Tosse cronica: dalla percezione alla soluzione

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SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

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Consensus intersocietaria: Società Scientifiche coinvolte

AIPO	Associazione Italiana Pneumologi Ospedalieri
AIST	Associazione Italiana Studio Tosse
CNR	Centro Nazionale Ricerche
ISS	Istituto Superiore di Sanità
SIAAIC	Società Italiana di Allergologia, Asma e Immunologia Clinica
SIGG	Società Italiana di Gerontologia e Geriatria
SIMG	Società Italiana di Medicina Generale
SINGEM	Società Italiana di Neuro-Gastro-Enterologia e Motilità
SIP	Società Italiana di Pneumologia

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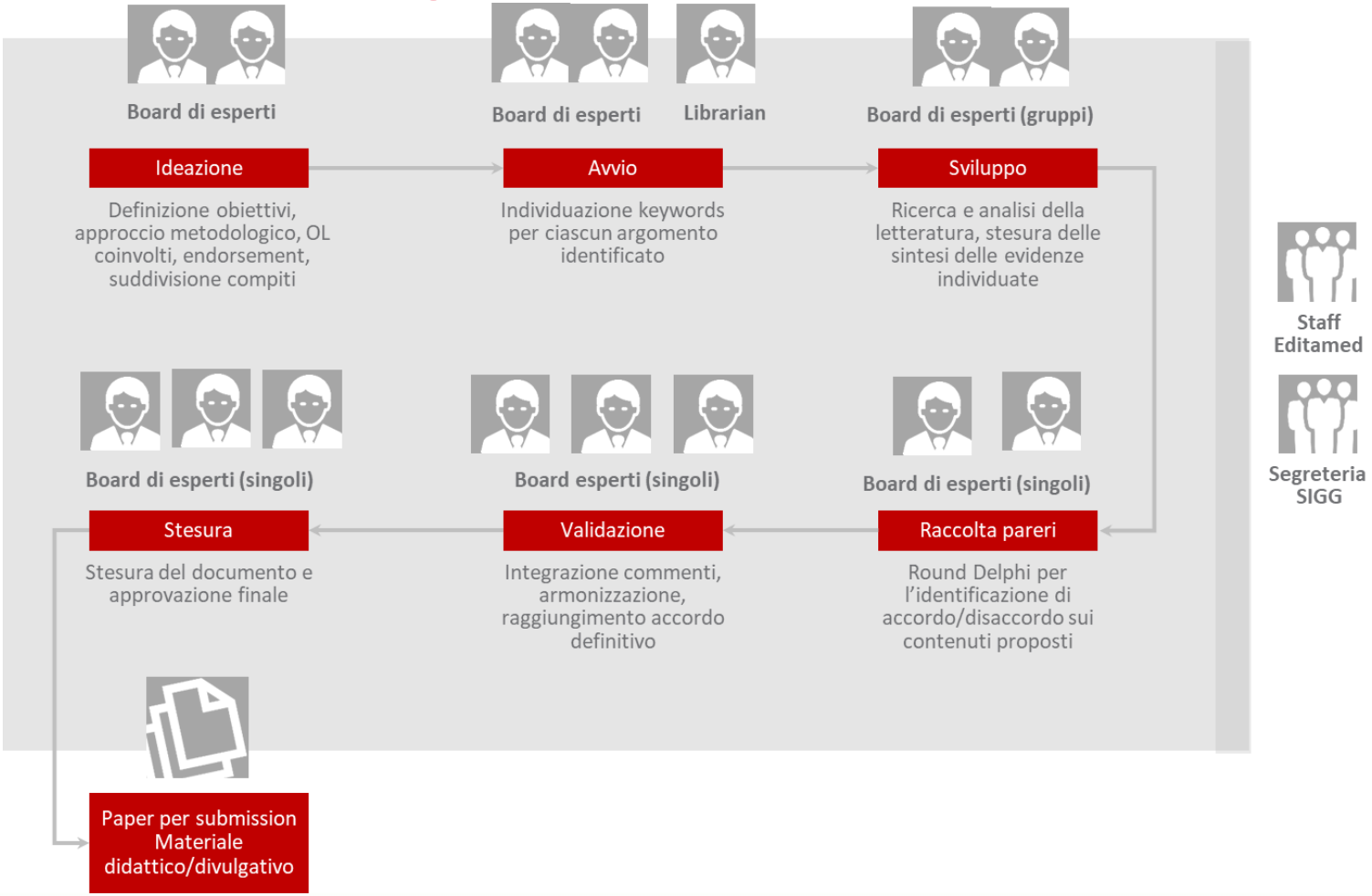
Overview del progetto



Tipologia di progetto

Chronic Cough: from perception to solution

Finalizzato a:
Definire l'approccio diagnostico e le possibilità terapeutiche del paziente con tosse cronica
Proporre un algoritmo diagnostico-terapeutico

OBIETTIVO:
Elaborare un documento intersocietario, che riporti indicazioni frutto dell'accordo tra i partecipanti

TARGET DEL DOCUMENTO
Tutti i professionisti coinvolti nella gestione del paziente con tosse cronica

Outline

Definizione

Dimensioni del problema

Basi patogenetiche

Aspetti diagnostici

Aspetti terapeutici

La dimensione geriatrica

Prospettive

Definizione (Morice AH et al. Eur Respir J 2020; 55: 1901136)

To define a chronic cough on the basis of longevity is clearly an arbitrary paradigm. Early studies used 3 months based on the Medical Research Council definition of chronic bronchitis [8]. More recent guidelines have adopted 8 weeks in adults [9] and 4 weeks in children [10]. Inclusion criteria for studies of novel antitussives require a cough refractory to treatment to be present for over a year. While some patients cough on a daily basis over many years, for others the disease has a relapsing and remitting course, making a definition based purely on a temporal basis difficult to sustain.

La tosse: effetto di un meccanismo complesso, vario e variabile

(Respiratory Physiology & Neurobiology 2017; 243: 60–76)

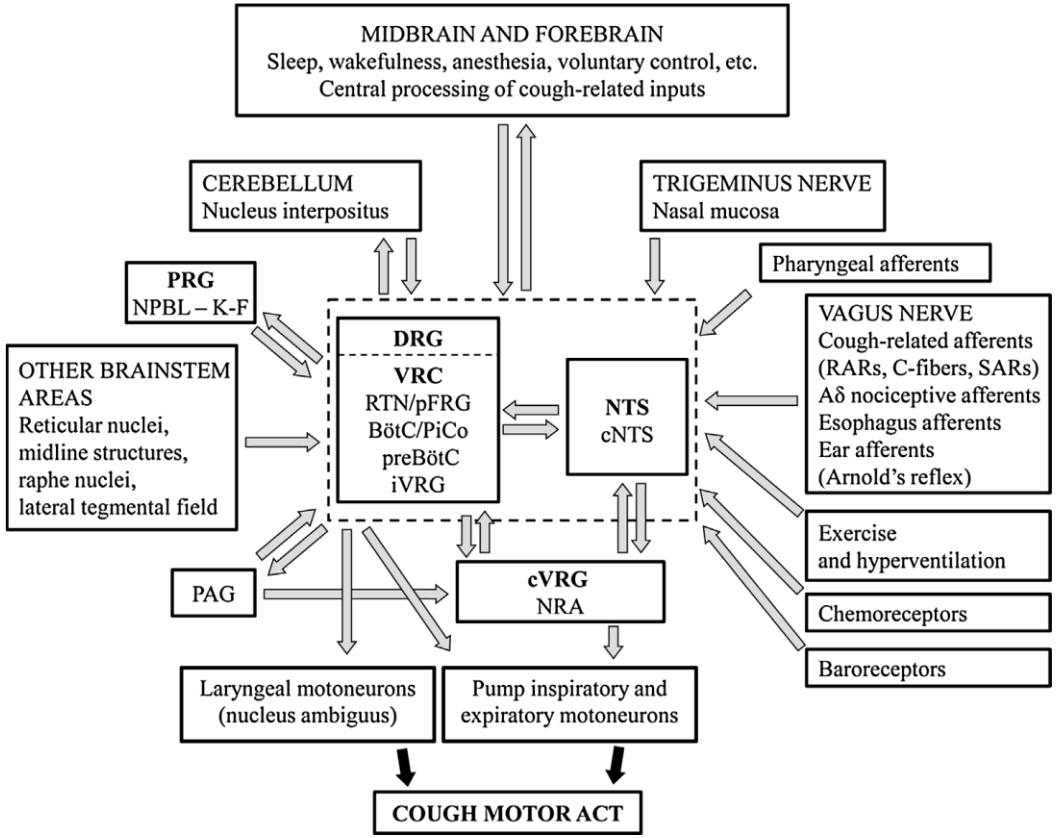


Fig. 2. Tentative block diagram summarizing the main central and peripheral neural mechanisms involved in the generation and regulation of the cough motor act. Abbreviations: BötC, Bötzinger complex; cNTS, caudal aspect of the nucleus tractus solitarii; cVRG, caudal ventral respiratory group; DRG, dorsal respiratory group; iVRG, inspiratory portion of the ventral respiratory group; K-F, Kölliker-Fuse nucleus; NPBL, nucleus parabrachialis lateralis; NRA, nucleus retroambigualis; NTS, nucleus tractus solitarii; PAG, periaqueductal grey; PiCo, Postinspiratory complex; preBötC, preBötzinger complex; PRG, pontine respiratory group; RARs, rapidly adapting receptors; SARs, slowly adapting receptors; RTN/pFRG, retrotrapezoid nucleus/parafacial repiratory group; VRC, ventral respiratory column.

