Eur Respir J 2004; 24: 481–492
DOI: 10.1183/09031936.04.00027804
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European Respiratory Journal
ISSN 0903-1936

ERS TASK FORCE

The diagnosis and management of chronic cough

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Background

Chronic cough, here defined as a cough of >8 weeks duration, is a common and frequently debilitating symptom [1, 2] that is often viewed as an intractable problem. However, the experience of specialist cough clinics is that a very high success rate, in the order of 90%, can be achieved (table 1) [3–15]. The key to successful management is to establish a diagnosis and to treat the cause of cough. Truly idiopathic cough is rare and misdiagnosis common, particularly because of the failure to recognise that cough is often provoked from sites outside the airway. These guidelines aim to distil the lessons from these reports and provide a framework for a logical care pathway for patients with this highly disabling symptom.

There are three common causes of chronic cough that arise from three different anatomical areas. This varied presentation explains the major reason for the success of multidisciplinary cough clinics compared with general clinics [16]. As asthma, reflux and rhinitis are the realms of different specialists who have little experience in the diagnosis of conditions outside their expertise, a patient with chronic cough may not undergo full evaluation. This problem is exacerbated by the frequently atypical presentation of patients with cough. Thus, patients with cough-predominant asthma may not exhibit bronchoconstriction, and patients with reflux-associated cough may have no associated reflux symptoms such as heartburn.

Management strategy

Current management strategies for cough have undergone cost-effectiveness analysis [17]. The approach to "test all, then treat" was the most expensive, but had the shortest treatment duration. In contrast, treating sequentially, starting with rhinitis, was the cheapest option but had the longest treatment duration. Therefore, the challenge is to balance the cost with time to treatment success. Thus, in patients without asthma and post-nasal drip, an empirical 2-week treatment trial of high-dose proton pump inhibitor was more reliable than investigations such as manometry and pH testing in

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Table 1. – Commonest causes of chronic cough in patients investigated in specialist clinics

Reference	Patients (female)	Patients improved %	Diagnosis % of total			
			Asthma syndrome	Oesophageal disease	Rhinitis	Most common other %
IRWIN *et al.* 1981[3]	49 (27)	98	25	10	29	Chronic bronchitis 12
POE *et al.* 1982 [4]	109 (68)	96	36	0	8	Post infectious 27
POE *et al.* 1989 [5]	139 (84)	88	35	5	26	Idiopathic 12
IRWIN *et al.* 1990 [6]	102 (59)	99	24	21	41	Chronic bronchitis 5
HOFFSTEIN *et al.* 1994 [7]	228 (139)	91	25	24	26	Post infectious 21
O'CONNELL *et al.* 1994 [8]	87 (63)	68	6	10	13	Idiopathic 22
SMYRNIOS *et al.* 1995 [9]	71 (32)	97	24	15	40	Chronic bronchitis 11
MELLO *et al.* 1996 [10]	88 (64)	98	14	40	38	Bronchiectasis 4
MARCHESANI *et al.* 1998 [11]	87 (68)	91	14	5	56	Chronic bronchitis 16
MCGARVEY *et al.* 1998 [12]	43 (29)	82	23	19	21	Idiopathic 18
PALOMBINI *et al.* 1999 [13]	78 (51)		59	41	58	Bronchiectasis 18
BRIGHTLING *et al.* 1999 [14]	91	93	31	8	24	Post-viral 13
SIMPSON G *et al.* 1999 [15]	86 (51)	92	6	22	28	Post-viral 13
Total n	1258		317	250	430	
Mean %		91	25	20	34	

Data are presented as n and %.

diagnosing patients with reflux-associated cough. There was a 3–5 fold cost saving with this empirical approach [18]. Combining both laboratory investigation and empirical therapy may offer the best management strategy. Which combination clearly depends on the resources available. These guidelines suggest two pathways, one using an empirical approach and one of recommended investigations, and these strategies should be considered in parallel.

The epidemiology of chronic cough

Chronic cough in adults

Acute cough is the single most common cause of consultation [19]. The prevalence of chronic cough, arbitrarily defined here as a cough of >8 weeks duration, is difficult to estimate since response rates vary according to the question posed. There is no doubt that chronic cough is a major cause of morbidity being reported by 3–40% of the population [20–22]. A European Respiratory Society-supported survey of 18,277 subjects aged 20–48 from 16 countries worldwide reported nocturnal cough in 30%, productive cough in 10% and nonproductive cough in 10% [1].

Cigarette smoking has a dose-related influence on the prevalence of productive cough [1]. However, smokers rarely seek medical advice specifically for cough. The majority of patients referred to specialist cough clinics are females (table 1). Females appear to have an intrinsically heightened cough response. Cough challenge is augmented in females [23–25] and a higher frequency of angiotensin converting enzyme (ACE) inhibitor-induced cough is also reported [26]. The reason for this marked sex difference is unknown.

There are wide variations in the reported incidence of the three common causes of cough illustrated in table 1. This reflects differences in the population and in the strategy for establishing a diagnosis. Either a battery of tests may be employed or alternatively a therapeutic trial with reduction in cough taken as indicating aetiology. The current authors suggest a combined approach, since a response to therapy is not necessarily specific. Whilst an improvement in cough with proton pump inhibitors may be reasonably linked to gastro-oesophageal disease, the suggestion that sedating antihistamines have a specific site of activity is clearly incorrect. The successful treatment of chronic cough leads to a major improvement in quality of life, which may be severely impaired at presentation [2].

