

Management of cough

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**Murray & Nadel's Textbook of Respiratory
Medicine**

CHEST Guideline

ERS guidelines

**KAAACI Evidence-Based Clinical Practice
Guidelines for Chronic Cough in Adults and
Children in Korea**

European Journal of Internal Medicine

**Management of chronic refractory cough in
adults**

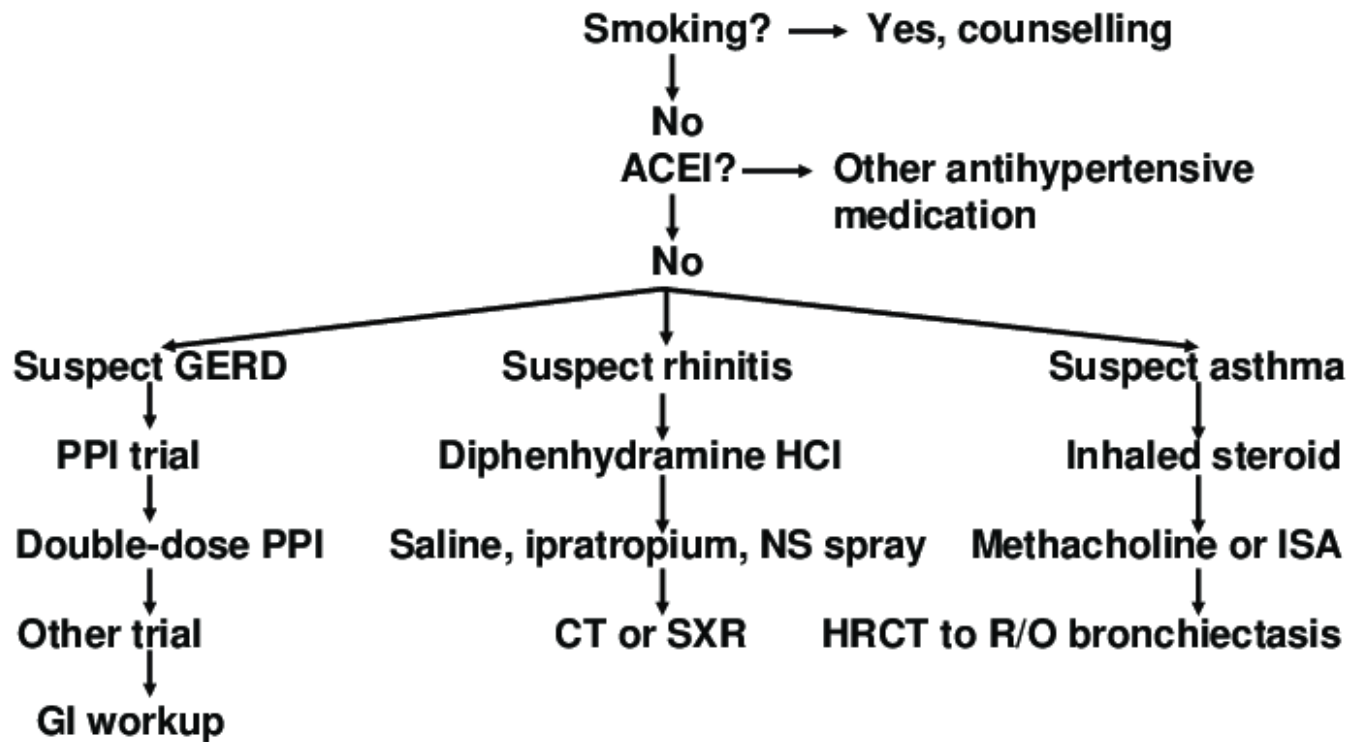
**we summarize non-pharmacologic and pharmacologic
management of adult patients with cough**

guidelines suggest :

- ❑ diagnostic algorithm to identify underlying diseases , then specific treatments for underlying disease.
- ❑ may be more than one associated cause
- ❑ PND, asthma, and GERD :three most common conditions associated with chronic cough, and a diagnostic approach to exclude these conditions early on is sensible.
- ❑ Other triggers and diseases:smoking, drugs such ACE-I, occupational irritants, foreign bodies, COPD, Eosinophilic bronchitis, and bronchiectasis,chest neoplasms, CF, ILD
- ❑ **chronic idiopathic cough (unexplained chronic cough):**
After excluding causes, triggers and diseases, patients experience chronic cough of unclear etiology
- ❑ **chronic refractory cough (CRC) :** cough persists despite optimal treatment of underlying disease

