Cough in chronic lung disease: a state of the art review

Author

Hirons, Barnaby, Rhatigan, Katherine, Kesavan, Harini, Turner, Richard D, Birring, Surinder S, Cho, Peter SP

Published

2023

Journal Title

Journal of Thoracic Disease

Version

Version of Record (VoR)

DOI

10.21037/jtd-22-1776

Review Article on Novel Insights into Chronic Cough

Cough in chronic lung disease: a state of the art review

Barnaby Hirons[1,2]^, Katherine Rhatigan[1,2], Harini Kesavan[1], Richard D. Turner[3,4], Surinder S. Birring[1,2], Peter S. P. Cho[1,2]

[1]Department of Respiratory Medicine, King's College Hospital, London, UK; [2]Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College London, London, UK; [3]Department of Respiratory Medicine, Gold Coast University Hospital, Queensland, Australia; [4]School of Medicine and Dentistry, Griffith University, Queensland, Australia

Contributions: (I) Conception and design: B Hirons, PSP Cho, SS Birring; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: B Hirons, PSP Cho, SS Birring; (V) Data analysis and interpretation: B Hirons, PSP Cho, SS Birring, RD Turner; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Peter S. P. Cho. Chest Unit, Department of Respiratory Medicine, Cheyne Wing, King's College Hospital, Denmark Hill, London SE5 9RS, UK; Centre for Human and Applied Physiological Sciences, School of Basic and Medical Biosciences, Faculty of Life Sciences and Medicine, King's College London, London, UK. Email: p.cho@nhs.net.

Abstract: Chronic cough (CC; ≥8 weeks in duration) is a common and burdensome feature of respiratory diseases. The understanding of cough has progressed significantly in recent years, albeit largely in refractory (unexplained) chronic cough (RCC) in the absence of other respiratory conditions. The prevalence of CC in respiratory diseases is poorly described, but estimates have been reported: asthma (8–58%), chronic obstructive pulmonary disease (COPD; 10–74%), bronchiectasis (82–98%), interstitial lung disease (ILD; 50–89%) and sarcoidosis (3–64%). CC in respiratory conditions generally predicts impaired health status and more severe disease. It is associated with increased symptom burden and disease severity in asthma, COPD, bronchiectasis and ILD, higher exacerbation frequency in asthma and bronchiectasis, and increased mortality and lung transplantation in idiopathic pulmonary fibrosis (IPF). Physiologically, heightened cough reflex sensitivity (CRS) has been reported and postulated to be mechanistic in isolated RCC. Cough reflex hypersensitivity (CRH) has also been reported in asthma, COPD, bronchiectasis, ILD and sarcoidosis. Unlike recent advances in isolated RCC, there are limited studies and understanding of central cough neuropathways in other respiratory conditions. Of note, dysfunctional central voluntary cough suppression neuropathways and physiology were observed in isolation in RCC; cough suppression is preserved in COPD. Understanding in the mechanism of RCC cannot be simply extrapolated to other respiratory conditions. The restricted understanding of cough mechanisms in these conditions has limited cough-specific therapeutic options in this context. There is currently an unmet need to expand our understanding of cough in chronic respiratory conditions, both in order to improve the quality of life of patients, and to improve knowledge of cough in general. This review aims to describe the prevalence, impact, pathophysiology and management of CC in asthma, COPD, bronchiectasis, ILD and sarcoidosis.

Keywords: Cough; asthma; chronic obstructive pulmonary disease (COPD); bronchiectasis; interstitial lung disease (ILD)

Submitted Dec 08, 2022. Accepted for publication Sep 01, 2023. Published online Sep 21, 2023.
doi: 10.21037/jtd-22-1776
View this article at: https://dx.doi.org/10.21037/jtd-22-1776

^ ORCID: 0000-0002-5049-6820.

Introduction

Cough is common in a wide range of chronic respiratory diseases (1-5). It is important, not only as a feature of significant disease (such as lung cancer or tuberculosis), but as a symptom due to its effect on the patient. Chronic cough (CC, defined as lasting greater than 8 weeks) of any cause is associated with both significant impairments in quality of life and potentially more severe underlying disease (6-9). Characteristics of cough, such as sputum production and diurnal variation, may vary between diseases, suggesting potentially different underlying mechanisms (10).

Understanding of the physiology of cough has progressed significantly over the last 20 years. The majority of research focused on refractory chronic cough (RCC), defined as CC that persists or has no identifiable cause despite exhaustive investigations and treatment, respectively (11). Important concepts in this context have been cough reflex hypersensitivity (CRH), possibly arising peripherally with sensitisation of airway afferent nerves, and dysregulation of central cough neural networks (12,13). The former is supported by observations of heightened cough reflex sensitivity (CRS) to tussive agents and the symptom profile in RCC, and has led to the hypothesis of cough hypersensitivity syndrome (CHS) (14,15). Meanwhile, recent functional neuroimaging and physiological studies have demonstrated dysfunction of central cough control neuropathways in RCC (16-18).

CRH has also been demonstrated in other chronic respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease (ILD) and sarcoidosis (4,19-23). Whilst the mechanism of cough in chronic respiratory disease awaits further evaluation, reports of CRH suggest potential similarities with RCC akin to CHS (12,13,16-18).

The landscape of potentially therapeutic options for RCC is rapidly evolving. Recently, a phase 3 study of the novel antitussive gefapixant, reported very promising results in the disease (16). Gefapixant is a novel antitussive and is postulated to attenuate CRH through direct antagonism of pulmonary C fibres (24). Given the potential mechanistic similarities in cough between RCC and other respiratory diseases, a closer examination of cough in chronic respiratory diseases may reveal shared therapeutic options.

This review will provide an overview of the prevalence, impact on quality of life, mechanism, and management of CC in a range of chronic respiratory diseases. Much effort to date in the understanding of physiology of cough has revolved around CRS, thus this review will focus on CRS mechanistically.

Asthma

Asthma is characterised by airway obstruction, inflammation and hyper-reactivity (25), and affects 12% of the UK general population over their lifetime (26). Of the different asthma phenotypes, cough variant asthma (CVA) and eosinophilic bronchitis (EB) are well described with regards to CC (11,27); what follows will focus more on cough in "classic" asthma rather than focus on CVA and EB.

Prevalence

There is a paucity of studies that report the prevalence of CC in asthma. Studies to date have reported considerably different prevalence of CC in asthma (8% to 58%) (7,28,29) (*Tables 1*,*2*). Of note, Osman *et al*. reported 90 (58%) moderate-severe asthma participants with cough (28), whilst only 70 (8%) of the asthma participants in the Copenhagen General Population Study (CGPS) reported CC (7). The difference in reported prevalence may be attributable to CC definitions employed in these studies. Osman *et al*. reported cough over 1 week duration whilst the CGPS reported over 8 weeks. In addition, different disease severity, management and study designs may be contributory. Of interest, those with CC were predominantly females in a European study of uncontrolled asthma (n=1,701) (30). This epidemiological similarity with RCC lends support to potential shared mechanistic commonalities with cough in asthma (29,30).

Impact

CC in asthma is associated with increased symptom burden, airway obstruction, exacerbation frequency, and healthcare utilisation (7,29) (*Table 3*). In the CGPS, asthma participants with CC had higher symptom prevalence (wheeze, dyspnoea, sputum and chest tightness), more severe airway obstruction [forced expiratory volume in 1 second (FEV_1) ≤60%], frequent bronchitis or pneumonia (≥6 episodes in 10 years) and healthcare utilisation [≥3 general practice (GP) consultations in 12 months] compared to those without CC (7). In addition, CC in asthma has been reported to be associated with higher Global Initiative for Asthma (GINA) severity (29), whilst higher objective cough frequency measurements were associated with poorer disease control

Table 1 Evidence summary of cough in chronic respiratory disease

Cough characteristics	Asthma	COPD	Bronchiectasis	ILD	Sarcoidosis
Prevalence of cough	8–58%	10–74%	82–98%	50–89%	3–64%
Impact of cough	↑ GINA severity	↑ SGRQ/CAT	↑ BSI	↑ Mortality[†]	↓ FVC[#]
	↑ ACQ	↓ FEV_1	↑ CT severity	↑ CT severity	↓ ACE[#]
	↓ FEV_1	↑ Exacerbations[#]	↑ Exacerbations	↓ FVC	↑ Dyspnoea
	↑ Exacerbations	↑ Dyspnoea	↑ Sputum burden	↓ DLCO	
	↑ Dyspnoea			↑ Dyspnoea	
Impaired QoL, LCQ range	13–18	13–19	12–16	15–17	15–17
Cough reflex sensitivity	↑	↑	↑	↑	↑

↑, increased; ↓, decreased; [†], data conflicting. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; GINA, Global Initiative for Asthma; SGRQ, St George's Respiratory Questionnaire; CAT, COPD Assessment Tool; BSI, Bronchiectasis Severity Index; FVC, forced vital capacity; ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; CT, computed tomography; ACE, angiotensin converting enzyme; DLCO, diffusing capacity of the lungs for carbon monoxide; QoL, Quality of Life; LCQ, Leicester Cough Questionnaire (range, 3–21, lower score indicates worse cough-specific health status).

in a study by Marsden *et al*. [Asthma Control Questionnaire 6 (ACQ6); r=0.4] (49). The mechanisms of the relationships of cough with exacerbation frequency and healthcare utilisation remain unclear.

Cough in asthma is associated with impaired cough-specific health status, as has been assessed with the Leicester Cough Questionnaire (LCQ, range, 3–21; higher scores indicate better health status) (64). Whilst impaired cough-specific health status in asthma has been reported universally, LCQ health status varies considerably internationally (*Table 4*). It is unclear why such differences exist though cultural and study design differences may be attributable. Of note, impairment in LCQ health status is similar between asthma patients with CC and non-asthma patients with CC (7,65); from the CGPS, median [interquartile range (IQR)] LCQ 16.8 (14.8–18.9) *vs.* LCQ 17.4 (15.4–18.9) respectively (7). This suggests that cough is likely an independent contributor to impaired health status in asthma, and has a similar impact on health status to CC in other contexts (28,81). The former is further supported by reports that effective cough management in asthma can yield health status improvement. Fukuhara *et al*. reported that a reduction in cough frequency (CFreq) with effective treatment was associated with improved LCQ scores (r=0.6) (65). In addition, a separate Japanese study reported improved LCQ with Tiotropium in asthma with CC (66). Taken together, cough in asthma may represent a clinically more severe phenotype with considerable health status impairment, and effective cough-targeted treatment may alter the impact.

Pathophysiology

CRS, assessed with standardised tussive inhalation challenges, is heightened in asthma (22,50,51,82,83). In tussive challenges, C2 and C5 are commonly reported endpoints, and refer to concentration thresholds of tussive agent required to elicit at least 2 and 5 coughs in 15 seconds respectively (82).

