### Treatment of cough in

### lung diseases

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IM - REVIEW



### The pathogenetic mechanisms of cough in idiopathic pulmonary fibrosis

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#### Accepted Manuscript

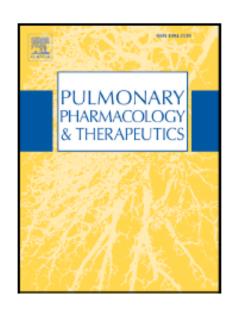
Idiopathic pulmonary fibrosis-associated cough: Mechanisms and management

Katherine Myall, Joanne E. Kavanagh, Surinder S. Birring

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Reference: YPUPT 1794



Diffuse Lung Disease How I Do It



### Managing Cough in Idiopathic Pulmonary Fibrosis



Yosafe Wakwaya, MD; Deepa Ramdurai, MD; and Jeffrey J. Swigris, DO, MS

- Patients complain of a chronic dry cough in 80% of cases
- A cough is often the first symptom
- Gastroesophageal reflux may promote coughing in IPF
- Antacid therapy decreases acidic reflux but does not have an effect on cough frequency in patients with IPF.
- Coughing is often the first symptom of this interstitial lung disease, preceding dyspnea by years.
- Coughing is more common in IPF patients who have never smoked than in smokers.
- ▶ In one study, 62% of patients with IPF had moderate-to-severe OSA.
- Chronic cough is common in patients with OSA, and treatment of OSA with CPAP has been shown to improve cough severity.

#### Gastroesophageal reflux

- ▶ Bile salts and pepsin may be abundant in (BAL) fluid from IPF patients
- ▶ The development of IPF facilitated by recurrent lung insult due to H. pylori
- ▶ Non-acid reflux seems to influence coughing in IPF more than acid reflux.
- ▶ Pharmacological therapy with pump inhibitors does not improve cough symptoms.
- Therapy with proton pump inhibitors is able to increase non-acid reflux.
- Prokinetic therapies, maybe targets of treatment.
- Pulmonary fibrosis causes traction lower esophageal sphincter and aggravating gastric reflux.

# Architectural distortion of the lungs & Increased cough reflex sensitivity

- ▶ The airway traction in IPF may promote the development of a cough.
- Stimulation of chemical cough receptors may be related to subclinical inflammation.
- inflammatory cells overexpressed in BAL and sputum of IPF patients, eosinophils and mast cells are involved in fibrosis and cough development.

#### Comorbidities

Table 1 Comorbidities associated with Cough in IPF				
IPF comorbidities	Mechanisms of cough			
OSAS	Profibrotic hypoxaemia			
GER	Non-acid reflux, increase TGF-β			
BRONCHIECTASIS	C-fibre nerve activity			
COPD	Hypersecretion mucous glandular			
ASTHMA	Bronchial hyperactivity			

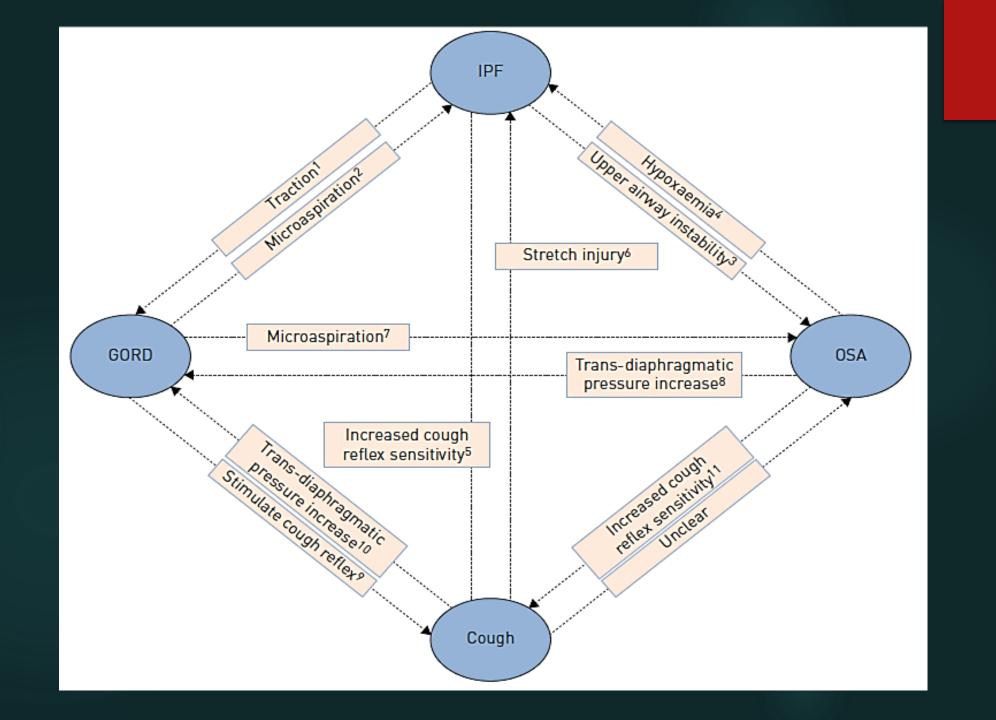
Fig. 1 Pathogenetic mechanisms of cough in idiopathic pulmonary fibrosis (IPF)

