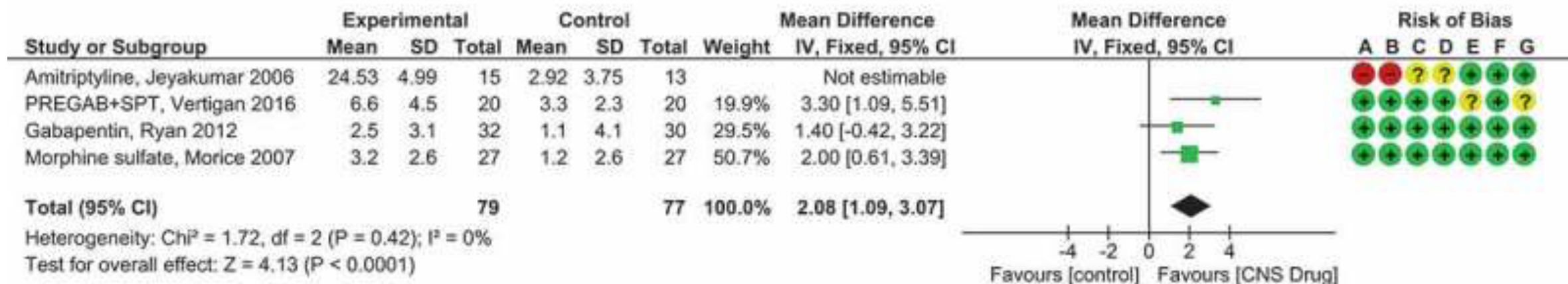
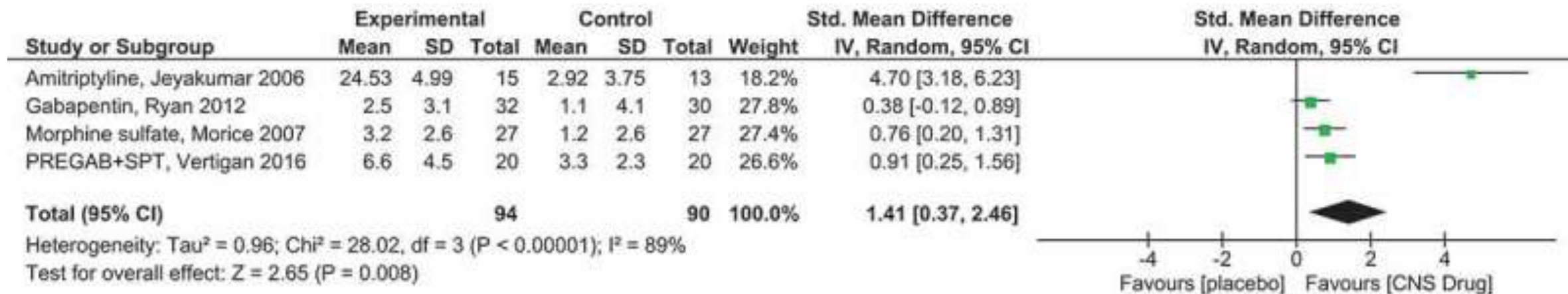
As the erythromycin study assessed LCQ as a secondary outcome, a meta-analysis on the two macrolide antibiotics could be performed. It can be seen that there is a small effect from azithromycin over placebo treatment on LCQ in refractory CC patients, MD [95% CI] 1.70 [-0.66 to 4.06]. There was no effect of erythromycin over placebo on LCQ in patients with refractory CC, MD [95% CI] 0 [-2.72 to 2.72], therefore the overall pooled estimate of effect was not significant, MD [95% CI] of 0.97 [-0.81 to 2.75],  $p = 0.29$ .

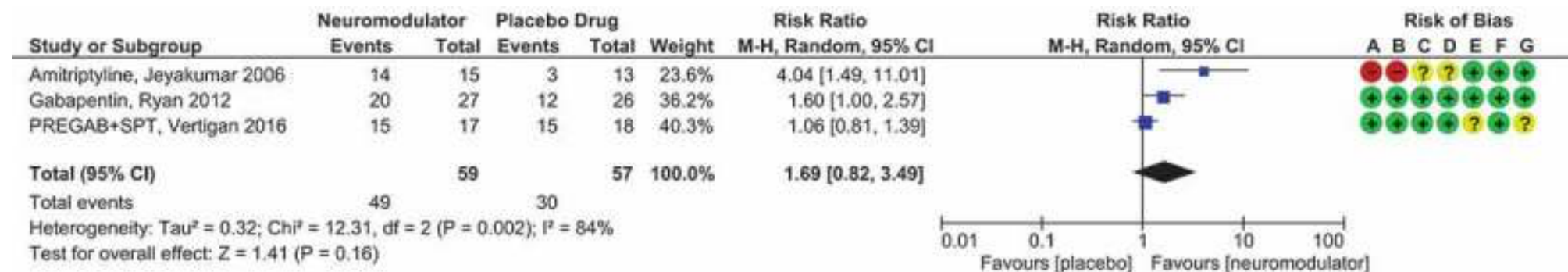
## PA101 cromolyn sodium formulation for refractory CC

PA101 is a novel formulation of cromolyn sodium delivered via a high-efficiency eFlow nebulizer (PARI, Germany) that achieves significantly higher lung deposition compared to previous formulations. Cromolyn blocks calcium ion influx into mast cells preventing the degranulation of mast cells in the lungs.

STUDY#1. The results of this study suggest that the mechanism of cough in IPF might be disease specific as it responds to PA101 treatment while refractory CC without IPF does not respond to PA101 treatment.