Dimensioni del problema: prevalenza

2-4% nelle regioni in via di sviluppo (Song WJ et al. Eur Respir J 45:1479–1481)

Circa il 10% nelle regioni sviluppate (Song WJ et al. Eur Respir J 45:1479–1481)

Prevalenza età-correlata: 14,5% a 80 anni (Campi G et al. Aging Clin Exp Res 32:741–746)

Le dimensioni del problema

Statement	Type	Strength of recommendation/quality of evidence
Prevalence data are uncertain because epidemiological studies on CC demonstrate poor comparison due to heterogeneous study populations, settings, and screening tools	Statement of fact	–

CC, chronic cough

Le dimensioni del problema: effetti della tosse cronica

Statement	Type	Strength of recommendation/quality of evidence
Chronic cough has an important impact on social life and relationships, giving rise to serious psychological consequences for patients and their families	Statement of fact	—
We recommend searching for potential complications of CC (e.g., syncope, GE reflux, mood disturbance, arrhythmias, headache, chronic chest pain, costal fractures, urinary incontinence, herniation or prolapse of abdominal–pelvic organs)	Recommendation	A/Moderate
We suggest exploring the impact of CC on health status via the use of validated questionnaires, either generic (e.g., SF36) or cough specific (e.g., Leicester Cough Questionnaire)	Recommendation	B/moderate

CC, chronic cough; GE, gastroesophageal

Dimensioni del problema: l'interesse dell'ERS nell'argomento Tosse cronica (McGarvey L et al. Eur Respir J 2019; 53: 1900787)

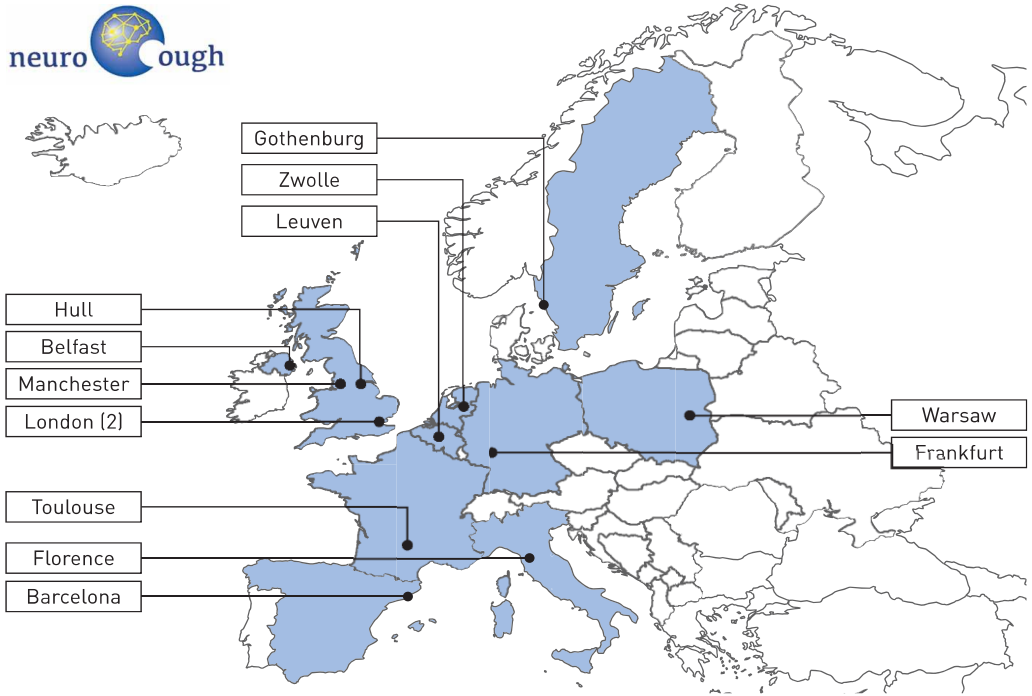


FIGURE 1 New understanding in the treatment of cough (NEUROCOUGH): first-wave specialist cough centres participating in the Europe-wide registry of chronic cough patients.

Dimensioni del problema: l'interesse dell'ERS nell'argomento Tosse cronica (McGarvey L et al. Eur Respir J 2019; 53: 1900787)

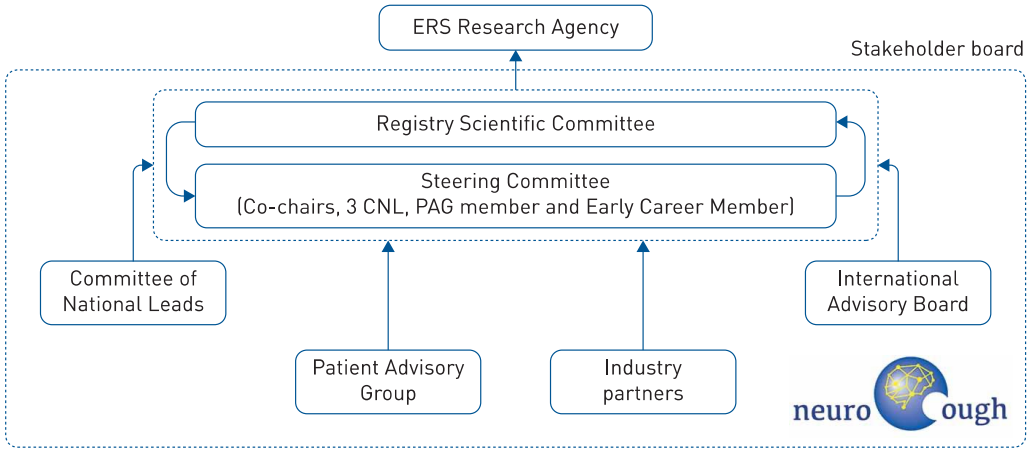


FIGURE 2 New understanding in the treatment of cough (NEUROCOUGH) structure: an operational model for the Clinical Research Collaboration. ERS: European Respiratory Society; CNL: members of the Committee of National Leads; PAG: Patient Advisory Group.

Linee guida ERS per l'adulto (Morice AH et al. Eur Respir J 2020; 55: 1901136)