#### **GER COMORBIDITIES** MICROASPIRATION INDUCING TGF-β OVERPRODUCTION INCREASE OF TRANS-DIAPHRAGMATIC OSA PRESSURE ASTHMA TRACTION LEADING TO A WEAKER COPD/EMPHYSEMA LOWER OESOPHNAGEAL SPHINCTER BRONCHIECTASIS PATHOGENETIC MECHANISMS OF COUGH IN IPF

TONUS

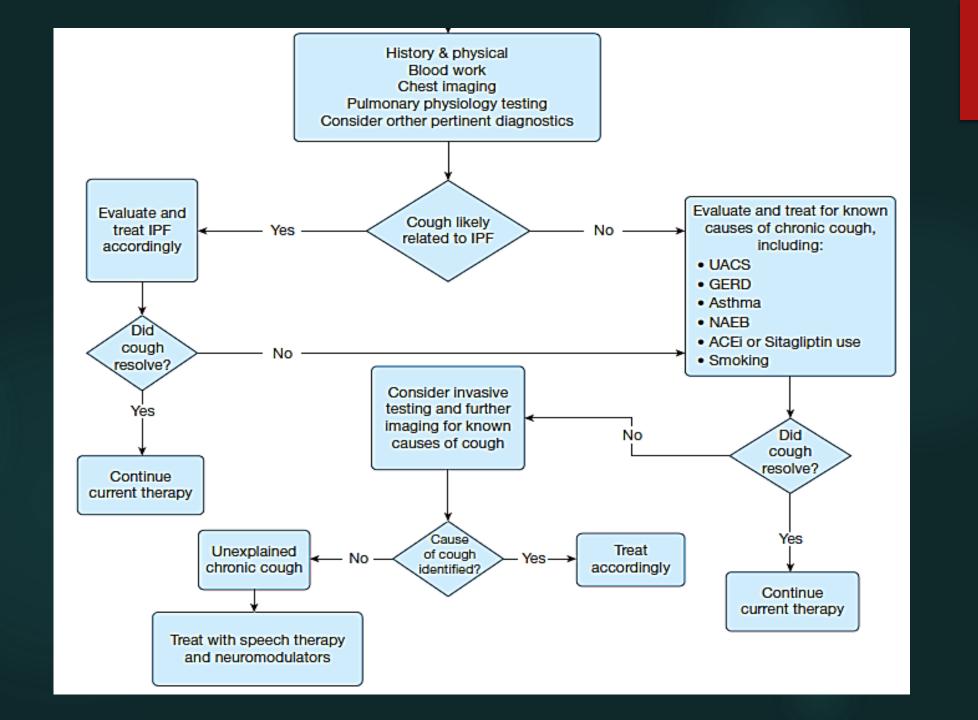
#### **IPF**

- ARCHITECTURAL DISTORTION OF THE LUNGS
- INCREASED COUGH REFLEX SENSITIVITY
- GENETIC FACTORS (MUC5B)
- INFLAMMATION



### How We Evaluate Cough in Patients With IPF

- comorbid conditions
- when a patient with IPF is receiving immunosuppressive therapy, we rule out infection.
- ▶ hemoptysis, hoarseness, weight loss, recurrent pneumonia, or dysphagia,7 the use of drugs (eg, angiotensin-converting enzyme inhibitors, sitagliptin), or environmental/occupational



- ▶ Cough also predicted disease progression at 6 months.
- both IPF and COPD patients had a higher sputum eosinophil count.
- If cough in IPF were related to eosinophilic airway inflammation, one would expect resolution with prednisolone treatment.

- ▶ Thalidomide as an IPF drug, improves symptoms of cough.
- ▶ The commonest side effects were constipation, dizziness and malaise.
- ► Thalidomide has anti-inflammatory and anti-angiogenic effects, similar to currently used anti-fibrotic drugs.
- ▶ Laparoscopic antireflux surgery also no effect on cough was found.
- Recent study showed that omeprazole may have a positive effect on cough in IPF.
- Next step is treatment with conventional antitussive therapies, such as cough syrups, dextromethorphan, and codeine.
- ▶ Pirfenidone seemed to reduce cough.