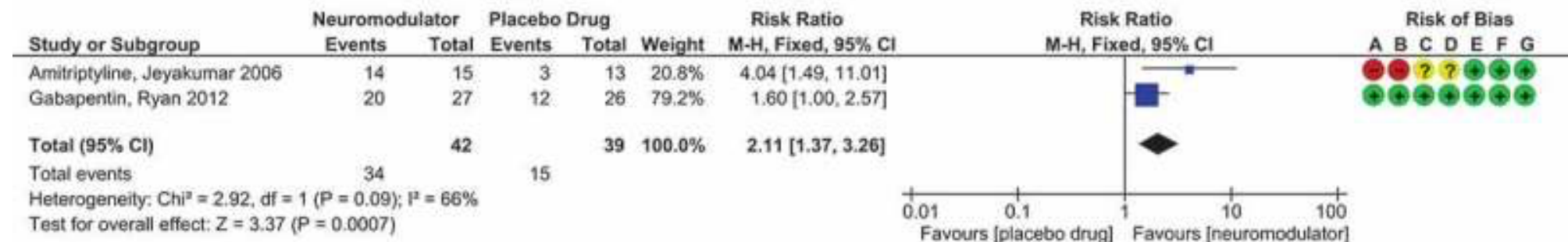
During the next 5 years, clinical trials in CC are planned with medications that target **P2X3, NK1, TRPV4, TRPM8, and ALPHA7-Nicotinic receptors**. Current research into central cough inhibition pathways with fMRI imaging techniques have highlighted areas in the **brain for central sensitization** and therapies that target this are worth investigating.





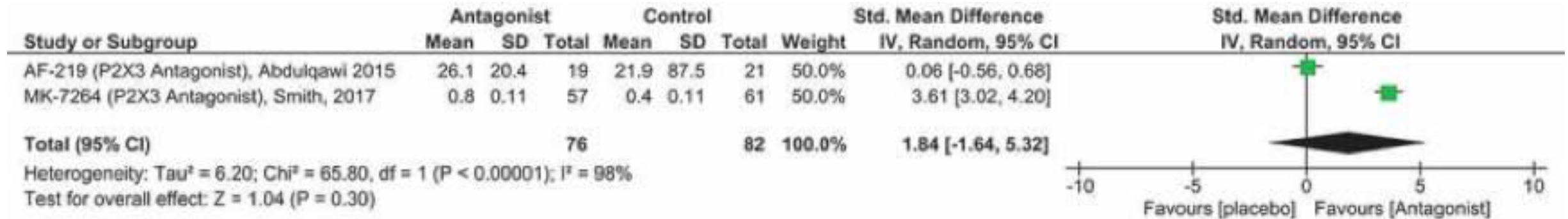
#### Risk of bias legend

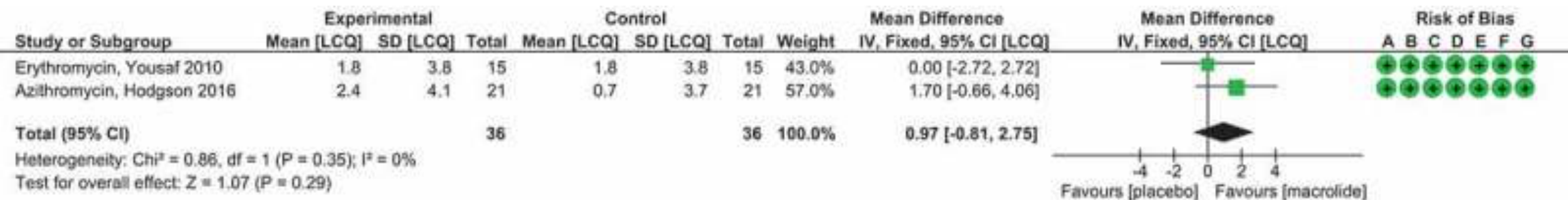
- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias



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## **ITER TERAPEUTICO PRATICO:**

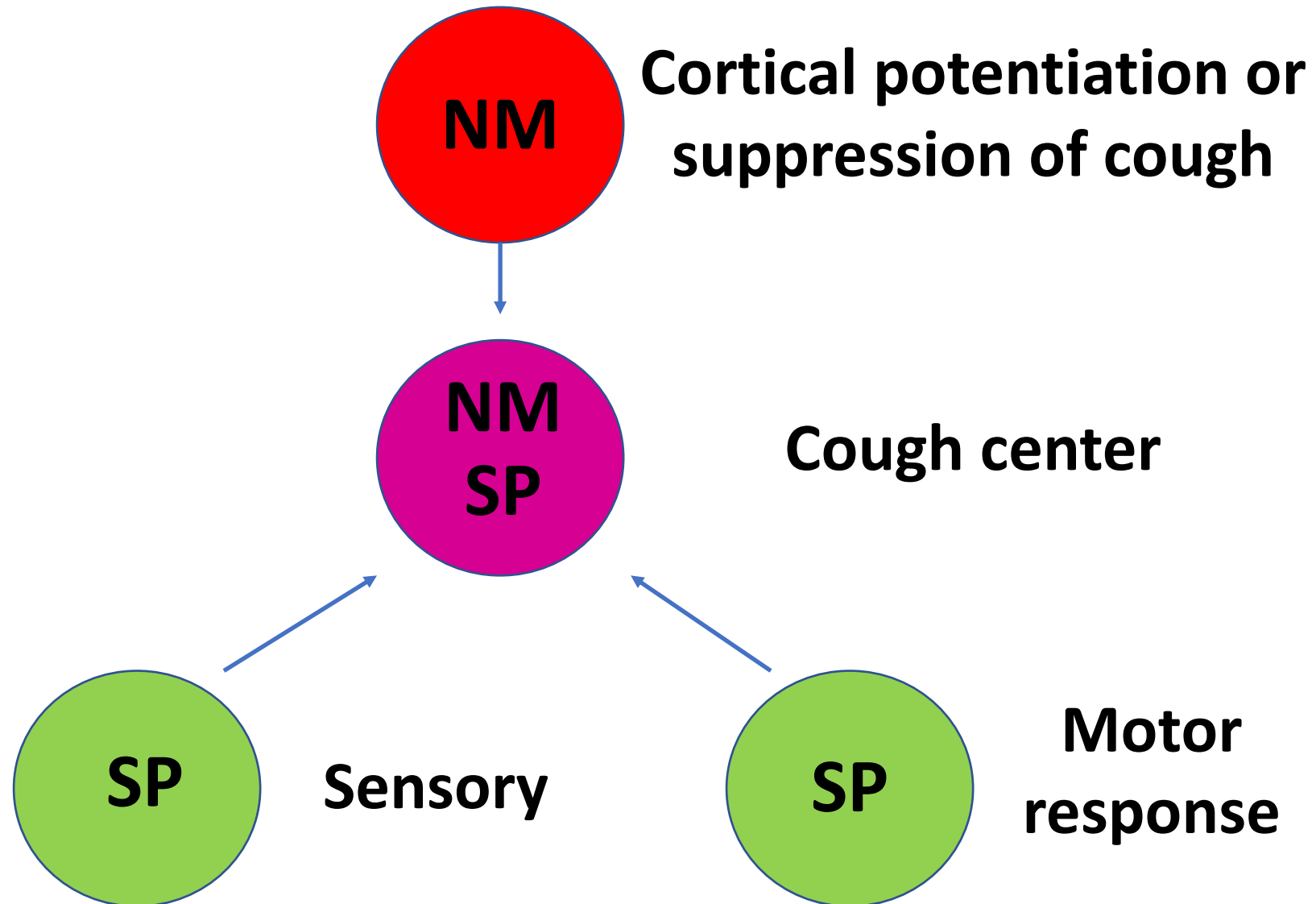
TRATTAMENTO DELLA PATOLOGIA DI BASE CAUSA DELLA TOSSE CRONICA.