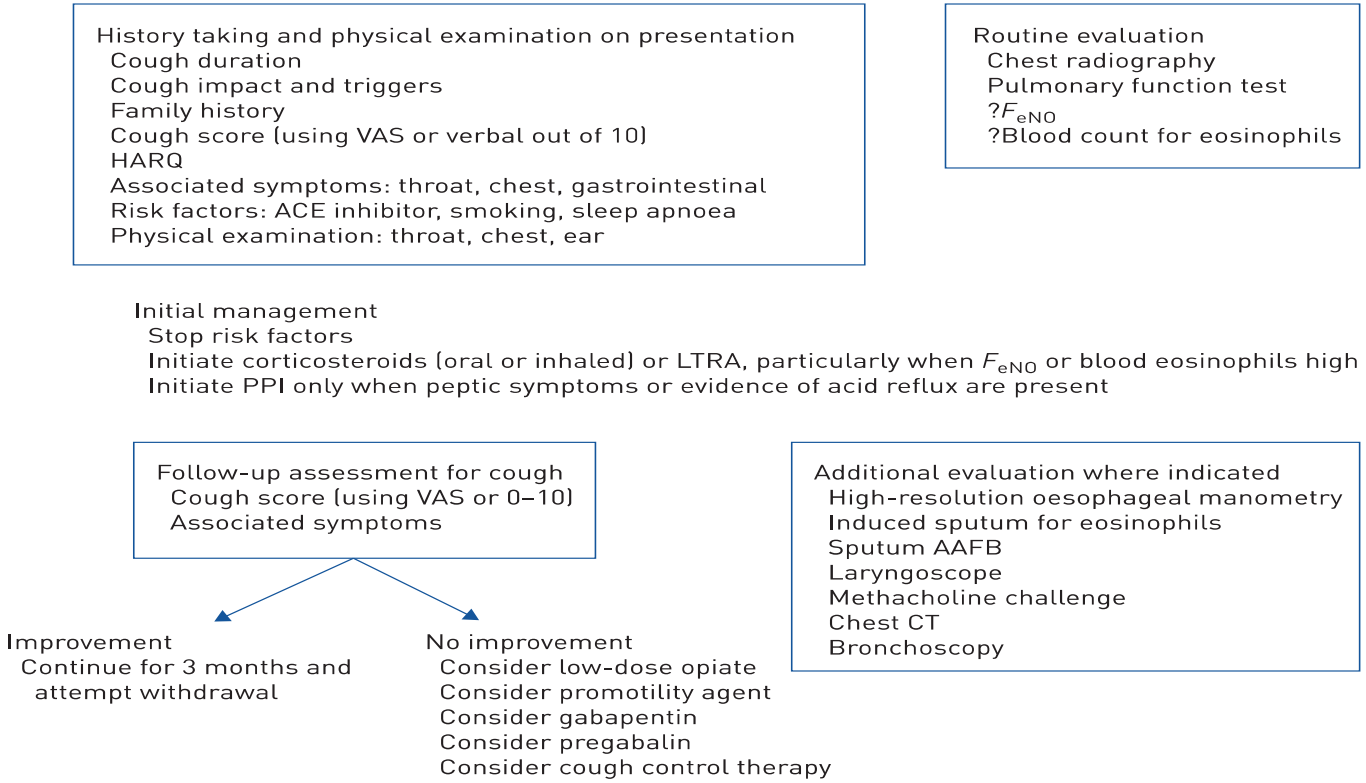
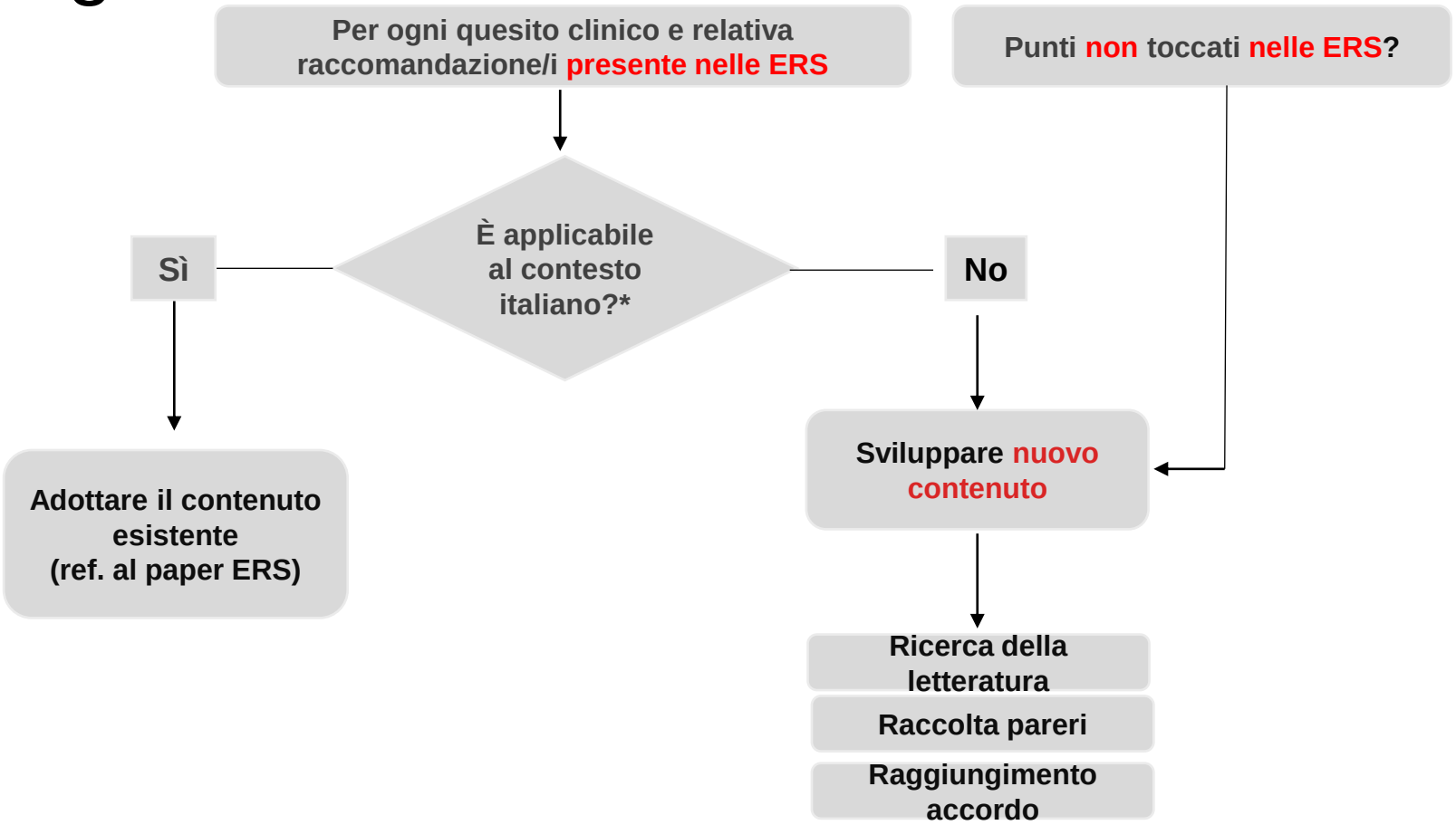


FIGURE 1 Cough assessment in adults. VAS: visual analogue scale; HARQ: Hull Airway Reflux Questionnaire; ACE: angiotensin-converting enzyme; F_{eNO}: exhaled nitric oxide fraction; LTRA: leukotriene receptor antagonist; PPI: proton-pump inhibitor; AAFB: alcohol and acid-fast bacilli; CT: computed tomography.

Linee guida ERS vs documento intersocietario



* Valutazione sulla base di diverso setting, **tipo di specialista coinvolto (primary vs secondary care)**, disponibilità di risorse (economiche/expertise/disponibilità farmaco), fattibilità etc

Argomenti e gruppi di lavoro

	ARGOMENTO	GRUPPO DI LAVORO
1	Definizione ed epidemiologia	
2	Basi patogenetiche ed eziologia	
3	Approccio diagnostico	
4	Possibilità terapeutiche	
5	Peculiarità epidemiologiche e cliniche in rapporto al tipo di specialista	
6	Sviluppo dell'algoritmo diagnostico e terapeutico	

Attività

KEYWORDS	Identificazione delle keywords, per ciascun tema/argomento, per avviare la ricerca della letteratura
RICERCA DELLA LETTERATURA	Ricerca degli articoli sulla base delle keywords identificate
ANALISI DELLA LETTERATURA	Il board, suddiviso in gruppi di lavoro, avrà il compito di individuare i paper di interesse e visionarli per estrarre i dati utili
STESURA SINTESI EVIDENZE E BOZZA CONTENUTI	Ciascun gruppo di lavoro scriverà una sintesi delle evidenze identificate per ciascuno degli argomenti. Proporrà quindi una prima bozza di indicazioni per ciascun argomento
RACCOLTA PARERI (DELPHI)	La bozza prodotta sarà condivisa tra tutti i membri del board in modo da raccogliere, attraverso votazioni strutturate, l'accordo o il disaccordo su ciascun contenuto
VALIDAZIONE FINALE	Raggiungimento dell'accordo sugli aspetti controversi e approvazione finale (testo + algoritmo)
STESURA PAPER E SUBMISSION	Il paper finale, a firma del board, sarà sottoposto per pubblicazione a rivista internazionale

Aspetti ezio-patogenetici

Una patogenesi variabile: tre esempi di meccanismi della tosse (Grabczak EM et al. **EXPERT REVIEW OF RESPIRATORY MEDICINE https://doi.org/10.1080/17476348.2020.1811686)**

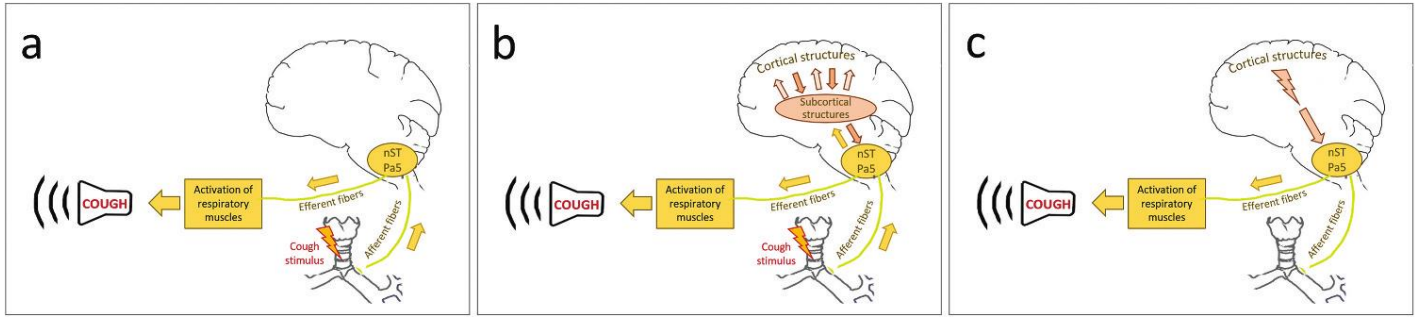


Figure 1. Schematic presentation of three different mechanisms of cough.

(a) Reflexive involuntary subconscious cough. After activation of cough receptors, the impulse is transferred into the brainstem (nST or Pa5), where it activates efferent fibers resulting in cough. The reflex is evoked without conscious control. (b) Provoked conscious cough. The impulse elicited in vagal terminals is modulated by cortical structures before cough is evoked. (c) Non-provoked voluntary cough – cough evoked by central stimulus without peripheral input.nST – nucleus of solitary tract, Pa5 – paratrigeminal nucleus.