#### Treating cough in IPF: UACS

- ► For UACS, we initiate therapy with saline sinus rinses and nasal glucocorticoids and add nasal antihistamines and/or nonsedating oral antihistamines and/or leukotriene antagonists when allergies contribute to nasal symptoms.
- We also add nasal anticholinergics when vasomotor rhinitis is present.

#### Treating cough in IPF: GERD

- ▶ In patients thought to have, we recommend lifestyle modifications and proton pump inhibitors for antacid therapy.
- agents that promote increased lower esophageal sphincter tone and/or esophageal motility (if appropriate).

### Treating cough in IPF: asthma and NAEB

 Both asthma and NAEB may be treated with inhaled corticosteroids, but we do not typically initiate empirically

# Treating cough in IPF: Treating the underlying disease

- Neuromodulators in idiopathic chronic cough found that gabapentin, pregabalin, amitriptyline, and baclofen led to an improvement in cough severity.
- ▶ gabapentin, starting at low doses (eg, 100-300 mg) at night.
- morphine sulfate (5-10 mg, twice daily) led to a significant improvement in cough.

# Treating cough in IPF: Treating the underlying disease

- ▶ IPF cough when they are hypoxemic, and in such patients supplemental oxygen can dramatically improve cough
- Speech therapy has also been demonstrated to temporarily improve cough.

# Treating cough in IPF: Treating the underlying disease:

- ► Short term (eg, 2 weeks), low-dose (eg, 10-20 mg) prednisone is effective at substantially reducing cough in patients with IPF.
- ▶ 12 weeks of thalidomide led to significant improvement in cough and its impacts in a small cohort of patients with IPF.
- Observational data with pirfenidone treatment have shown significant reductions in both objective and subjective measures of cough severity after 12 weeks of therapy(cough frequency reduced by 34%).

TABLE 1 ] Therapeutic Treatment Trials for Cough in Idiopathic Pulmonary Fibrosis

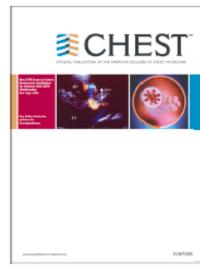
		Systematic Evaluation for Causes of Known Chronic			
Study/Year	Study Design	Cough	Intervention	Duration	Outcome
Dutta et al <sup>39</sup> / 2019, n = 45	Pilot, single-center, double-blind, RCT	No	Omeprazole, 20 mg twice daily	3 mo	A nonsignificant 39% reduction in geometric mean cough frequency per hour (95% CI, 0.34 to 1.093)
Kilduff et al <sup>26</sup> / 2014, n = 18	Cohort	Yes	Omeprazole, 40 mg twice daily or lansoprazole, 30 mg twice daily plus ranitidine, 300 mg at night	8 wk	No significant change in cough frequency $(P = .70)$
van Manen et al <sup>40</sup> / 2017, n = 43	Multicenter, prospective, observational study	No	Pirfenidone, 2,403 mg/d	12 wk	A clinically significant 34% reduction in 24-h objective cough counts (95% CI, -48% to -15%; P = .002)
Horton et al <sup>41</sup> / 2012, n = 23	Randomized, double- blind, crossover trial	No	Thalidomide, 50-100 mg at night	12 wk	CQLQ scores significantly improved with thalidomide, decreasing by 11.4 points (95% CI, –15.7 to –7.0; P < .001)
Birring et al <sup>42</sup> / 2017, n = 24	Randomized, double- blind, placebo- controlled trial	Yes	Inhaled cromolyn sodium (PA101) three times daily via oral inhalation	14 d	There was a significant 31.1% reduction in mean daytime cough frequency ( $P = .0241$ )
Hope-Gill et al <sup>33</sup> / 2003, n = 6	Cohort study	No	Prednisolone, 40-60 mg/d	4 wk	Significant reduction in visual analog scale score (P < .05)

- ▶ Recent ACCP guidelines therefore suggest that patients with refractory cough and ILD should first be assessed for progression or complications from their underlying disease but then go on have trials of therapy (trials of gabapentin) as per unexplained chronic cough guidelines.
- ► ACCP guidelines also recommended that patients who have IPF but no evidence of gastrooesophageal reflux are not routinely prescribed PPIs.

#### Accepted Manuscript

Improved cough and cough-specific quality of life in patients treated for sclerodermarelated interstitial lung disease (SSc-ILD): Results of Scleroderma Lung Study II

Donald P. Tashkin, MD, Elizabeth R. Volkmann, MD, Chi-Hong Tseng, PhD, Michael D. Roth, MD, Dinesh Khanna, MD, Daniel E. Furst, MD, Philip J. Clements, MD, Arthur Theodore, MD, Suzanne Kafaja, MD, Grace Hyun Kim, PhD, Jonathan Goldin, MD, Edgar Ariolla, PharmD, Robert M. Elashoff, PhD



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Reference: CHEST 868

- ► Cough is a common symptom of scleroderma-related interstitial lung disease (SSc-ILD) but less frequent and less intrusive than in HP or IPF.
- cough might be an indicator of extent of lung disease in SSc-ILD.
- ► changes in cough might serve as a surrogate marker of the efficacy of disease-modifying therapy for SSc-ILD.
- ▶ substantial decline in the proportion of patients with frequent cough during treatment with either CYC or MMF.