Chronic cough in childhood

Recurrent cough is perhaps one of the commonest symptoms in childhood and, although most cough is related to viral infections, there are a great number of differential diagnoses to consider when cough frequency or severity are abnormal. How often do normal children cough? Questionnaire data suggest that $\leqslant$10% of preschool and early school-aged children have persistent, chronic cough unrelated to colds, and without wheeze [27–29]. Cough without wheeze was associated with environmental factors, including dampness in the home and air pollution, and is strongly related to socioeconomic status. Parental smoking is associated with increased prevalence of chronic cough, amounting to 50% in children aged <11 yrs with two smoking parents [30]. Again these data rely on questionnaires and parental reports that are unreliable [31]. A study where cough was measured objectively has shown that healthy children (mean age: 10 yrs) have, on average, 10 cough episodes (ranging $\leqslant$34) per 24 h, mostly in the daytime [32]. This number will increase during respiratory infections, of which 5–8 may occur per year in healthy children, with duration of 7–9 days. This will cause additional cough during another 50 days per year [33]. It is likely that younger children will have more infections and, hence, even more cough, but objective data are scarce. Children of preschool age reported chronic cough without colds in 22% [34]. Coughers were not more likely to develop asthma and atopy than noncoughers and had similar lung function and airway responsiveness. A problem with follow-up data is selection bias as a result of selective loss-to-follow-up in asymptomatic children [35]. It seems that coughing children have similar airway responsiveness than controls, but may have temporarily increased airway responsiveness during cough episodes [36].

Clinical history and examination of the patient with chronic cough

A careful clinical history may provide important diagnostic clues that allow for targeted therapeutic trials without the

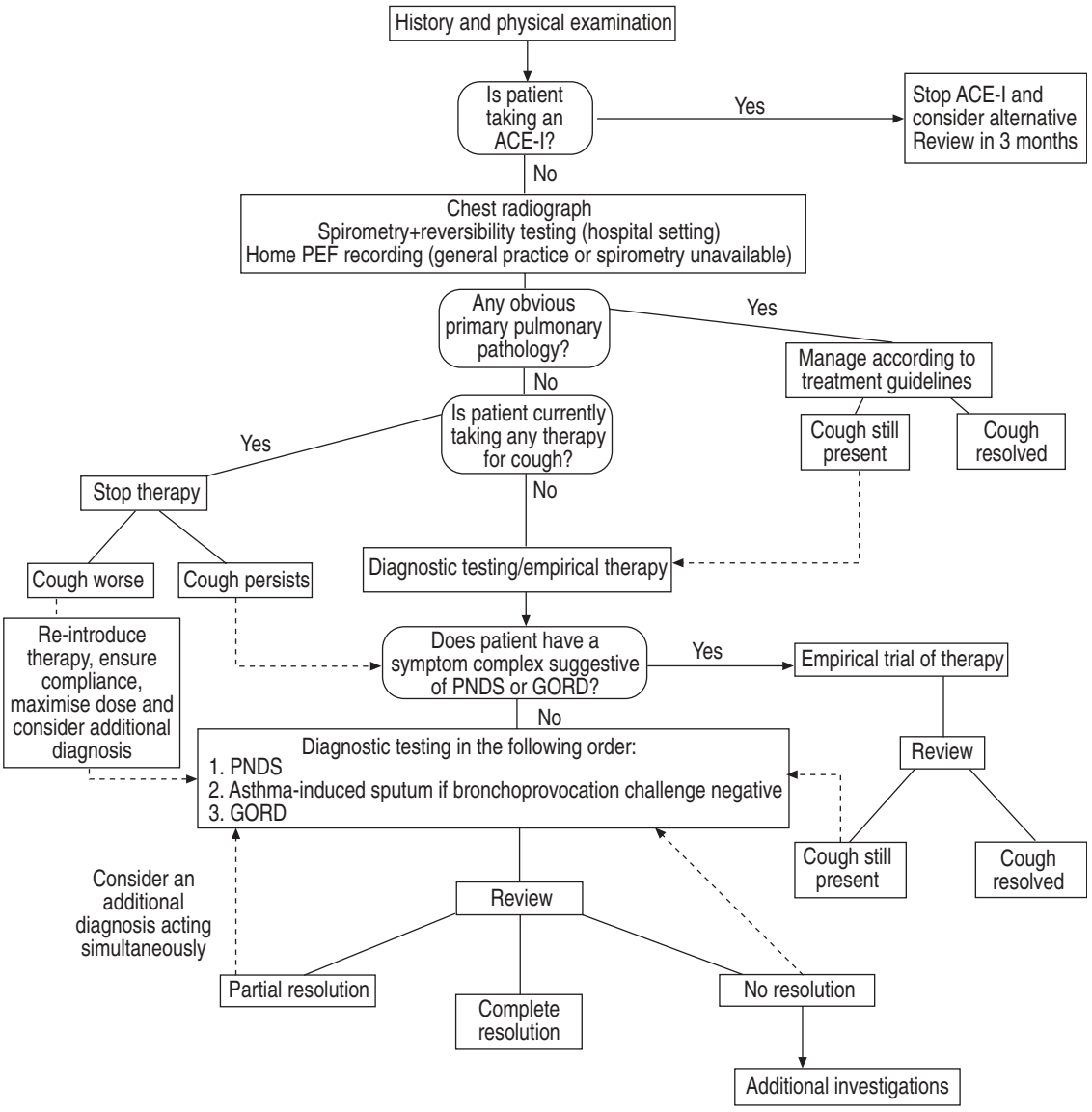

Fig. 1. – Overview of the evaluation of chronic cough in an adult. ACE-I: angiotensin converting enzyme inhibitor; PEF: peak expiratory flow; PNDS: post-nasal drip syndrome; GORD: gastro-oesophageal reflux disease.

need for further investigation (fig. 1). The smoking history and the quantity and character of sputum (if any) should be detailed in full. Chronic cough in cigarette smokers is dose-related [1] and may be productive of mucoid or mucopurulent secretions as a result of chronic bronchitis, or may be dry, as a result of the irritant effects of cigarette smoke. Examination may reveal signs of airflow obstruction. Production of significant volumes (more than one cup per day) of sputum suggests particular pathologies. In the most common, bronchiectasis, the secretions are purulent and related to changes in posture. Examination may reveal digital clubbing, halitosis, localised or generalised coarse crepitations or signs of airflow obstruction. Diagnosis of these causes of productive cough is usually straightforward and strategies for intervention and treatment are well defined [37]. Chronic dry or poorly productive cough poses a greater diagnostic challenge.