(Mazzone SB et al. *Pulmonary Pharmacology & Therapeutics 2019; 55: 62–66)*

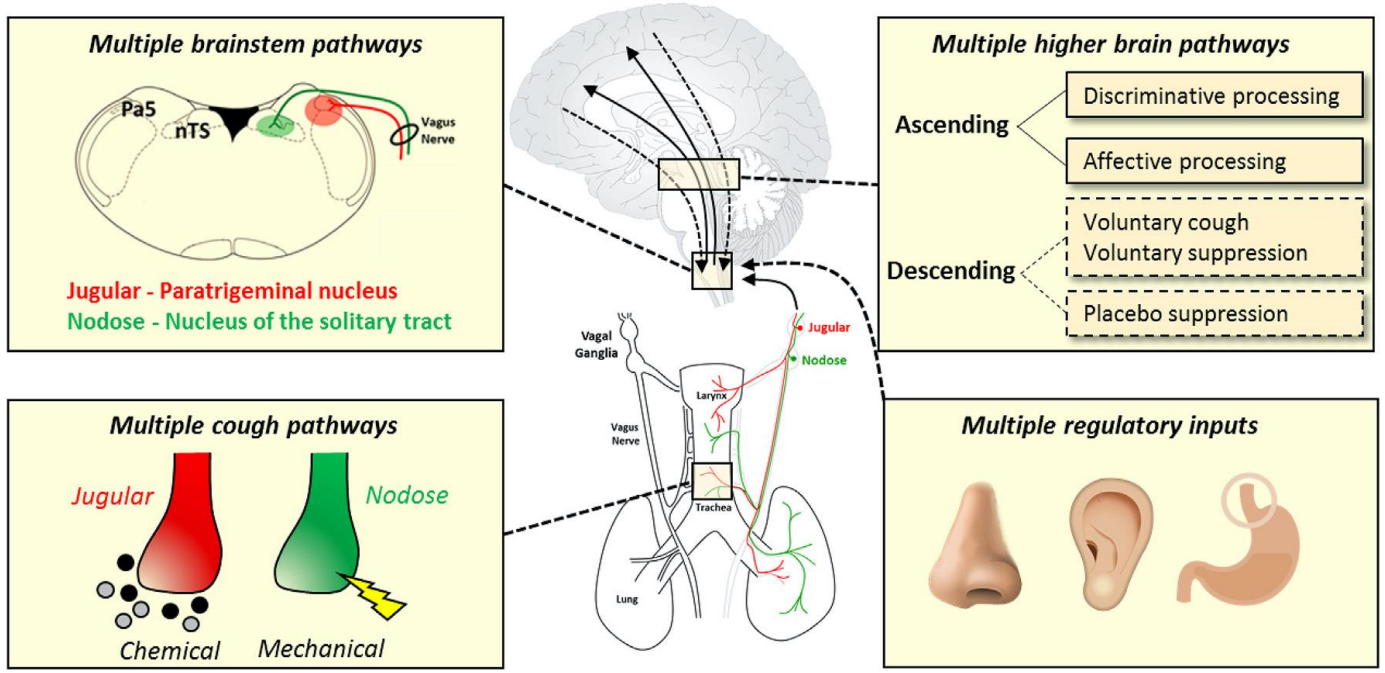


Fig. 1. Heterogeneous neural processes regulating cough. Two distinct vagal sensory pathways monitor the airways for cough evoking stimuli. Nodose sensory neurons are specialized to detect mechanical stimuli whereas jugular neurons respond to a wide variety of chemical mediators. Sensory inputs from non-pulmonary sources, including the nose, ear and esophagus can facilitate or inhibit cough evoked from the airways. In the brainstem, nodose and jugular sensory inputs terminate in different processing nuclei which contribute to distinct brainstem and brain cough sensory circuits that presumably encode different aspects of airway sensation. Cough can additionally be induced, facilitated or inhibited by descending pathways that provide volitional control over coughing. Other descending modulatory pathways can be recruited by cognitive processes that shape expectations, including the endogenous placebo system in the brain. Collectively these diverse neurobiological mechanisms regulate cough, and changes in the functioning of each may contribute differentially to the development of chronic cough in disease.

Aspetti patogenetici: tre set di recettori e fibre periferici (Satia I et al. Biochemical Pharmacology 179 (2020) 113901)

Fibra/recettore	Descrizione
C fibers	Networks of un-myelinated nerves with a conduction velocity of one m/sec can be found throughout the airways, are sensitive to chemical stimuli including inflammatory mediators (e.g. bradykinin, prostaglandins), environmental stimuli (e.g. pollutants, temperature) and are characteristically activated by capsaicin via the transient receptor potential vanilloid type 1 (TRPV1) receptor but also express transient receptor potential ankyrin-1 (TRPA1). It is currently thought that activation of jugular c-fibres evoke coughs whilst no- dose c-fibres do not, and may in fact be inhibitory to cough
Aδ fibres	The proximal airways are also innnervated by sub- epithelial myelinated nerves with a conduction velocity of five m/sec and which are also known as 'cough receptors', as they evoke cough. They respond to punctate mechanical stimuli, low osmo- larity and acidity but are insensitive to capsaicin and inflammatory mediators
Low Pressure Mechanosensors - (SARs) and (RARs):	from SARS and RARs is 15–18 m/sec suggesting Aβ range [43,44]. Both SARs and RARs are important in detecting lung volume, airway calibre, bronchoconstriction and airway oedema RARs are activated by dynamic lung inflation, pulmonary oedema, lung collapse, negative airway luminal pressures but quiescent during static lung inflations

E differenti possibili mediatori target (Grabczak EM et al. EXPERT REVIEW OF RESPIRATORY MEDICINE https://doi.org/10.1080/17476348.2020.1811686)

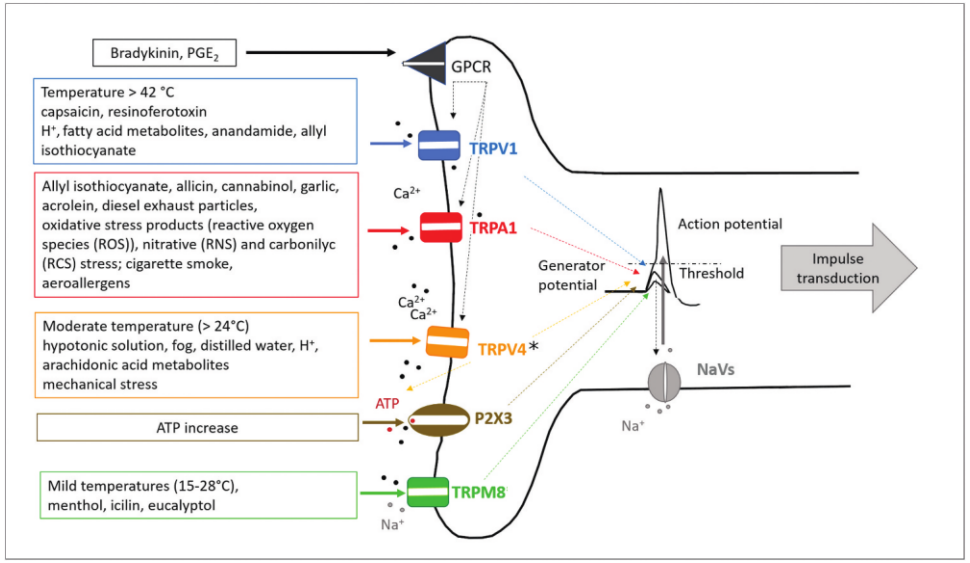
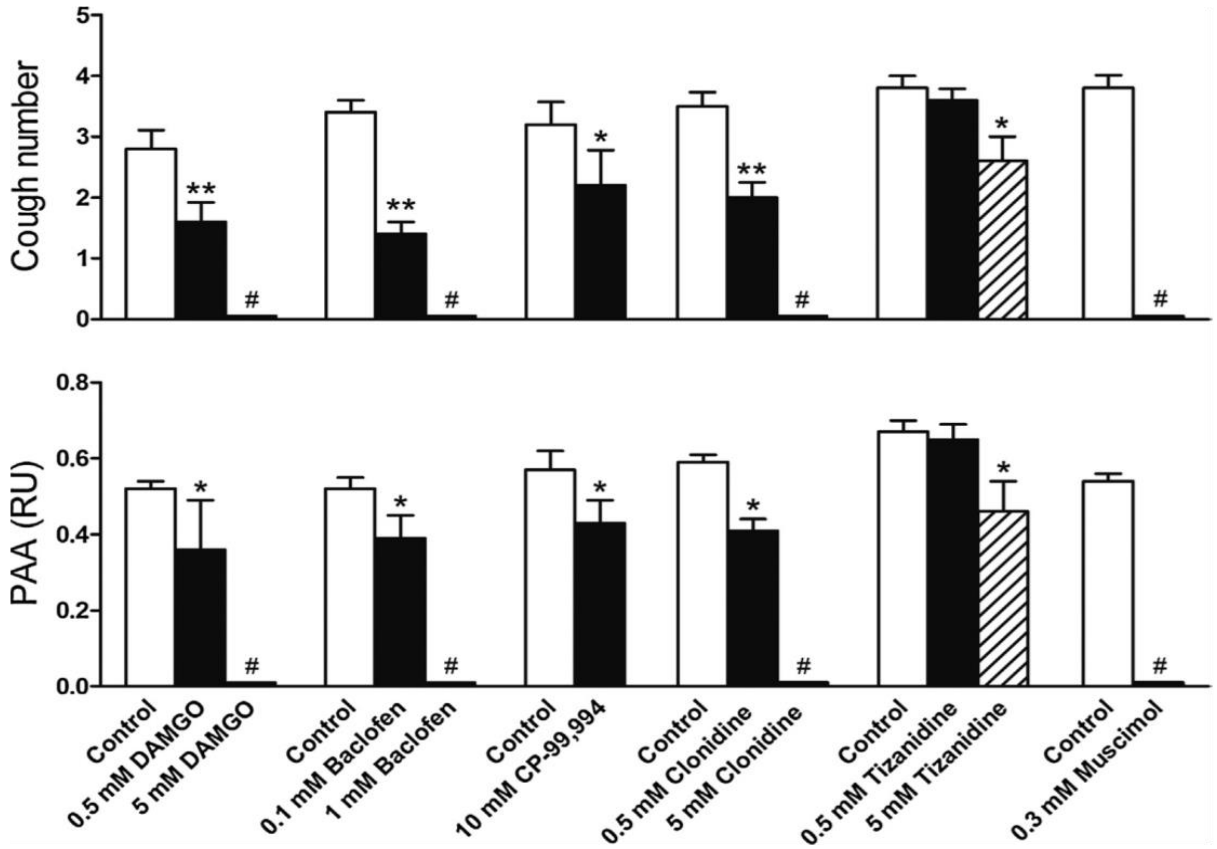