- ► Reduction in cough might serve as a useful secondary marker of the therapeutic response in SSC-ILD.
- ► Therefore, attributing chronic cough to a specific type of ILD depends on excluding the presence of other conditions such as asthma, UACS, and GERD
- SSc-ILD, a randomized controlled trial found that 12 months of treatment with oral cyclophosphamide improved cough frequency scores

Evidence-Based Medicine



# Treatment of Interstitial Lung Disease Associated Cough CHEST Guideline and Expert Panel Report



Surinder S. Birring, MD; Joanne E. Kavanagh, MBChB; Richard S. Irwin, MD, Master FCCP; Karina A. Keogh, MD, FCCP; Kaiser G. Lim, MD, FCCP; Jay H. Ryu, MD, FCCP

#### Pulmonary Pharmacology & Therapeutics 35 (2015) 122-128



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#### Cough in interstitial lung disease

Justin Garner a,\*, Peter M. George a,b, Elisabetta Renzoni a,b



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#### REVIEW



### Cough, an unresolved problem in interstitial lung diseases

Mirjam J.G. van Manen and Marlies S. Wijsenbeek

#### Purpose of review

Many patients with interstitial lung diseases (ILDs), especially fibrotic ILDs, experience chronic cough. Cough has a major impact on wellbeing, affecting both physical and psychological aspects of life. The pathophysiology of cough in ILDs is poorly understood and currently no good antitussive therapy exists.

#### Recent findings

Research on cough in ILDs is increasing. A recent proof-of-concept study with nebulized sodium cromoglycate for patients with idiopathic pulmonary fibrosis (IPF)-related cough showed a promising effect on cough. Observational data suggest that antifibrotic pirfenidone might reduce cough in IPF. Studies on the effect of acid inhibition on cough in ILDs show contradicting results.

#### Sarcoidosis

- ▶ Pulmonary involvement is observed in over 90% of patients with sarcoidosis.
- ▶ The prevalence of cough is estimated at between 30 and 50%.
- ► For patients with pulmonary sarcoidosis, we suggest that inhaled corticosteroids should not be routinely prescribed to treat the chronic cough.
- granulomatous mucosal inflammation causing airflow limitation and hyperresponsiveness.
- corticosteroid (oral or inhaled) in individuals with pulmonary sarcoidosis, authors concluded an improvement in symptoms (including cough) over 6 to 24 months of treatment.

#### Hypersensitivity pneumonitis

- ▶ Airflow limitation due to bronchiolitis in non-fibrotic disease.
- Proportion of patients with fibrotic HP have a clinical course and progression of disease like individuals with IPF.
- ▶ Targeting co-factors such as rhino sinusitis and gastro-oesphageal reflux.
- corticosteroid
- cough in HP is very similar to that seen in IPF with 83% and 87% of individuals

#### Connective tissue disease and ILD

- ▶ In Sjogren's syndrome, cough can occur as a consequence of lymphocytic destruction of the glandular epithelial mucosa of the trachea causing airway desiccation or xerotrachea.
- ▶ topical lubrication in the form of nebulised saline for xerotrachea, and either inhaled or systemic corticosteroid therapy for lymphocytic inflammation.
- ► There is a positive correlation between the extent of fibrosis in SSC and the frequency and severity of cough, which is responsive to immunosuppressive therapy with Cyclophosphamide.

# The role of gastro-esophageal reflux disease (GERD) in ILD

- ▶ It is now well established that GERD (Acid and non-acid reflux) is one of the most common causes of chronic cough.
- ▶ In patients with SSc associated ILD, worsening GERD (dysmotility and dilatation) has been associated with more severe pulmonary fibrosis.
- ▶ In IPF the majority of reflux was non-acid as opposed to acid.
- Treatment with high dose PPIs paradoxically increased non-acid reflux and although reducing acid reflux, had no effect on cough.

#### Treatment of cough in ILD

- ▶ Targeting co-factors such as rhinosinusitis and gastro-oesphageal reflux.
- ▶ In the Scleroderma Lung Study (SLS I), cough frequency and severity responded to 12 months treatment with oral Cyclophosphamide.
- ► Neuropathic aetiology for cough is suggested by improvement in chronic idiopathic cough after treatment with Amitriptyline and Gabapentin.
- Nebulised lidocaine has been found to be beneficial in patients with refractory cough.
- Corticosteroids may be helpful in alleviating chronic cough in some cases of interstitial lung disease.

