CHEST

Treatment of Interstitial Lung Disease Associated Cough

CHEST Guideline and Expert Panel Report

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BACKGROUND: Chronic cough in interstitial lung disease (ILD) causes significant impairment in quality of life. Effective treatment approaches are needed for cough associated with ILD.

METHODS: This systematic review asked: Is there evidence of clinically relevant treatment effects for therapies for cough in ILD? Studies of adults aged > 18 years with a chronic cough ≥ 8 weeks' duration were included and assessed for relevance and quality. Based on the systematic review, guideline suggestions were developed and voted on by using CHEST guideline methodology.

RESULTS: Eight randomized controlled trials and two case series (≥ 10 patients) were included that reported data on patients with idiopathic pulmonary fibrosis, sarcoidosis, and scleroderma-related ILD who received a variety of interventions. Study quality was high in all eight randomized controlled trials. Inhaled corticosteroids were not supported for cough associated with sarcoidosis. Cyclophosphamide and mycophenolate were not supported for solely treating cough associated with scleroderma-associated ILD. A recommendation for thalidomide to treat cough associated with idiopathic pulmonary fibrosis did not pass the panel vote. In view of the paucity of antitussive treatment options for refractory cough in ILD, the guideline panel suggested that the CHEST unexplained chronic cough guideline be followed by considering options such as the neuromodulator gabapentin and speech pathology management. Opiates were also suggested for patients with cough refractory to alternative therapies.

CONCLUSIONS: The evidence supporting the management of chronic cough in ILD is limited. This guideline presents suggestions for managing and treating cough on the best available evidence, but future research is clearly needed. CHEST 2018; 154(4):904-917

KEY WORDS: chronic cough: interstitial lung disease; refractory; sarcoidosis; scleroderma; treatment; unexplained

ABBREVIATIONS: CINAHL = Cumulative Index of Nursing and Allied Health Literature; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LCQ = Leicester Cough Questionnaire; PPI = proton pump inhibitor; RCT = randomized controlled trial; VAS = Visual Analogue Score

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Summary of Recommendations and Suggestions

1. For patients with ILD who present with a troublesome cough, we suggest that patients be assessed for progression of their underlying ILD, or complications from immunosuppressive treatment (eg, drug side effect, pulmonary infection) and also be considered for further investigation/treatment trials for their cough according to guidelines for acute, subacute and chronic cough. (Ungraded Consensus-Based Statement)

2. 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. (Ungraded Consensus-Based Statement)

3. For patients with pulmonary sarcoidosis, we suggest that inhaled corticosteroids should not be routinely prescribed to treat the chronic cough. (Grade 2C).

4. For patients with ILD and refractory chronic cough, we suggest trials of therapies recommended for patients with unexplained chronic cough according to the CHEST guidelines, with treatments such as gabapentin and multimodality speech pathology therapy, or entering into clinical trials if available. (Ungraded Consensus-Based Statement)

5. 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 a palliative care setting with reassessment of the benefits and risks at 1 week and then monthly before continuing. (Ungraded Consensus-Based Statement)

Interstitial lung disease (ILD) comprises a wide range of acute and chronic pulmonary disorders that affect both the airways and lung parenchyma with variable amounts of inflammation and fibrosis. Cough is a common symptom associated with ILD and may be the presenting symptom in some patients. Cough in idiopathic pulmonary fibrosis (IPF) has been the best studied of all ILDs, and a chronic cough is present in up to 80% of patients with IPF, although the proportion of patients with a troublesome cough is likely to be less than this.[1] Cough in IPF has been assessed with validated tools, such as 24-h cough monitoring and health-related Quality of Life questionnaires.[2] The health-related quality of life impairment in cough associated with IPF is significant and comparable with unexplained chronic cough.[2,3]

The presence of cough in IPF also has prognostic significance. A study of 242 patients with IPF found that cough predicted disease progression, independent of disease severity.[4] Cough was more prevalent in patients with more advanced pulmonary fibrosis. An important challenge when assessing cough in patients with ILD is to establish whether the cough is a consequence of the underlying inflammation or fibrosis, or due to the presence of a co-morbidity. In IPF, while the mechanism of cough may be mechanical distortion associated with lung parenchymal fibrosis,[5] heightened cough reflex sensitivity, gastro-esophageal reflux, and airway inflammation have all been reported in patients with IPF and may therefore be potentially important mechanisms.[6-8]

Cough is also a common symptom in patients with pulmonary sarcoidosis. A study by Sinha et al[9] reported that 50% of patients had a chronic cough and this was associated with poor health-related quality of life. Furthermore, there was a significant association between the frequency of cough measured objectively with 24-h cough monitoring and health-related quality of life. In the study by Sinha et al,[9] cough reflex sensitivity assessed with capsaicin was the only independent predictor of the frequency of coughing. Lung function, disease activity, and severity were not predictors of cough frequency. In scleroderma-related ILD, cough is also a prevalent symptom and is associated with more severe ILD.[10,11]

The present systematic review addresses the problem of chronic cough associated with ILDs, including sarcoidosis and scleroderma, in the areas of management and future directions.

Methods

The methodology of the CHEST Guideline Oversight Committee was used to select the Expert Cough Panel chair and the international panel of experts to perform the systematic review, synthesis of the evidence, and development of the recommendations and suggestions.[12]

Systematic Review Question

The key clinical question for this systematic review, developed by the writing group, was: "Is there evidence of clinically relevant treatment effects for therapies for cough in ILD." The literature search was generated following the creation of a PICO (Population, Intervention, Comparison, Outcome) element table (Table 1).