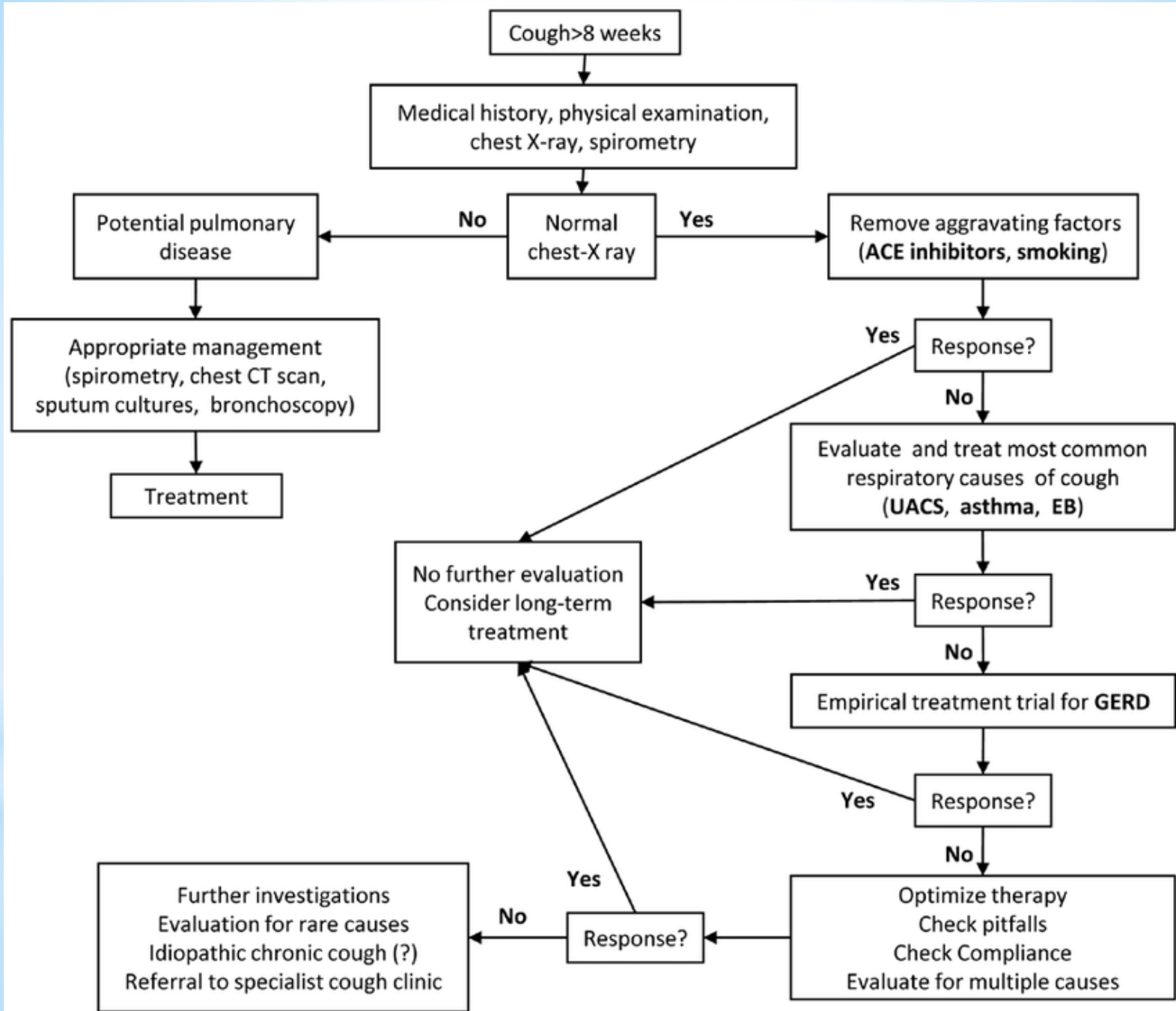
Educator management algorithm

Consenting patients randomized to educator



PHARMACOLOGIC APPROACH:

- * **ANTITUSSIVE THERAPIES** : by inhibition of central mechanisms within brainstem or peripheral cough sensors in airways.
- * An ideal antitussive :suppresses hyper tussive component of cough in disease allowing protective cough to be active.



ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

- patient with cough who is taking ACE inhibitor, first step in workup is stop drug and reevaluate if cough persists.
- replace it with alternative therapies, such : angiotensin II receptor antagonists.

Acute cough: usually due to viral or bacterial upper respiratory tract infection.

COUGH OF COMMON COLD

- ☐ usually self-limiting
- ☐ starts within first 48 hours with accompanying symptoms of postnasal drip, throat-clearing, sore throat, nasal obstruction, and nasal discharge
- ☐ usually resolve within 2 weeks.
- ☐ usually self-medicate with antitussive preparations, despite a lack of good evidence for their effectiveness in acute cough.
- ☐ Codeine ineffective
- ☐ dextromethorphan : variable , small effect
- ☐ Honey provide symptomatic relief

- ☐ cough due to acute viral airway infections should be treated only with fluids and humidity

Acute cough caused by an exacerbation of underlying diseases, such as an upper airway cough syndrome secondary to rhino sinusitis, asthma, COPD, or pneumonia.

UPPER AIRWAY COUGH SYNDROME (UACS)

POSTNASAL DRIP (RHINOSINUSITIS)

- ❑ Most common causes
- ❑ best treatment: topical administration of corticosteroid drops in head-down position, with concomitant use of antihistamines.
- ❑ Topical steroids offer a local effect with a minimum of side effects.
- ❑ severe symptoms controlled initially by short course of oral steroids, followed by topical therapy
- ❑ topical anticholinergic spray to nose: ipratropium bromide, dry excessive nasal secretions provide additional benefit.
- ❑ Topical decongestant vasoconstrictor sprays useful therapy for a few days, but rebound nasal obstruction develop after prolonged use
- ❑ Antibiotic therapy: necessary in acute sinusitis involving bacterial infection with mucopurulent secretions persisted at least 10 days.

ASTHMA AND ASSOCIATED EOSINOPHILIC CONDITION

- ☐ two conditions presenting with chronic cough, cough-variant asthma and eosinophilic bronchitis, eosinophils predominate in airways
- ☐ inhaled or oral corticosteroids, inhibit eosinophilia, effective in controlling cough

Cough associated with asthma should be treated:

- ☐ combination :ICS & LABA, over a prolonged period (3-6 months)
- ☐ Cough-variant asthma responds to leukotriene receptor antagonists.
- ☐ trial corticosteroids: prednisolone 40 mg/day - 2 weeks ,in asthmatic patients ,cough despite adequate inhaled anti asthma medication

GASTROESOPHAGEAL REFLUX DISEASE

☐ Reduction of acid production : H₂- blockers or PPI

recommended :objective evidence of heightened esophageal acid exposure on pH monitoring or with complaints of heartburn benefit from acid-suppressive therapy provided for 2 months.

☐ esophageal-tracheobronchial cough reflex suppressed by perfusion distal esophagus with lidocaine

☐ inhalation of anticholinergic agent, ipratropium bromide

Both guidelines recommend against use PPIs in absence of GERD

☐ no good evidence for use prokinetics :domperidone or metoclopramide, associated with potential side effects

☐ effectiveness of anti reflux surgery, laparoscopic fundoplication in chronic cough associated with GERD whose cough failed to respond to medical therapy, unclear.

☐ Conservative measures

- weight reduction
- a high protein, low-fat diet
- No eating 2-hour prior to reclining
- elevation of head of bed
- Avoidance of reduce lower esophageal tone
- avoidance of coffee and smoking may be useful.

CHRONIC BRONCHITIS/COPD

- ❖ productive cough in chronic bronchitis is exacerbated by upper respiratory infections with common viruses or respiratory bacteria or by exposure to irritating dusts or environmental pollutants.
- ❖ Cessation cigarette smoking : accompanied by reduction in cough, most often within 4 to 5 weeks.
- ❖ Treatment of chronic airflow obstruction with short-acting and/or long-acting β_2 -adrenoceptor agonists and anticholinergic agents, particularly in presence of dyspnea.
- ❖ Suppression of inflammatory process in small airways tried with combination of inhaled corticosteroids and long acting β -agonists.
- ❖ Mucolytic therapy may reduce incidence of exacerbations.