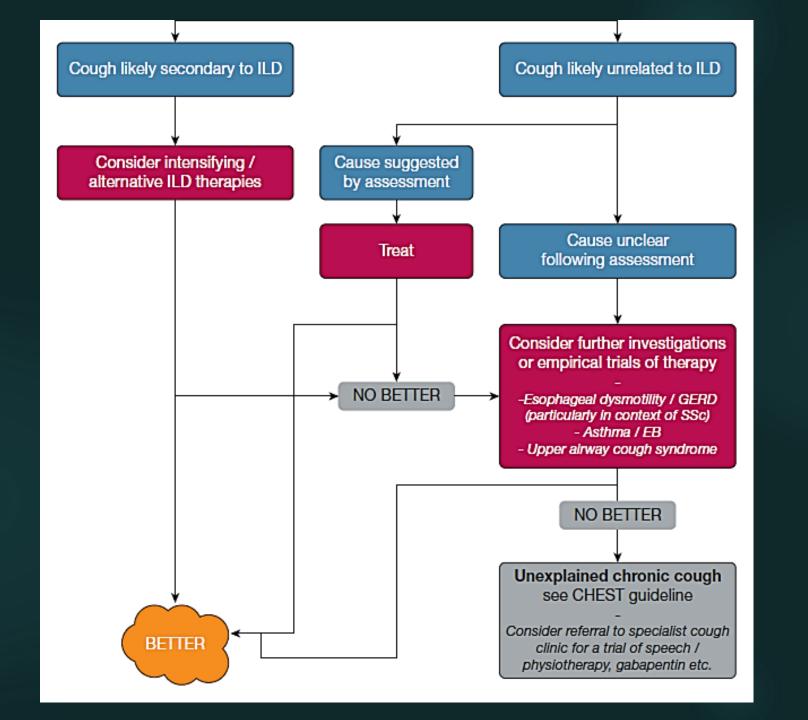
A new promising therapy for chronic cough in ILDs could be AF- 219 (P2X3 receptor antagonist), which reduces objective cough by 75% in a phase II trial in chronic cough disease



- ► Low doses of morphine, ranging from 5 to 10mg twice a day have shown to clinical significantly improve and reduce overall daily cough scores by 40% in an randomized controlled trial in chronic cough patients.
- Morphine might be used to treat severe cough in patients with advanced fibrotic ILDs.
- ► For patients with ILDs and chronic cough who do not respond to any antitussive treatment, speech and language therapy might be a good noninvasive option.

- ► For patients with IPF, chronic cough and a negative workup for acid gastroesophageal reflux, we suggest that proton pump inhibitor therapy should not be prescribed.
- ► For patients with ILD and refractory chronic cough, treatments such as gabapentin and speech pathology therapy, or entering into clinical trials if available.
- ► For patients with chronic cough due to ILD, when alternative treatments have failed and the cough is adversely affecting their quality of life, we suggest that opiates be recommended for symptom control.

- ▶ In patients with chronic cough, before diagnosing ILD as the sole cause, common etiologies such as upper airway cough syndrome (UACS), which was previously referred to as postnasal drip syndrome, asthma, and GERD should be considered.
- As these common causes may also share clinical features with specific ILDs, a diagnosis of ILD as the cause of cough should be considered a diagnosis of exclusion.



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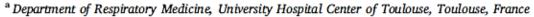
#### Pulmonary Pharmacology & Therapeutics

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#### Chronic cough and obesity

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<sup>&</sup>lt;sup>b</sup> Center for Pathophysiology Toulouse Purpan, INSERM U1043, CNRS UMR 5282, Toulouse III University, Toulouse, France



### chronic cough (CC)

- ► Asthma and reflux diseases, which are considered key factors in the onset of CC, are more severe symptoms in obese patients.
- OSA and diabetes may also be involved in the development of CC.
- ▶ 20% of patients with chronic cough were obese.
- Should we manage chronic cough in obese patients differently from nonobese patients?
- an obese asthma phenotype with non eosinophilic inflammation.
- ▶ inhaled corticosteroids and long acting beta agonists are **not** as effective in asthma control in obese patients compared to non-obese patients.

- ▶ PPIs have a similar effect on chronic cough in obese and non-obese patients.
- high level of FENO is associated with cough variant asthma (CVA) and may predict the response to inhaled corticosteroids.
- Obese individuals have a slight but significant increase in FENO.
- ► The prevalence of OSA in obese patients is nearly twice that of normal weight Adults.
- ▶ GERD was statistically associated with chronic cough in patients with OSA.
- Upper and lower airway inflammation is observed in OSA and may also contribute to chronic cough.
- ► CPAP treatment on chronic cough in OSA patients.
- weight loss has been suggested as an option in obese patients with asthma.