TABLE 1] Eligibility Criteria

Criteria	Study Requirements
Inclusion	■ Published any time prior to time of search (February 2016) ■ English language ■ Any study design, case series (≥ 10 subjects)
Population	■ Age > 18 years ■ Diagnosis of ILD, IPF, or sarcoidosis
Intervention	■ Any pharmacological intervention or non-pharmacological intervention
Control/comparison	■ Usual care/standard therapy or placebo (if applicable to study design)
Outcome	■ Assessment of cough (measured using validated/standardized tool)

ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis.

Literature Search

The search methods used for this systematic review conformed to those outlined in "Methodologies for the development of CHEST guidelines and expert panel reports."[12] PubMed and the Cochrane Database of Systematic Reviews were searched for systematic reviews, and Scopus (includes EMBASE [Excerpta Medica database]), PubMed, CINAHL (Cumulative Index of Nursing and Allied Health Literature), and the Cochrane Central Register of Controlled Trials were searched for other papers. All databases were searched from the earliest available date until February 2016. The search terms used are included in e-Appendix 1.

Eligibility criteria were reached by consensus between all of the authors (Table 1). Given the relative paucity of data in this field, we included all study types including case series of ≥ 10 patients. The titles and abstracts were reviewed independently by two of the authors (S.S.B. and J.E.K.) to identify potentially useful publications, based on the inclusion and exclusion criteria. Where differences occurred, consensus was achieved between the two reviewers. While a third independent reviewer was available if consensus could not be reached, lack of consensus did not occur. The full text of those abstracts selected as potentially relevant were then reviewed independently (again by S.S.B. and J.E.K.) against the eligibility criteria. The inclusion of a standardized cough outcome measure was acceptable as a primary or secondary end point. Systematic reviews fulfilling the Population, Intervention, Comparison, Outcome criteria were selected in the preliminary search for further analysis.

Quality Assessment

All studies included at full text stage were randomized controlled trials (RCTs), and a quality assessment for each study was carried out using the Cochrane risk of bias tool.[13] To assess the quality of any systematic reviews, the Documentation and Appraisal Review Tool was used.[14] There is no standardized tool available for quality assessing case series, and these studies were assessed on criteria suggested by the Agency for Healthcare Research and Quality.[15]

Intervention Fidelity Assessment

During full text review, the methodology was examined (including online supplementation where available) to determine whether the investigators had systematically excluded common alternative causes of cough in their patient population prior to the intervention.

Grading Recommendations

Each recommendation is graded for the strength of the recommendation and quality of evidence, as is the case for all CHEST guidelines.[12] The strength of recommendation is graded as either strong (grade 1; likely to apply to almost all patients) or weak (grade 2; conditional and only applying to selected patients). This grading is based on the quality of the evidence, the balance of risk vs potential benefit, the acceptability to patients, and resource considerations (eg, cost, availability, practicality/burden). The overall quality of evidence for each recommendation is graded as high (grade A), moderate (grade B), or low (grade C). A structured consensus-based Delphi approach was used to provide expert advice on guidance statements.[16] In this regard, for a recommendation or suggestion to be approved by the Expert Cough Panel, 75% of the eligible panel members had to vote, and 80% of those voting had to strongly agree or agree with the statement. All panelists had the opportunity to vote during the Delphi exercise; none were recused because of any conflicts of interest (e-Table 1). A patient representative who is a member of the Expert Cough Panel provided patient-centered input for this guideline and approved of the suggestions contained herein.

Results

Figure 1 summarizes the results of the systematic review. The majority of publications were excluded by title or abstract alone because they did not meet the inclusion criteria (702 of the 723 identified by the literature search). Twenty-six full text publications were reviewed and a further 16 excluded. The most common reasons for exclusion at this stage were studies that did not use a standardized or validated cough end point or reviews that were non-systematic. Finally, three systematic reviews that met our inclusion criteria were excluded because the only relevant studies they contained were already included in our review.[17-19] Three papers[20-22] met the inclusion criteria but were published after the initial search and were subsequently included on agreement of all the authors of the expert panel report. This process resulted in 10 studies included in this review (Table 2). Of these, five concerned IPF, three investigated the use of inhaled corticosteroids in pulmonary sarcoidosis, and two investigated immunosuppressive therapies in scleroderma-related ILD.