Doherty *et al*. demonstrated CRS was heightened in asthma compared to healthy controls; C5: 62.5 *vs.* >500 µM (P<0.001) respectively. In addition, CRS was associated with cough severity visual analogue scale (VAS) (r=–0.32) and subjective cough frequency (r=–0.38) (22). Findings of CRH in asthma and associations between CRH and objective CFreq have since been replicated by different authors (22,50,51,82,83) (*Table 5*).

CRH appears to be associated with disease control and a specific phenotype. Satia *et al*. reported heightened CRS was associated with poorer asthma control (51). In a separate study, CRH was reported to be associated with worse asthma control, frequent exacerbations (≥2 per annum) and hospitalisation but not FEV_1 (84). In addition, Satia *et al*. and Kanemitsu *et al*. both reported heightened CRS was more pronounced in non-atopic compared to atopic disease (51,84).

Taken together, CRH appears to play a mechanistic role in cough in asthma and represents a more severe phenotype though the precise mechanism remains under-explored.

Table 2 Prevalence of chronic cough in respiratory disease

Disease	Study	Prevalence in disease
Asthma	Çolak *et al*., CGPS. Cross-sectional population study (n=14,740). 6% had asthma, Denmark (7)	8% reported CC
	Osman *et al*., observational study of moderate-severe asthma in clinic (n=162), UK (28)	58% reported cough in last week. 12% reported cough as dominant symptom of concern
	de Marco *et al*., observational study of community asthmatics (n=856), UK (29)	30% reported CC
	Morjaria *et al*., *post-hoc* analysis prospective study uncontrolled asthma (n=1,701), UK (30)	Cough reported on median 323 days/year. Cough predominant in females and high BMI
COPD	Landt *et al*., 2020, CGPS. Cross-sectional population study (n=43,271). 19% had COPD, Denmark (6)	10% reported CC
	Agusti *et al*, 2010, observational, longitudinal, controlled study of stable COPD patients (n=2,164), Spain (31)	Chronic bronchitis in 35%
	Kim *et al*., 2011, COPDGene observational study, stable COPD (n=1,061), USA (32)	Chronic bronchitis in 27%
	Burgel *et al*., 2009, cross-sectional multicentre study, stable COPD (n=433), France (33)	Chronic bronchitis in 74%
	Mejza *et al*., 2017, observational data (n=24,855), 33 international centres (34)	Prevalence of chronic bronchitis in population: range (0–10.8%). 10.8% in Lexington (USA); 0% in Ile-Ife (Nigeria) and Blantyre (Malawi)
Bronchiectasis	Pasteur *et al*., 2010. BTS guidelines, UK (35)	>90% have chronic productive cough
	Özgün Niksarlioglu *et al*., 2016, stable bronchiectasis (n=133), Turkey (36)	82% reported cough
	King *et al*., 2006, newly presenting bronchiectasis (n=103), Australia (37)	98% reported CC
IPF	Ryerson *et al*., 2011, registry of IPF (n=242), USA (8)	84.3% reported cough
	Guenther *et al*., 2018, baseline registry data in IPF (n=525), Europe (38)	53.2% reported dry cough at presentation
	Behr *et al*., 2015, consecutive IPF patients (n=502), Germany (39)	74.7% reported current cough
	Glaspole *et al*., 2017, registry of IPF patients (n=516), Australia (40)	88.5% reported cough
	Cheng *et al*., 2017, consecutive IPF (n=77), Australia (41)	87% reported cough
	Lan *et al*., 2020, survey (n=53), Australia (42)	81% reported cough
Other-ILD	Guenther *et al*., 2018, baseline registry data in other-ILD (n=561), Europe (38)	50.2% reported dry cough at presentation
	Cheng *et al*., 2017, consecutive SSc-ILD (n=67), Australia (41)	68% reported cough
	Cheng *et al*., 2017, consecutive CHP (n=32), Australia (41)	83% reported cough
	Lan *et al*., 2020, survey of ILD, 30% IPF (n=179), Australia (42)	72% reported cough; 66% of CTD-ILD; 71% of NSIP
	Tashkin *et al*., 2017, SSc-ILD enrolled in SLS2 (n=142), USA (43)	61.3% reported frequent cough
	Theodore *et al*., 2012, SSc-ILD enrolled in SLS1 (n=156), USA (44)	73% reported cough
Sarcoidosis	Sinha et al., 2016, consecutive sarcoidosis (n=32), UK (4)	56% reported CC
	Pietinalho *et al*., 1996, consecutive sarcoidosis in Mjölbolsta, Finland (n=573), and Sapporo, Japan (n=467) (45)	Mjölbolsta: 33% reported cough; Sapporo: 3% reported cough
	Nardi *et al*., 2011, retrospective cohort stage IV sarcoidosis, n=142, France (46)	51.4% reported cough
	Kovacova *et al*., 2019, retrospective cohort (n=101), Slovakia (47)	64% reported cough
	Al-Khouzaie *et al*., 2011, retrospective cohort (n=33), Saudi Arabia (48)	54% reported cough

CGPS, Copenhagen General Population Study; CC, chronic cough; BMI, body mass index; COPD, chronic obstructive pulmonary disease; BTS, British Thoracic Society; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; SSc, systemic sclerosis; CHP, chronic hypersensitivity pneumonitis; CTD, connective tissue disease; NSIP, nonspecific interstitial pneumonia; SLS, scleroderma lung study.

Table 3 Impact: cough and clinical outcomes in respiratory disease

Disease	Impact on clinical outcomes
Asthma	In individuals with CC compared to those without:
	Higher symptom prevalence (wheeze, dyspnoea, sputum and chest tightness), frequency of bronchitis or pneumonia (≥6 episodes in 10 years) and healthcare utilisation (≥3 GP consultations in 12 months) (7)
	More likely FEV_1 ≤60% (7)
	More likely to have severe asthma (GINA classification) (29)
	Objective CFreq higher in uncontrolled *vs*. well controlled asthma and associated with ACQ6 (r=0.4) (49)
	Objective time spent coughing associated with LCQ (r=−0.54) (50)
	Cough not associated with airway eosinophil and neutrophil counts, serum eosinophil and IgE, IL-5, IL-8, TNF-α and FeNO (7,51-54)
COPD	CC is stronger predictor of airflow obstruction in smokers than wheeze and dyspnoea (55)
	In individuals with CC compared to those without:
	Increased dyspnoea, sputum production, episodes acute bronchitis or pneumonia, healthcare utilisation, and lower FEV_1 (6)
	Risk of exacerbation conflicting: 2 studies found association, 1 did not (33,56,57)
	Cough frequency associated with sputum neutrophils, but not eosinophils (1,58)
Bronchiectasis	Objective CFreq higher in stable bronchiectasis compared to health. CFreq correlated with LCQ scores (r=−0.52). CFreq independently associated with sputum VAS and 1-year exacerbation frequency, but not FEV_1 or FVC (59)
ILD	IPF: self-reported cough significantly associated with disease severity (symptoms, desaturation, lung function), and progression but not prognosis or transplantation (8)
	Conflicting associations between LCQ scores and outcome:
	Saunders *et al*. In IPF, impaired LCQ at baseline associated with higher MRC dyspnoea score, but not lung function or mortality (60)
	Lee *et al*. In ILD (61% IPF), impaired LCQ associated with increased mortality, hospitalisation, and lung transplantation (61)
	IPF, CHP and SSc-ILD: worse lung function (FEV_1, FVC, DLCO), and dyspnoea score were predictors of cough (41)
	SSc-ILD: self-reported cough associated with impaired LCQ, dyspnoea and disease severity (DLCO and radiological) in 2 studies (43,44)
Sarcoidosis	Patient-reported cough associated with symptoms of dyspnoea, fever, and chest pain, but not arthralgia or erythema nodosum. Also associated with lower FEV_1 and FVC, but not radiographic staging, sex, or smoking status (47)
	Objective CFreq higher in sarcoidosis compared to health and associated with cough severity VAS (r=0.62) and LCQ (r=−0.61) (4)
	No association between serum ACE and objective CFreq (4,62)
	Objective CFreq not associated with lung function (FEV_1, FVC, DLCO), number of organs involved, immunosuppressive treatment or radiological staging (4)
	In individuals with reported cough compared to those without:
	Associated with presence of endobronchial findings, biopsy-proven tracheitis, and airway neutrophilia, but not lymphocytes, eosinophils, or $CD4^+/CD8^+$ ratios (47,63)

CC, chronic cough; GP, general practice; FEV_1, forced expiratory volume in one second; GINA, Global Initiative for Asthma; CFreq, cough frequency; ACQ, Asthma Control Questionnaire; LCQ, Leicester Cough Questionnaire; IgE, immunoglobulin E; IL, interleukin; TNF-α, tumour necrosis factor α; FeNO, fractional exhaled nitric oxide; COPD, chronic obstructive pulmonary disease; VAS, visual analogue scale; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MRC, medical research council; CHP, chronic hypersensitivity pneumonitis; SSc, systemic sclerosis; DLCO, diffusing capacity of the lungs for carbon monoxide; ACE, angiotensin converting enzyme.

Table 4 Impact: cough-specific health status in respiratory disease

Disease	Impact on cough-specific health status
Asthma	Cough-specific health status LCQ is impaired in asthma; range, 12.6–17.8 (2,7,50,64-66)
	LCQ associated with objective time spent coughing (r=−0.54), but not age or sex (50)
COPD	Cough-specific health status LCQ appears impaired in COPD; range, 13.4–18.7 (1,67-69)
	LCQ is worse in COPD than health, lowest in COPD current smokers (1)
	Cough for >3 months/year associated with worse health-related QoL (SGRQ-C) (70)
	Cough-specific CQLQ health status associated with nocturnal, but not daytime, CFreq (r=0.50) (71)
Bronchiectasis	Cough-specific health status LCQ is impaired in stable bronchiectasis; range, 11.7–16.0 (2,23,59,72-74)
	Worse LCQ associated with increased disease duration, HRCT severity, sputum, and BSI (23)
	LCQ score may discriminate between mild and severe disease (75)
	Raised subjective cough score in stable bronchiectasis increases risk of anxiety and depression (OR 1.64 and 1.57 respectively) (76)
ILD	Cough-specific health status LCQ is impaired in unselected ILD; range, 14.9–16.5 (6,43,60,61,77)
	CC in IPF and cough severity VAS (r=0.2) are associated with impaired generic health status (SGRQ) (40)
	Conflicting associations between LCQ and outcome:
	Saunders *et al*. In IPF, impaired LCQ at baseline associated with higher MRC, but not lung function or mortality (60)
	Lee *et al*. In ILD (61% IPF), impaired LCQ associated with increased mortality, hospitalisation, and lung transplantation (61)
Sarcoidosis	Cough-specific health status LCQ is impaired in sarcoidosis; range, 14.8–16.9 (4,78-80)
	Worse LCQ and cough severity VAS in black compared to white patients, and worse VAS in females. VAS and LCQ not associated with age, lung function, radiological severity, or smoking status (80)

LCQ, Leicester Cough Questionnaire; COPD, chronic obstructive pulmonary disease; QoL, quality of life; SGRQ-C, St. George's respiratory questionnaire for COPD; CQLQ, Cough Quality of Life Questionnaire; CFreq, cough frequency; HRCT, high-resolution computed tomography; BSI, Bronchiectasis Severity Index; OR, odds ratio; ILD, interstitial lung disease; CC, chronic cough; IPF, idiopathic pulmonary fibrosis; VAS, visual analogue scale; MRC, medical research council.