### **ITER TERAPEUTICO PRATICO PER LA SINDROME DA IPERSENSIBILITA' ALLA TOSSE**

1. INIZIARE CON SEDATIVI DELLA TOSSE (destrometorfano [Bronchenolo sciroppo 1 cucchiaino x 3-4\*]) + ANTIISTAMINICI 1<sup>a</sup> GENERAZIONE (Actifed soluzione 5/10 ml x 3-4);
2. TRATTAMENTO LOGOPEDICO
3. FARMACI NEUROMODULATORI

**NM:** Neuro Modulatory; **SP:** Speech Pathology

Cortex  
Brainstem  
Larynx



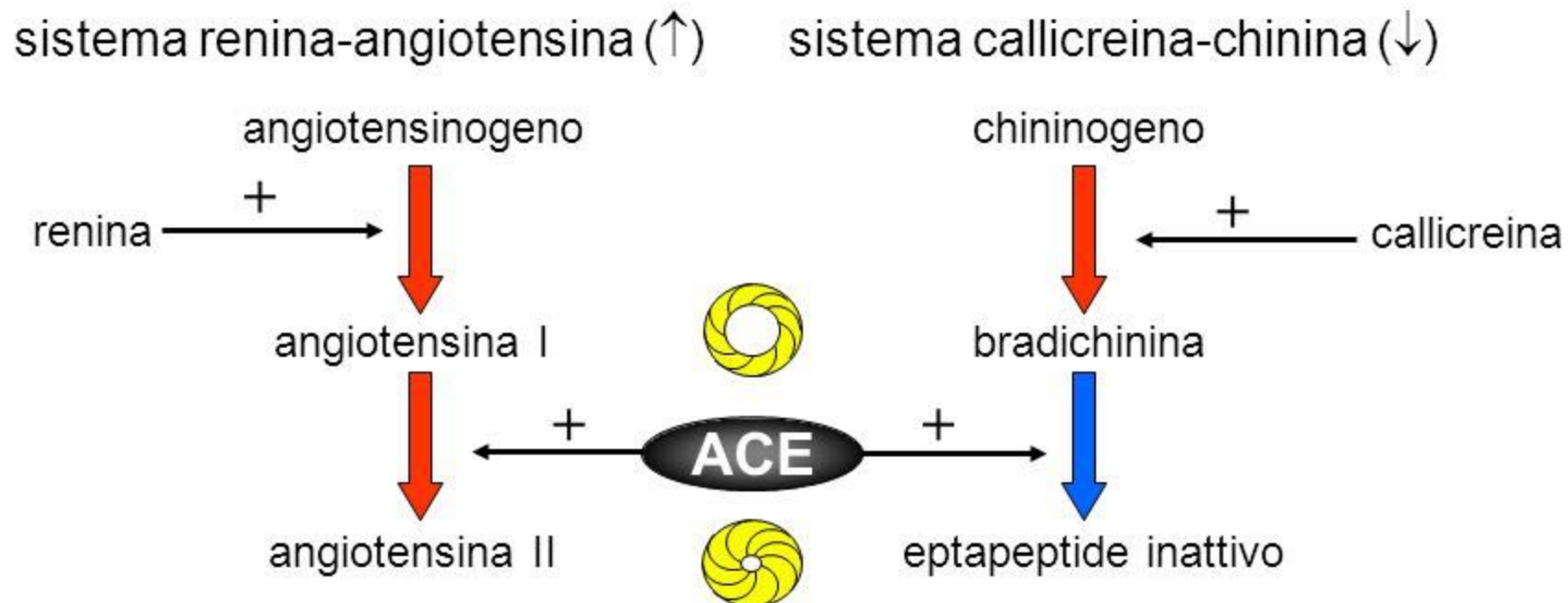
# **TOSSE CRONICA E ACE-INIBITORI**

## **Angiotensin-converting enzyme (ACE) inhibitor medications.**

Chronic cough is a frequent side effect of ACE inhibitor treatment. Its incidence is estimated between 3.9% and 35%. A large analysis of almost 27,500 patients with vascular disease identified that female gender, age 65 years and concomitant use of lipid lowering agents were clinical predictors of ACE inhibitor induced dry cough (OR 1.92, 95% CI 1.68–2.18; OR 1.53, 95% CI 1.35–1.73 and OR 1.37, 95% CI 1.18–1.59, respectively). Several genetic variants (CLASP1, ABO, KCNIP4) have also been identified as risk factors for ACE inhibitor induced cough.