A history of ACE-inhibitor therapy should be sought as $\leqslant 15\%$ of patients on ACE-inhibitors develop dry cough soon after commencement of therapy [38]. The cough usually abates with cessation of treatment, but resolution may take several months and cough may persist in a small minority. Upper respiratory infection (URI) is commonly accompanied by cough, which usually abates promptly as the acute infection clears [39, 40]. However, in previously healthy individuals, dry cough may persist after URI, and some patients with chronic dry cough give a convincing history of URI at the time of onset of their cough [42].

Several studies have shown that in nonsmokers with normal chest radiography who are not taking ACE-inhibitors, chronic cough is usually due to asthma, rhinosinusitis or gastro-oesophageal reflux (GOR) (table 1). Dual pathology may be present [9, 15]. Symptoms suggesting these underlying diagnoses may be absent, but important clues within the history frequently go unrecognised. Abnormal physical signs are rare in patients with chronic dry cough.

Wheeze, chest tightness and dyspnoea outside a paroxysm of coughing suggest asthma, but may be entirely absent in cough-variant asthma (CVA). Variability from day to day and nocturnal exacerbation is suggestive. The cough may be triggered by exercise and/or cold air but this also occurs with nonasthmatic cough. Wheeze may be audible on examination, but is usually absent in CVA. Rhinosinusitis may be suggested

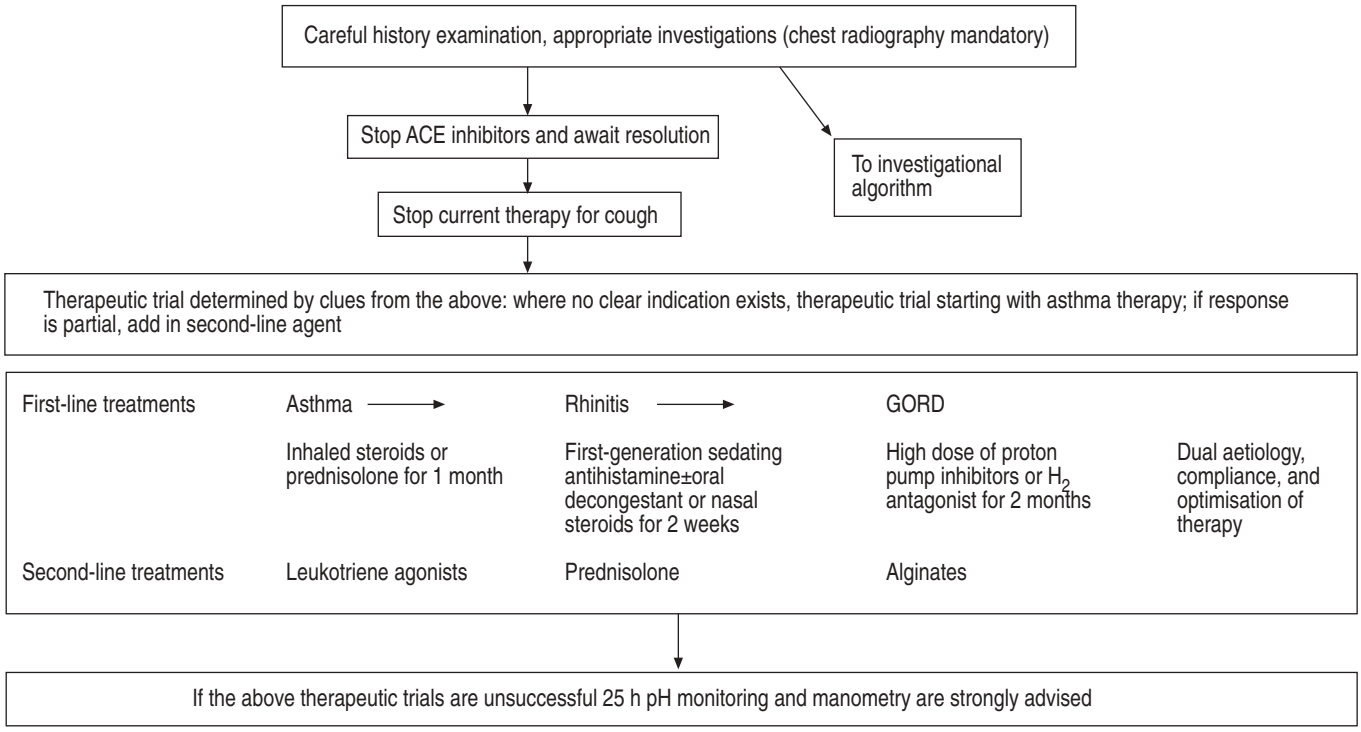

Fig. 2. – Therapeutic algorithm. ACE: angiotensin-converting enzyme; GORD: gastro-oesophageal reflux disease.

by a history of nasal obstruction or congestion, rhinorrhoea, sneezing, purulent nasal discharge, facial pain, post-nasal drip (the sensation of secretions dripping down the back of the throat) or repetitive throat-clearing. Examination of the pharynx may reveal erythema, a "cobblestone" appearance of the posterior pharyngeal mucosa, or mucoid or purulent secretions dripping from the nasopharynx. Unfortunately, many pharyngeal signs and symptoms also occur in reflux disease. GOR may be suggested by the presence of classic symptoms such as dyspepsia, heartburn, or waterbrash, but symptoms such as hoarse voice, aphonia, and globus are increasingly recognised. Reflux is usually caused by transient relaxation of the low oesophageal sphincter (LOS) [42]. Thus, cough may occur after meals or during eating or when supine, bending or stooping. Cough usually diminishes during sleep as the LOS closes and recurs on adopting an upright posture. Talking or laughing may precipitate reflux cough since the diaphragm is an important component of the LOS. GOR is more common in, although not restricted to, overweight patients.