Cough in bronchiectasis

most effective mechanism for clearing airway secretions.

Chest physiotherapy to improve airway clearance remains essential.

Long-term macrolide therapy may lead to an improvement in exacerbations and lung function.

■ cough controlled:

inhaled β_2 -agonists improve mucociliary clearance and reverse associated bronchoconstriction,

intermittent antibiotic therapy.

□ antitussives not recommended, but, of severe cough, some suppressive effect may be clinically beneficial.

POST INFECTIOUS

- ☐ initial trigger :upper respiratory tract infection
- ☐ cough expected to last for only a week persists for many months
- ☐ Inhaled corticosteroids , variable success.
- ☐ Oral steroids may be successful.
- ☐ Macrolide antibiotics or trimethoprim-sulfamethoxazole effective in eliminating *B. pertussis* but do not alter subsequent clinical course.

IDIOPATHIC PULMONARY FIBROSIS

cough :

- refractory to antitussive therapy
- harms quality of life.
- usually experience higher rates of cough.
- often associated with other comorbidities, such as PND, GERD, or cough-variant asthma.

Comorbid conditions need to be treated.

- ✓ Conventional antitussive therapies, opiates, not effective.
- ✓ Corticosteroid therapy may sometimes work.
- ✓ new antifibrotic treatment for IPF, **pirfenidone**, shown in an observational study reduce cough frequency and subjective cough measures.
- ✓ trial of **thalidomide** indicated some beneficial effect

OTHER CONDITIONS

causing cough include bronchogenic carcinoma, metastatic carcinoma, sarcoidosis, chronic aspiration, interstitial lung disease, or left ventricular failure, obstructive sleep apnea and chronic tonsillar enlargement.

Nocturnal cough with OSA presents with snoring, nocturnal heart burn, and symptoms of rhinitis.

Continuous positive airway pressure (CPAP) therapy with humidification is usually effective.

CHRONIC COUGH OF UNKNOWN CAUSE (IDIOPATHIC COUGH)

- ☐ Up to 46% of patients with chronic cough
- ☐ Idiopathic cough is more commonly found in women aged between 50 and 70 years with a cough onset at menopause and associated with autoimmune disorders.
- ☐ **Assessment of laryngeal dysfunction , important aspect of management of chronic idiopathic cough.**

- ❖ Neuromodulator
 - ❖ PPI
 - ❖ Ipratropium bromid
 - ❖ Non pharmacologic (speech treatment)
 - ❖ □ ICS (sputum eosinophil)
- ❖ patients with unexplained chronic cough and negative tests for bronchial hyper responsiveness and eosinophilia (sputum eosinophils, exhaled nitric oxide), suggest ICS not be prescribed (Grade 2B)
- ❖ guidelines differ in their recommendations of inhaled corticosteroids (ICS) and morphine.

Treatment medications
for unexplained CC

When treatment cause of cough not effective or not available, therapies directed at eliminating symptom of cough irrespective of cause of cough should be tried

Which patients should be considered neuromodulatory therapy?

- ❑ chronic cough persists after treatment of underlying disease, symptomatic approach with neuromodulators considered
- ❑ both opioid and non-opioid: suppress cough via activity on central cough center
- ❑ effectiveness of neuromodulators suggests chronic cough , a neuropathic condition
- ❑ act on enhanced neural sensitization that underlies idiopathic or refractory cough

NARCOTIC AND NON-NARCOTIC ANTI TUSSIVES

Opiates : morphine, diamorphine, codeine most effective antitussive agents.

Codeine :

- methylether of morphine
- most commonly prescribed antitussive.
- little effect on cough in selected COPD or against acute cough of common cold
- used cautiously in reduced hepatic function, used without dose modification in renal failure.
- side effect: Drowsiness , nausea, vomiting constipation.
- Rarely, allergic cutaneous reactions: erythema multiform
- cause physical dependence, but on a smaller scale than morphine.
- codeine not effective in chronic refractory cough, not recommended by ERS guidelines,

Dihydrocodeine has no particular advantage over codeine and may cause more addiction than codeine.