Peripheral airway afferent neurones can be sensitised by various inflammatory markers, and potentially lead to heightened CRS. Indeed, serum neutrophils, leukocytes and fibrinogen may be higher in asthma patients with CC compared to those without (7). If CRH was secondary to inflammatory sensitisation in asthma, the agent responsible remains elusive. Eosinophilic airway inflammation does not appear to be the sole driver of cough; neither fractional exhaled nitric oxide (FeNO) nor serum eosinophil count was associated with CRS to capsaicin (51). The relationship between FeNO or eosinophil count with CRS to other tussive agents is under explored. In addition, airway neutrophils, immunoglobulin E (IgE), interleukin (IL)-5, IL-8 and tumour necrosis factor α (TNF-α) seem to not be associated with cough in asthma (7,51-54). The precise mechanism of cough likely involves multiple receptors and neuropathways as in RCC (12,13,16-18).

Management

Inhaled corticosteroid (ICS) is an established treatment in asthma and is recommended in CC to assess response (11). The specific therapeutic effect on cough may not be due to attenuation of CRS—there seems to be no change in the threshold of capsaicin-induced cough with the use of ICS in asthma (22).

Tiotropium and leukotriene receptor antagonists (LTRAs) are also established treatment for asthma. In an observational study of patients with asthma and CC unresponsive to combination inhaled treatment with long-acting beta agonist (LABA) and ICS (n=17), tiotropium was associated with substantial improvements in median cough severity VAS (from 53 at baseline to 26 mm following treatment), LCQ scores (12.8 to 16.3) and asthma control test scores (17.6 to 20.5), with no significant change in

Table 5 Pathophysiology: cough reflex sensitivity in respiratory disease

Disease	Observed traits of cough reflex sensitivity
Asthma	CRS heightened in asthma compared to health (22,50,51,82,83)
	CRH associated with worse asthma control, frequent exacerbations (≥2 per annum) and hospitalisation but not FEV_1 (84)
	CRS associated with cough severity VAS (r=−0.32) and subjective cough frequency (r=−0.38) (22)
	CRS associated with objective CFreq and ACQ. CRS not associated with FeNO or serum eosinophils (51)
	Methacholine-induced bronchoconstriction increases CRS (85)
	CRH more likely in non-atopic compared to atopic asthma (51,84)
COPD	CRS heightened in COPD compared to health (1,19,22,86)
	CRS is associated with objective CFreq (1,3,71)
	Change in CRS between exacerbation and 6-week recovery associated with future exacerbation rate (ρ=−0.69) (87)
	CRS not significantly different between current/ex/never smokers (1)
Bronchiectasis	CRS heightened in stable bronchiectasis compared to health (23,88)
	CRH associated with duration, disease severity (BSI and HRCT), Pseudomonas aeruginosa, female, cough symptom score, worse LCQ (23)
ILD	CRS heightened in IPF and SSc-ILD compared to health (21,89)
	No association between CRS and cough severity VAS, lung function (FEV_1, FVC, DLCO), or radiological disease severity (21,89)
	In SSc, CRS higher in those with ILD than without (90)
Sarcoidosis	CRS heightened in sarcoidosis compared to health (4)
	CRS associated with objective CFreq (r=−0.64) (4)
	CRH associated with lower serum ACE level (r=0.72) (4,62)

CRS, cough reflex sensitivity; CRH, cough reflex hypersensitivity; FEV_1, forced expiratory volume in 1 second; VAS, visual analogue scale; CFreq, cough frequency; ACQ, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; COPD, chronic obstructive pulmonary disease; BSI, Bronchiectasis Severity Index; HRCT, high-resolution computed tomography; LCQ, Leicester Cough Questionnaire; IPF, idiopathic pulmonary fibrosis; SSc, systemic sclerosis; ILD, interstitial lung disease; FVC, forced vital capacity; DLCO, diffusing capacity of the lungs for carbon monoxide; ACE, angiotensin converting enzyme.

FEV_1 (66). In this study, tiotropium was associated with a reduction in CRS in those patients demonstrating improvements in cough severity VAS of ≥15 mm; however, the mechanism for CRS attenuation remains unclear (66).

Two LTRAs, zafirlukast and montelukast, have been shown to improve cough severity VAS and objective cough frequency with no significant change to FEV_1 in two small randomised controlled trials (RCTs) (n=8 and 14) and an observational study (91-93). CRS was improved by both LTRAs through an uncertain mechanism (91,92). Further studies are required to assess the efficacy and mechanism of action of long-acting muscarinic antagonist (LAMA) and LTRAs in CC in asthma (*Table 6*).

Azithromycin is an immunomodulatory and anti-inflammatory antibiotic (25). In a RCT in RCC the drug was associated with improved cough severity VAS and LCQ compared to placebo in patients with concurrent asthma (n=7) (108). Recently, biological therapies, such as mepolizumab (anti-IL-5), are increasingly employed in the management of asthma (25). The impact of biological therapies on cough in asthma has been under explored to date. In an observational study (n=11), Faruqi *et al*. reported a reduction in mean 24-hour objective CFreq with mepolizumab over 6 months (94).

Summary

CC is prevalent in asthma, and significantly impairs quality of life. The presence of CC is associated with increased disease severity and poor control. CC is associated with the presence of airway inflammation and may improve with anti-inflammatory treatment. There is heightened CRS in patients with asthma. A clear relationship between airway inflammation and sensitisation of the cough reflex has however not yet been established. Further work should particularly evaluate treatments that target airway sensory nerves.

Table 6 Management of chronic cough in respiratory disease

Disease	Intervention	Study	Outcome
Asthma	Gefapixant	RCT (n=732), comorbid asthma in 41% (16)	Improved objective CFreq, cough severity VAS and LCQ
	Tiotropium	Noncontrolled study of asthma with CC on LABA/ICS (n=17) (66)	Improved cough severity VAS, LCQ and ACT with no change to FEV_1. CRS reduced when VAS reduced ≥15 mm
	LTRAs: Zafirlukast and Montelukast	2 RCTs (n=8 and 14) and an observational study (n=14) (91-93)	Improved cough severity VAS, objective CFreq, and CRS with no change to FEV_1
	Mepolizumab	Observational study (n=11) (94)	24 h objective CFreq improved from baseline of 172 to 71 at 6 months
	Azithromycin	RCT, *post-hoc* analysis of patients with asthma (n=7) (95)	LCQ and cough severity (VAS) improved compared to placebo; difference 6.19, P<0.01, and –3.1, P<0.01, respectively
COPD	Smoking cessation	Observational study (n=68) (1)	Current smokers had worse objective CFreq, cough severity VAS and LCQ compared to COPD ex-smokers
	Pulmonary rehabilitation	Observational study in consecutive COPD (n=49) (67)	Significant improvement in LCQ and CASA-Q
	Azithromycin	RCT of COPD with chronic bronchitis (n=84) (69)	Treatment conferred benefit to LCQ (difference 1.3, P=0.01)
	Codeine	RCT of COPD with cough (n=21) (96)	No benefit to cough severity VAS, objective CFreq or CRS
Bronchiectasis	BHPT	Observational study of stable bronchiectasis (n=53) (73)	Cough severity VAS and LCQ improved
	Twice daily chest physiotherapy	RCT of stable bronchiectasis (n=20) (74)	Improved LCQ
	Atorvastatin	RCT of stable bronchiectasis colonised with Pseudomonas aeruginosa (n=27) (97)	No change in LCQ, improvement in SGRQ
	Atorvastatin	RCT of stable bronchiectasis (n=82) (98)	Improved LCQ
ILD	Thalidomide	Cross-over study in IPF (n=98) (99)	Improved cough severity VAS, CQLQ and SGRQ. High rates of adverse events
	Cyclophosphamide and mycophenolate	*Post-hoc* analysis of trials SLS1 (n=158) and SLS2 (n=142) in SSc-ILD (43,44)	Both improved self-reported cough
	Omeprazole	RCT in IPF (n=45) (77)	No effect on objective CFreq or LCQ
	Oral prednisolone	Uncontrolled trial in IPF (n=6) (89)	Improved CRS and cough severity VAS
	Azithromycin	RCT cross-over trial in IPF (n=25) (100)	No benefit in LCQ, cough severity VAS, or objective CFreq
	Nebulised sodium cromoglycate	Phase 2b RCT in IPF (n=108) (101)	Despite promising phase 2a results, gave no benefit in LCQ, cough severity VAS, or objective CFreq
	Pirfenidone	Observational study in IPF (n=43) (102)	Improved cough severity VAS, LCQ and objective CFreq
	Gefapixant	Cross-over RCT in IPF (n=51) (103)	No effect on cough severity VAS, CQLQ and objective CFreq. Cough severity diary scores improved with treatment
Sarcoidosis	Azithromycin	Noncontrolled, open-label trial (n=21) (78)	Reduced objective CFreq, cough severity (VAS) and LCQ
	Inhaled corticosteroid	3 RCTs in sarcoidosis (n=21, 29 and 44) (104-106)	No benefit to reported cough
	Nebulised VIP	Open phase 2 study (n=20) (107)	Improved self-reported cough and reduced bronchoalveolar TNF-α

RCT, randomised controlled trial; CFreq, cough frequency; VAS, visual analogue scale; LCQ, Leicester Cough Questionnaire; CC, chronic cough; LABA/ICS, long-acting beta agonist/inhaled corticosteroid; ACT, asthma control test; FEV_1, forced expiratory volume in one second; CRS, cough reflex sensitivity; LTRA, leukotriene receptor antagonists; COPD, chronic obstructive pulmonary disease; CASA-Q, Cough and Sputum Assessment Questionnaire; BHPT, bronchopulmonary hygiene physical therapy; SGRQ, St. George's respiratory questionnaire; IPF, idiopathic pulmonary fibrosis; CQLQ, Cough Quality of Life Questionnaire; SLS, scleroderma lung study; SSc, systemic sclerosis; ILD, interstitial lung disease; VIP, vasoactive intestinal peptide; TNF-α, tumour necrosis factor α.

COPD

COPD affects an estimated 2% of the UK population (4.5% aged over 40) and is associated with considerable impairment in health status (109-112).