Symptoms suggestive of asthma, rhinosinusitis or GOR positively predict these conditions in half of patients presenting to a specialist clinic [15]. Although cough may be the sole presenting symptom in all of these conditions [43, 44], this should not discourage a careful history.

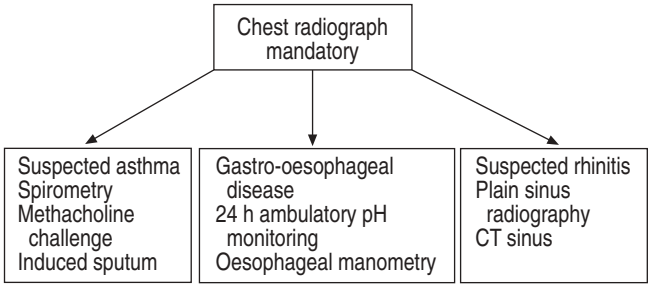

Fig. 3. – Investigational algorithm. CT: computed tomography.

Baseline investigations for patients with chronic cough

The following recommendations broadly parallel those made in the consensus panel report of the American College of Chest Physicians [45]. The baseline evaluation should include a number of investigations that reflect the pulmonary and extrapulmonary conditions known to commonly cause chronic cough (figs. 2 and 3). The diagnostic approach will depend on what tests are available to the physician either in hospital or general practice. A chest radiograph is mandatory at an early stage as a significant abnormality will alter the diagnostic algorithm and avoid unnecessary investigation.

Spirometry, preferably flow/volume, both before and after an inhaled bronchodilator may demonstrate significant airway reversibility, establishing the diagnosis of asthma. If spirometry is unavailable or is normal, and a diagnosis of asthma is considered probable from the history, serial measurements of peak expiratory flow at home may demonstrate significant diurnal variability [46].

In CVA, these investigations may be normal and bronchoprovocation testing should be considered. A negative test reliably rules out asthma as a cause [12], but does not exclude a steroid-responsive cough [14]. The extended role of bronchoprovocation testing will be discussed later.

Plain sinus radiography alone has low specificity, but improves when combined with history and findings at ear, nose and throat (ENT) inspection [47]. Although computed tomography (CT) imaging of the sinuses has superior specificity to plain radiography, it adds little to the routine evaluation of patients with chronic cough [12].

If symptoms of GOR seem prominent on history, then an empirical trial of an anti-reflux regimen should precede investigation of the upper gastrointestinal tract. The choice and timing of such investigations will be discussed later.

The diagnostic yield from fibreoptic bronchoscopy in the routine evaluation of chronic cough is low, *i.e.* ~5% [45]. However, it has significant diagnostic potential in selected patients where the more common causes have been rigorously excluded [48]. Aspirated foreign bodies occur more commonly in children, but can occur in adults. In such cases, evaluation of the airway and extraction of the foreign body may require rigid bronchoscopy [49]. Bronchoscopy also provides the opportunity for airway sampling (either mucosal biopsy or bronchial lavage).

The addition of high-resolution CT scanning of the thorax to baseline investigations is unlikely to be cost-effective [16]. Diagnoses including diffuse parenchymal lung disease or bronchiectasis not appreciated on history or chest radiograph may be identified.

Asthmatic cough and eosinophilic bronchitis

Several prospective studies have demonstrated asthma to be among the most common causes of chronic cough (24–29%) in nonsmoking adults [6, 12, 50]. Usually, cough is associated with the more typical symptoms of dyspnoea and wheezing. However, in a subgroup of asthmatics, cough is the predominant or sole complaint [43]. This condition is termed CVA.

The patient with CVA may present a diagnostic challenge since, often, physical examination and pulmonary function studies are entirely normal. In such instances, bronchial provocation studies may be considered. Although demonstration of bronchial hyperresponsiveness (BHR) by methacholine inhalation challenge (MIC) testing is commonly regarded as the diagnostic gold standard for CVA, the clinician must bear in mind that a positive MIC is merely consistent with, but not diagnostic of, CVA. A definitive diagnosis cannot be made until resolution of cough is achieved with specific antiasthmatic therapy.

In general, treatment of CVA is similar to that of typical ("classic") asthma. Cough as a result of CVA usually improves within 1 week of initiation of an inhaled bronchodilator. However, complete resolution of cough may require $\leqslant 8$ weeks of combination therapy with inhaled bronchodilators and corticosteroids [51]. Dry powder inhalers or metered-dose inhalers with spacers are recommended for the administration of inhaled steroids. It must be noted that, in some patients with CVA, cough may actually be exacerbated by inhaled steroid therapy, as a result of a constituent of the aerosol. For example, the more common occurrence of cough after inhalation of beclomethasone diproprionate relative to triamcinolone acetonide is attributed to a component of the dispersant in the former [52]. In such cases, as well as in cases of partial response to inhaled steroids, or when cough is severe, a diagnostic therapeutic trial of oral corticosteroids (prednisone 40 mg *q.d.* or equivalent for 1 week) alone or followed by inhaled therapy is appropriate.

Recent studies suggest that leukotriene-receptor antagonists, the newest therapeutic agents for asthma, may be particularly effective in treating CVA. A 14-day course of zafirlukast has been shown to improve cough, as well as to inhibit objectively measured cough reflex sensitivity in patients with CVA, including a subgroup whose cough had been refractory to inhaled steroids [53].

Eosinophilic bronchitis (EB), a fairly recently recognised entity, presents with chronic cough and sputum eosinophilia (>3%). This type of cough usually responds well to inhaled corticosteroids, thereby probably causing many patients with this condition to be misdiagnosed with CVA. However, patients with EB differ from typical asthmatics in that they do not demonstrate reversible airflow obstruction or hyperresponsiveness to methacholine. In a recent prospective study, EB was shown to be the cause of chronic cough in 13% of patients referred to a specialist for evaluation [14]. Whether EB represents a distinct clinical entity or shares a pathophysiological spectrum with CVA remains to be elucidated. The recommended therapy for asthmatic cough is given as follows: inhaled broncodilators, inhaled corticosteroids, leukotriene receptor antagonists and oral corticosteroids.