Figure 3. Afferent nerve terminals with receptors involved in cough reflex and their exemplary agonists.

ATP – adenosine triphosphate, GPCR – G protein-coupled receptor, PGE_2 – prostaglandin E_2, NaVs – voltage-gated sodium channels, TRPA1 – transient receptor potential ankyrin 1, TRPM8 – transient receptor potential melastatin 8, TRPV1 – transient receptor potential vanilloid 1, TRPV4- transient receptor potential vanilloid 4.* There are no sufficient data for expression of TRPV4 channels on sensory neurons in the lungs (as presented schematically on Figure 3). In fact TRPV4 are expressed in macrophages, epithelial and endothelial cells and activate nerve terminals in an indirect way.

Nel modello sperimentale, molti possibili rimedi (Mutolo D et al. Brain Res. Bull. 2007; 74: 284–293; Cinelli E et al. Respir. Physiol. Neurobiol. 2015; 219, 9–17.



Statement	Type	Strength of recommendation/quality of evidence
Individuals with CC have a cough hypersensitivity, which is also evoked by low intensity stimuli	Statement of fact	—
Cough hypersensitivity results from peripheral (vagal afferent receptors) and/or central (hyperactivity of the neural circuits and of the areas that regulate the cough reflex) sensitization	Statement of fact	—
Reduction in the efficacy of the descending inhibitory pathways may contribute to cough hypersensitivity, up to the possible development of a positive modulation similar to that involved in the establishment of chronic pain	Statement of fact	—
Interindividual variability in the mechanisms underlying CC makes the efficacy of central and peripheral pharmacological interventions poorly predictable	Statement of fact	—

CC, chronic cough

Ricerca della causa: approccio base

Statement	Type	Strength of recommendation/quality of evidence
Because the diagnostic workup of CC generally allows identification of one or more underlying causes, we recommend focusing the initial assessment (history and clinical examination) on the most common etiologies (e.g., asthma, UACS, reflux cough, lifestyle and medications, and other inflammatory/infiltrative lung diseases)	Recommendation	A/mModerate
If the first-line workup is inconclusive, further diagnostic investigations are needed to exclude a diagnosis of UCC	Recommendation	A/moderate

CC, chronic cough; UACS, uUpper airways cough syndrome; UCC, unexplained chronic cough

We recommend defining refractory CC (RCC) as a cough that persists despite optimal treatment for the presumed common and uncommon conditions

We recommend defining unexplained CC (UCC) in all circumstances when no diagnosable cause for CC has been found, despite extensive assessment for common and uncommon causes

Ricerca della causa: quando eseguire prove respiratorie e laringoscopia

Statement	Type	Strength of recommendation/quality of evidence
We recommend using respiratory function tests (spirometry) in all individuals with CC with inconclusive medical visit and chest X-ray	Recommendation	A/moderate
When lung function tests are normal, we recommend using the bronchoprovocation test with methacholine when the clinical history is suggestive of asthma or eosinophilic bronchitis	Recommendation	A/moderate
The methacholine test has a low specificity, and a positive result does not confirm asthma diagnosis while a negative result excludes it	Statement of fact	

CC, chronic cough

Statement	Type	Strength of recommendation/quality of evidence
We recommend performing laryngoscopy on all patients with CC who have suspected upper airway etiology	Recommendation	A / moderate
We suggest performing fiberoptic investigation (e.g., VNPL) when traditional laryngoscopy is not feasible (e.g., due to impeding reflexes or anatomical abnormality) and to objectify clinical signs of potential post-nasal drip or to rate laryngeal clinical signs potentially associated with GE reflux	Recommendation	C /low

CC, chronic cough; GE, gastroesophageal; VNPL, video nasopharyngolaryngoscopy

Ricerca della causa: il reflusso gastro-esofageo

Statement	Type	Strength of recommendation/quality of evidence
We recommend using MII-pH monitoring in patients with CC who do not have typical GERD signs or symptoms and in whom other more common causes of cough have been ruled out	Recommendation	A / high
We recommend performing MII-pH after suspending antisecretory therapy for at least 10 days; the test must be performed in specialized centers because establishing a causal link between episodes of reflux and cough is crucial and requires technical expertise	Recommendation	A / high

CC, chronic cough; GERD, gastroesophageal reflux disease; MII-pH, esophageal multichannel intraluminal pH-impedance

Statement	Type	Strength of recommendation/quality of evidence
A PPI trial is recommended in patients with CC who display concomitant typical reflux symptoms (n.b., the trial should be avoided in patients without typical reflux symptoms). The trial must be undertaken with a twice daily standard dose of PPI for at least 2 months. Lack of response should promote the search for other causes of CC	Recommendation	A / moderate

CC, chronic cough; PPI, proton pump inhibitor

Ricerca della causa: l'escreato (se presente)

Statement	Type	Strength of recommendation/quality of evidence
We suggest using microscopic and cultural sputum examination in cases of productive cough, to exclude the presence of chronic infection	Recommendation	B / moderate

Statement	Type	Strength of recommendation/quality of evidence
In the absence of sputum, bronchoscopy with broncho-alveolar lavage may be indicated in the presence of high suspicion of infection or interstitial lung disease	Recommendation	C / moderate

Statement	Type	Strength of recommendation/quality of evidence
Evidence of eosinophilic inflammation can be determined by induced sputum examination	Statement of fact	
FeNO testing and blood eosinophil count are non-invasive means to determine the presence of airway eosinophilia	Statement of fact	
FeNO levels, if increased, are predictive of a positive response to inhaled corticosteroids	Statement of fact	

FeNO, fractional exhaled nitric oxide

Ricerca della causa: quando fare prove allergometriche e HRCT

Statement	Type	Strength of recommendation/quality of evidence
We recommend performing allergy tests in all patients with CC if atopic sensitization is suspected	Recommendation	A / moderate
We recommend using the prick test as the first-line investigation for allergic respiratory disease	Recommendation	A / moderate
Given its better diagnostic specificity, we suggest searching for specific IgE with CRD	Recommendation	B / moderate

CC, chronic cough; CRD, component resolved diagnosis

Statement	Type	Strength of recommendation / quality of evidence
We do not recommend the use of HRCT as a first line investigation in patients with CC who display both normal physical examination and chest X-ray	Recommendation	D / moderate

Statement	Type	Strength of recommendation / quality of evidence
We suggest using HRCT only when the common causes of CC have been excluded, or in the presence of bibasilar Velcro-like crackles, or if an occupational or pharmacological risk profile is present	Recommendation	C / moderate

CC, chronic cough; HRCT, high-resolution chest computed tomography

Ricerca della causa: neuropatie e deficit di vitamina B12 (Chung KF et al. Lancet 2013)