Prevalence

In the CGPS, 8,181 (19%) participants had COPD, of which 796 (10%) reported CC (6) (*Table 1*). Meanwhile, chronic bronchitis (daily cough with sputum for ≥3 months of the year for ≥2 years), as a phenotype of COPD, has been more widely investigated. The estimated prevalence of chronic bronchitis in patients with COPD varies considerably at up to 74% (31-33,113) (*Table 2*). Meanwhile, Burden of Obstructive Lung Disease (BOLD) study reported the prevalence of chronic bronchitis across 33 international centres (0–10.8%) across the population (34). In BOLD, chronic bronchitis was associated with older age, current smoking, family history of chronic respiratory disease and lower education level (34). In a French secondary care study (n=433), 321 (74%) stable COPD patients reported chronic bronchitis (33). The considerably varied prevalence observed may be secondary to cultural differences, disease severity and study designs.

Impact

CC is a predictor of airflow obstruction in smokers (55), and is associated with significant symptom burden in COPD (6). In the CGPS, COPD participants with CC experienced more breathlessness and sputum production, more acute bronchitis or pneumonia, more healthcare utilisation, and had lower FEV_1 compared to those without CC (6). Meanwhile, there is conflicting evidence on whether CC in stable COPD is predictive of exacerbation frequency (114). Burgel *et al*. and Seemungal *et al*. reported that patient-reported daily cough is a predictor of frequent exacerbations, whilst Hurst *et al*. did not find such an association (33,56,57); the difference perhaps relating in part to the shortcomings of subjective assessments in comparison to objective cough frequency monitoring. Recently, Cho *et al*. reported that the change in CRS between exacerbation and 6-week recovery was associated with future exacerbation rate (ρ=–0.69) (87) (*Table 3*).

Cough in COPD is associated with considerably impaired health status (1,115-118) (*Table 4*). Jones *et al*. reported cough as one of the top five factors contributing towards impaired COPD-specific health status with the COPD Assessment Tool (CAT) (118). Cough-specific health status LCQ appears to be impaired in stable COPD patients with cough (1,67-69) (*Table 4*). Of note, the extent of cough-specific health status impairment is similar between COPD patients with CC and RCC (3). Smith *et al*. reported that nocturnal cough frequency was associated with worse cough-specific health status (r=0.50) in COPD, thus suggesting that cough is likely a determinant of health status in COPD (71).

Pathophysiology

COPD is characterised by airway and systemic inflammation and, as is postulated in asthma, inflammatory mediators can sensitise airway afferent neurones and heighten CRS (119-121). Supporting this idea, several authors have documented CRS to be heightened in COPD compared to health (1,19,22,86), with a possible association with objectively-measured CFreq (1,3,71) (*Table 5*). As in asthma, eosinophilic inflammation does not appear to be the driver of cough in COPD. Two studies have reported an association between cough frequency and sputum neutrophils, but not eosinophils (1,58).

Recently, Cho *et al*. reported a heightened CRS both in participants with COPD and CC, and in a separate group with isolated RCC, in comparison to a third group of healthy controls. However, those with COPD were able to voluntarily suppress evoked cough to a much greater extent than patients with RCC (3). In inhaled tussive challenges, threshold capsaicin concentrations to induce cough, with and without attempted voluntary cough suppression, were associated with objective daily cough frequency (ρ=–0.42 and –0.43 respectively) (3). Taken together, CRS likely plays a mechanistic role though the mechanism is poorly understood and is likely to involve neuropathway sensitisation. In contrast, the dysfunction of central voluntary inhibitory neuropathways may play much less of a part in CC associated with COPD than in other contexts (3).

Smoking is strongly associated with COPD but there have been limited attempts to investigate the mechanistic role of smoking in CC in COPD (1,122). Sumner *et al*. reported that current smoker status was associated with a higher objective daily CFreq in patients with COPD, compared to both those with COPD who were ex-smokers, and current smokers without COPD. However, this difference in CFreq was not reflected in CRS to capsaicin, threshold inhaled concentrations of which were not

significantly different between these two COPD groups (1). This raises the possibility that ongoing tobacco smoke exposure exerts its observed effect on daily cough frequency through a different mechanism to that governing capsaicin-evoked cough pathways in COPD.

Management

There is a plethora of established COPD-specific pharmacological and non-pharmacological interventions, though a lacuna remains in cough-specific management (110,111) (*Table 6*). That Sumner *et al*. reported COPD current smokers had worse objective CFreq, cough severity VAS scores and cough-specific health status (LCQ scores) compared to COPD ex-smokers (1) reiterates the benefits of smoking cessation in all COPD patients (111).

In terms of pharmacological therapy, a Cochrane review reported that mucolytics such as carbocisteine reduce exacerbation risk and may improve COPD-specific health status (123); however, the efficacy of these medications on cough remains unexplored. Cough has been relatively under explored as an endpoint in terms of COPD inhaled therapy. Doherty *et al*. reported no relationship between CRS and ICS treatment, whilst CRS was heightened with inhaled anti-cholinergic therapy (22). Smith *et al*. observed the effects of inhaled medications on objective CFreq in COPD (71). Cough counts were reduced with long acting β2-agonists, increased with inhaled anticholinergics, and unchanged by ICS (71). Azithromycin can be used in COPD patients with frequent exacerbations (111). In a RCT (n=84) of stable COPD patients with chronic bronchitis (FEV_1 <80%), LCQ scores modestly improved with azithromycin compared to placebo (mean difference 1.3 points; P=0.01) (69).

There has been limited success with non-COPD specific pharmacological therapies (*Table 6*). Codeine is commonly used as an anti-tussive but had no significant impact on cough severity VAS, objective CFreq, or CRS in a placebo-controlled study in COPD (96). Meanwhile, in an observational study of stable COPD (n=49), Rebelo *et al*. reported significant improvement in LCQ and the Cough and Sputum Assessment Questionnaire (CASA-Q) following pulmonary rehabilitation (67). Whilst promising, further studies are required to evaluate the potential benefit from inhaled therapies, azithromycin, and pulmonary rehabilitation in COPD-associated cough.

Summary

CC is prevalent in COPD and significantly impairs quality of life. The presence of CC is associated with increased symptom severity and worse lung function though the relationship with exacerbation risk remains unclear. CRS is heightened in COPD patients with cough, much like in RCC. However, in contrast to RCC in the absence of other lung disease, the ability to suppress evoked cough in COPD appears intact. The limited evidence on CRS in COPD does suggest that inflammation is potentially mechanistic in cough and disease severity. Further studies should investigate the culprit of CRH and its associations with disease severity in COPD. Treating cough in COPD tends to largely involve treating the underlying disease and has variable success whilst smoking cessation remains critical.

Bronchiectasis

Bronchiectasis is a heterogenous disorder characterised by complex interplay between infection, airway inflammation, failure of mucociliary clearance and airway structural damage (124).

Prevalence

Chronic productive cough is the cardinal symptom of bronchiectasis, and guidelines report a prevalence of over 90% (35) (*Table 1*). Özgün Niksarlioglu *et al*. reported cough in 109 (82%) of stable bronchiectasis patients in Turkey (36). In contrast, King *et al*. reported CC in 101 (98%) patients referred to a specialist bronchiectasis clinic in Australia (37) (*Table 2*). The cause of these disparities is unclear, and may relate to the aetiology of bronchiectasis, disease severity or treatment, and cultural differences. Regardless, the prevalence of cough in bronchiectasis is high.

Impact

In stable bronchiectasis, cough-specific health status is impaired; LCQ score range, 11.7–16.0 (2,23,59,72-74) (*Table 4*). In addition, Guan *et al*. reported significantly worse LCQ health status with increased disease duration, high-resolution computed tomography (HRCT) severity, sputum burden (sputum purulence score and 24 h volume), and Bronchiectasis Severity Index (BSI) score (23). Not only

do LCQ scores significantly differ with disease severity, the questionnaire is able to discriminate between mild and severe stable disease [area under the curve (AUC) 0.8 and 0.84 respectively] as per microbiological and radiological criteria (75) (*Table 3*).

Increased CFreq appears to be associated with cough-specific health status and exacerbation frequency (59). Spinou *et al*. reported higher objective CFreq in consecutive stable bronchiectasis patients (n=54) compared to health, and CFreq was associated with LCQ score (r=–0.52) (59). Objective CFreq was independently associated with patient-reported sputum severity VAS and one-year exacerbation frequency, but not spirometry [FEV_1 or forced vital capacity (FVC)] (59). In addition, cough may be associated with psychological co-morbidities. Gao *et al*. reported increased risk of anxiety and depression with raised daytime cough symptom scores [odds ratio (OR) 1.64 and 1.57 respectively] in stable bronchiectasis (76).

Pathophysiology

Bronchiectasis is associated with airway inflammation, and appears to lead to peripheral airway afferent nerve sensitisation and heightened CRS. Torrego *et al*. and Guan *et al*. reported heightened CRS in stable bronchiectasis compared to health, and this may relate to disease severity (23,88) (*Table 5*). Heightened CRS was associated with disease duration, disease severity (BSI and HRCT findings), *Pseudomonas aeruginosa* colonisation, female sex, increased cough symptom score and worse LCQ scores (23). The studies to date have not investigated the relationship of CRS with objective CFreq or validated subjective cough measures, thus the mechanistic role of CRH remains unclear.

Sputum burden is likely to play a mechanistic role in cough in bronchiectasis, but there are a lack of studies directly exploring the mechanical and chemical stimulation of airway sensory nerves by the excessive sputum load in the disease. Such challenging work is awaited.

Management

Bronchiectasis is a suppurative condition with an increased risk of infection, thus the absolute suppression of cough is not recommended (124). However, much of the excessive cough in the disease may be maladaptive above that which is physiologically helpful to aid sputum clearance. To our knowledge, there is no study that has investigated cough-specific interventions in bronchiectasis and cough severity is perhaps not sufficiently explored as an outcome measure in bronchiectasis. Management of bronchiectasis involves airway clearance, bronchial hygiene, prompt treatment of infections, treatment of any underlying conditions, consideration of regular antibiotics, mucolytics, and pulmonary rehabilitation (124) (*Table 6*).

Atorvastatin has anti-inflammatory effects and has shown promise in bronchiectasis (97,98). In an RCT (n=82) of stable bronchiectasis, treatment improved LCQ (mean change 1.5) compared to placebo (98). However, in a separate cross-over RCT (n=27) of stable bronchiectasis colonised with *Pseudomonas aeruginosa*, there was improvement in health status with St George's Respiratory Questionnaire (SGRQ) but not LCQ scores (97). Further studies incorporating objective cough frequency and cough severity ratings are needed before atorvastatin can be recommended for cough in the disease.