Questions in cough-variant asthma and eosinophilic bronchitis

The following three major questions in the "differential" pathogenesis of (cough-variant) asthma and eosinophilic bronchitis are still unsolved. 1) Is there a single confounding factor for all three diseases, or are asthma, CVA and EB different diseases which share some common features? 2) Which is the cause of the increased cough receptor sensitivity in CVA, EB and cough predominant asthma and is it related to the development of the BHR in asthma and CVA? 3) Is there a pathogenic role for the eosinophil in asthma, CVA and EB or is the eosinophilic inflammation merely a marker of the underlying disease?

Increased cough receptor sensitivity has been reported in humans after inhalation of prostaglandin (PG) E_2 [54, 55], PGF2α [55] and, in addition, after the inhalation of cyclooxygenase and thromboxane inhibitors in asthmatic patients. In the animal model, there is good evidence that bradykinin [56], PGI_2 and platelet activating factor [57] and substance P [58] might enhance the cough reflex, but the mediator responsible in the three diseases is the subject of speculation.

It has long been hypothesised that tachykinins such as substance P or neurokinin (NK) A are involved in the pathogenesis of BHR, which might be released as a result of an increased sensitivity of the nonadrenergic, noncholinergic neuron system caused by epithelial shedding [59]. Nevertheless, the studies on various NK receptor antagonists in humans were not able to conclusively support the role of these substances in the development of BHR or other asthma-related symptoms [59].

Cough and gastro-oesophageal reflux

Several studies have implicated GOR as one of the commonest causes of chronic cough [3, 6, 10, 44, 60, 61]. Stimulation of vagally innervated oesophageal receptors [62], dysmotility [63], and/or aspiration of refluxed gastric content [64] are regarded as the primary causes of GOR-related cough. Whilst a history of classic GOR symptoms, such as heartburn, may be helpful in suggesting the diagnosis, cough due to GOR may be an isolated symptom [63–65]. GOR is usually associated with transient relaxation of the LOS [66], and an understanding of the LOS physiology provides diagnostic pointers. Except in severe disease the LOS closes during sleep and so GOR cough is rarely troublesome at night, returning when the patient gets up. Diaphragmatic relaxation during talking decreases LOS tone. Eating causes LOS relaxation *via* a pharyngeal-oesophageal reflex. Reflux may reach the upper airways, leading to a wide range of symptoms including dysphonia, sore throat and globus.

The best single test for diagnosing cough due to GOR is the 24-h oesophageal pH monitoring (OpHM) [46]. Abnormal reflux indexes on OpHM that may be used in the diagnosis of GOR-related cough have been reported [12, 67]. The recording of cough events by means of a diary or event marker during OpHM is particularly useful, since patients with normal standard reflux indexes may still have acid-related

cough if a temporal relationship between GOR episodes and cough can be established [61]. Prospective studies have shown that the positive and negative predictive value of reflux indexes derived from OpHM approximated 89 and 100%, respectively [9, 67]. In contrast, OURS *et al.* [68] reported that only 35% of patients with chronic cough and abnormal pH profiles responded favourably to proton pump inhibitor therapy, and concluded that OpHM is not a reliable predictor of acid-related cough. Resistance to acid suppression [69], short treatment duration [6, 62], cough mediation by nonacid reflux [70] and coexistence of other causes of cough can all be invoked to account for the discrepancy. When OpHM is not available, or the results obtained with this technique are controversial, an empirical trial of anti-reflux therapy may represent a useful and reasonable diagnostic alternative in patients with chronic cough of suspected gastro-oesophageal origin. If an empirical trial is chosen, high-dose treatment must be continued for $\leqslant$3–4 months before GOR as a cause of cough can reasonably be excluded [6].

Although no clinical trial had been addressed to evaluate the effects of nonpharmacological interventions in reducing GOR-induced cough, many patients seem to benefit from sleeping with an elevated head, smoking cessation, weight reduction, a diet rich in protein and low in fat, and in food and beverages that may relax the LOS, such as alcohol, chocolate, mint, onion, coffee, tea, cola, citrus fruits. Association of conservative and lifestyle measures with H_2-antagonists and/or prokinetic agents for a period of ~3 months resolves GOR-induced cough in 70–100% of patients [46]. Proton pump inhibitors′ administration for 8 weeks produces a significant, long-lasting reduction in GOR-induced cough [71], and increases the cough threshold in patients with reflux oesophagitis [72]. Failure of proton pump inhibitors must be considered only after adequate dosage (40 mg *b.i.d.*) has been used for $\geqslant$12 weeks. Prokinetic agents exert their effects by increasing LOS tone and facilitating gastric emptying. They are usually employed in association with H_2-antagonists or pump inhibitors. When used as monotherapy in children, prokinetic agents have been shown to produce high response rates in the suppression of cough [46]. However, the risk of fatal arrhythmia with cisapride mitigates against its routine use [73]. Anti-reflux surgery (open or laparoscopic fundoplication) is the treatment of choice for those patients with proven GOR disease whose cough persists after >3 months of appropriate medical treatment, including high dosage of proton pump inhibitors. Surgery is particularly indicated for patients who present with symptoms and signs of recurrent aspiration in the respiratory tract. Surgical therapy has been shown to be more effective in those patients with normal oesophageal motility [74]. Evidence is provided from controlled trials in certain references [6, 9, 46, 66, 67, 74].