## Management of chronic cough in obese patients

Consider the 4 most common causes of chronic cough and treat if present

- GERD

If clinically suspected, test with PPI and diet lifestyle change

- Asthma

Spirometry with reversibility ± bronchial challenge test

Allergy evaluation

Treatment: ICS ± LABA, LTRA, trigger avoidance, weight loss

- Upper Airways Cough Syndrome

Sinus imaging, nasofibroscopy, allergy evaluation

Treatment: antihistamine and/or nasal corticosteroids

- Non-asthmatic Eosinophilic Bronchitis

Sputum eosinophilia, FENO, allergy evaluation

Treatment: ICS, trigger avoidance

## Management of chronic cough in obese patients

- c. Consider 2 emergent causes in obese patients
  - OSA

Sleep questionnaire and, if positive, nocturnal polygraphy

Treatment: CPAP treatment

Diabetes

Blood glucose levels and, if abnormal, HbA1c

Treatment: specific diabetic treatments

- d. Weight loss interventions if the patient is motivated
- e. Further investigations if cough proves refractory:
  - 24-h oesophageal pH/Impedance monitoring
  - HRCT (high-resolution computed tomography), sinus CT scan
  - Swallowing evaluation
  - Bronchoscopy
  - Environmental assessment

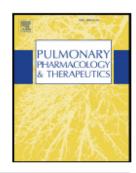
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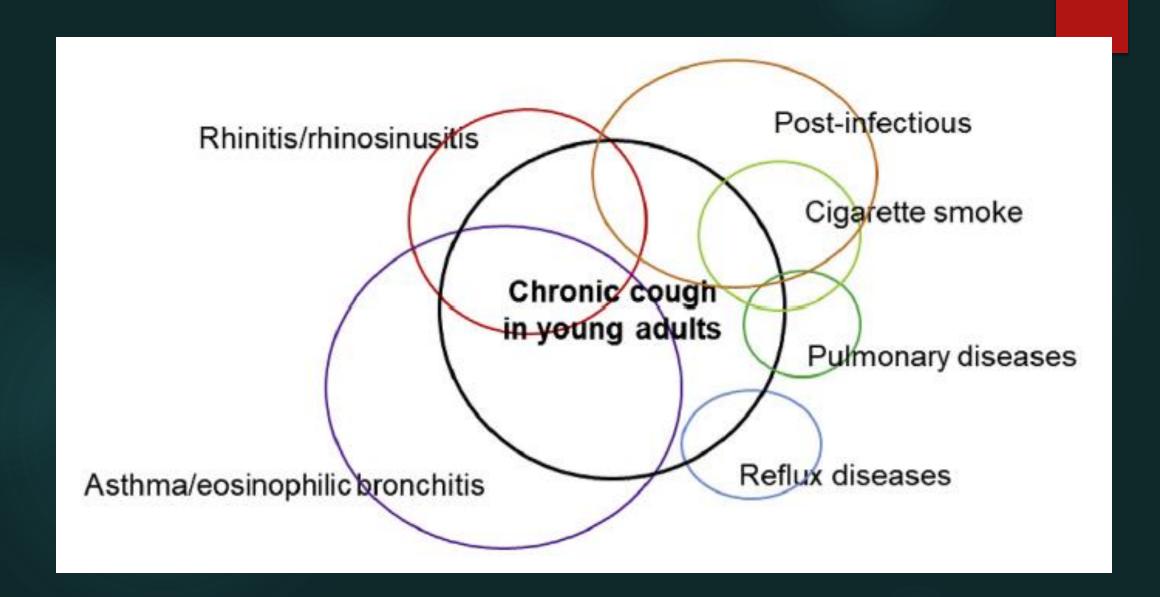