Chest physiotherapy and bronchopulmonary hygiene physical therapy (BHPT) have been shown to benefit cough severity and health status in bronchiectasis (73,74,124); the latter involves patient education and airway clearance technique training. A small RCT of stable bronchiectasis patients naïve to chest physiotherapy (n=20) reported improvements in cough-specific health status after 3-months of twice daily chest physiotherapy using an oscillatory positive expiratory pressure device compared to control (3 months of no chest physiotherapy); median increase (IQR) in LCQ scores 1.3 (–0.17 to 3.25) *vs.* 0 (–1.5 to 0.5) respectively (P=0.002) (74). In a separate observational study (n=53), cough severity VAS and LCQ scores improved following BHPT; mean difference [95% confidence interval (CI)] VAS 15.8 mm (9.6 to 22 mm) and LCQ 3.1 (2.4 to 3.9) (all P<0.001) (73) (*Table 6*). Effective airway clearance may therefore lead to an improvement in cough severity and cough-specific health status; however, such therapies should be assessed in larger studies (125).

Summary

CC is highly prevalent in bronchiectasis and significantly impairs quality of life. CC appears associated with increased disease severity and exacerbation risk. There is heightened CRS in patients with bronchiectasis, but the mechanisms of cough remain unclear. There is also limited cough-specific therapy, with chest physiotherapy perhaps having the most evidence.

ILD

ILD encompasses over 300 entities with differing aetiologies and prognoses (126). All ILDs involve a degree of interstitial

inflammation and can lead to fibrosis (127). IPF is the most common, accounting for more than 60% of patients (99). To date, most cough literature in ILD relates to IPF.

Prevalence

The reported prevalence of cough in IPF varies between 53% and 89%, and most studies report a rate >80% (8,38-42,127) (*Table 1*). There are considerable differences in the prevalence of cough amongst different aetiologies of ILD (*Table 2*). The cause of these disparities remains unexplained but may relate to different definitions of cough and ILD, study design, severity of disease, comorbidities, smoking, and cultural differences. The prevalence of cough in ILD other than IPF is under-investigated. In a cross-sectional study of ILD (n=164), 72% of all participants reported cough; 81% in IPF, 66% in connective tissue disease ILD, and 71% in non-specific interstitial pneumonia (42). In systemic sclerosis-associated interstitial lung disease (SSc-ILD), cough is reported in 61–71% of patients (41,43,44). In a small observational study (n=32), cough was reported in 83% of chronic hypersensitivity pneumonitis (HP) (41).

Impact

CC in IPF is associated with disease severity and health status impairment (8,40,41,60,61,128), though again few studies have explored this in other ILDs (*Tables 2,5*). CC in IPF and cough severity VAS scores (r=0.2) were associated with impaired SGRQ in an Australian national observational study (n=516) (40). In an US IPF registry analysis, self-reported cough was associated with disease severity according to symptoms, exertional desaturation and lung function, and progression but not prognosis or transplantation (8). In addition, Lan *et al*. reported participants with ILD and cough had more severe disease as measured by FEV_1, FVC, gas transfer factor [diffusing capacity of the lungs for carbon monoxide (DLCO)], 6-minute walk test and physician assessment compared to ILD participants without cough (42).

Cough-specific LCQ health status is impaired in ILD with a reported range of 14.9–16.5 (maximum possible score 21) (6,43,60,61,77) (*Table 4*). A UK prospective study of IPF (n=484) reported impaired LCQ scores were associated with higher medical research council (MRC) dyspnoea scores but not lung function or mortality (60). In contrast, Lee *et al*. reported impaired LCQ was associated with increased mortality, hospitalisation, and lung transplantation in a study of the US Pulmonary Fibrosis Foundation registry (n=1,447; 61% IPF) (61). Every 1-point decrease in LCQ score was associated with a 7.4% increased risk of mortality at 12 months; hazard ratio (HR) (95% CI) 1.074 (1.020–1.130, P=0.006). The different disease groups investigated in the studies may be attributable to the contrasting findings. Of note, LCQ scores were not significantly different between ILDs, and there was no association with lung function decline (61).

Outside of IPF, self-reported cough was associated with impaired LCQ, breathlessness and disease severity (DLCO and radiological features) in two separate studies in SSc-ILD (43,44). Recently, Cheng *et al*. reported greater patient-reported cough severity (VAS) in IPF compared to both chronic HP and SSc-ILD; median (IQR) VAS 39 [17–65] *vs.* 29 [11–48] *vs.* 18 [0–33] mm respectively (P<0.01) (41). In addition, worse lung function (FEV_1, FVC, DLCO) and dyspnoea score were predictors of cough in IPF, chronic HP and SSc-ILD (41). The impact of cough should be investigated in large studies in individual ILDs.

Pathophysiology

ILD is associated with inflammation and interstitial distortion, which may lead to cough through sensitisation and stimulation of both chemoreceptors and mechanoreceptors, respectively (43,129). To our knowledge, there is no study that has directly investigated the role of mechanoreceptors in cough in ILD. However, Jones *et al*. reported that indirectly activating mechanoreceptors by chest wall percussion evoked cough in 85% of patients with IPF (n=27) compared to 17% of healthy controls (130). As in other respiratory diseases, effort in understanding the mechanisms of cough has largely focused on CRS, and such effort has borne fruit to some extent.

Heightened CRS to inhaled capsaicin and substance P has been observed in IPF and SSc-ILD compared to healthy volunteers (21,89) (*Table 5*). The mechanism of such CRH in ILD is unclear, though it appears to be associated with pathophysiology of the lung disease itself rather than, for example, generalised systemic inflammation. Supporting this idea, in a study of subjects with progressive systemic sclerosis, Lalloo *et al*. reported significantly higher cough severity VAS and heighten CRS to capsaicin in participants with associated ILD compared to those without (90).

Despite the demonstration of heightened CRS in ILD, the extent to which hypersensitivity drives cough in this

group is not certain. The profile of cough in ILD is similar to that in RCC; similar self-reported laryngeal sensations and triggers are common to both contexts, including airway irritants (smoke, aerosols, fumes), talking, exertion and position change (42,131). On the other hand, the studies above did not explore the associations of CRS with cough severity VAS or objective cough frequency to consolidate the concept of CRH in cough in ILD (21,89).

Management

ILD-associated cough is often refractory to treatment (5,8,132), and in this context most cough-specific therapies have only been investigated in IPF (*Table 6*). With ILD associated with inflammation and heightened CRS, much effort has understandably been invested in assessing the efficacy of immunomodulatory therapies in ILD-associated cough.

Various immunomodulators have been investigated in IPF-associated cough, and the results have been largely disappointing (133). In a small study of IPF with cough (n=6), prednisolone was associated with improvement in CRS and cough severity VAS (89). However, long-term corticosteroid treatment in IPF does not improve prognosis and is associated with considerable morbidity (134). Thalidomide is a potent immunomodulatory and anti-inflammatory drug, and was associated with improved cough severity VAS, Cough Quality-of-Life Questionnaire (CQLQ), and SGRQ scores in a cross-over study of IPF-associated cough (99). Unfortunately, thalidomide was also associated with substantial adverse event rates (77%), such as constipation and dizziness, which might limit clinical application (99,135). Azithromycin, an immunomodulatory and anti-inflammatory antibiotic, has demonstrated benefit in various cough metrics in sarcoidosis and COPD (69,78). However, a small RCT of the drug in IPF (n=25) demonstrated no improvement in LCQ, cough severity VAS, or objective CFreq (100). Inhaled sodium cromoglycate, a mast cell degranulation inhibitor which can inhibit C-fibre sensory nerve activity, significantly improved cough severity VAS, LCQ and objective CFreq in IPF in an initial small RCT (n=24) (136). However, these findings were not reproduced in a subsequent larger scale study (n=81) of longer duration (12 weeks *vs.* 14 days) (101). A large initial placebo effect is frequently observed in cough trials which may explain the differing findings in these studies (137). The mostly disappointing findings above perhaps reflect our limited understanding of cough physiology in ILD, thus impeding the development of targeted therapy.

To our knowledge, pirfenidone is the only disease attenuating therapy that has been investigated in relation to cough. Pirfenidone, an antifibrotic agent (138), significantly improved cough severity VAS, LCQ and objective CFreq in IPF in an observational study (n=43) (102), but the findings need to be replicated in larger randomised studies.

Therapies with demonstrated efficacy in isolated RCC have been investigated in IPF, though with limited success (*Table 6*). Gastro-oesophageal reflux disease (GORD) is a potential cause of CC and a common co-morbidity in ILD (127). However, omeprazole had no significant effect on objective CFreq or patient-reported outcomes, including LCQ scores, in an RCT (n=45) of patients with IPF (77). The P2X3 inhibitor gefapixant improved cough severity diary (CSD) score, but had no effect on cough severity VAS scores, CQLQ score or objective CFreq in a cross-over RCT (n=51) in IPF (103). This suggests the ATP/P2X pathway is less important in CC associated with IPF than in RCC in other contexts. Meanwhile, two separate RCTs are underway, nalbuphine (a mixed opioid agonists/antagonist) and morphine for CC in IPF, and early results are promising (139,140).

Outside of IPF, there are some early promising findings regarding the efficacy of systemic treatment of cough in ILD. In *post-hoc* analyses of two studies investigating cyclophosphamide and mycophenolate in SSc-ILD, the drugs were associated with significant improvements in self-reported cough (43,44). These observations however require further confirmation, and neither cyclophosphamide nor mycophenolate are currently recommended for cough in SSc-ILD (133).

Summary

CC is highly prevalent in ILD and significantly impairs quality of life. CC may be associated with increased disease severity, mortality and lung transplantation. The symptom profile of cough and the demonstration of CRH in ILD suggest similar specific underlying physiological processes to those governing cough to in 'classical' RCC (in the absence of other lung disease). The lack of therapeutic response to P2X3 antagonist in ILD however casts doubt on this idea. Investigations of therapies for cough in ILD have enjoyed the most success with immune and inflammatory modulating therapies, albeit in early exploratory studies, perhaps suggesting specific immune and inflammatory pathways as culprits for further attention.

Sarcoidosis

Sarcoidosis is an idiopathic multisystem granulomatous disorder which commonly affects the lungs, skin, and eyes. It is more common in African-Caribbean populations with both genetic and environmental factors playing a role in susceptibility (141).

Prevalence

Cough prevalence in sarcoidosis varies geographically, ranging from 3% in Japan, 33% in Finland, to 48–64% in Saudi Arabia and Europe (4,45-48) (*Table 1*). A paucity of studies investigating the prevalence and predictors of cough in sarcoidosis mean the mechanism of this geographical variation remains unexplained (*Table 2*).

Impact

Cough in sarcoidosis appears to be associated with other symptoms of the disease. Kovacova *et al*. reported that self-reported cough was associated with concurrent dyspnoea, fever, and chest pain, but not arthralgia or erythema nodosum in a retrospective study (47). Presence of cough has also been associated with lower FEV_1 and FVC values, but not radiological staging of thoracic sarcoidosis (Scadding), sex, or smoking status (47). Recently, Sinha *et al*. demonstrated that objective CFreq was higher in patients with sarcoidosis (n=32) compared to healthy volunteers, and correlated with the subjective markers cough severity VAS (r=0.62) and LCQ scores (r=–0.61) (4) (*Table 3*).