Rhinitis and sinusitis

The important ENT causes of chronic cough are post-nasal drip, GOR (discussed elsewhere) and problems arising from the ear. The diagnosis may be particularly problematic here, since chronic cough may be multifactorial and attributing the contribution of each component can be difficult. For example, many patients with asthma have rhinitis and often have post-nasal drip. The contribution of the post-nasal drip to the chronic cough is controversial and may be difficult to establish. Some suggest that nasal or sinus secretions dripping into the hypopharynx and larynx stimulate local cough receptors [46, 75]. However, the transport of mucus from the nose and sinuses to the pharynx is a physiological process present in all individuals. Many patients with rhinosinusitis, or who have had sinus surgery, have large amounts of (both physiological and inflammatory) mucus within the throat. Whilst they sense post-nasal drip, they do not have a chronic cough. A questionnaire of patients with chronic sinusitis or polyps (W.J. Fokkens, Academic Medical Centre, Amsterdam, Netherlands; unpublished data) revealed only 60% with post-nasal drip, whereas 74% coughed. In patients without asthma, the figures dropped to 51% and 65%, respectively. Only 18% of nonasthmatics without post-nasal drip had an episodic dry cough. Thus, chronic rhinosinusitis with or without post-nasal drip can cause coughing and may be a marker of disease in the lower airway.

Since post-nasal drip is not a disease, but a symptom, the differential diagnosis is wide and includes allergic rhinitis, vasomotor rhinitis, viral or bacterial infections, and nasal polyps. If suspected, an extensive ENT examination including nasal endoscopy should be performed. If it is a predominant aspect of the syndrome, nasal lavage with saline solution may be helpful. The saline should be inserted with a large (20 mL) syringe or with a nasal douche. Nasal inflammation can be treated with topical corticosteroids. However, a considerable body of evidence supports the use of first generation sedating antihistamines in chronic cough, often in combination with sympathomimetic "decongestants" [48]. Antihistamines do not influence nasal congestion [76]. In children with allergic rhinitis, chronic cough may be the predominant symptom [77], and therapy should be directed at the upper airway, inhaled steroids yielding a poor response.

Problems arising from the ear

Irritation of the auricular branch of the vagal nerve (Arnold′s nerve) stimulates cough. This reflex is present in 2.3% of patients and can be elicited by palpation of the postero-inferior wall of the external acoustic meatus. Impacted cerumen, foreign bodies, syringing of the ear or a hair lying against the tympanic membrane can all stimulate the reflex [78]. Coughing caused by middle-ear pathology has also been reported [79], but is rare.

Irritation of the auditory canal can easily be detected during otoscopic examination. Removal of the irritant from the auditory canal will diminish symptoms within a few days [80].

Chronic cough in children

It is important to recognise clues suggestive of pathology that is characteristic for the paediatric age range (fig. 4). Chronic productive cough with purulent sputum is always reason for concern in children and is not a symptom of asthma. More or less specific diagnoses for the paediatric age range include cystic fibrosis, aspirated foreign body, congenital anatomic abnormalities and primary ciliary dyskinesia (PCD), and these can often be suspected from careful medical history taking and physical examination.

Asthma

In the first years of life, asthma may be suspected if chronic cough is associated with atopic eczema and a positive family history of allergy and asthma. However, an "asthmatic"-type of inflammation, characterised by eosinophilic cell infiltration, appears rare in young children with chronic cough [81]. Comparison of cough frequencies between children with known asthma and healthy controls of school-age showed no