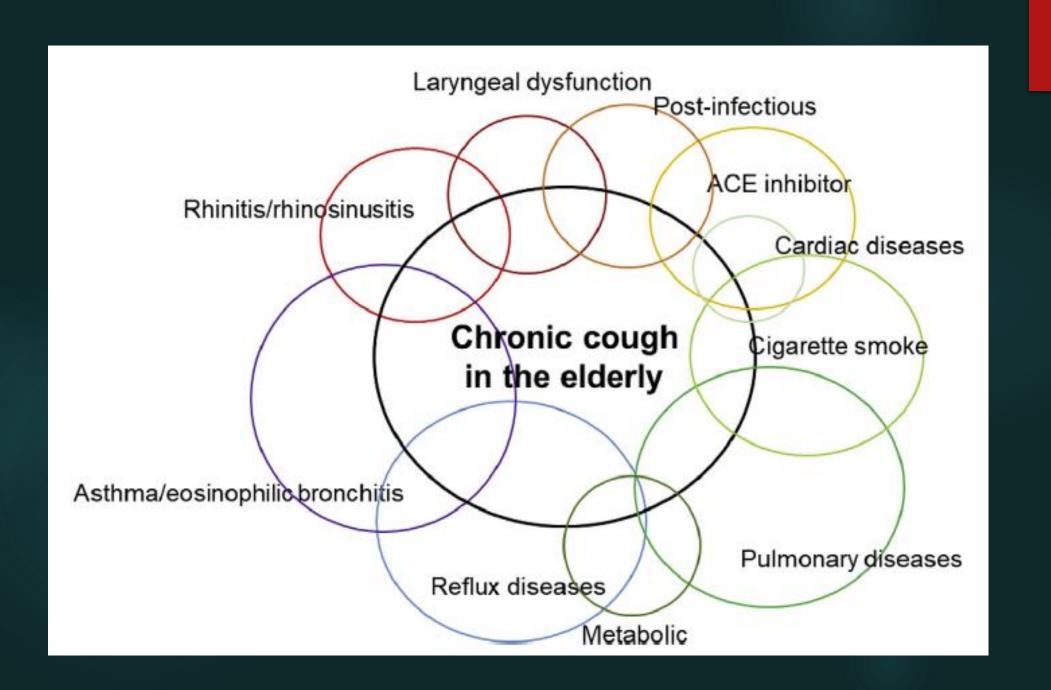
#### Chronic cough in the elderly





- Chronic cough a more heterogeneous condition in the elderly (age of ≥65 years) compared to younger Adults.
- chronic persistent cough was significantly associated with asthma and allergic rhinitis but also unexpectedly with poorly controlled diabetes mellitus and constipation.
- prevalence of abnormal chest X-rays was significantly higher in the elderly cough patients.
- ► The most common abnormal radiograph finding in the elderly was inactive tuberculosis.





- Triad (upper airway diseases, asthma, and GERD) accounted for about 85% of overall elderly patients with chronic cough.
- bronchiectasis, chronic bronchitis, Zenker's diverticulum with aspiration, ACEi use, left ventricular failure and bronchogenic carcinoma.
- ▶ first-generation H1-antihistamines
- ► Inhaled corticosteroid (ICS): reduced bone mineral density, fracture, cataracts, or adrenal insufficiency, pneumonia.
- Short-term courses of oral corticosteroids (OCS) (i.e., prednisolone 40 mg q.d. or equivalent for 1 week) are also often considered for diagnostic trials or rapid symptom relief in chronic cough patients.

Evidence-Based Medicine



## Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer CHEST Guideline and Expert Panel Report



Alex Molassiotis, RN, PhD; Jaclyn A. Smith, MBChB, PhD; Peter Mazzone, MD, MPH; Fiona Blackhall, MD, PhD; and Richard S. Irwin, MD, Master FCCP; on behalf of the CHEST Expert Cough Panel

TABLE 2	Causes of	Cough	Among	<b>Patients</b>	With
	Cancera				

Pleural disease-effusion, tumor

Lung parenchyma infiltration

Major airway or endobronchial tumor

Cough after radiation or after chemotherapy

COPD; chronic bronchitis

Bronchiectasis

Pericardial effusion

Upper airway cough syndrome due to a variety of rhinosinus conditions

Gastroesophageal reflux disease

Asthma

Lymphangitis carcinomatosis

Chest infection

Microembolism

Tracheoesophageal fistula

Vocal cord paralysis

Congestive heart failure

Postinfectious cough

Eosinophilic bronchitis

Angiotensin-converting enzyme inhibitor

aReviewed in Tse.20

- Cough among patients with lung cancer is a common.
- ▶ In adult patients with cough associated with lung cancer that persists despite cancer treatment, assessment any co-existing.
- ▶ In adult patients with lung cancer we suggest an initial trial with demulcents such as butamirate linctus (syrup) or simple linctus (syrup) or glycerin-based linctus (syrup) where available.
- ▶ In adult patients with lung cancer experiencing cough that does not respond to demulcents, we suggest pharmacological management using an opiate-derivative.

- ▶ In adult patients with lung cancer experiencing opioid-resistant cough, we suggest a peripherally acting antitussive (where available), such as levodropropizine, moguisteine, levocloperastine or sodium cromoglycate.
- ▶ In adult patients with lung cancer experiencing opioid-resistant cough that does not respond to peripheral antitussives, we suggest a trial with local anesthetics, including nebulized lidocaine/ bupivacaine or benzonatate.