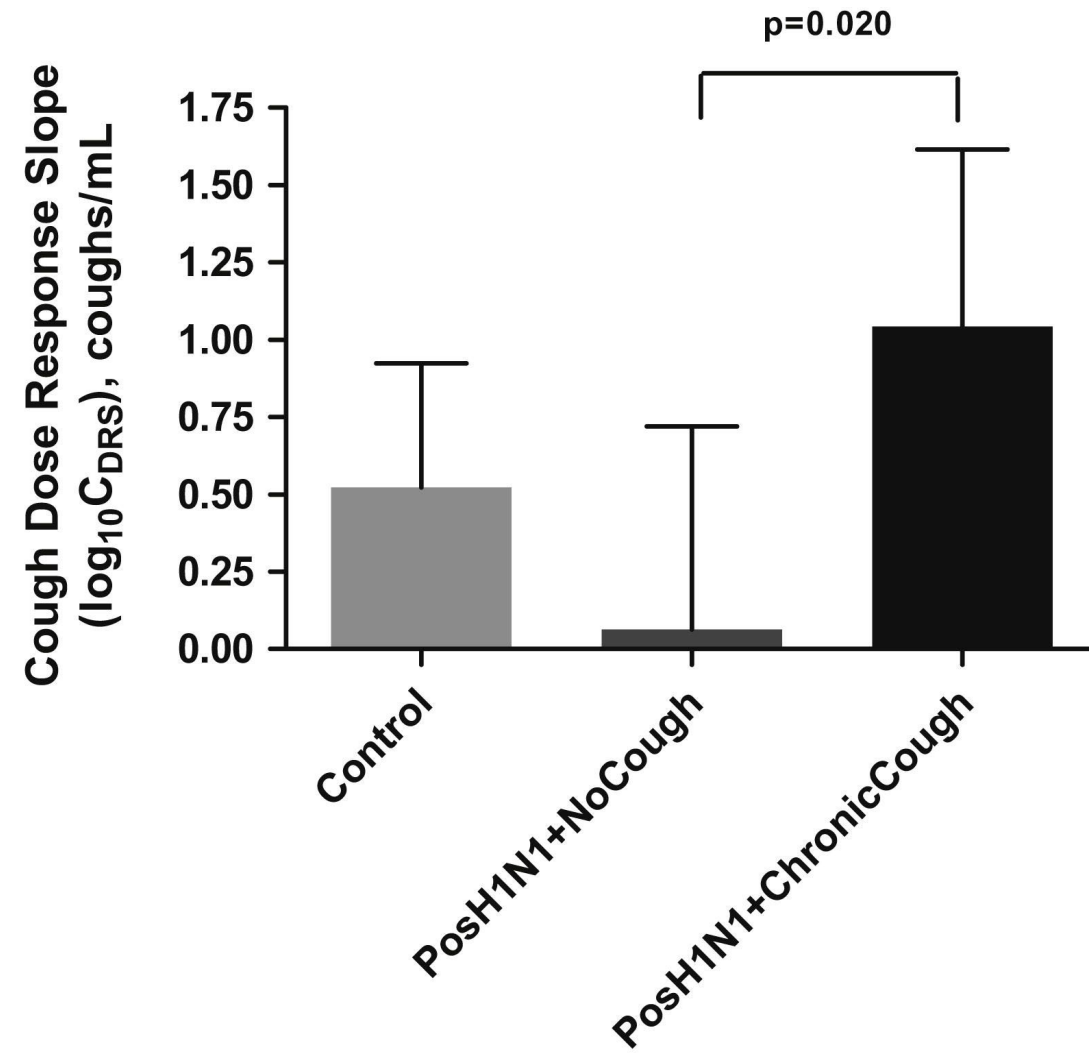
ACE inhibitor related cough usually occurs in the first weeks of treatment, but later occurrences (several months of treatment) are not infrequent. After discontinuation of ACE inhibitor treatment, cough usually disappears in a few weeks (3 months).

## Inibitori dell'enzima di conversione dell'angiotensina (ACE inibitori)



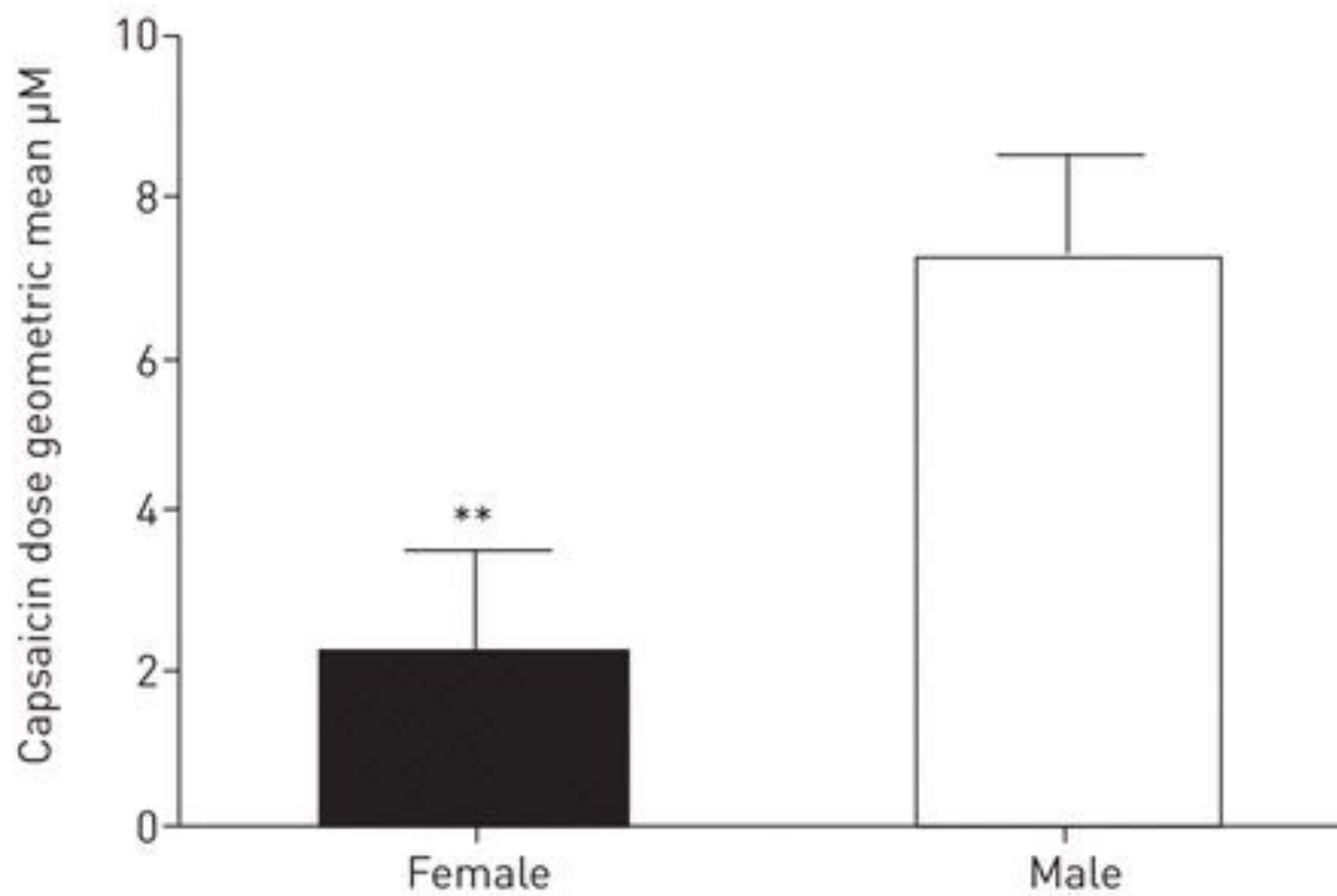
**teprotide:** piroGlu-Trp-Pro-Arg-Pro-Glu-Ile-Pro-Pro-OH  
(*Bothrops jararaca*)