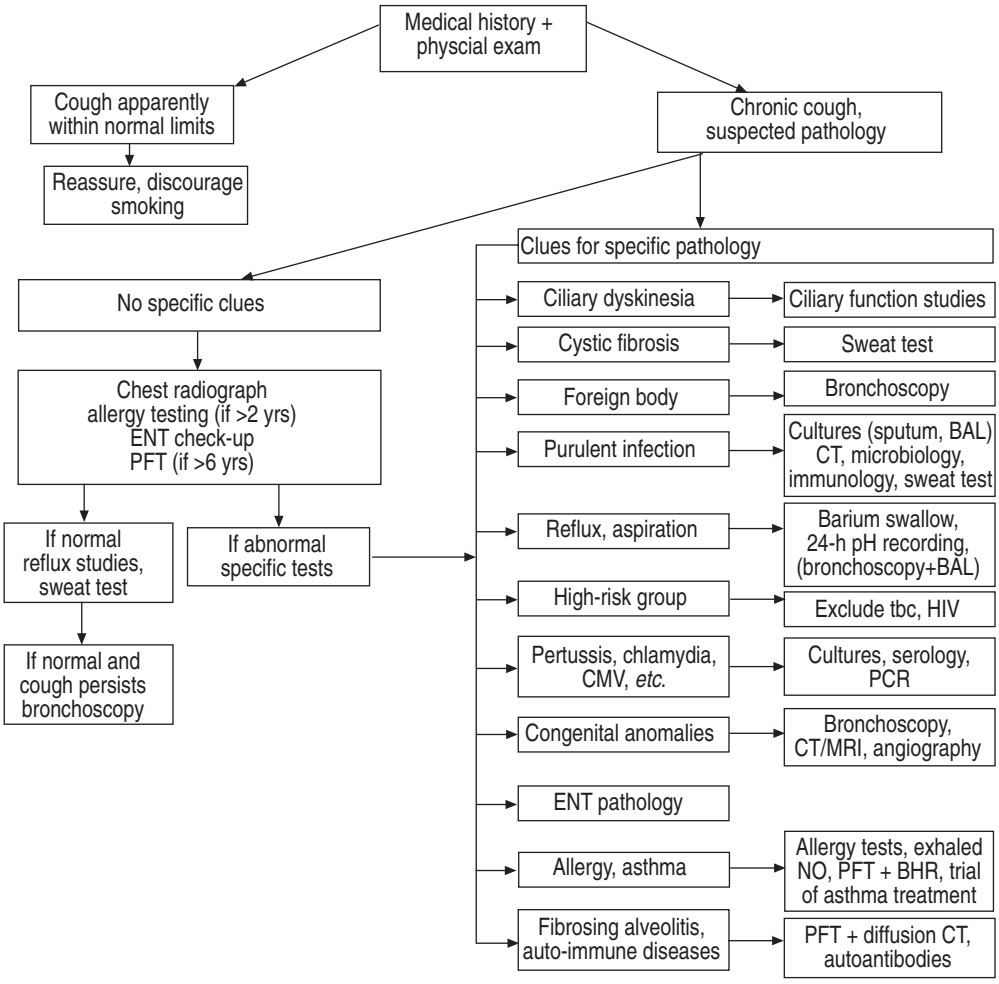

Fig. 4. – Diagnostic algorithm for the approach to children with chronic cough. ENT: ear, nose and throat; PFT: pulmonary function testing; BAL: bronchoalveolar lavage; CT: computed tomography; tbc: total blood count; CMV: cytomegalovirus; PCR: polymerase chain reaction; MRI: magnetic resonance imaging; NO: nitric oxide; BHR: bronchial hyperresponsiveness.

differences between attacks, but more severe cough during bronchoconstriction [82]. Night cough appeared unrelated to lung function and hyperresponsiveness in wheezing school age children [83]. Compared to cough with recurrent wheeze, cough without wheeze had a favourable prognosis in pre-school children, and tended to resolve before the age of 6 yrs in most cases [29]. The possible interactions between asthma and cough in children have been comprehensively reviewed by CHANG [84].

Reflux and aspiration

Reflux with or without aspiration of gastric content or food is probably one of the commonest paediatric causes of chronic respiratory symptoms, including cough and wheeze [85]. Some degree of GOR is common in infants and improves spontaneously with time. Apparently, this "normal" reflux is often not associated with cough. The presence of lipid laden macrophages in bronchoalveolar lavage (BAL) fluid may reflect chronic aspiration [86], but is not specific [87, 88].

Infections

BAL findings in a group of young children with chronic cough showed evidence of infectious mechanisms in a high percentage [81]. Many infections cause prolonged cough, including pertussis, tuberculosis, repeated viral infections and chronic ENT infections. In young infants, chlamydia, cytomegalovirus and ureaplasma urealytica infections may be involved as well. Pertussis causes cough for many months and does not respond to treatment. Recently, an epidemic increase of pertussis has been reported in vaccinated children, possibly as a result of immunisation-driven emergence of polymorphisms of the surface protein pertactin, making the micro-organisms less susceptible to vaccination-induced immunity [89, 90]. Tuberculosis may cause chronic cough due to airways obstruction by protruding or perforating lymph nodes, and secondary infection of obstructed lung segments.

Immunodeficiencies

If airway infections are unusually frequent or severe, a number of underlying diseases may be considered, including milder variants of primary immunodeficiencies. If chronic airway infection is accompanied by failure to thrive and malabsorption, cystic fibrosis should be ruled out by means of a sweat test.

Primary ciliary dyskinesia

PCD causes a combination of unusually severe ENT infections and lower airway infections. Situs inversus is

present in ~50% and may be recognised prenatally on routine echography.

Congenital anomalies

Tracheobronchomalacia may occur as isolated abnormality or as part of a syndrome, and causes a characteristic harsh cough. Tracheo-oesophageal fistula or laryngeal cleft causes cough due to aspiration, especially during meals. Any cause of airway compression or stenosis, including vascular rings and other vascular malformations may cause chronic respiratory symptoms. Increased infectious susceptibility of the airways may result from increased lung perfusion, as is the case with atrial or ventricular septal defects, or open ductus Botalli.

Foreign body aspiration

Aspirated foreign bodies may go unrecognised for prolonged periods of time, especially if the diagnosis is missed initially [91]. Foreign body aspiration is much more common in young males than in young females, and is especially frequent in children aged <4 yrs. The possibility of finding an unsuspected foreign body during bronchoscopy for chronic cough, without any clue in the medical history or physical examination is probably small, but GODFREY *et al.* [92] reported a high success rate of bronchoscopy in children in whom foreign body aspiration was considered possible but by no means clear.

Psychogenic cough

Psychogenic cough is uncommon in children. It may produce a characteristic "honk" sound and can be produced on request. The diagnosis should be preceded by exclusion of possible underlying disease, particularly Tourette's syndrome, which may present with an isolated cough in childhood [93].

Other tests in chronic cough

Cough challenges

Cough challenges to a tussigenic agent, such as capsaicin or citric acid, evaluate the sensory ("cough threshold") and motor components of the cough reflex. Cough challenges may provide an index of cough severity and can assess the strength of the reflex in patients with neurological disorders [94–96], but the presence of increased cough reflex is not disease-specific.

Objective assessment of cough

Objective assessment of spontaneous cough may be needed when the existence, severity or diurnal appearance of cough is unclear, or when additional information is needed to assess the aetiology of chronic cough [97]. Cough events can be detected by recording cough sound simultaneously with chest electromyography [98] or body movements on the bed [99]. Automatic cough counters based on digital signal processing of cough sound have been developed [100]. Airflow dynamics and sound spectra of cough have characteristic features in different pulmonary diseases, but the specificity is low [101]. In the cough of asthma, wheezing sound components are typical.

Sputum analysis

An elevated number of eosinophils and metachromatic cells are found in sputum samples of patients with asthma, CVA and EB [102, 103]. Recognition of airway eosinophilic inflammation may assist in the assessment of the cause of chronic cough, as well as in the selection of treatment options. In other cases, a neutrophilic inflammation may be more predominant [104].

Exhaled nitric oxide

Elevated nitric oxide (NO) levels in exhaled air reflect eosinophilic inflammation in the airways commonly found in atopic asthma. Exhaled NO values are lower in nonsmoking adult chronic cough patients without asthma symptoms than in asthmatics, the negative predictive value for the absence of asthma being 93% [105]. Measurements of exhaled NO may be useful in diagnostic evaluation of chronic cough.