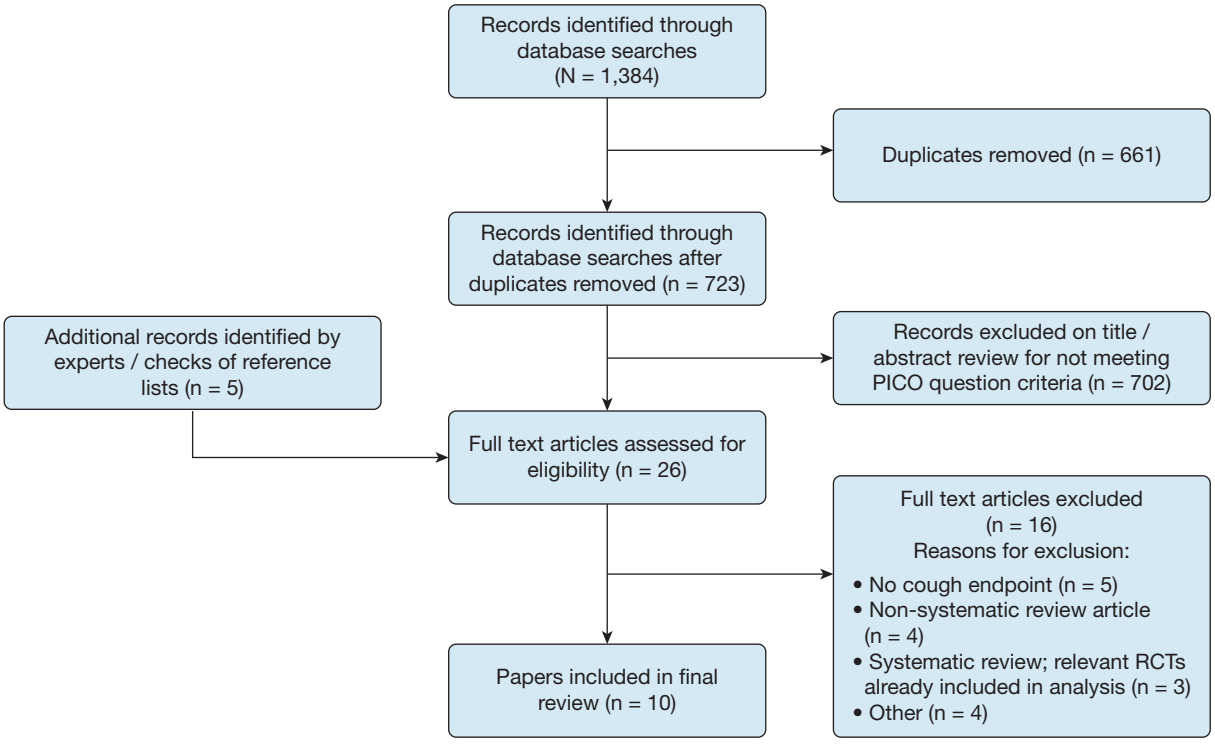

Figure 1 – *Systematic review flow diagram. PICO = Population, Intervention, Comparison, Outcome; RCT = randomized controlled trial.*

Quality Assessment

In general, the study quality was high in the trials selected for inclusion in the systematic review. In the eight RCTs included, the risk of bias was unclear in four of the studies in the area of selection (Table 3). A high risk of bias was identified in one study in selective outcome reporting.[23] This paper presents further, new analyses of the patients reported in an earlier study[24] and a post hoc subgroup analysis. The methodology used to determine the subgroups was unclear, and this paper was therefore categorized as high risk of selective outcome reporting. The two observational studies included have an inherent risk of bias, having no placebo group and therefore have to be interpreted with caution.

Diagnosis of Cough

Cough in a patient with ILD may be due to their underlying lung disease. However, because chronic cough occurs so commonly in the general population,[25] it is likely that in some cases other diseases may be responsible for the cough in patients with ILD (asthma, eosinophilic bronchitis, upper airway causes, drug therapy) or that cough may be unexplained. Patients with some ILDs are commonly treated with immunosuppressive therapies, and, therefore, infectious causes should also be considered.

Only one of the included studies[26] reported using a standardized diagnostic protocol to assess cough prior to their intervention; otherwise it is unclear whether alternative causes of cough were fully excluded (eg, asthma, upper airway cough syndrome). In four studies,[23,27-29] cough was not a major focus of the study and was only examined as a secondary or tertiary end point and often as part of a composite symptom score, so it is unlikely a cough diagnostic protocol was used. Horton et al[34] and Birring et al[20] did complete an assessment for identifiable causes of cough, but details of this assessment were not recorded. In the study of Theodore et al,[30] it is possible that enrolled patients had been assessed; however, this was not reported.

Suggestion 1. For patients with ILD who present with a troublesome cough, we suggest that patients be assessed for progression of their underlying ILD, or complications from immunosuppressive treatment (eg, drug side effect, pulmonary infection) and also be considered for further investigation/treatment trials for their cough according to guidelines for acute, subacute and chronic cough. (Ungraded Consensus-Based Statement)

Cough in IPF

While the major trials of pirfenidone[24,31,32] and nintedanib[33] have not reported data on the impact of

TABLE 2] Study Characteristics

Study	Study Design	Anatomical Workup for Chronic Cough	Duration	Intervention	No. Randomized [Intervention Arm; Placebo Arm]
IPF					
Azuma et al,[23] 2011	Post hoc analysis of a multicenter randomized double blind placebo controlled trial	No	12 mo	Pirfenidone 1,200 mg or 1,800 mg/d	275 [166; 109]
Horton et al,[34] 2012	Randomized double blind placebo controlled crossover	No	12 wk	Thalidomide 100 mg	24[a]
Kilduff et al,[26] 2014	Cohort study	Yes	8 wk	High dose PPI (omeprazole 40 mg bd or lansoprazole 30 mg bd) plus ranitidine 300 mg nocte	18
Birring et al,[20] 2017	Multicenter, randomized, double blind, placebo controlled, 2-cohort, 2-period crossover trial	Yes	14 d	Inhaled cromolyn sodium (PA101) via eFlow nebulizer 40 mg tds	24[a]
van Manen et al,[22] 2017	Multicenter, prospective, observational study	No	12 wk	Pirfenidone 2,403 mg/d[b]	43
Sarcoid					
Milman et al,[29] 1994	Randomized double blind placebo controlled	No	12 mo	Inhaled budesonide 1.2 or 2.0 mg/d	21 [9; 12]
du Bois et al,[28] 1999	Two center randomized double blind placebo controlled	No	6 mo intervention + 2 mo follow up	Inhaled fluticasone 2 mg/d	43 [21; 22]
Baughman et al,[27] 2002	Multicenter randomized double blind placebo controlled	No	48 wk	Inhaled fluticasone 880 μg bd	22 [10; 12]
Scleroderma					
Theodore et al,[30] 2012	Randomized double blind placebo controlled	No	12 mo	Oral cyclophosphamide 2 mg/kg monthly	158 [79; 79]
Tashkin et al,[21] 2017	Multicenter randomized double blind trial, 2 treatment arms	No	24 mo	Mycophenolate target dose 1,500 mg bd for 24 mo OR Cyclophosphamide target dose 2 mg/kg/d for 12 mo then placebo 12 mo	142[c]