# **TOSSE CRONICA E INFEZIONI BRONCOPOLMONARI VIRALI**

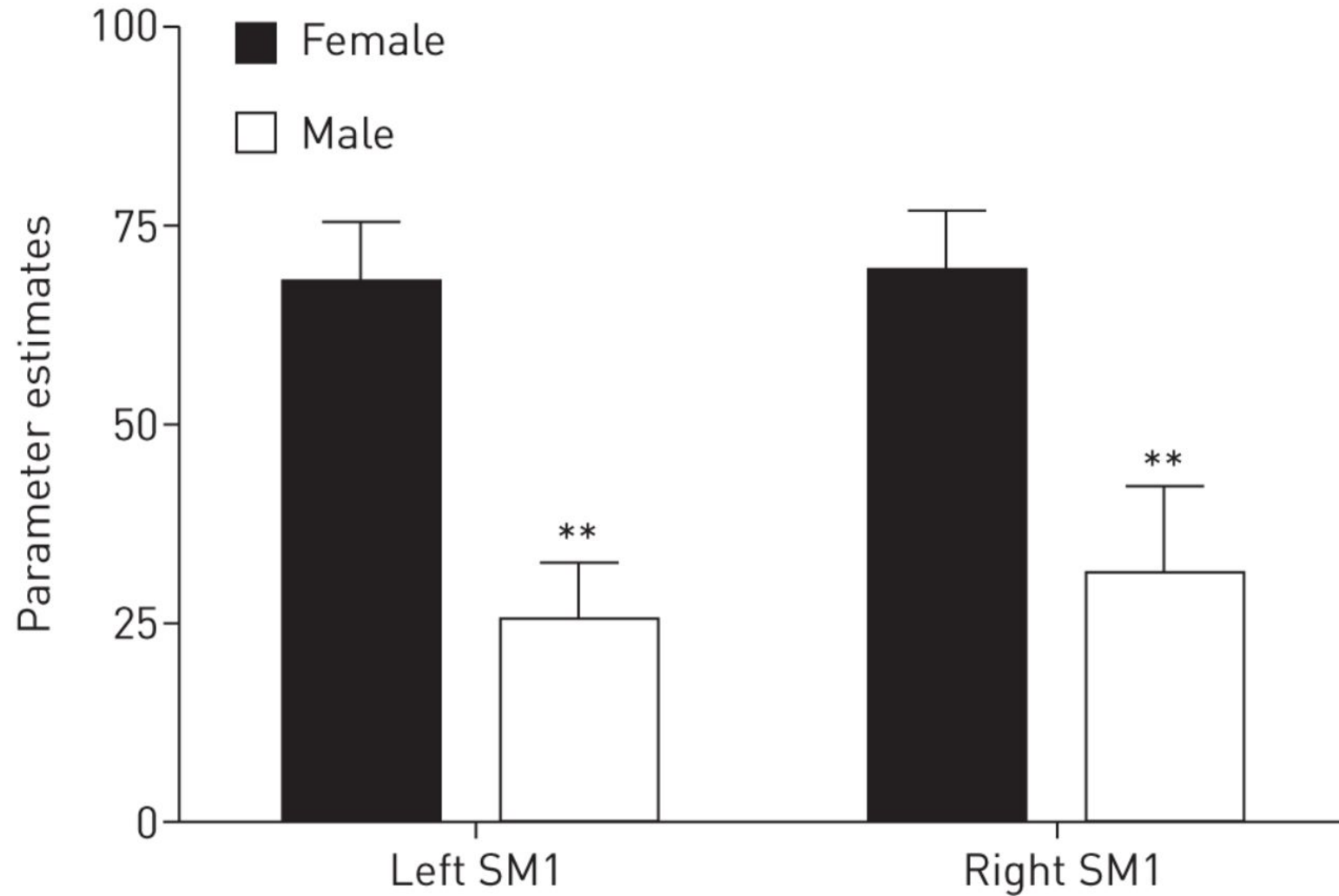


A **viral airway infection** usually induces a cough *lasting no more than 3 weeks*. **However**, a number of patients with chronic cough describe an initial “viral infection”. A recent review highlighted that the function of the airway sensory nerves can be altered by the viral infection. Indeed, viral infection of airways leads to a **stimulation of the sensory C-fibers** (afferent nerves) by inflammatory mediators and products of oxidative stress in the respiratory tract, as well as an increase in their excitability and a change in sensory nerve gene expression. Post-viral cough could be linked to an **alteration of the central neural networks** involved in cough, including a decrease in the cough reflex threshold. Viral infection also **induces the expression of cough receptors that can be inhibited by tiotropium**. However, the exact mechanisms involved in postinfection cough are not entirely elucidated. In case of a cough >8 weeks after an initial viral infection, an alternative diagnosis should be considered.