Cough-specific health status is impaired in sarcoidosis; the reported range of LCQ scores is between 14.8 and 16.9 in a secondary care setting (4,78-80) (*Table 4*). Judson *et al*. reported more severe cough (VAS) and worse LCQ health status in consecutive black patients compared to white patients, and more severe cough (VAS) in females (80). In addition, cough severity and health status were not associated with age, lung function, radiological severity, or smoking status (80).

Pathophysiology

Few have investigated the mechanisms of cough in sarcoidosis to date. Postulated mechanisms include airway inflammation or hyper-responsiveness, interstitial distortion, vagus nerve disruption, laryngeal and vocal cord involvement, granulomatous infiltration of the pulmonary vasculature, and heightened CRS (63,142).

Kovacova *et al*. reported that cough in sarcoidosis was associated with more positive endobronchial findings compared to those without cough (43% *vs*. 12% respectively) in the absence of cough-relevant co-morbidities (47). In addition, cough was associated with airway neutrophilia, but not lymphocyte counts, eosinophils, or $CD4^+$:$CD8^+$ ratios (47). In a retrospective study of tracheal biopsy in sarcoidosis, Ding *et al*. reported more self-reported cough in patients with tracheitis compared to those without (92% *vs*. 49% respectively) (63). Taken together, endobronchial sarcoidosis and airway neutrophilic inflammation are associated with cough though the precise mechanism remains unexplored.

The potential role of levels of serum angiotensin converting enzyme (ACE) in cough is conflicting (4,79). Sinha *et al*. reported heightened CRS was associated with lower serum ACE level (r=0.72) though there was no association between serum ACE and objective CFreq (4,62). Meanwhile, Gvozdenovic *et al*. reported lower serum ACE was associated with better LCQ health status in an observational study (n=275) (79).

Heightened CRS may play a mechanistic role in sarcoidosis-associated cough (*Table 5*). Sinha *et al*. reported heightened CRS in sarcoidosis compared to health, and capsaicin thresholds were associated with objective CFreq (r=–0.64) (4). Indeed, the profile of cough triggers in sarcoidosis were suggestive of CRH, and included smoky atmosphere (54%), tickle sensation in the throat (49%), perfume and scents (44%). In addition, objective CFreq was not associated with lung function (FEV_1, FVC, DLCO), number of organs involved, immunosuppressive treatment or radiological staging, thus suggesting CFreq and mechanism of cough are independent of disease severity (4).

Management

Few therapeutic options have been investigated in sarcoidosis-related cough (*Table 6*). Systemic corticosteroid is often indicated in sarcoidosis, although no specific trials for cough exist to our knowledge (143). Meanwhile, ICSs are ineffective in sarcoid-related cough as per three different RCTs (n=21, 29 and 44) (104-106). ICSs are therefore not recommended for cough in the disease (133).

Further uncontrolled studies of potential treatments for cough in sarcoidosis have shown promise but need RCT evaluation. Nebulised vasoactive intestinal peptide (VIP), a neurotransmitter with anti-inflammatory and immunomodulator properties, appeared to have

efficacy in an open label phase 2 study (n=20) (107). Bronchoalveolar TNF-α levels were significantly reduced following inhalation of the drug, and nine (75%) patients who received it reported amelioration of their CC (107). Recently, azithromycin significantly reduced objective CFreq in a non-controlled, open-label clinical trial (n=21); median cough frequency 228 *vs.* 81 coughs over 24 hours before and after three months of treatment (78). In addition, cough severity (VAS) and LCQ health status improved significantly, and CFreq improvement was associated with improvement in LCQ scores (r=–0.64) (78). The findings from these exploratory studies clearly need confirmation.

Summary

CC is prevalent in patients with sarcoidosis although the range is large and varies with geographical region. The presence of CC impacts on quality of life. There appears to be a relationship between CC and endobronchial disease, and symptoms in sarcoidosis. However, a relationship with disease severity or progression has not been reported. CC is associated with airway inflammation in sarcoidosis. Further studies are needed to evaluate if treating this inflammation improves cough. There is heightened CRS in patients with sarcoidosis. The relationship between this and sarcoidosis outcomes has not been well studied.

Future directions

CC is common in chronic respiratory diseases and frequently associated with impaired health status. Despite this, in chronic respiratory conditions, a paucity of studies have investigated the prevalence and predictors of CC and, unlike isolated RCC in the absence of other respiratory disease (144), no study has investigated cough-related healthcare utilisation and cost. Further investigations may reveal its true burden in a wide breath of respiratory diseases. Such studies will help to effectively direct future research efforts.

In the general field of CC, notable advancements in the understanding of neuropathophysiology have been made (13,18,145). Functional neuroimaging has provided novel insight into central mechanisms (18,122), whilst clinical and preclinical models have illuminated peripheral processes (13,145). In turn, effective pharmacological and non-pharmacological therapies, neuromodulators and speech pathology management respectively, have been developed for the management of RCC (146-149). In contrast, with limited investigations to date in most cases, the specific (additional) mechanisms of cough which may be unique to particular chronic respiratory diseases remain enigmatic. At present this is limiting options for treatment.

Potential avenues for investigating cough associated with chronic respiratory diseases may come about from a closer examination of the mechanisms of RCC. Indeed, such an approach has borne fruit; investigations into CRS have demonstrated an element of CRH in many chronic respiratory diseases (*Table 5*). Belvisi *et al*. demonstrated that different respiratory diseases have different cough reflex profiles with different tussive agents, thus proposed the idea of different 'neurophenotypes' of cough amongst respiratory diseases (83). Indeed, the differing CRS profiles between diseases may suggest different pathophysiology of cough. Further studies to investigate the CRS profile and mechanism of CRH in different respiratory diseases may provide insight into the potential for novel antitussives such as P2X3 inhibitors (16,150). Further understanding into the phenotypes of cough in different respiratory diseases may also enable individualised disease-specific treatment.

Recently, dysfunctional central voluntary cough suppression has been reported in RCC (13,18). Of note, in contrast to RCC, COPD patients with cough were able to voluntarily suppress an evoked cough despite presence of CRH in both conditions (3). This phenomenon lends further support to the concept of distinct phenotypes of cough, with different mechanisms, in different chronic respiratory diseases. In addition, it is not possible to simply extrapolate our understanding between RCC and other chronic respiratory diseases. Indeed, the central cough neural mechanisms remains enigmatic in both RCC and other diseases.

Conclusions

CC is a common symptom in chronic respiratory disease and is frequently associated with worse disease-specific outcomes and impaired health status. The mechanisms of cough in these diseases remain poorly understood. There is some evidence to suggest CRH may play a mechanistic role in diseases other than RCC. This is of particular interest given the findings of the recent phase 3 study of gefapixant, known to reduce CRS to adenosine triphosphate (16,24). Further studies should investigate the impact of cough in other respiratory diseases, including healthcare cost, to guide more directed interventions. In addition, a better understanding of the neurophysiology of cough in other diseases may help to

identify specific avenues of investigation for potential novel therapies, and may extend the useful indications for new drugs developed initially for RCC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Woo-Jung Song and Kian Fan Chung) for the series "Novel Insights into Chronic Cough" published in *Journal of Thoracic Disease*. The article has undergone external peer review.

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1776/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1776/coif). The series "Novel Insights into Chronic Cough" was commissioned by the editorial office without any funding or sponsorship. SSB has received personal fees for consultancy from Merck, Bellus, Trevi, Genentech, Nerre, Kinevant, Boehringer Ingelheim and Bayer. PSPC reports two ongoing grants: EPSRC and MERCK, outside of the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sumner H, Woodcock A, Kolsum U, et al. Predictors of objective cough frequency in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:943-9.
2. Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest 2008;134:295-302.
3. Cho PSP, Fletcher HV, Patel IS, et al. Cough hypersensitivity and suppression in COPD. Eur Respir J 2021;57:2003569.
4. Sinha A, Lee KK, Rafferty GF, et al. Predictors of objective cough frequency in pulmonary sarcoidosis. Eur Respir J 2016;47:1461-71.
5. Key AL, Holt K, Hamilton A, et al. Objective cough frequency in Idiopathic Pulmonary Fibrosis. Cough 2010;6:4.
6. Landt E, Çolak Y, Lange P, et al. Chronic Cough in Individuals With COPD: A Population-Based Cohort Study. Chest 2020;157:1446-54.
7. Çolak Y, Afzal S, Lange P, et al. Role and Impact of Chronic Cough in Individuals with Asthma From the General Population. J Allergy Clin Immunol Pract 2019;7:1783-1792.e8.
8. Ryerson CJ, Abbritti M, Ley B, et al. Cough predicts prognosis in idiopathic pulmonary fibrosis. Respirology 2011;16:969-75.
9. Kovacova E, Buday T, Vysehradsky R, et al. Cough in sarcoidosis patients. Respir Physiol Neurobiol 2018;257:18-24.
10. Smith JA, Ashurst HL, Jack S, et al. The description of cough sounds by healthcare professionals. Cough 2006;2:1.
11. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 2020;55:1901136.
12. Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. Lancet Respir Med 2013;1:414-22.
13. Cho PSP, Fletcher HV, Turner RD, et al. Impaired cough suppression in chronic refractory cough. Eur Respir J 2019;53:1802203.
14. Morice AH, Faruqi S, Wright CE, et al. Cough hypersensitivity syndrome: a distinct clinical entity. Lung 2011;189:73-9.
15. Chung KF, McGarvey L, Song WJ, et al. Cough hypersensitivity and chronic cough. Nat Rev Dis Primers 2022;8:45.
16. McGarvey LP, Birring SS, Morice AH, et al. Efficacy and safety of gefapixant, a P2X(3) receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-