bd = twice a day; PPI = proton pump inhibitor; tds = 3 times a day.
[a]Crossover trial design.
[b]Communication with first author. Target dose; patients were up titrated from 801 mg/day starting dose over a 2-week period.
[c]This study pooled the cough data from both treatment arms.

TABLE 3] Risk of Bias—Randomized Controlled Trials

Azuma et al,[23] 2011	Baughman et al,[27] 2002	Birring et al,[20] 2017	du Bois et al,[28] 1999	Horton et al,[34] 2012	Milman et al,[29] 1994	Tashkin et al,[21] 2017	Theodore et al,[30] 2012	Bias Domain
L	U	L	U	L	U	L	L	Random sequence generation (selection bias)
U	U	L	U	L	U	L	L	Allocation concealment (selection bias)
L	L	L	L	L	L	L	L	Blinding of participants and personnel (performance bias)
L	L	L	L	L	L	L	L	Blinding of outcome assessment (detection bias)
L	L	L	L	L	U	L	L	Incomplete outcome data addressed (attrition bias)
H	L	L	L	L	L	L	L	Selective outcome reporting (reporting bias)
L	L	L	L	L	L	L	L	Other bias

H = high risk of bias; L = low risk of bias; U = unclear risk of bias.

treatment on cough (Table 4), Azuma et al[23] used data from an earlier Japanese pirfenidone trial[24] to report on the impact of pirfenidone on cough in IPF. These data were not published in the initial study, but cough was included as part of a composite symptoms-based tertiary end point, together with dyspnea. Azuma et al report no significant difference overall in cough severity between the treatment arms (low and high dose pirfenidone) and placebo. A recent study by van Manen et al[22] investigated the effect of pirfenidone on IPF-associated

TABLE 4] Treatment Effects

	Cough Severity	Cough Frequency (Subjective)	Cough Frequency (Objective)	Cough QoL
Pirfenidone in IPF				
Azuma et al,[23] 2011	+	NA	NA	NA
van Manen et al,[22] 2017	+	NA	+	+
Thalidomide in IPF				
Horton et al,[34] 2012	+	NA	NA	+
Acid suppression in IPF				
Kilduff et al,[26] 2014	NA	NA	–	NA
Cromolyn in IPF				
Birring et al,[20] 2017	–	NA	+	–
Inhaled steroid in pulmonary sarcoidosis				
Milman et al,[29] 1994	–	NA	NA	NA
du Bois et al,[28] 1999	–	NA	NA	NA
Baughman et al,[27] 2002	–	NA	NA	NA
Oral cyclophosphamide in SSc-ILD				
Theodore et al,[30] 2012	–	–	NA	NA
Tashkin et al,[21] 2017	NA	+	NA	–
Mycophenolate in SSc-ILD				
Tashkin et al,[21] 2017	NA	+	NA	–

– = no statistically significant difference; + = statistically significant improvement; QoL= quality of life;NA = not measured; SSc-ILD = systemic sclerosis with interstitial lung disease. See Table 1 legend for expansion of other abbreviation.

cough using validated cough outcome tools (Leicester Cough Monitor and Leicester Cough Questionnaire [LCQ]). There was a 34% reduction in objective cough frequency and a clinically significant improvement in cough-related quality of life. The limitation of this study was the lack of a control group.

Horton et al[34] assessed cough as a primary end point in patients with cough and IPF. This was a crossover trial where all patients received 12 weeks of treatment with thalidomide 50 mg daily, increasing in all but one patient to 100 mg if there was no improvement in cough after 2 weeks. All patients receiving thalidomide routinely received sodium docusate and vitamin B supplementation. The trial recruited small numbers of patients (24 patients, of whom 20 completed the trial). There was a statistically significant improvement in Cough Quality of Life Questionnaire score (a validated quality of life questionnaire for cough) (decreased 11.37 points; $P < .001$), cough Visual Analogue Score (VAS) (decreased by 31.2 mm; $P < .001$), and the St. George's Respiratory Questionnaire (decreased 11.7 points; $P = .001$).

The side effect profile of thalidomide is an obvious concern, including its potential for teratogenicity. Significantly more patients receiving thalidomide than placebo reported adverse events (77% vs 22%; $P = .001$). The commonest side effects were constipation, dizziness, and malaise. There were no serious adverse events during treatment. Three patients required a dose reduction, and the four withdrawals from the study were due to lack of interest (n = 1) or disease progression and inability to return for study visits (n = 3). Despite most patients experiencing side effects, all participants accepted the offer of continuing thalidomide treatment at the end of the trial.