Molassiotis et al. Cough 2010, 6:9 http://www.coughjournal.com/content/6/1/9



REVIEW Open Access

## Clinical expert guidelines for the management of cough in lung cancer: report of a UK task group on cough

Alex Molassiotis<sup>1\*</sup>, Jaclyn A Smith<sup>2</sup>, Mike I Bennett<sup>3</sup>, Fiona Blackhall<sup>4</sup>, David Taylor<sup>5</sup>, Burhan Zavery<sup>6</sup>, Amelie Harle<sup>4</sup>, Richard Booton<sup>7</sup>, Elaine M Rankin<sup>8</sup>, Mari Lloyd-Williams<sup>9</sup>, Alyn H Morice<sup>10</sup>

- ► Cough is a common symptom in about 47-86% of lung cancer patients.
- Metoclopramide and Domperidone are frequently used to promote GI motility: non-acid reflux is suspected.
- prominent upper airway pathology, a trial of a topical corticosteroid is appropriate.
- Productive cough may indicate bronchiectasis, sinusitis or a lower respiratory tract infection.

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#### **EXPERIMENTAL**#

Carbamazepine, Thalidomide, Gabapentin, Baclofen Amitriptylline

#### LOCAL ANAESTHETICS

Nebulised Lidocaine/bupivacaine; Benzonatate\*

#### PERIPHERALLY-ACTING ANTITUSSIVES

Levodropropizine\*, Moguisteine\*, Levocloperastine

#### **OPIOIDS**

Morphine, Methadone linctus Dextromethorphan<sup>2</sup>, Codeine, Pholcodine, Hydrocodone\*

#### CONSIDER ORAL STEROID TRIAL

(if appropriate) - 2 weeks

Simple Linctus/Glycerol<sup>1</sup>

#### CANCER SPECIFIC

systemic chemotherapy/RT endobronchial therapy, Photodynamic therapy, palliative radiotherapy.

#### CO-MORBIDITIES

COPD, reflux, asthma, infections. Medication review.

hydiene techniques

Table 2 Recommended dosages for antitussives, demulcents and topical anaesthetics

Medication	Dosage		
Simple linctus	5 ml tds/qds		
Dextromethorphan	10-15 mg tds/qds		
Codeine	30-60 mg qds		
Pholcodine	10 ml tds		
Morphine (oramorph)			
Diamorphine	5-10 mg CSCI/24 hrs		
Methadone linctus	Single dose 2 mg (2 mL of 1 mg/mL solution)		
Dihydrocodeine*	10 mg tds		
Hydrocodone	5 mg bd		
Inhaled cromoglycate	10 mg qds		
Levodropropizine*	75 mg tds		
Moguisteine*	100-200 mg tds		
Levocloperastine*	20 mg tds		
Nebulised Lidocaine#	5 ml of 0.2% tds		
Nebulised Bupivacaine#	5 ml of 0.25% tds		
Benzonatate*	100-200 mg qds		
Prednisolone	30 mg daily for 2 weeks		

# Treating Cough Due to Non-CF and CF Bronchiectasis With Nonpharmacological Airway Clearance

▶ For children and adults with productive cough due to bronchiectasis related to any cause, we suggest that they be taught airway clearance techniques by professionals with advanced training in airway clearance techniques.

Asthma Guidelines and Consensus Statements



## Managing Chronic Cough Due to Asthma and NAEB in Adults and Adolescents CHEST Guideline and Expert Panel Report



Andreanne Côté, MD; Richard J. Russell, MBBS; Louis-Philippe Boulet, MD; Peter G. Gibson, DMed; Kefang Lai, MD, PhD; Richard S. Irwin, MD, Master FCCP; and Christopher E. Brightling, PhD; on behalf of the CHEST Expert Cough Panel\*

### Non-asthmatic eosinophilic bronchitis (NAEB)

- ► Asthma and non-asthmatic eosinophilic bronchitis (NAEB) are among the commonest causes of chronic cough in adults.
- ► The best therapeutic option for cough in asthma or NAEB is inhaled corticosteroids followed by leukotriene receptor antagonism.
- ▶ In patients with chronic cough due to asthma, measurement of airway inflammation and the presence of eosinophilic airway inflammation is likely to be associated with a more response to corticosteroids.
- blood or sputum eosinophil counts and fractional exhaled nitric oxide (FENO)

- ► In patients with chronic cough due to asthma as a unique symptom (cough variant asthma [CVA]) we suggest that inhaled corticosteroids should be considered as first line treatment.
- If response is incomplete in those with CVA or if cough is the remaining isolated symptom following treatment with inhaled corticosteroids in patients with asthma in whom cough was one of their symptoms we suggest stepping-up the inhaled corticosteroid dose and considering a therapeutic trial of a leukotriene inhibitor after reconsideration of alternative causes of cough.

- Beta-agonists could also be considered in combination with ICS.
- ▶ In patients with chronic cough due to non-asthmatic eosinophilic bronchitis (NAEB), we suggest ICS as first-choice treatment.
- ▶ In patients with chronic cough due to NAEB, if response to ICS is incomplete, we suggest stepping-up the inhaled corticosteroid dose and considering a therapeutic trial of a leukotriene inhibitor after reconsideration of alternative causes of cough.