	Cough as a symptom	Other symptoms and clinical features	Cough-reflex sensitivity
Laryngeal (laryngeal sensory neuropathy, post-viral vagal neuropathy, irritable larynx)	Yes (common)	Frequent throat clearing, hoarseness, weak voice, stridor, paradoxical vocal-cord dysfunction, globus sensation	Increased
Hereditary sensory neuropathy	Yes (rare)	Distal muscle weakness and wasting, reflux	Increased
Vitamin B_{12} deficiency	Yes (rare)	Anaemia, myelopathy, optic neuropathy, dementia	Increased
Diabetic autonomic neuropathy	Yes (when associated with oesophageal dysmotility)	Pain, autonomic dysfunction, sensory loss	Reduced
Neurosarcoidosis of vagus nerve	Yes (rare)	Facial pain, vocal-cord palsy	Unknown
Vagal neurofibroma	Yes (rare)	Pain , swelling, hoarseness	Unknown

Table: **Local and generalised sensory neuropathies, cough, and cough-reflex sensitivity**

Tosse cronica: possibili terapie

Terapia non farmacologica

Statement	Type	Strength of recommendation / quality of evidence
We suggest the use of logopedic treatment as a valid and safe non-pharmacological intervention for patients with CC	Recommendation	B / low
We recommend that logopedic treatment is guided by otorhinolaryngologist assessment	Recommendation	A / low

CC, Chronic cough

Terapia farmacologica: ICS

Statement	Type	Strength of recommendation / quality of evidence
We suggest the use of ICS for 2–4 weeks in cases of cough-variant asthma or eosinophilic bronchitis and, in the absence of a well-established pathogenetic mechanism, in the broader adult population with CC	Recommendation	B / moderate
We do not recommend the use of an ICS trial as a diagnostic *ex juvantibus* test for bronchial asthma	Recommendation	D / moderate
We suggest ICS as a valid therapeutic choice for the treatment of patients with CC with high suspicion of bronchial asthma	Recommendation	B / low
We suggest considering the addition of an antileukotriene agent (e.g., montelukast), when response to ICS is incomplete	Recommendation	C / Moderate

CC, chronic cough; ICS, inhaled corticosteroids

Terapia farmacologica: gli antibiotici

Statement	Type	Strength of recommendation / quality of evidence
We suggest using antibiotic therapy only in the presence of bacterial infection, as documented by microbiologic or radiologic findings	Recommendation	B / moderate

Terapia farmacologica: i neuromodulatori

Statement	Type	Strength of recommendation / quality of evidence
We suggest considering the use of neuromodulators (e.g., gabapentin and pregabalin) as an 'off-label' treatment for CC	Recommendation	C / moderate
We recommend progressive dose titration and close monitoring of patients prescribed with a neuromodulator for CC, since the clinical response can be extremely variable, and the risk of side effects high—especially in older patients with multiple comorbidities	Recommendation	A / hHigh
We recommend carefully discussing the risk–benefit balance with the patient before starting neuromodulator therapy for CC	Recommendation	A / high

CC, chronic cough

Terapia farmacologica: i sedativi centrali

Statement	Type	Strength of recommendation / quality of evidence
In adult patients with RCC/UCC, the use of an 'off-label' drug (e.g., low-dose morphine, 5–10 mg twice daily) for the shortest possible time is indicated after careful evaluation of the risk/benefit profile and following patient consent	Recommendation	A / high
Codeine might be prescribed in patients with UCC only when other treatments have failed because of the drug's highly variable interindividual metabolism and undesirable side effect profile	Recommendation	C / hoderate

CC, chronic cough; RCC, refractory chronic cough; UCC, unexplained chronic cough

But ACCP stresses the potential role of amitriptyline (Gibson P et al. CHEST 2016; 149(1):27-44)

TABLE 8] Effects of Neuromodulator Therapies on Cough in LCQ and CQLQ

Study	Change in LCQ From Baseline	Change in CQLQ From Baseline	MID and Comments
Jeyakumar et al,[22] 2006	NA	Amitriptyline: 24.53; guaifenesin-codeine: 2.92 (Note: Wang Gang estimated the scores according to Fig 1 provided by the author)	MID based on 2 methods: GRCS (10.58 ± 10.63) and Punum Ladder (21.89 ± 15.38]).[37]
Morice et al,[25] 2007	LCQ: morphine, 3.2; placebo, 1.2 Subdomains in LCQ (95% CI): physical, −1.1 to −4.3; psychological, −1.1 to −3.9; social, −1.7 to −3.0	NA	MID in LCQ is 1.3 ± 3.2 and MID for subdomains in LCQ is 0.2 ± 0.8 in physical, 0.8 ± 1.5 in psychological, and 0.2 ± 1.1 in social.[38]
Ryan et al,[34] 2012	LCQ: gabapentin, 2.5; placebo, 1.1		

CQLQ = cough-specific quality-of-life questionnaire; GRCS = Global Rating of Change Scale; LCQ = Leicester Cough Questionnaire; MID = minimum important difference. See Table 2 legend for expansion of other abbreviation.

A supporto dei sedativi centrali con effetto analgesico (Mutolo D. Respiratory Physiology & Neurobiology 2017; 243: 60–76)

Some of the main similarities between cough and pain.

Afferent fibres	
Aδ, C	Cough, pain
Receptors on sensory afferents	
$TRPV_1$,$TRPA_1$, ASICs	Cough, pain
ATP and adenosine receptors	Cough, pain
Bradykinin and prostaglandins receptors	Cough, pain
Histamine receptors	Cough, pain
Serotonin receptors	Cough, pain
Peripheral sensitization	Cough, pain
Central sensitization	Cough, pain
Corresponding clinical features	
Upper airway tickling sensation	Cough
Paresthesia	Pain
Hypertussia	Cough
Hyperalgesia	Pain
Allotussia	Cough
Allodynia	Pain

...and suggests gabapentin 900 mg bid! (Gibson P et al. CHEST 2016; 149(1):27-44)

TABLE 7] Overall Summary Treatment Effects from RCTs of UCC

Citation	Intervention	Cough Severity	Cough Frequency	Cough QOL
Nonpharmacologic				
Vertigan et al[23]	Speech therapy	+	NA	NA
Inhaled corticosteroid				
Rytila et al[27]	Mometasone 400 μg once daily	?+	NA	NA
Ribeiro et al[29]	Beclomethasone 500 μg tid	+	NA	NA
Pizzichini et al[39]	Budesonide 400 mg bid	–	NA	NA
Neuromodulators				
Khalid et al[24]	TRPV antagonist SB-705498 600 mg single dose	–	–	–
Ryan et al[34]	Gabapentin 900 mg bid	+	+	+
Morice et al[25]	Morphine 10 mg bid	+	NA	+
Jeyakumar et al[22]	Amitriptyline 10 mg nocte	NA	NA	+
Other				
Shaheen et al[36]	Esomeprazole 40 mg bd	–	NA	–
Yousaf et al[35]	Erythromycin 250 mg qd	NA	?	–
Sher et al[19]	Memantine 20 mg daily	NR	NR	NR
Holmes et al[26]	Inhaled ipratropium bromide 80 μg qid	+	NA	NA

– = no effect; NR = not reported; + = positive effect; QOL = quality of life; ? = possible effect in direction shown; RCT = randomized controlled trial; UCC = unexplained chronic cough. See Table 2 legend for expansion of other abbreviations.

Terapia farmacologica: PPI

Statement	Type	Strength of recommendation / quality of evidence
We recommend PPI therapy in patients with CC only in the presence of typical reflux symptoms (e.g., heartburn, regurgitation) and/or objectively documented acid reflux	Recommendation	A / moderate
We do not recommend the use of prokinetics or topical agents (e.g., alginates) as first choice therapy, but rather, as adjunctive treatment	Recommendation	D / moderate

CC, chronic cough; PPI, proton pump inhibitors

Terapia farmacologica: inibitori recettori P2X3

Statement	Type	Strength of recommendation / quality of evidence
The new anti-cough agents, which target specific channel receptors, have shown some effectiveness in reducing the frequency and intensity of cough, improving QoL in patients suffering from RCC and UCC	Statement of fact	
The first of these agents (i.e., gefapixant) demonstrates a good tolerability profile, except for dose-dependent dysgeusia	Statement of fact	