Based on this evidence, the authors made a recommendation to the CHEST Expert Cough Panel that thalidomide be considered in those with IPF and chronic cough where alternative causes of cough were ruled out (Grade 2c). Only 67% of the panel voted in favor of this recommendation, and so it failed to pass and was removed (an approval score of 80% is required). It is likely that the practical barriers to prescribing thalidomide in many countries, side effects, and the limited evidence from a single, small trial were concerns among the CHEST Expert Cough Panel. The potential of thalidomide should be further investigated.

A recent proof of concept study investigated the efficacy of a novel inhaled cromolyn sodium formulation (PA101) in IPF patients with chronic cough.[20] PA101 is a high concentration cromolyn formulation delivered via a high efficiency eFlow nebulizer that achieves significantly higher drug deposition in the lung compared with existing formulations. There was a 31% decrease in daytime mean cough frequency (the primary outcome measure) at day 14 with treatment when adjusted for placebo, but no statistically significant change in cough-specific quality of life (measured by LCQ) or cough severity (measured by VAS score). The drug was well tolerated with no severe or serious adverse events reported. PA101 cromolyn is not currently available to prescribe, and further studies investigating its efficacy are awaited.

Proton pump inhibitors (PPIs) have long been used in IPF and have been recommended in the 2015 American Thoracic Society IPF guidelines.[35] This was a conditional recommendation and was based on two observational studies suggesting a slower decline in vital capacity in IPF patients taking PPI therapy. Kilduff et al[26] investigated the efficacy of high dose PPI and H2 receptor antagonist for 8 weeks in a small group of 18 patients with IPF. They assessed cough and gastro-esophageal reflux disease (GERD) objectively with esophageal pH and impedance testing and cough monitoring. This was an uncontrolled study, but there was no change in objective cough counts with PPI despite a decrease in acid reflux events. This finding is in keeping with current evidence in unexplained chronic cough, where no benefit in cough severity or quality of life has been observed with high dose esomeprazole in RCTs.[36,37] The CHEST unexplained chronic cough guideline therefore recommends against using PPIs in patients with a negative workup for acid gastro-esophageal reflux.

Suggestion 2. For patients with IPF, chronic cough and a negative workup for acid gastroesophageal reflux, we suggest that proton pump inhibitor therapy not be prescribed. (Ungraded Consensus-Based Statement)

Cough in Sarcoidosis

Three trials investigating inhaled steroids in sarcoidosis were included (Table 4). The type of patients included in each study differed, as did the dose of inhaled steroid used. Baughman et al[27] studied 22 patients with acute sarcoidosis. All patients were given concomitant oral steroids according to a standardized protocol. Ten patients were randomized to also take 880 μg of fluticasone twice a day for 48 weeks, while the other 12 took a placebo inhaler. Cough was evaluated in a

systematic way, although not using a validated cough tool. Cough was reported as "better" in more patients in the treatment arm (eight of 10 in the treatment arm vs six of 11 in the placebo arm); however, there was no statistically significant difference ($P = .36$). There was no reduction in oral steroid requirements in the treatment arm.

du Bois et al[28] also investigated the efficacy of inhaled fluticasone but, in contrast, in patients with established sarcoidosis (> 1 year from time of diagnosis) and at a slightly higher dose compared with Baughman et al[27] (2000 μg daily vs 1760 μg daily). Seventy-five percent of patients were concomitantly taking oral prednisolone, but this was balanced across the placebo and treatment groups. Cough was evaluated by a four-point severity scale. This study also recruited a relatively small number of patients (n = 43), and although all patients reported a decrease in cough severity at the end of the trial, there was no significant difference between the fluticasone and placebo arms.

Milman et al[29] conducted a study in 1994 to investigate inhaled budesonide in established sarcoidosis. The number of subjects recruited was small, with 29 patients enrolled, of whom 14 were treated with budesonide. There was no difference in cough severity, assessed with a four-point scale, between the treatment and placebo arms ($P = .87$). In the small subgroup on oral prednisolone (eight patients) there was no significant difference in the change in oral prednisolone dose with treatment vs placebo.

Suggestion 3. For patients with pulmonary sarcoidosis, we suggest that inhaled corticosteroids should not be routinely prescribed to treat the chronic cough. (Grade 2C)

Cough in Scleroderma-related ILD

The only studies included relating to connective tissue disease both concern scleroderma-related ILD. Theodore et al[30] reported cough data from the Scleroderma Lung Study[10] that randomized 158 patients to receive either cyclophosphamide or placebo for 1 year (with a further 12 months' follow up). A cough index (which included a score of severity, frequency and presence of phlegm) was assessed at baseline and three monthly intervals. Patients with cough (73%) were more likely to have severe lung disease (established with Transfer Factor of the Lung for Carbon Monoxide and CT scans) and more diffuse scleroderma. The change in cough index with cyclophosphamide therapy compared with placebo was not significantly different. There was a trend for greater improvement in reported cough frequency in the treatment group, but this did not reach statistical significance ($P = .56$).

Tashkin et al reported cough data from the Scleroderma Lung Study II[11] that randomized 142 patients to either cyclophosphamide for 1 year followed by placebo for 1 year or to mycophenolate for 2 years. Given the interesting findings concerning cough in the first scleroderma lung study, the investigators included the LCQ as a secondary outcome measure. The presence of "frequent cough" was determined by the responses to two questions in the St. George's questionnaire. The paper reported the number of frequent coughers and LCQ scores from both treatment arms combined and compared these to pretreatment scores, not against placebo. There was a decrease in the number of patients who reported frequent cough (from 61.7% to 45.7%; $P = .0051$), but there was no significant difference in the LCQ scores.