# **TOSSE CRONICA NEL SESSO FEMMINILE**



**Quantification of the size of the regional responses in the right and left primary somatosensory cortices (SM1) of females and males, as represented by mean parameter estimates.**



Alyn H. Morice et al. Eur Respir J 2014;44:1149-1155

# **PREVALENZA DELLA TOSSE CRONICA NEL SESSO FEMMINILE**

1. ALTA INCIDENZA DI USO DI ACEi (J Clin Epidemiol 1995; 48: 851)
2. ASSOCIAZIONE ESTROGENI-TRPV1 (Lung 2011; 189: 257)
3. *PATTERN* DI ATTIVAZIONE CEREBRALE AUMENTATO e/o ALTERAZIONI DEL SISTEMA INIBITORIO DISCENDENTE (Lancet Respir Med 2013; 1: 414)

## **TOSSE CRONICA e BRONCHIOLITE**

Cough may be the initial manifestation, or may develop during the clinical course, of nonbronchiectatic suppurative airway disease (bronchiolitis). While infrequently encountered, these small airways disorders are seen commonly enough by the practicing pulmonologist to warrant serious consideration in the correct clinical setting.

# Clinical Classification of Bronchiolitis

## Clinical Class

## Specific Examples

Infections

M. pneumoniae, respiratory syncytial virus

Inhalational mechanism

Toxins

Respiratory bronchiolitis (tobacco smoke), sulfur dioxide

Antigens

Hypersensitivity pneumonitis

Systemic diseases

Collagen vascular disease, inflammatory bowel disease, immunodeficiency

Drug reactions

Penicillamine, amiodarone

Allograft recipients

Lung and bone marrow transplant

Idiopathic disorders

Bronchiolitis obliterans (cryptogenic constrictive bronchiolitis), follicular bronchiolitis, DPB

# Recommendations

In patients with cough and incomplete or irreversible airflow limitation, direct or indirect signs of small airways disease seen on HRCT scan, or purulent secretions seen on bronchoscopy, nonbronchiectatic suppurative airways disease (**bronchiolitis**) **should be suspected** as the primary cause. Level of evidence: E/A 2.

In patients with cough in whom more common causes have been excluded, because bacterial suppurative airways disease may be present and clinically unsuspected, **bronchoscopy** is required before excluding it as a cause. Level of evidence: B

3. In patients in whom bronchiolitis is suspected, a **surgical lung biopsy** should be performed when the combination of the clinical syndrome, physiology, and HRCT findings do not provide a confident diagnosis. Level of evidence: E/A

4. In patients with infectious bacterial bronchiolitis, **prolonged antibiotic therapy** improves cough and is recommended. Level of evidence: B

5. In patients with toxic/antigenic exposure or drug-related bronchiolitis, **cessation of the exposure or medication plus corticosteroid therapy** for those with physiologic impairment is appropriate. Level of evidence: E/A

# INFLAMMATORY BOWEL DISEASE (IBD)

The lung may be affected in the patient with an IBD (ie, **ulcerative colitis** [UC] or **Crohn disease**). Direct involvement by the underlying disease, pulmonary toxicity secondary to a medication, or infection may occur. The underlying disease may involve the entire airway, from larynx to the alveolus repeating the abnormalities found in the bowel including inflammatory (lymphocytic, neutrophilic, and granulomatous), fibrotic, and destructive changes.

**Specific Treatment.** Removal of the affected bowel has not been shown to be beneficial and may lead to an increase in symptoms. In observational studies, therapy with **corticosteroids, both oral and inhaled**, has been associated with improvement in cough, particularly when the large airways (bronchitis) are involved. With involvement of the smaller airways, the responses to corticosteroids appear to depend on the underlying pathology, with granulomatous and lymphocytic disease being more responsive than bronchiolitis obliterans or necrotizing bronchiolitis.

# **TOSSE CRONICA IN DIALISI PERITONEALE**

Patients receiving PD are more likely to develop a cough than other patients with end-stage renal disease who are receiving hemodialysis. Although both groups of patients frequently receive medications, such as **ACEi** and **β-blockers**, that can trigger cough and both may be at increased risk for **fluid overload** and pulmonary edema, the increased risk associated with PD appears to relate to **gastroesophageal reflux**, likely from the peritoneal dialysate.

CHEST 2006; 129:202S

# **TOSSE CRONICA e ASPIRAZIONE DI CIBI/LIQUIDI NELLA DISFAGIA ORO-FARINGEA**

Cough may be an indicator of aspiration due to oral-pharyngeal dysphagia.

Aspiration was observed on radiologic evaluation in over one third of **acute stroke** patients and in > 40% of patients undergoing **cervical spine surgery**. Cough while **eating** may indicate aspiration, but aspiration may be clinically silent. Subjective patient and caregiver reports of cough while eating are useful in identifying patients who are at risk for aspiration.

**Objective measures** of voluntary cough and tussigenic challenges to inhaled irritants are under investigation to determine their capacity to predict the risk for aspiration and subsequent pneumonia.

The **treatment** of dysphagic patients by a multidisciplinary team, including early evaluation by a speech-language pathologist, is associated with improved outcomes. Effective clinical interventions such as the use of compensatory swallowing strategies and the alteration of food consistencies can be based on the results of instrumental swallowing studies. The efficacy of swallowing exercises and electrical muscle stimulation is under study. Surgical interventions may be considered in selected patients, but studies proving efficacy are generally lacking.

# **TOSSE CRONICA DOPO CHIRURGIA PER TUMORE AL POLMONE**

There are few studies on the pathogenesis of **chronic cough after lung cancer surgery**. Based on these studies, airway inflammation is a common feature of patients with chronic cough.<sup>4, 15</sup> According to a previous study,<sup>15, 16, 17</sup> the mechanism of chronic cough caused by surgery mainly includes the following: **(i)** local inflammation caused by surgery in lung tissues and peripheral nerves; **(ii)** physical changes to small airways after surgery, such as local torsion caused by poor ventilation; **(iii)** surgical scars and chronic stimulation from foreign bodies, such as sutures in the trachea; and **(iv)** local pleurisy and pleural effusion. In this study, we found that right lung cancer, difficult airway, acute cough and a history of COPD are independent predictors of chronic cough after surgery. Right lung cancer dissection and extensive lymph node dissection of the superior mediastinum, damage to vessels and nerves on the anterior wall of the trachea and partial cavity formation after surgery are the main causes of chronic cough. Difficult airway can lead to prolonged intubation time. Furthermore, repeated stimulation of the tracheal mucosa is the main cause of increased acute cough, and poor control of acute cough and COPD leads to chronic inflammation. Notably, COPD is an important cause of chronic cough.