Pholcodine as effective as codeine

Morphine and diamorphine :

- only for severe distressing cough cannot relieved by other antitussives
- confined patients: terminal illness , bronchial carcinoma
- Diamorphine preferred to morphine because lower incidence of nausea and vomiting.

ERS guidelines recommend a trial of low dose slow-release morphine (5–10 mg twice daily) in adults with CRC.

opioids also relieve anxiety and pain.

Opioids cause:

- * sedation
- * respiratory depression
- * constipation
- * Exacerbate wheezing through release of histamine, but this is rare.
- * physical dependence,
- * GI colic.

Tramadol:

- ❖ opioid similar to codeine and morphine.
- ❖ neither recommended nor discouraged by guidelines

Dextromethorphan :

- probably most commonly used non-opioid agent
 - as effective as codeine in suppressing acute and chronic cough when given orally, with one study showing its superiority over codeine.
 - Antitussive efficacy of a single 30-mg dose demonstrated against cough associated with upper respiratory tract infections in adults.
 - However, in children, shown ineffective in cough due to upper respiratory tract
 - Side effects few at usual dose but, at higher doses, dizziness, nausea, vomiting, and headaches reported.
 - avoided :hepatic insufficiency .
 - caution : patients on monoamine oxidase inhibitors in whom central nervous depression and death reported
- dextromethorphan neither recommended by guidelines

☐ noscapine and levo propoxyphene: non-narcotic preparations
their antitussive efficacy has not been proved.

☐ Other drugs acting on cough receptors include benzonatate,
which inhibits vagal stretch lung receptors, with a possible
central effect.

OTHER NON-NARCOTIC ANTITUSSIVES

☐ Amitriptyline

A prospective, randomized, controlled open trial comparing effectiveness of amitriptyline versus codeine/guaifenesin for chronic cough following an upper respiratory tract infection showed that **amitriptyline led to a complete response** cough in most subjects while none of codeine/guaifenesin group had a complete response.

☐ All patients treated with a single dose 10 mg of amitriptyline for 21 days. At least a 40% reduction in self reported symptoms

☐ Amitriptyline is neither recommended nor discouraged by guidelines

Gabapentin and pregabalin : GABA analogs bind to voltage-gated calcium channels and inhibit centrally neurotransmitter release.

Gabapentin:

CRC for more than 8 w, gabapentin , 10 weeks significantly improved cough-specific quality of life (Leicester Cough Questionnaire score), cough severity (visual analogue scale) and cough reflex sensitivity

- CHEST Expert Cough Panel recommends
- ERS also suggest a trial of gabapentin or pregabalin in adults with CRC

cough hypersensitive syndrome

disorder characterized by troublesome coughing triggered by low levels of thermal, mechanical, or chemical exposure, with a persistent tickling sensation in the throat that leads to paroxysms of coughing triggered by changes in ambient temperature; taking a deep breath; laughing; talking; and exposure to cigarette smoke, aerosol sprays, perfumes, or certain odors.

neuromodulatory therapies should tried.

LOCAL ANESTHETICS(Lidocaine aerosol inhaled)

- ☐ nonselective blocker sodium channels
- ☐ efficacy for cough reduction.
- ☐ inhibiting sensory neural activity
- ☐ also removes reflexes that protect lung from noxious substances
- ☐ a nebulizer (e.g., lidocaine or bupivacaine) administered to intractable cough with variable results, reserved for selective individual cases.
- ☐ in palliative management of cough associated with malignancies.
- ☐ effects transient
- ☐ avoided in asthma , induce severe bronchoconstriction.
- ☐ safe option , 2-week trial identify patients derive most therapeutic benefit.

❑ ipratropium bromide :significant reduction in cough severity and a good safety in chronic persistent cough

❑ Tiotropium: modulate airway sensory nerve activity
and thereby cough reflex, through a mechanism unrelated to its anticholinergic activity

* **EXPECTORANTS AND MUCOLYTICS**

- ❑ small reduction in exacerbation of bronchitis with oral acetylcysteine, accompanied by **small improvement in cough**
- ❑ **Aromatic agents :eucalyptus and menthol have decongestant effects in nose and useful in short-term relief of cough.**
- ❑ **Menthol inhibits capsaicin-induced cough**

* POTENTIAL NEW ANTITUSSIVES

Because of relative low efficacy of current antitussives, several new classes of antitussives developed on basis of understanding of cough reflex and of membrane receptors and channels on cough sensors

New cough suppressants :include new opioids or blockers of ion channels on vagal afferent

TRP channels target for cough suppression. TRPV1 agonists : patients with chronic cough increased TRPV1-positive nerve fibers in their airways.