The paper by Tashkin et al also reported an association between the presence of GERD-related GI symptoms and frequent cough. Of those patients with frequent cough, 77% reported GERD-related GI symptoms at baseline compared with 59% of non-coughers ($P = .025$). In the small number of patients in whom GERD had resolved by 24 months (n = 8), there was a clinically significant improvement in mean LCQ score (from 14.3 to 17.9). In contrast, LCQ scores were unchanged in patients who had persistent GERD at the end of the study.

Refractory or Unexplained Cough in ILD

Patients with ILD and refractory cough have severely impaired quality of life.[2] In view of the limited treatment options for cough, the authors felt it was reasonable to manage such patients according to the CHEST unexplained chronic cough guideline, particularly in those with advanced disease and poor quality of life.[38]

One treatment option recommended in the CHEST unexplained chronic cough guideline is multimodality speech pathology therapy[39] that has been reported to decrease objective cough frequency and improve quality of life in patients with unexplained chronic cough.[40] A similar efficacy has been reported for the Physiotherapy, Speech and Language Therapy Intervention.[41] These therapies include educating patients about cough, teaching cough suppression techniques, vocal hygiene, and psychoeducational counseling. Gabapentin, a

neuromodulator, is also recommended, and in one RCT it decreased cough severity, frequency and improved quality of life in patients with refractory chronic cough.[42] Side effects were experienced by 10 of the 32 patients in the treatment group and were most commonly confusion, dizziness, dry mouth, fatigue, and nausea. There was a clinically and statistically significant improvement in the mean LCQ score of 1.8 adjusted for placebo effect. A more recent study combined the use of pregabalin and speech therapy and found a larger improvement in LCQ and cough VAS compared with speech therapy alone, suggesting that a combined approach may offer additional benefit.[43]

Suggestion 4. For patients with ILD and refractory chronic cough, we suggest trials of therapies recommended for patients with unexplained chronic cough according to the CHEST guidelines, with treatments such as gabapentin and multimodality speech pathology therapy, or entering into clinical trials if available. (Ungraded Consensus- Based Statement)

This review found no studies that met the inclusion criteria on the use of opiates for management of chronic cough in ILD patients. There is a single RCT investigating slow-release morphine (5 mg twice daily) in refractory chronic cough patients.[44] This was a positive study with a significant improvement in quality of life (a mean increase of 3.2 points in the LCQ score). The most common side effects were constipation and drowsiness; however, the drug was well tolerated, and no patients withdrew from the study due to adverse events. Opiates were not recommended by the CHEST Cough Panelists for unexplained cough, because such a recommendation narrowly failed the guideline acceptance voting threshold of 80%. Nevertheless, the authors of this guideline agree that opiates should be considered for ILD patients with intractable cough when the cough has a substantial impact on quality of life and when all alternative treatments have failed. Low dose opiates may be helpful for symptomatic relief, and this will be particularly appropriate in the palliative care setting. There are guidelines for the use of opiates for symptomatic relief of dry cough in patients receiving palliative care[45]; and, in the United States, the Centers for Disease Control and Prevention has published primary care physician guidelines for opiate use in the treatment of chronic pain that includes helpful advice regarding the potential harms of opiate use and managing risk.[46]

Suggestion 5. 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 a palliative care setting, with reassessment of the benefits and risks at 1 week and then monthly before continuing. (Ungraded Consensus-Based Statement)

Discussion

Diagnosis

ILDs are a broad range of conditions that can affect the airways, lung parenchyma, and pulmonary vasculature. The involvement of any of these compartments can lead to development of cough. Cough in patients with ILD can also be caused by ILD drug therapy, infections, and the presence of co-morbid conditions, such as GERD, upper airways disease, and asthma. It can therefore be challenging to determine the cause of a cough in a patient with ILD. The approach to investigating patients with ILD-associated cough needs to be individualized to the patient, and therefore a general approach such as that suggested in Figure 2 has limitations and should be used only as a guide. ILD is likely to be the cause of cough in a patient with evidence of disease progression, temporal association between onset of cough and disease progression, and a favorable response to ILD therapy.

When cough persists, other causes should be investigated as per the CHEST Chronic Cough Guidelines, specifically evaluating patients for the presence of asthma, nonasthmatic eosinophilic bronchitis, upper airways cough syndrome due to a variety of rhinosinus conditions, and/or GERD.[38] If a cause is not established and the patient is significantly troubled by their cough, in the opinion of this guideline group, it is reasonable to follow the CHEST unexplained chronic cough guideline approach for managing cough patients because it is possible that some patients with ILD and an unexplained cough have dysfunctional cough sensory nerves.[47] The term "cough hypersensitivity syndrome" has been proposed to address such patients.[48] In IPF, there is evidence of increased cough reflex sensitivity to both capsaicin and nerve-derived mediator substance P, and increased levels of nerve growth factor have been reported in the airways of patients with IPF.[49]

Therapy

The approach to treating cough depends on a number of factors that include the type of ILD, the availability of