The question of **how to prevent and reduce chronic cough in lung cancer patients after surgery** remains unsolved. The main aspects to consider include the following: **First**, tubeless anesthesia technology can be used to minimize the stimulation of airways in some patients. **Second**, when cleaning lymph nodes, more attention should be paid to protect nerves and vessels around the trachea and bronchi and to reduce postoperative scar formation. **Third**, early intervention for patients with acute cough may reduce the incidence of chronic cough. **Fourth**, for patients who are diagnosed with chronic cough, acupuncture therapy can be administered to relieve symptoms.

# **TOSSE CRONICA NOTTURNA**

**A nocturnal cough needs to be assessed by intensity, severity, frequency, and sensitivity. Some clues in the assessment of a nocturnal cough:**

A cough worsening on supine posture: Post nasal drip, esophageal reflux, chronic bronchitis, bronchiectasis, and heart failure.

Presence of clear sputum: Hypersensitivity mechanism.

Purulent sputum: Sinusitis, bronchiectasis; rule out tuberculosis.

Blood tinged sputum: Malignancies, tuberculosis, and bronchiectasis.

A non-productive cough: ACEI therapy.

Improvement of a cough with antihistaminic treatment confirms the diagnosis of UACS.

The red flag symptoms of chronic nocturnal cough are copious sputum (bronchiectasis), hemoptysis (malignancy, tuberculosis), systemic symptoms (tuberculosis, lymphoma, lung primary or secondaries) and significant dyspnoea (CCF, COPD, fibrotic lung disease). Ask about a history of fever, weight loss, night sweats, and progressive fatigue.

# **TOSSE CRONICA NELLA FIBROSI POLMONARE IDIOPATICA**

# MECCANISMI:

1. MODULAZIONE NEUROSENSORIALE VIE AEREE CENTRALE AD OPERA DI NEUROTROFINE GENERATE NEL TESSUTO FIBROTICO (Pulm Pharmacol Ther 2004; 17: 347);
2. DISTORSIONE MECCANICA DELLE VIE AREE AD OPERA DEL TESSUTO FIBROTICO (Cough 2011; 7: 2)
3. MRGE (AJRCCM 1998; 158: 1804)

# **TOSSE CRONICA NELLA BRONCHITE EOSINOFILA NONASMATICA**

# Chronic Cough Due to Nonasthmatic Eosinophilic Bronchitis

Nonasthmatic eosinophilic bronchitis is a common cause of chronic cough. It is characterized by the presence of eosinophilic airway inflammation, similar to that seen in asthma. However, in contrast to asthma, nonasthmatic eosinophilic bronchitis is not associated with variable airflow limitation or airway hyperresponsiveness. The differences in functional association are related to differences in the localization of mast cells within the airway wall, with airway smooth muscle infiltration occurring in patients with asthma, and epithelial infiltration in patients with nonasthmatic eosinophilic bronchitis.

Diagnosis is made by the confirmation of eosinophilic airway inflammation usually with induced sputum analysis after the exclusion of other causes for chronic cough on clinical, radiologic, and lung function assessment.

The cough usually responds well to treatment with inhaled corticosteroids. The dose and duration of treatment differ between patients. The condition can be transient, episodic, or persistent unless treated, and occasionally patients may require long-term prednisone treatment.

# **SINDROME DELLA TOSSE SOMATICA**

**CHEST 2015; 148: 24**  
**J Thorac Dis 2017; 9: 831**

1. In adults or children with chronic cough, we suggest that the presence or absence of **night time cough or cough with a barking or honking character** should not be used to diagnose or exclude psychogenic or habit cough (Grade 2C).

2. In adults with a persistently troublesome chronic cough, we suggest that the presence of **depression and/or anxiety** not be used as diagnostic criteria for psychogenic cough because patients with a persistently troublesome chronic cough can develop these psychologic symptoms when their coughs remain untreatable (Grade 2C).

3. In adults and children with chronic cough that has remained medically unexplained after a comprehensive evaluation based upon the most current evidence-based management guideline, we recommend that the **diagnosis of tic cough** be made when the patient manifests the core clinical features of tics that include suppressibility, distractibility, suggestibility, variability, and the presence of a premonitory sensation whether the cough is single or one of many tics (Grade 1C).

## **TIC FONETICI SEMPLICI**

Tosse

Sniffing (Tirare su dal naso)

Barking (Latrare)

Throat clearing (schiarirsi la gola)

Screaming (urlare)

Sucking (suzione)

Clicking (fare un suono secco)

Snorting (sbuffare)

Chirping (cinguettare)

Blowing (soffiare)

4. In adults and children with chronic cough, we suggest **against using the diagnostic terms habit cough and psychogenic cough** (Ungraded Consensus-Based Statement).

5. In adults and children with chronic cough, we suggest **substituting the diagnostic term tic cough for habit cough** to be consistent with the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) classification of diseases and because the definition and features of a tic capture the habitual nature of cough (Ungraded Consensus-Based Statement).

*Remarks:* A simple cough tic in children may respond to suggestion therapy alone, as if it were just a “habit.” A cough tic in isolation that persists for more than one year would be referred to by DSM-5 criteria as a chronic vocal tic disorder. This is distinct from Tourette syndrome that involves both motor and vocal tics.

6. When disseminating research findings on tic cough, we suggest **adding the parenthetical term (*habit*) (eg, tic cough [*habit*]) for three years**, to help smooth the adoption of the new name, avoid confusion in the medical literature, and facilitate bibliographic database searches (Ungraded Consensus-Based Statement).

7. In adults and children, we suggest **substituting the diagnostic term somatic cough disorder for psychogenic cough** to be consistent with the DSM-5 classification of diseases (Ungraded Consensus-Based Statement).

*Remarks:* The term “psychogenic” has disappeared from the DSM classification of diseases because functional imaging studies have started showing cerebral correlates for disorders previously thought to be of a pure psychogenic nature.

8. When disseminating research findings on somatic cough disorder, we suggest **adding the parenthetical term (*psychogenic*) (eg, somatic cough disorder [*psychogenic*]) for three years**, to help smooth the adoption of the new name, avoid confusion in the medical literature, and facilitate bibliographic database searches (Ungraded Consensus-Based Statement).