Bronchial hyperresponsiveness

BHR to direct stimuli, inhaled histamine or methacholine is characteristic for asthma and CVA. These tests are best used to exclude asthma [106]. In chronic nonasthmatic cough patients gross BHR is not found [107]. The positive predictive power of these tests can be used for excluding diseases associated with chronic cough.

Quality of life

Chronic cough has a profound impact on the psychosocial function of patients. A number of measures have been developed to quantify these effects and their response to treatment. The two most validated measures have been produced by FRENCH *et al.* [2] for North American practice and the Leicester Cough Questionnaire [108] for Europe.

Novel therapies for the treatment of chronic cough

Currently, there are no effective treatments for cough with an acceptable therapeutic ratio and more selective drugs with a more favourable side-effect profile are needed. Several novel mechanisms (table 2) have been identified, which may lead to the identification of drugs (table 3) that reduce the increased sensitivity of sensory fibres, which leads to exaggerated cough. Many potential drugs are effective in inhibiting induced cough in animals and are yet to be tested in man. Novel drugs may be divided into those inhibiting the underlying causes of the cough *e.g.* anti-inflammatory drugs for the treatment of cough in asthma or CVA, or novel proton pump inhibitors for treating GOR or compounds that inhibit sensory nerve activity directly irrespective of the cause of increased sensitivity, *i.e.* a nonspecific antitussive.

Ligands acting at G protein-coupled receptors

Opioids inhibit cough *via* activation of μ-, δ- and κ-opioid receptors [109], and currently used antitussives bind to the μ-opioid receptor and are associated with characteristic side-effects. Nociceptin, which binds to opioid receptor-like (ORL)-1 receptors, inhibits sensory nerve function in guinea pig airways, and *i.v.* or centrally administered nociceptin

Table 2. – Neural mechanisms of cough

Cerebral cortex
Voluntary cough
Voluntary cough suppression
Involuntary facilitation (?)
Brainstem
Integrative inputs
Interaction with breathing
Motor outputs
Sensory inputs, larynx and lower airways
Rapidly adapting receptors
Aδ-nociceptors
C-fibre receptors
Motor responses
Respiratory muscles
Laryngeal muscles
Upper airway muscles
Bronchial muscle
Bronchial glands
Cardiovascular system

Table 3. – Potential targets for antitussive drugs

Cerebral cortex
Placebo effect
Brainstem
Opioid receptors
ORL1 receptors
GABA-B (and A?) receptors
Glycine receptors
Tachykinin receptors
5-HT receptors
Glutamate receptors
Peripheral sensory nerve endings antagonists
Vanilloid receptors (VRL1, TRPV1)
BK and BKca receptors
Neurokinin receptors
Opioid receptors
ORL1 receptors
Na^+ channel receptors (TTX-sensitive, insensitive) *e.g.* local anaesthetics
Purine receptors
Acid-sensing ion channels
Inflammatory and immunological mediators
Peripheral sensory endings agonists
K^+ channels
GABA-B receptors

ORL1: Opioid receptor-like 1 receptors; GABA: gamma aminobutyric acid; 5-HT: 5-hydroxytryptamine; VRL1: vanilloid receptor like-1 receptor; TRPV1: Transient receptor potential vanilloid; BK: bradykinin; BKCa: large conductance calcium-activated potassium channel; TTX: tetrodotoxin.

inhibits cough by activating inhibitory ORL1 receptor on sensory nerve terminals [110, 111]. Gamma aminobutyric acid $(GABA)_B$ receptor agonists have a similar inhibitory profile on the tussive response [112]. NK-receptor antagonists, such as the NK_2-receptor antagonist, SR 48968, inhibit citric acid-induced cough in conscious guinea pigs [113], possibly *via* both a central and/or peripheral mechanism of action [114]. The NK_3-receptor competitive antagonist, SB 235375, is also effective against citric acid-induced cough and an $NK_1/NK_2/NK_3$-receptor antagonist, SCH 206272, inhibits capsaicin-induced cough in the guinea-pig [115]. However, an NK_1-receptor antagonist had no antitussive action in man [116]. Bradykinin B_2-receptor antagonists may have utility as antitussive drugs [57]. $Cannabinoid_2$-receptor agonists show antitussive activity in animal models [117].

Ion channel modulators

Since the actions of the sensory nerve stimulant capsaicin on sensory nerves may be mediated by activation of the heat-sensitive channel, vanilloid receptor-1, blocking these channels may be a good target for suppressing cough [118]. The cold and menthol-sensitive receptor (CMR)-1 is a member of the transient receptor potential family of excitatory ion channels [119] expressed in primary sensory neurons, and menthol, which activates CMR-1 receptors, inhibits citric acid-induced cough in normal volunteers [120]. The cotransporter inhibitor, frusemide, reduces the potentiation of capsaicin-induced cough by prostaglandin $F_{2\alpha}$ but has no effect on capsaicin-induced cough alone. Changes in local ionic concentrations by frusemide, particularly chloride ions within the vicinity of epithelial cough receptors, may be responsible for this inhibitory effect [121]. Large conductance calcium-activated potassium channels and ATP-sensitive potassium channel openers reduce citric acid-induced cough in guinea pigs [122].

Conclusions

Our understanding of the diagnosis and treatment of chronic cough has undergone a radical change in the past 20 yrs. The experience of specialist clinics has demonstrated that most chronic cough is treatable, provided the characteristic features of the three important causes of cough: asthma, reflux, and rhinitis, are recognised. Awareness of the way in which the treatment of cough differs from other symptoms has also increased. The frequent delay in improvement of cough with therapy demonstrates that appreciation of the plasticity of the reflex, and the factors which control it, are fundamental for current understanding and future treatments. As cough is a vital protective reflex for the airways, this predicates that the goal of cough treatment must be the restoration of a normal cough reflex. The increasing knowledge of the molecular and physiological organisation of the putative cough receptors will help us to achieve this in the not too distant future.

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