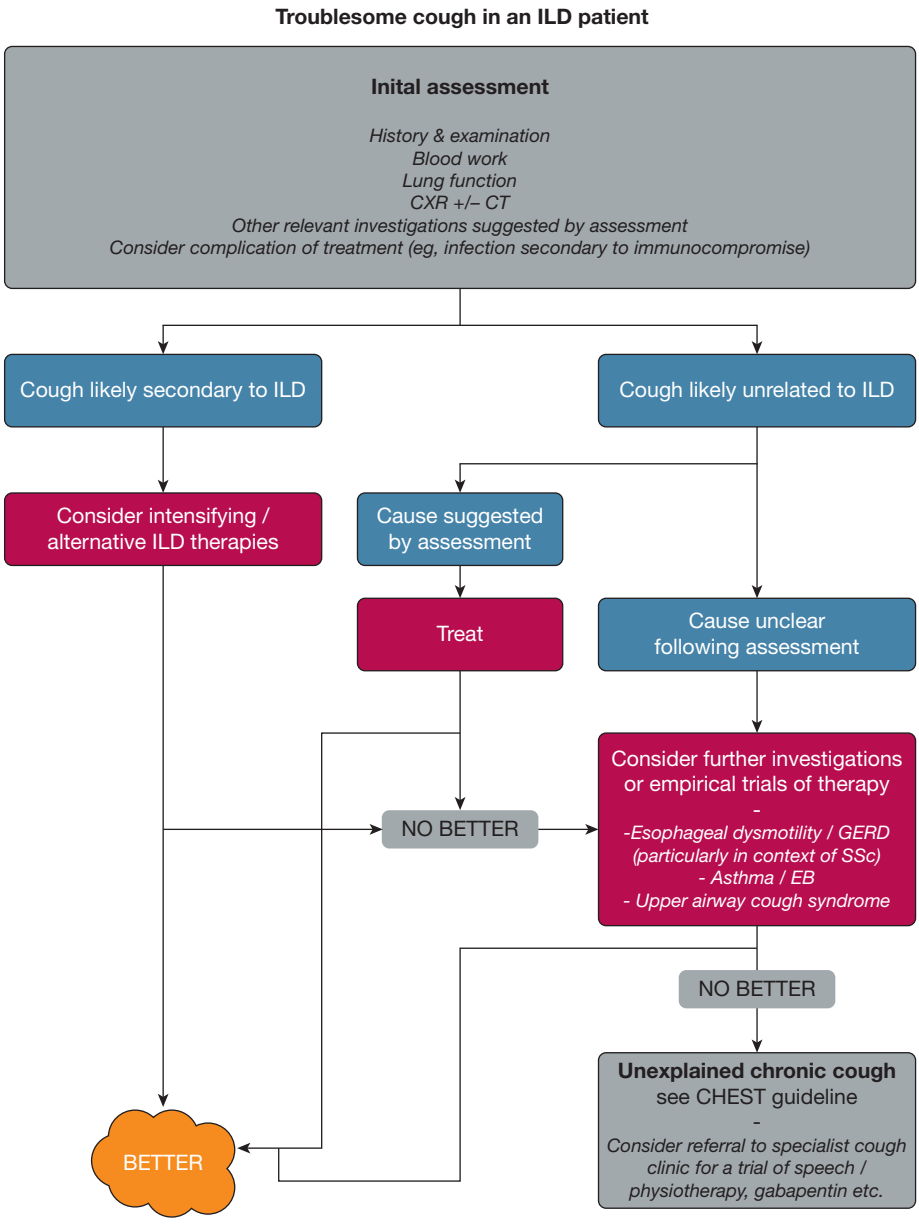

Figure 2 – *A proposed algorithm detailing a management approach to troublesome cough in an interstitial lung disease (ILD) patient. CXR = chest radiograph; EB = eosinophilic bronchitis; GERD = gastro-esophageal reflux disease; SSc = systemic sclerosis.*

effective treatments for ILD, the risk/benefit profile of ILD and antitussive treatments, and the presence of co-morbid conditions that can cause cough. When ILD is the suspected cause of cough, treatment for the underlying ILD should be considered on an individual basis, particularly in patients with clear evidence of disease progression.

IPF: In IPF, antifibrotic therapy with pirfenidone and nintedanib should be prescribed according to American Thoracic Society/European Respiratory Society Guidelines, and not specifically for cough.[35] It is possible that antifibrotic therapy may reduce the severity of cough as suggested by the findings of an uncontrolled study,[22] but this needs confirmation in larger clinical trials.

There are no controlled studies that have evaluated the use of systemic corticosteroids for IPF-associated cough. The efficacy of corticosteroids for suppressing cough was evaluated in an open-label study of six patients by Hope-Gill et al,[49] which did report a reduction in cough; however, this did not meet our review inclusion criteria. Corticosteroids in IPF (in combination with

azathioprine and N-acetyl-cysteine; "triple therapy") have been associated with increased mortality compared with placebo,[50] and the use of corticosteroids in IPF should therefore be limited to patients who may be experiencing an exacerbation of IPF or who have co-existing asthma or eosinophilic bronchitis.

Thalidomide has been investigated in IPF-associated cough in a single-center trial that included a small number of patients.[34] Thalidomide led to a significant improvement in quality of life. The mechanism of action is thought to be antiinflammatory, and possibly reduced cough sensory nerve activity.[51,52] Thalidomide was, however, associated with significant side effects.[34] While thalidomide is not suggested for use in IPF-associated cough, the Committee does encourage further study of thalidomide for cough because it might be helpful.

A recent pilot study of a novel formulation of inhaled cromolyn sodium (PA101) showed promise.[20] There was a >30% reduction in objective cough frequency between the treatment and placebo periods that is likely to be clinically significant. Although there was no significant change in the subjective cough severity and quality of life measures with treatment, the study was not powered to detect these, and the treatment duration was short. The drug was well tolerated in this pilot study. A larger trial with a longer treatment period is needed to further assess its efficacy.