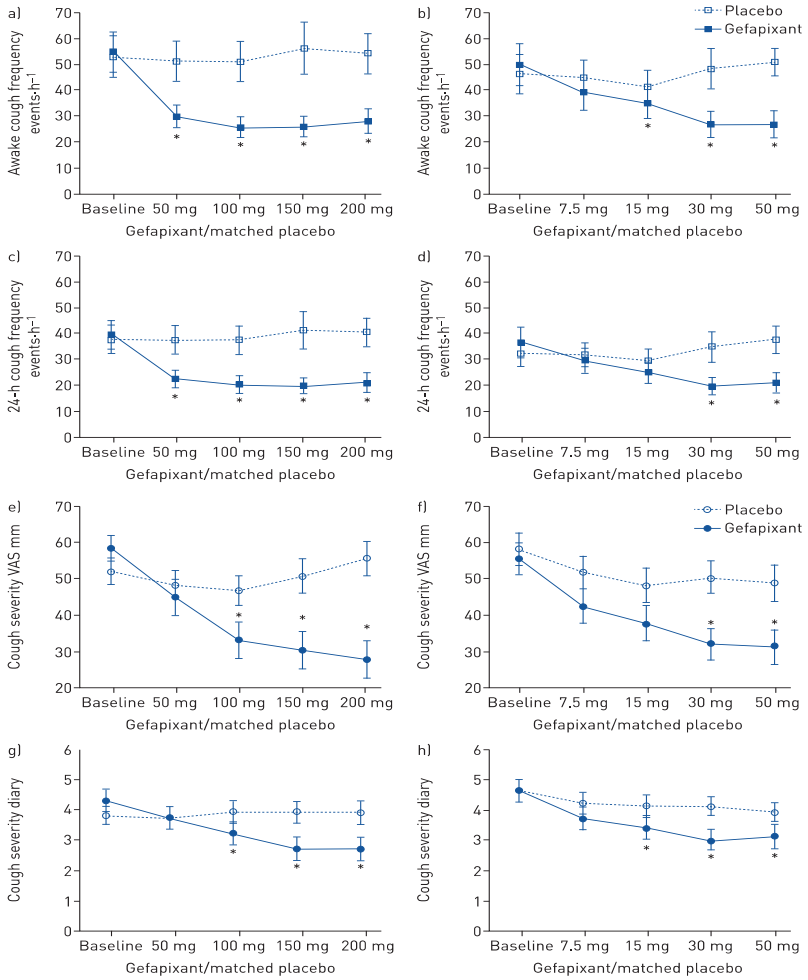
QoL, quality of life; RCC, refractory chronic cough; UCC, unexplained chronic cough

Il razionale per provare gli antagonisti del recettore P2X3 (Grabczak EM et al. EXPERT REVIEW OF RESPIRATORY MEDICINE https://doi.org/10.1080/17476348.2020.1811686)

At the present time, P2X3 receptor antagonists seem to be the most promising antitussive molecules. However, their beneficial effect does not apply to all patients with refractory CC and their efficacy in reducing cough related to different underlying respiratory conditions (e.g. COPD, interstitial lung diseases) is unknown. An antitussive effect has been reported for several other molecules that act at receptors such as TRPM8 and sodium channels/NaVs (e.g. carcainium or lidocaine). There is an urgent need for better characterization of different …

Gefapixant: efficace, ma…

(Smith JA et al. Eur Respir J 2020; 55: 1901615)



… dysgeusia or hypogeusia are very common for gefapixant=50 mg

	Placebo (n=63)	Gefapixant 7·5 mg (n=63)	Gefapixant 20 mg (n=63)	Gefapixant 50 mg (n=63)	Gefapixant combined (n=189)
Any adverse event	39 (62%)	44 (70%)	54 (86%)	58 (92%)	156 (83%)
Discontinued due to adverse event	2 (3%)	2 (3%)	3 (5%)	10 (16%)	15 (8%)
Serious adverse event	0	0	0	1 (2%)	1 (1%)
Adverse event related to treatment*	22 (35%)	19 (30%)	43 (68%)	55 (87%)	117 (62%)
Adverse events of special interest†					
Renal or urological event	3 (5%)	1 (2%)	2 (3%)	1 (2%)	4 (2%)
Taste related event‡	4 (6%)	6 (10%)	31 (49%)	51 (81%)	88 (47%)
Oral paraesthesia or hypoaesthesia	8 (13%)	6 (10%)	7 (11%)	13 (21%)	26 (14%)
Most common adverse events					
Dysgeusia	3 (5%)	6 (10%)	21 (33%)	30 (48%)	57 (30%)
Hypogeusia	1 (2%)	0	11 (18%)	15 (24%)	26 (14%)
Headache	3 (5%)	4 (6%)	12 (19%)	4 (6%)	20 (11%)
Upper respiratory tract infection	2 (3%)	5 (8%)	9 (14%)	6 (10%)	20 (11%)
Ageusia	1 (2%)	0	3 (5%)	13 (21%)	16 (9%)
Paraesthesia oral	5 (8%)	4 (6%)	5 (8%)	4 (6%)	13 (7%)
Cough	2 (3%)	2 (3%)	5 (8%)	5 (8%)	12 (6%)
Hypoaesthesia oral	3 (5%)	2 (3%)	4 (6%)	5 (8%)	11 (6%)
Nausea	0	0	4 (6%)	6 (10%)	10 (5%)
Urinary tract infection	2 (3%)	3 (5%)	5 (8%)	2 (3%)	10 (5%)

*Adverse events determined by the investigator to be possibly, probably, or definitely related to study treatment. †Prespecified. ‡Taste-related adverse events included dysgeusia, hypogeusia, and ageusia.

Table 4: **Summary of safety and tolerability**

Sivopixant, dotato di maggiore selettività per P2X3, può proteggere dalla disgeusia? Numeri troppo piccoli per dirlo (Niimi A et al. Eur Respir J 2022; 59: 2100725)

TABLE 5 Treatment-related adverse events (AEs)

	Sivopixant (n=31)		Placebo (n=31)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Patients with any treatment-related AEs	4 (12.9)	4	1 (3.2)	1
Nervous system disorders	2 (6.5)	2	0	0
Dysgeusia	1 (3.2)	1	0	0
Hypogeusia	1 (3.2)	1	0	0
Gastrointestinal disorders	1 (3.2)	1	1 (3.2)	1
Hypoesthesia oral	1 (3.2)	1	1 (3.2)	1
Hepatobiliary disorders	1 (3.2)	1	0	0
Drug-induced liver injury	1 (3.2)	1	0	0

Treatment-related AEs are defined as events in which causality cannot be denied among AEs reported after initial administration of study drugs.

Ma anche un dosaggio di gefapixant 30 mg può essere efficace e meglio tollerato

Per inciso, la forza del placebo vs Gefapixant 45 mg b i d

(McGaevey LP et al. *Lancet* 2022; 399: 909–23)

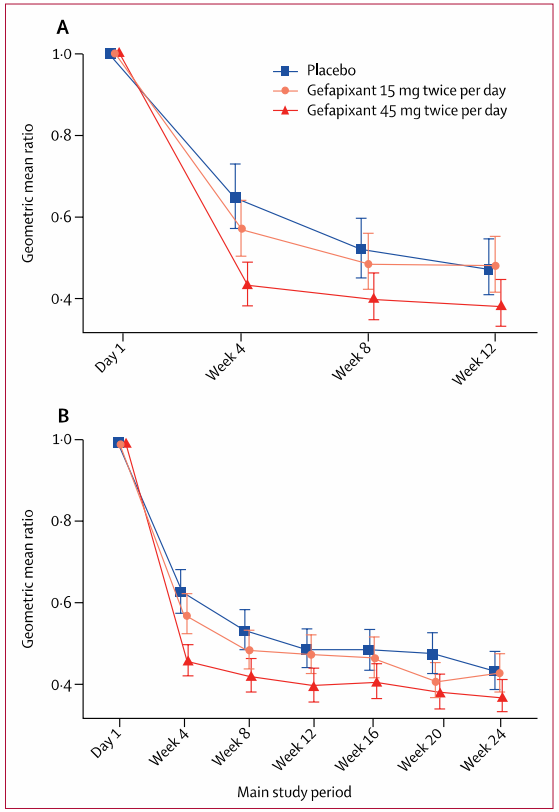


***Figure 2*: 24-h cough frequency over 12 weeks in COUGH-1 (A) and 24 weeks in COUGH-2 (B)**
Error bars are 95% CIs.

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day
COUGH-1			
Number of participants	243	244	243
Any adverse event	184 (75·7%)	186 (76·2%)	208 (85·6%)
Serious adverse events	14 (5·8%)	17 (7·0%)	13 (5·3%)
Adverse events related to treatment*	47 (19·3%)	49 (20·1%)	158 (65·0%)
Adverse events of special interest			
Taste-related adverse events	11 (4·5%)	31 (12·7%)†	144 (59·3%)†
Most common adverse events (>8% in a single treatment group)			
Ageusia	0	3 (1·2%)	33 (13·6%)†
Back pain	19 (7·8%)	14 (5·7%)	20 (8·2%)
Dysgeusia	8 (3·3%)	22 (9·0%)‡	88 (36·2%)†
Headache	31 (12·8%)	34 (13·9%)	29 (11·9%)
Hypogeusia	1 (0·4%)	5 (2·0%)	13 (5·3%)†
Nasopharyngitis	51 (21·0%)	47 (19·3%)	50 (20·6%)
Taste disorder	2 (0·8%)	2 (0·8%)	24 (9·9%)†
COUGH-2			
Number of participants	432	442	440
Any adverse event	349 (80·8%)	373 (84·4%)	399 (90·7%)
Serious adverse events	25 (5·8%)	24 (5·4%)	25 (5·7%)
Adverse events related to treatment*	91 (21·1%)	145 (32·8%)	312 (70·9%)
Adverse events of special interest			
Taste-related adverse events	36 (8·3%)	89 (20·1%)†	303 (68·9%)†
Most common adverse events (>8% in a single treatment group)			
Ageusia	6 (1·4%)	13 (2·9%)	67 (15·2%)†
Dysgeusia	28 (6·5%)	56 (12·7%)‡	193 (43·9%)†
Headache	67 (15·5%)	74 (16·7%)	70 (15·9%)
Hypogeusia	3 (0·7%)	17 (3·8%)‡	60 (13·6%)†
Influenza	35 (8·1%)	30 (6·8%)	24 (5·5%)
Nasopharyngitis	70 (16·2%)	93 (21·0%)	70 (15·9%)
Nausea	32 (7·4%)	26 (5·9%)	47 (10·7%)
Taste disorder	1 (0·2%)	8 (1·8%)‡	37 (8·4%)†
Upper respiratory tract infection	27 (6·3%)	38 (8·6%)	30 (6·8%)

Data are n or n (%). Difference in percentage versus placebo for taste-related adverse events were tested for significance. Taste-related adverse events included ageusia, dysgeusia, hypergeusia, hypogeusia, and taste disorder; dysgeusia is defined as a change in taste to something specific, such as salty or sweet, taste disorder is defined as a non-specific change in taste, ageusia is defined as loss of taste, hypergeusia is defined as increased taste, and hypogeusia is defined as diminished taste. *Determined to be possibly, probably, or definitely related to study treatment by the investigator. †p≤0·001. ‡p≤0·05.