blind, randomised, parallel-group, placebo-controlled, phase 3 trials. Lancet 2022;399:909-23.
17. Mazzone SB, Canning BJ. Central nervous system control of the airways: pharmacological implications. Curr Opin Pharmacol 2002;2:220-8.
18. Ando A, Smallwood D, McMahon M, et al. Neural correlates of cough hypersensitivity in humans: evidence for central sensitisation and dysfunctional inhibitory control. Thorax 2016;71:323-9.
19. Cho PSP, Fletcher HV, Patel IS, et al. Cough reflex sensitivity in exacerbations of chronic obstructive pulmonary disease. Eur Respiratory Soc 2018;52:PA4056.
20. Prudon B, Birring SS, Vara DD, et al. Cough and glottic-stop reflex sensitivity in health and disease. Chest 2005;127:550-7.
21. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin induced cough in cryptogenic fibrosing alveolitis. Thorax 2000;55:1028-32.
22. Doherty MJ, Mister R, Pearson MG, et al. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax 2000;55:643-9.
23. Guan WJ, Gao YH, Xu G, et al. Capsaicin cough sensitivity and the association with clinical parameters in bronchiectasis. PLoS One 2014;9:e113057.
24. Morice AH, Kitt MM, Ford AP, et al. The effect of gefapixant, a P2X3 antagonist, on cough reflex sensitivity: a randomised placebo-controlled study. Eur Respir J 2019;54:1900439.
25. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022.
26. Asthma statistics | British Lung Foundation [Internet]. Available online: https://statistics.blf.org.uk/asthma
27. Niimi A. Cough and Asthma. Curr Respir Med Rev 2011;7:47-54.
28. Osman LM, McKenzie L, Cairns J, et al. Patient weighting of importance of asthma symptoms. Thorax 2001;56:138-42.
29. de Marco R, Marcon A, Jarvis D, et al. Prognostic factors of asthma severity: a 9-year international prospective cohort study. J Allergy Clin Immunol 2006;117:1249-56.
30. Morjaria JB, Rigby AS, Morice AH. Asthma phenotypes: do cough and wheeze predict exacerbations in persistent asthma? Eur Respir J 2017;50:1701366.
31. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010;11:122.
32. Kim V, Han MK, Vance GB, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. Chest 2011;140:626-33.
33. Burgel PR, Nesme-Meyer P, Chanez P, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest 2009;135:975-82.
34. Mejza F, Gnatiuc L, Buist AS, et al. Prevalence and burden of chronic bronchitis symptoms: results from the BOLD study. Eur Respir J 2017;50:1700621.
35. Pasteur MC, Bilton D, Hill AT, et al. British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010;65:577.
36. Özgün Niksarlioglu EY, Özkan G, Günlüoğlu G, et al. Factors related to depression and anxiety in adults with bronchiectasis. Neuropsychiatr Dis Treat 2016;12:3005-10.
37. King PT, Holdsworth SR, Freezer NJ, et al. Characterisation of the onset and presenting clinical features of adult bronchiectasis. Respir Med 2006;100:2183-9.
38. Guenther A, Krauss E, Tello S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respir Res 2018;19:141.
39. Behr J, Kreuter M, Hoeper MM, et al. Management of patients with idiopathic pulmonary fibrosis in clinical practice: the INSIGHTS-IPF registry. Eur Respir J 2015;46:186-96.
40. Glaspole IN, Chapman SA, Cooper WA, et al. Health-related quality of life in idiopathic pulmonary fibrosis: Data from the Australian IPF Registry. Respirology 2017;22:950-6.
41. Cheng JZ, Wilcox PG, Glaspole I, et al. Cough is less common and less severe in systemic sclerosis-associated interstitial lung disease compared to other fibrotic interstitial lung diseases. Respirology 2017;22:1592-7.
42. Lan NSH, Moore I, Lake F. Understanding cough in interstitial lung disease: a cross-sectional study on the adequacy of treatment. Intern Med J 2021;51:923-9.
43. Tashkin DP, Volkmann ER, Tseng CH, et al. Improved Cough and Cough-Specific Quality of Life in Patients Treated for Scleroderma-Related Interstitial Lung Disease: Results of Scleroderma Lung Study II. Chest 2017;151:813-20.
44. Theodore AC, Tseng CH, Li N, et al. Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: findings from the Scleroderma Lung Study. Chest 2012;142:614-21.
45. Pietinalho A, Ohmichi M, Hiraga Y, et al. The mode

of presentation of sarcoidosis in Finland and Hokkaido, Japan. A comparative analysis of 571 Finnish and 686 Japanese patients. Sarcoidosis Vasc Diffuse Lung Dis 1996;13:159-66.
46. Nardi A, Brillet PY, Letoumelin P, et al. Stage IV sarcoidosis: comparison of survival with the general population and causes of death. Eur Respir J 2011;38:1368-73.
47. Kovacova E, Vysehradsky R, Kocan I, et al. Retrospective Study of Factors Potentially Influencing Occurrence of Cough in Slovak Patients with Sarcoidosis. Can Respir J 2019;2019:3808206.
48. Al-Khouzaie TH, Al-Tawfiq JA, Al Subhi FM. Sarcoidosis in the eastern region of Saudi Arabia. Ann Thorac Med 2011;6:22-4.
49. Marsden PA, Satia I, Ibrahim B, et al. Objective Cough Frequency, Airway Inflammation, and Disease Control in Asthma. Chest 2016;149:1460-6.
50. Marsden PA, Smith JA, Kelsall AA, et al. A comparison of objective and subjective measures of cough in asthma. J Allergy Clin Immunol 2008;122:903-7.
51. Satia I, Tsamandouras N, Holt K, et al. Capsaicin-evoked cough responses in asthmatic patients: Evidence for airway neuronal dysfunction. J Allergy Clin Immunol 2017;139:771-779.e10.
52. De Diego A, Martínez E, Perpiñá M, et al. Airway inflammation and cough sensitivity in cough-variant asthma. Allergy 2005;60:1407-11.
53. Niimi A, Amitani R, Suzuki K, et al. Eosinophilic inflammation in cough variant asthma. Eur Respir J 1998;11:1064-9.
54. Thomson NC, Chaudhuri R, Messow CM, et al. Chronic cough and sputum production are associated with worse clinical outcomes in stable asthma. Respir Med 2013;107:1501-8.
55. Van Schayck CP, Loozen JM, Wagena E, et al. Detecting patients at a high risk of developing chronic obstructive pulmonary disease in general practice: cross sectional case finding study. BMJ 2002;324:1370.
56. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.
57. Seemungal TA, Donaldson GC, Paul EA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418-22.
58. Contoli M, Baraldo S, Conti V, et al. Airway inflammatory profile is correlated with symptoms in stable COPD: A longitudinal proof-of-concept cohort study. Respirology 2020;25:80-8.
59. Spinou A, Lee KK, Sinha A, et al. The Objective Assessment of Cough Frequency in Bronchiectasis. Lung 2017;195:575-85.
60. Saunders P, Saini G, Marshall RP, et al. Cough Related Quality of Life in Patients with Idiopathic Pulmonary Fibrosis - Initial Findings from the PROFILE Cohort. Am J Respir Crit Care Med 2017;195:A1543.
61. Lee J, White E, Freiheit E, et al. Cough-Specific Quality of Life Predicts Disease Progression Among Patients With Interstitial Lung Disease: Data From the Pulmonary Fibrosis Foundation Patient Registry. Chest 2022;162:603-13.
62. Sinha A, Lee KK, Patel AS, et al. S136 The association between cough reflex sensitivity and serum ACE level in patients with sarcoidosis. Thorax 2011;66:A62-3.
63. Xin-Min D, Qin-Zhi X, Yun-You D, et al. Impact of tracheal mucosa involvement on clinical characteristics of sarcoidosis. South Med J 2011;104:315-8.
64. Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 2003;58:339-43.
65. Fukuhara A, Saito J, Birring SS, et al. Clinical Characteristics of Cough Frequency Patterns in Patients with and without Asthma. J Allergy Clin Immunol Pract 2020;8:654-61.
66. Fukumitsu K, Kanemitsu Y, Asano T, et al. Tiotropium Attenuates Refractory Cough and Capsaicin Cough Reflex Sensitivity in Patients with Asthma. J Allergy Clin Immunol Pract 2018;6:1613-1620.e2.
67. Rebelo P, Oliveira A, Paixão C, et al. Minimal Clinically Important Differences for Patient-Reported Outcome Measures of Cough and Sputum in Patients with COPD. Int J Chron Obstruct Pulmon Dis 2020;15:201-12.
68. Bellas H, Connolly B, Birring S, et al. Effect of cough on health-related quality of life in COPD. Eur Respir J 2012;40:P612.
69. Berkhof FF, Doornewaard-ten Hertog NE, Uil SM, et al. Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: a randomised controlled trial. Respir Res 2013;14:125.
70. Lee H, Jhun BW, Cho J, et al. Different impacts of respiratory symptoms and comorbidities on COPD-specific health-related quality of life by COPD severity. Int J Chron Obstruct Pulmon Dis 2017;12:3301-10.

71. Smith J, Owen E, Earis J, et al. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest 2006;130:379-85.
72. Nicolson CH, Stirling RG, Borg BM, et al. The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012;106:661-7.
73. Mutalithas K, Watkin G, Willig B, et al. Improvement in health status following bronchopulmonary hygiene physical therapy in patients with bronchiectasis. Respir Med 2008;102:1140-4.
74. Murray MP, Pentland JL, Hill AT. A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. Eur Respir J 2009;34:1086-92.
75. Murray MP, Turnbull K, MacQuarrie S, et al. Validation of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. Eur Respir J 2009;34:125-31.
76. Gao YH, Guan WJ, Zhu YN, et al. Anxiety and depression in adult outpatients with bronchiectasis: Associations with disease severity and health-related quality of life. Clin Respir J 2018;12:1485-94.
77. Dutta P, Funston W, Mossop H, et al. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. Thorax 2019;74:346-53.
78. Fraser SD, Thackray-Nocera S, Shepherd M, et al. Azithromycin for sarcoidosis cough: an open-label exploratory clinical trial. ERJ Open Res 2020. doi: 10.1183/23120541.00534-2020.
79. Gvozdenovic BS, Mihailovic-Vucinic VV, Vukovic MH, et al. Predictors of cough-specific and generic quality of life in sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis 2020;37:158-68.
80. Judson MA, Chopra A, Conuel E, et al. The Assessment of Cough in a Sarcoidosis Clinic Using a Validated instrument and a Visual Analog Scale. Lung 2017;195:587-94.
81. Clark VL, Gibson PG, McDonald VM. What matters to people with severe asthma? Exploring add-on asthma medication and outcomes of importance. ERJ Open Res 2021;7:00497-2020.
82. Morice AH, Fontana GA, Belvisi MG, et al. ERS guidelines on the assessment of cough. Eur Respir J 2007;29:1256-76.
83. Belvisi MG, Birrell MA, Khalid S, et al. Neurophenotypes in Airway Diseases. Insights from Translational Cough Studies. Am J Respir Crit Care Med 2016;193:1364-72.
84. Kanemitsu Y, Fukumitsu K, Kurokawa R, et al. Increased Capsaicin Sensitivity in Patients with Severe Asthma Is Associated with Worse Clinical Outcome. Am J Respir Crit Care Med 2020;201:1068-77.
85. Satia I, Badri H, Woodhead M, et al. The interaction between bronchoconstriction and cough in asthma. Thorax 2017;72:1144-6.
86. Wong CH, Morice AH. Cough threshold in patients with chronic obstructive pulmonary disease. Thorax 1999;54:62-4.
87. Cho PSP, Fletcher HV, Turner RD, et al. The Relationship Between Cough Reflex Sensitivity and Exacerbation Frequency in Chronic Obstructive Pulmonary Disease. Lung 2020;198:617-28.
88. Torrego A, Haque RA, Nguyen LT, et al. Capsaicin cough sensitivity in bronchiectasis. Thorax 2006;61:706-9.
89. Hope-Gill BD, Hilldrup S, Davies C, et al. A study of the cough reflex in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2003;168:995-1002.
90. Lalloo UG, Lim S, DuBois R, et al. Increased sensitivity of the cough reflex in progressive systemic sclerosis patients with interstitial lung disease. Eur Respir J 1998;11:702-5.
91. Takemura M, Niimi A, Matsumoto H, et al. Clinical, physiological and anti-inflammatory effect of montelukast in patients with cough variant asthma. Respiration 2012;83:308-15.
92. Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. J Asthma 2002;39:291-7.
93. Spector SL, Tan RA. Effectiveness of montelukast in the treatment of cough variant asthma. Ann Allergy Asthma Immunol 2004;93:232-6.
94. Faruqi S, Sykes DL, Crooks MG, et al. Objective Assessment of Cough: An Early Marker of Response to Biological Therapies in Asthma? Lung 2020;198:767-70.
95. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:659-68.
96. Smith J, Owen E, Earis J, et al. Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol 2006;117:831-5.
97. Bedi P, Chalmers JD, Graham C, et al. A Randomized Controlled Trial of Atorvastatin in Patients With Bronchiectasis Infected With Pseudomonas Aeruginosa: A Proof of Concept Study. Chest 2017;152:368-78.
98. Mandal P, Chalmers JD, Graham C, et al. Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial. Lancet Respir Med 2014;2:455-63.
99. Horton MR, Santopietro V, Mathew L, et al.

Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis: a randomized trial. Ann Intern Med 2012;157:398-406.
100. Guler SA, Clarenbach C, Brutsche M, et al. Azithromycin for the Treatment of Chronic Cough in Idiopathic Pulmonary Fibrosis: A Randomized Controlled Crossover Trial. Ann Am Thorac Soc 2021;18:2018-26.
101. Martinez FJ, Wijsenbeek MS, Raghu G, et al. Phase 2B Study of Inhaled RVT-1601 for Chronic Cough in Idiopathic Pulmonary Fibrosis: A Multicenter, Randomized, Placebo-controlled Study (SCENIC Trial). Am J Respir Crit Care Med 2022;205:1084-92.
102. van Manen MJG, Birring SS, Vancheri C, et al. Effect of pirfenidone on cough in patients with idiopathic pulmonary fibrosis. Eur Respir J 2017;50:1701157.
103. Martinez FJ, Afzal AS, Smith JA, et al. Treatment of Persistent Cough in Subjects with Idiopathic Pulmonary Fibrosis (IPF) with Gefapixant, a P2X3 Antagonist, in a Randomized, Placebo-Controlled Clinical Trial. Pulm Ther 2021;7:471-86.
104. Baughman RP, Iannuzzi MC, Lower EE, et al. Use of fluticasone in acute symptomatic pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2002;19:198-204.
105. du Bois RM, Greenhalgh PM, Southcott AM, et al. Randomized trial of inhaled fluticasone propionate in chronic stable pulmonary sarcoidosis: a pilot study. Eur Respir J 1999;13:1345-50.
106. Milman N, Graudal N, Grode G, et al. No effect of high-dose inhaled steroids in pulmonary sarcoidosis: a double-blind, placebo-controlled study. J Intern Med 1994;236:285-90.
107. Prasse A, Zissel G, Lützen N, et al. Inhaled vasoactive intestinal peptide exerts immunoregulatory effects in sarcoidosis. Am J Respir Crit Care Med 2010;182:540-8.
108. Hodgson D, Anderson J, Reynolds C, et al. The Effects of Azithromycin in Treatment-Resistant Cough: A Randomized, Double-Blind, Placebo-Controlled Trial. Chest 2016;149:1052-60.
109. Jones PW. COPD assessment test --rationale, development, validation and performance. COPD 2013;10:269-71.
110. Chronic obstructive pulmonary disease in over 16s: diagnosis and management NICE guideline; 2018. Available online: www.nice.org.uk/guidance/ng115
111. Global Initiative for Chronic Obstructive Lung Disease Global Initiative for Chronic Obstructive Lung Disease, pocket guide to COPD diagnosis, management, and prevention, A Guide for Health Care Professionals. 2020; Available online: www.goldcopd.org
112. Chronic obstructive pulmonary disease (COPD) statistics [Internet] British Lung Foundation; 2023. Available online: https://statistics.blf.org.uk/copd
113. Halbert RJ, Natoli JL, Gano A, et al. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006;28:523-32.
114. Miravitlles M. Cough and sputum production as risk factors for poor outcomes in patients with COPD. Respir Med 2011;105:1118-28.
115. Miravitlles M, Molina J, Naberan K, et al. Factors determining the quality of life of patients with COPD in primary care. Ther Adv Respir Dis 2007;1:85-92.
116. Miravitlles M, Anzueto A, Legnani D, et al. Patient's perception of exacerbations of COPD--the PERCEIVE study. Respir Med 2007;101:453-60.
117. Monteagudo M, Rodríguez-Blanco T, Llagostera M, et al. Factors associated with changes in quality of life of COPD patients: a prospective study in primary care. Respir Med 2013;107:1589-97.
118. Jones PW, Brusselle G, Dal Negro RW, et al. Patient-centred assessment of COPD in primary care: experience from a cross-sectional study of health-related quality of life in Europe. Prim Care Respir J 2012;21:329-36.
119. Kwong K, Lee LY. PGE(2) sensitizes cultured pulmonary vagal sensory neurons to chemical and electrical stimuli. J Appl Physiol (1985) 2002;93:1419-28.
120. Ho CY, Lee LY. Ozone enhances excitabilities of pulmonary C fibers to chemical and mechanical stimuli in anesthetized rats. J Appl Physiol (1985) 1998;85:1509-15.
121. Lieu T, Undem BJ. Neuroplasticity in vagal afferent neurons involved in cough. Pulm Pharmacol Ther 2011;24:276-9.
122. Ando A, Mazzone SB, Farrell MJ. Altered neural activity in brain cough suppression networks in cigarette smokers. Eur Respir J 2019;54:1900362.
123. Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2019;5:CD001287.
124. Hill AT, Sullivan AL, Chalmers JD, et al. British Thoracic Society Guideline for bronchiectasis in adults. Thorax 2019;74:1-69.
125. McCallion P, De Soyza A. Cough and bronchiectasis. Pulm Pharmacol Ther 2017;47:77-83.
126. Garner J, George PM, Renzoni E. Cough in interstitial lung disease. Pulm Pharmacol Ther 2015;35:122-8.
127. Brown KK. Chronic cough due to chronic interstitial

pulmonary diseases: ACCP evidence-based clinical practice guidelines. Chest 2006;129:180S-5S.
128. Yount SE, Beaumont JL, Chen SY, et al. Health-Related Quality of Life in Patients with Idiopathic Pulmonary Fibrosis. Lung 2016;194:227-34.
129. Madison JM, Irwin RS. Chronic cough in adults with interstitial lung disease. Curr Opin Pulm Med 2005;11:412-6.
130. Jones RM, Hilldrup S, Hope-Gill BD, et al. Mechanical induction of cough in Idiopathic Pulmonary Fibrosis. Cough 2011;7:2.
131. Hirons B, Rhatigan K, Kesavan H, et al. Triggers and impact of chronic cough in interstitial lung disease. Eur Respir J 2022;60:7.
132. Swigris JJ, Stewart AL, Gould MK, et al. Patients' perspectives on how idiopathic pulmonary fibrosis affects the quality of their lives. Health Qual Life Outcomes 2005;3:61.
133. Birring SS, Kavanagh JE, Irwin RS, et al. Treatment of Interstitial Lung Disease Associated Cough: CHEST Guideline and Expert Panel Report. Chest 2018;154:904-17.
134. Flaherty KR, Toews GB, Lynch JP 3rd, et al. Steroids in idiopathic pulmonary fibrosis: a prospective assessment of adverse reactions, response to therapy, and survival. Am J Med 2001;110:278-82.
135. Wakwaya Y, Ramdurai D, Swigris JJ. Managing Cough in Idiopathic Pulmonary Fibrosis. Chest 2021;160:1774-82.
136. Birring SS, Wijsenbeek MS, Agrawal S, et al. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. Lancet Respir Med 2017;5:806-15.
137. Eccles R. The Powerful Placebo Effect in Cough: Relevance to Treatment and Clinical Trials. Lung 2020;198:13-21.
138. National Institute for Health and Care Excellence. Pirfenidone for treating idiopathic pulmonary fibrosis [Internet]. London, NICE, 2018 [cited 2022 Apr 20]; [TA504]. Available online: www.nice.org.uk/guidance/ta504
139. Wu Z, Banya W, Chaudhuri N, et al. PAciFy Cough-a multicentre, double-blind, placebo-controlled, crossover trial of morphine sulphate for the treatment of pulmonary Fibrosis Cough. Trials 2022;23:184.
140. Molyneaux PL, Forbes W, Bortey E, et al. S15 Efficacy of oral nalbuphine extended release for the treatment of chronic cough in idiopathic pulmonary fibrosis: analysis of a phase 2 study. Thorax 2022;77:A13-4.
141. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007;357:2153-65.
142. Tully T, Birring SS. Cough in Sarcoidosis. Lung 2016;194:21-4.
143. Thillai M, Atkins CP, Crawshaw A, et al. BTS Clinical Statement on pulmonary sarcoidosis. Thorax 2021;76:4-20.
144. Cho PSP, Shearer J, Simpson A, et al. Healthcare utilization and costs in chronic cough. Curr Med Res Opin 2022;38:1251-7.
145. Belvisi MG, Birrell MA, Wortley MA, et al. XEN-D0501, a Novel Transient Receptor Potential Vanilloid 1 Antagonist, Does Not Reduce Cough in Patients with Refractory Cough. Am J Respir Crit Care Med 2017;196:1255-63.
146. Slinger C, Mehdi SB, Milan SJ, et al. Speech and language therapy for management of chronic cough. Cochrane Database Syst Rev 2019;7:CD013067.
147. Chamberlain Mitchell SA, Garrod R, Clark L, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. Thorax 2017;72:129-36.
148. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet 2012;380:1583-9.
149. Vertigan AE, Kapela SL, Ryan NM, et al. Pregabalin and speech pathology combination therapy for refractory chronic cough: a randomized controlled trial. Chest 2016;149:639-48.
150. Smith JA, Kitt MM, Morice AH, et al. Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. Lancet Respir Med 2020;8:775-85.

Cite this article as: Hirons B, Rhatigan K, Kesavan H, Turner RD, Birring SS, Cho PSP. Cough in chronic lung disease: a state of the art review. J Thorac Dis 2023;15(10):5823-5843. doi: 10.21037/jtd-22-1776