Sarcoidosis: In sarcoidosis, three trials of inhaled corticosteroids did not demonstrate a significant reduction in cough. The findings of the trials by du Bois et al[28] and Baughman et al[27] did report trends toward improvement in cough. Further trials are needed to clarify the efficacy of inhaled corticosteroids, ideally in carefully selected patients with active, airway-centered disease and a clinically significant cough.

Scleroderma: Two connective tissue disease ILD studies met the inclusion criteria of this guideline. They evaluated immunosuppressive therapy in scleroderma-associated ILD.[21,30] Both studies demonstrated an association between cough and the severity of ILD. Theodore et al found no significant improvement in cough with cyclophosphamide. Tashkin et al, however, did report a decrease in subjective cough frequency with treatment (cyclophosphamide or mycophenolate), but this was not associated with a significant improvement in quality of life. The clinical significance of these therapies is therefore not clear, and we suggest that immunosuppressive therapy be prescribed for the underlying lung disease, rather than specifically for cough. Further trials in scleroderma-associated ILD are needed, with cough as the primary focus.

GERD: GERD is highly prevalent in both patients with ILD, such as IPF, and scleroderma-associated ILD and is therefore a potential cause of cough. There were no RCTs of PPI therapy in ILD-associated cough. There was a small open-label study of high dose acid suppression therapy in IPF cough that did utilize validated objective and subjective cough end points[26]; however, there was no improvement in cough with PPI therapy. In patients with unexplained chronic cough and no ILD, two RCTs did not demonstrate antitussive efficacy.[36,37] The CHEST unexplained chronic cough guidelines therefore recommended that, in patients with a negative workup of acid gastro-esophageal reflux that included esophageal pH monitoring, PPI therapy should not be prescribed.[38] A similar approach in IPF cough seems reasonable. In patients with scleroderma-associated ILD, esophageal dysfunction is a key feature of the disease, and improvement in cough has been associated with improvements in GERD in the study by Tashkin et al.[21] Therefore, a thorough approach investigating both acid and nonacid reflux in scleroderma-associated ILD is reasonable until studies that guide best management become available.

Other Antitussive Therapies: Neuromodulators, Speech/Physiotherapy, and Opiates: The severity of cough in ILD, particularly IPF, and its impact on quality of life warrants consideration of further antitussive therapy options. In unexplained chronic cough, there are several RCTs that support the use of neuromodulator drugs, such as gabapentin and pregabalin,[42,43] morphine,[44] and nonpharmacological interventions such as speech pathology therapy[39,40] and physiotherapy, speech, and language intervention.[41] There are no studies that evaluated the efficacy of these therapies in ILD, and they are urgently needed. The Guideline Panel acknowledged the paucity of evidence for use of general antitussive therapy in ILD but recommended that they should be considered because of the lack of availability of treatment options, and for use in a palliative care setting. Opiates are likely the most controversial of these treatment options, due to concerns about safety, and the potential for abuse and addiction. Indeed, morphine narrowly missed the 80% voting endorsement requirement of the CHEST unexplained chronic cough guidelines due to such concerns.[38] However, given the severity of lung disease and the poor prognosis associated with many ILDs, the panel felt that morphine should be considered as a potential treatment

for ILD cough when quality of life is severely impacted. It is already used to some extent by clinicians to relieve both cough and dyspnea in ILD and for IPF patients with debilitating cough.[53]

Summary of Systemic Review Results and Its Limitations

The present systemic review evaluated 10 trials that investigated therapeutic interventions in ILD-associated cough. Cough was often not the primary focus of these studies, and was reported in retrospective analyses. The sample sizes were relatively small, and a variety of outcome assessments were used, not all of which were adequately validated. None of the interventions have been replicated in other RCTs. It is likely that there was heterogeneity in the patient population under study that restricts the general reliability of the results. Intervention fidelity is recognized as a key aspect in the diagnosis of unexplained chronic cough, and this factor was incompletely reported in the studies included in this review that indicates a possibility for indication-bias in the studies evaluated. These aspects of study design limit the strength of the conclusions.

Future Directions

A better estimate of the prevalence, severity, and predictors of cough in ILD is needed in larger population studies. Cough may be a potential biomarker in ILD, and therefore its potential to assess disease severity and guide prognosis should be evaluated. There is a clear need for RCTs of antitussive therapy in ILD. Validated cough outcome measures such as objective cough monitoring, visual analogue severity scales, and quality of life questionnaires, such as the Cough Quality of Life Questionnaire and LCQ, should be used.[54-56] Registries for patients with ILD, such as IPF, should record the presence and severity of cough, and this can be done with very simple tools such as the VAS or the Borg scale. There are now numerous targets identified for novel antitussive therapies for unexplained cough. The antagonist of the P2X3 sensory nerve ion channel is one of the most promising and advanced in development. A RCT of a P2X3 antagonist in IPF-associated cough has been completed but not reported.[57] The novel cromolyn formulation PA101 shows promise in a proof of concept trial but needs further evaluation.[20] Other antitussive targets include the neurokinin-1, TRPV4, and alpha-7 nicotinic receptors.[58-60] Further studies of thalidomide and similar drugs are also warranted.

Conclusions

Cough associated with ILD can be due to underlying lung disease, and co-morbid conditions such as upper airway disease or GERD. In some patients it remains unexplained. The approach to managing ILD-associated cough needs to be individualized for the patient. Further clinical trials of neuromodulator therapies and speech pathology/physiotherapy-based cough suppression are needed.

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Additional information: The e-Appendix and e-Table can be found in the Supplemental Materials section of the online article.

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