***Table 3*: Summary of adverse events by 52 weeks in COUGH-1 and COUGH-2**

L'inquadramento del malato con la tosse cronica: uno straordinario esempio di VMD (Kum E et al. ERJ Open Res 2022; 8: 00667-2021)

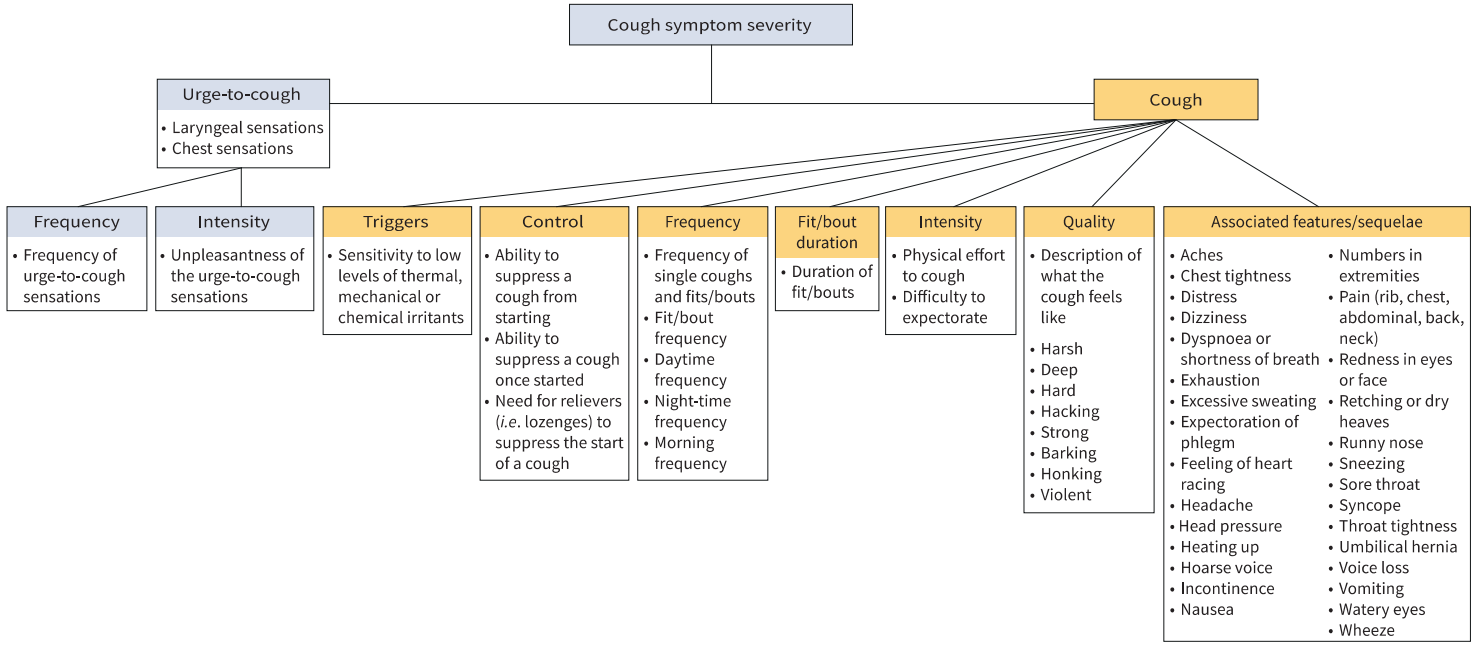


FIGURE 1 Conceptual framework of cough symptom severity in patients with refractory or unexplained chronic cough (RCC/UCC).

CHRONIC COUGH DIAGNOSIS ALGORITHM

cough persisting for > 8 weeks

MULDISCIPLINARY APPROACH – 'COUGH CLINIC'

FIRST LEVEL INVESTIGATIONS

- **HISTORY:** CC duration, circadian rhythm, triggers, family history, associated symptoms
- **PHYSICAL EXAMINATION:** chest, throat, nose and ear
- **Complications of CC:** e.g. sleep and mood disturbances, urinary incontinence, visceral hernia, rib fracture
- **Impact on QoL:** LCQ, SF-36
- **DRUG HISTORY/RISK FACTORS:** e.g., ACEI, environmental and occupational pollutants
- **CHEST X-ray, spirometry**

SECOND LEVEL INVESTIGATIONS

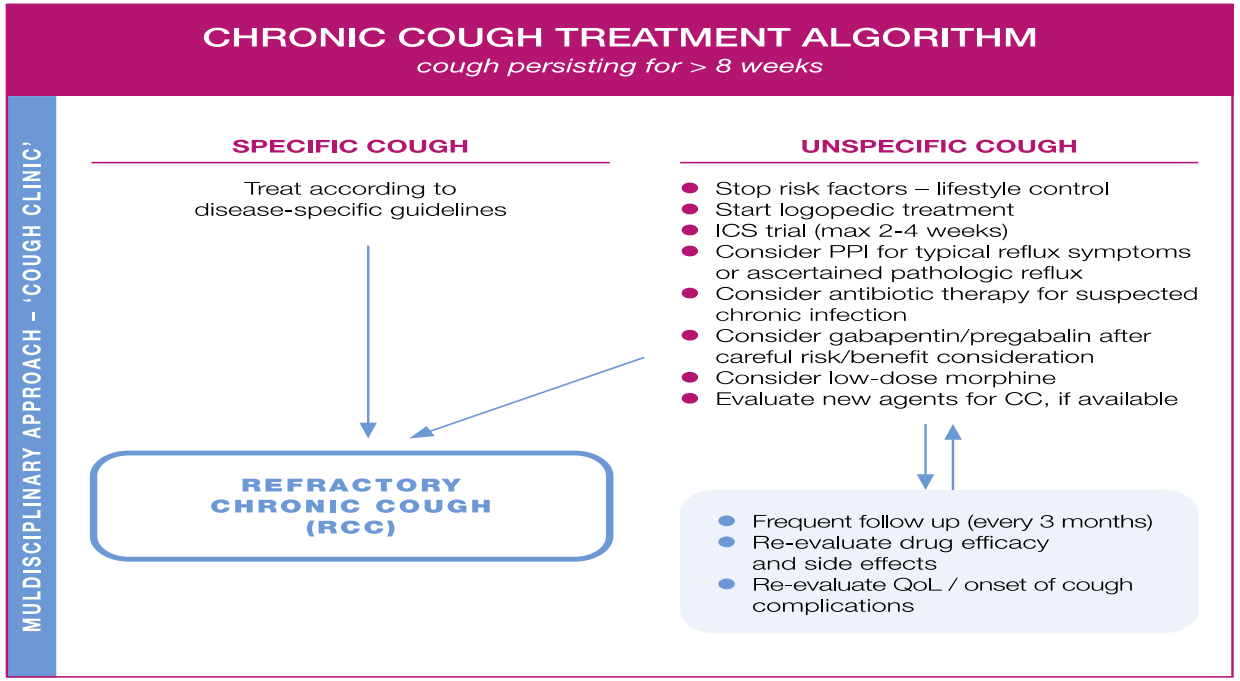
In selected cases:	chest HRCT, ICS trial
PULMONOLOGIST	FeNO, bronchoprovocation test, induced sputum analysis, bronchoscopy
OTORHINOLARYNGOLOGIST	Rhino-Pharingeal-Laryngoscopy
ALLERGOLOGIST	Skin prick tests, serum IgE
GASTROENTEROLOGIST	pH-impendence monitoring, PPI trial
GERIATRICIAN	Comprehensive Geriatric Assessment

EXPLAINED COUGH

Asthma, cough-variant asthma, eosinophilic bronchitis, smoking, COPD, medications, UACS, reflux cough (less common causes: interstitial lung diseases, bronchiectasis)

UNEXPLAINED CHRONIC COUGH (UCC)

De Vincentis A et al. Aging Clin Exp Res. 2022 Jul;34(7):1529-1550.



De Vincentis A et al. Aging Clin Exp Res. 2022 Jul;34(7):1529-1550.