9. In adults and children, we suggest that the **diagnosis of somatic cough disorder can only be made after an extensive evaluation has been performed that includes ruling out tic disorders and uncommon causes and the patient meets the DSM-5 criteria** (see [Table 1](#)) for a somatic symptom disorder (Grade 2C).

## **(Table 1) Diagnostic Criteria**

- A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.
  
- B. Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
  - 1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
  - 2. Persistently high level of anxiety about health or symptoms.
  - 3. Excessive time and energy devoted to these symptoms or health concerns.
  
- C. Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 mo).

DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition. Reprinted with permission from the American Psychiatric Association.

La **sindrome di Tourette** (o **sindrome di Gilles de la Tourette**) è un disturbo neurologico che esordisce nell'infanzia scomparendo spesso durante l'adolescenza, caratterizzato dalla presenza di tic motori e fonatori incostanti, talvolta fugaci e altre volte cronici, la cui gravità può variare da estremamente lievi a invalidanti.

In molti pazienti emergono alcune comorbidità (diagnosi di patologie diverse dalla sindrome di Tourette), come il disturbo da deficit dell'attenzione/iperattività (ADHD) e il disturbo ossessivo/compulsivo (DOC). Le altre condizioni sono spesso secondarie a peggioramento nel quadro clinico del paziente e quindi è fondamentale identificarle correttamente e trattarle.

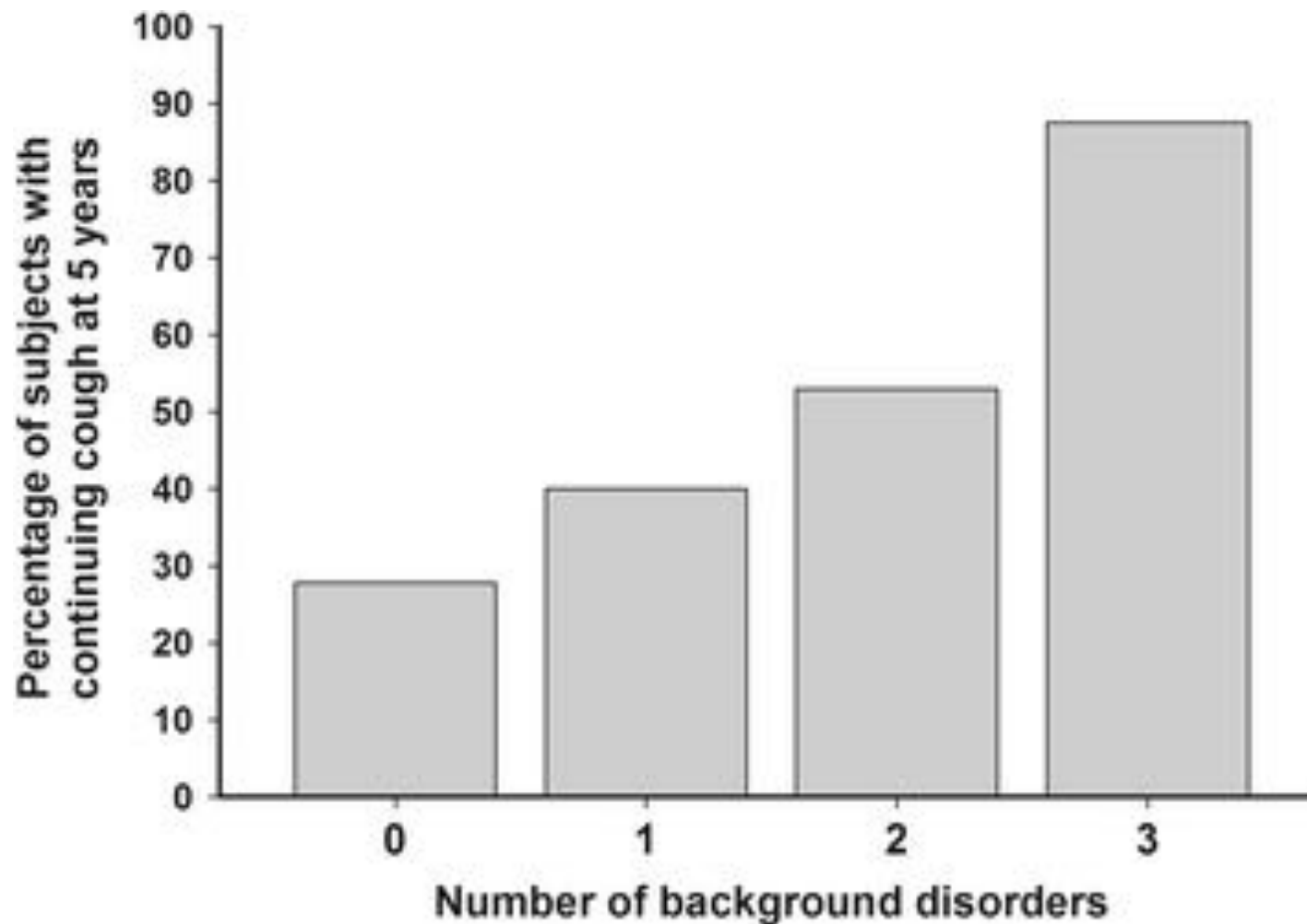
La sindrome prende il nome dal neurologo francese Georges Gilles de la Tourette, che la descrisse nell'Ottocento, anche se era già stata individuata e inquadrata sin dal Seicento; la sindrome in realtà non fu quasi considerata fino a pochi decenni dalla fine del XX secolo.



Dopamine receptor-blocking drugs, the so-called neuroleptics, are effective in controlling the tics of Tourette syndrome.

N Engl J Med, 2001; 345:1184–1192

# **PROGNOSI LONG-TERM DELLA TOSSE CRONICA**



The proportion of subjects who suffered from continuing regular cough at five years' follow-up related to the number of self-reported background disorders (esophageal reflux disease, asthma, or chronic rhinitis). Eighteen subjects reported no background disorders, 25 reported one disorder, 17 reported two disorders, and 8 reported three disorders.  $P = 0.03$  between the groups (Chi-square test),  $p = 0.007$  for the trend between the number of background disorders and continuing cough (univariate logistic regression analysis)