Agonists TRPA1:cinnamaldehyde, acrolein, allyl isothiocyanate (akamustard oil), cause cough, TRPA1 antagonists are tested in cough.

orally NOP1 receptor agonist (*nociceptin opioid 1*) tested in subacute cough: no significant efficacy

NaV1.7subunit : control of cough responses. there are no specific blockers of NaV1.7

Memantine, channel blocker, inhibits cough and currently being tested

ATP P2X2/3 antagonist, gefapixant, in suppressing chronic cough in phase II clinical trials with a reduction in cough frequency of 75% is currently undergoing phase III testing.

notable side effect of gefapixant is a reduction in taste because P2X2 receptors are not only expressed by airway sensory nerves but also by gustatory nerves involved in taste processing.

Alpha-7 cholinergic receptors may be expressed on central pathways that mediate cough inhibition

centrally acting neurokinin 1 receptor antagonists are also currently in trial for chronic refractory cough, showing improvements in cough frequency and patient quality of life in early phase II trials

Non-pharmacologic treatment

COUGH SUPPRESSION THERAPIES

SPEECH PATHOLOGY MANAGEMENT: refractory chronic cough

VCD: involuntary vocal fold adduction during inspiration

Patients should understand goals of therapy, suppress cough despite triggering sensation, and enhance patients' ability to voluntarily control cough.

consisting : educational component about cough, relaxed throat breathing techniques, and psycho educational counseling ,vocal hygiene training , speech therapy, breathing exercises

Vocal hygiene education :avoiding passive smoking, avoiding mouth breathing, and behavioral management GERD

breathing exercises : breathing control/diaphragmatic breathing, relaxed breathing control techniques described to relax throat, neck, shoulder muscles

administered by voice and speech and language specialist or respiratory physiotherapist in sessions every four weeks

❑ ERS guidelines: physiotherapy/speech and language therapy considered for CRC ,an alternative to drug treatment

❑ ACCP guidelines :identifying patients with oral-pharyngeal dysphagia, or presence of conditions associated with high risk of aspiration, are potential candidates for speech pathology Treatment

■ Despite efficacy and advantages of speech pathology intervention, limited guidance to when patients referred for treatment.

ERS

Treatment of chronic cough

Should anti-asthmatic drugs (anti-inflammatory or bronchodilator drugs) used to treat patients with chronic cough?

- ❖ suggest short-term ICS trial (2-4 weeks) in adult patients with chronic cough (conditional recommendation, low quality evidence).
- ❖ suggest a short-term anti-leukotriene trial (2-4 weeks) in chronic cough, particularly in those with asthmatic cough (conditional recommendation, low quality evidence).
- ❖ 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-acids

- *Should anti-acid drugs (PPIs and H2 antagonists) be used to treat patients with chronic cough?*
- **suggest: clinicians do not routinely prescribe anti-acid drugs in adult patients with chronic cough** (conditional recommendation, low quality evidence).

should drugs with promotility activity be used to treat patients with chronic cough?

- ☐ currently insufficient evidence to recommend routine use of macrolide therapy in chronic cough.
- ☐ A one month trial of macrolides can be considered in cough of chronic bronchitis refractory to other therapy .conditional recommendation, low quality evidence).
- ☐ No RCTs undertaken with pro-motility agents, such as baclofen, metoclopramide or domperidone, in patients with chronic cough.

Neuromodulators

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

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).

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

Non-pharmacological cough control therapy

Should non-pharmacological therapy (cough control therapy) be used to treat patients with chronic cough?

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

Antibiotics for chronic wet cough in children

In children with chronic wet cough with normal chest x-ray, normal spirometry and no warning signs, should a trial of antibiotics be used?

A trial of antibiotics is suggested in children with chronic wet cough with normal chest x-rays, normal spirometry and no warning signs (conditional recommendation, low quality evidence).

**Chronic cough management is often complex,
requiring an individualized treatment plan.**

THANK YOU