CE ARTICLE

Chronic cough: Stepwise application in primary care practice of the ACCP guidelines for diagnosis and management of cough

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Keywords
Chronic cough; primary care; case study; management; ACCP Evidence-Based Guidelines; nonasthmatic eosinophilic bronchitis.

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Received: February 2008;
accepted: July 2008

doi:10.1111/j.1745-7599.2009.00432.x

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Abstract

Purpose: To illustrate decision points encountered when using evidence-based guidelines for diagnosis and management of chronic cough by means of a composite case study based on primary care practice.
Data source: The American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines for Diagnosis and Management of Cough, and review of the scientific literature on cough and related topics.
Conclusions: The ACCP guidelines offer a systematic approach that uses trials of empirical therapies to diagnose and resolve the very common, often perplexing complaint of chronic cough. The major diagnoses reached are upper airway cough syndrome, cough-variant asthma, gastroesophageal reflux disease, and nonasthmatic eosinophilic bronchitis.
Implications for practice: Cough is the most common reason that patients seek an office visit. Many coughs resolve spontaneously, but coughs that persist significantly impair the quality of life. Use of the ACCP guidelines allows a stepwise empirical approach to the problem of unexplained chronic cough. This approach greatly increases the percentage of chronic coughs that are accurately diagnosed and effectively treated, and avoids unnecessary diagnostic testing.

Introduction

Cough is the most common principal reason for visiting primary care offices in the United States (Cherry, Woodwell, & Rechsteiner, 2007). It is an important normal defense mechanism that clears the airways, but when frequent and persistent, it is a cause of significant physical, emotional, functional, and psychosocial suffering (French, Irwin, Fletcher, & Adams, 2002). Physical complications of cough occur in every system, particularly in the cardiovascular (hypotension, arrythmias, syncope), gastrointestinal (GI) (reflux, anorexia), and genitourinary (urinary incontinence) systems (Irwin, 2006a). Sleeplessness and exhaustion, absence from work, difficulty speaking, social embarrassment and withdrawal, and fear of serious disease are adverse outcomes of cough that further impair the quality of life (French, Irwin, Curley, & Krikorian, 1998). Depressive symptoms are common, but improve as the cough improves (Dicpinigaitis, Tso, & Banauch, 2006).

Specific and effective treatment is possible only after an accurate diagnosis is reached, but diagnosing persistent cough is often challenging for the clinician. The American College of Chest Physicians (ACCP) has updated its evidence-based clinical practice guidelines for the diagnosis and management of cough (Irwin, Baumann, Bolser et al., 2006). The *therapeutic-diagnostic* approach (based on trials of empirical therapy) reaches a diagnosis in more than 90% of cases of previously unexplained chronic coughs seen by pulmonary specialists. Accurate diagnosis is confirmed by resolution or marked improvement of the cough by specific treatment. This case study illustrates how the ACCP guidelines can be used in a family practice setting and highlights decision points in the diagnosis

and management of chronic cough by the primary care clinician.

Case study of unexplained chronic cough

Initial presentation

Mr. Alvin S. is a 63-year-old farmer who consults you about his dry cough of 6 weeks' duration. Knowing that patients have particular social or psychological reasons for seeking advice about common, self-resolving symptoms such as cough (Cornford, 1998), you inquire why Alvin decided he needs a primary care consultation. He says his cough gives him dry heaves, embarrasses him in public, and wakes his wife and himself at night. He fears that because he has smoked for many years the cough signifies lung cancer.

The most common cough is an acute one, which follows a viral infection and resolves within a few weeks with or without treatment (Irwin & Madison, 2000). Chronic cough in immune-competent patients has been found in multiple studies to have three dominant causes, alone or in combination. These are (a) upper airway cough syndrome (UACS, formerly postnasal drip syndrome), (b) asthma (classical or cough-variant [CVA]), and (c) gastroesophageal reflux disease (GERD). Angiotensin-converting-enzyme (ACE) inhibitors and chronic bronchitis due to smoking are also associated with cough. Other causes include eosinophilic bronchitis, bronchiectasis, interstitial lung disease, tuberculosis, left ventricular failure, and aspiration (Pratter, 2006a). A cause of prolonged cough that is often overlooked in adults is *Bordatella pertussis* infection (whooping cough) (Cornia, Lipsky, Saint, & Gonzales, 2007). Although cough is present in more than 65% of patients who receive a diagnosis of lung cancer, fewer than 2% of patients whose primary complaint is chronic cough receive a diagnosis of lung cancer (Kvale, 2006).

All coughs start out as acute, but at what point is a cough considered chronic? According to expert opinion, acute coughs disappear within 3 weeks; after 3 weeks coughs are termed ''subacute'' and after 8 weeks are considered chronic (Irwin & Madison, 2000). Some patients can suffer for years.

Decision Point 1

The majority of subacute coughs are postinfectious (Irwin & Madison, 2000). Can you assume Alvin's cough is postinfectious and will resolve soon, or is it persistent enough to need more extensive consideration? Although still subacute in duration, the cough is causing distress and fear of underlying cancer. You therefore take an extensive history and perform a complete physical examination.

History

Significant features of the general medical history include: Alvin has smoked two to three cigarettes per day for many years, he has been treated for hypertension for several years but forgets the name of his medication, his blood lipids were borderline high in the past, and he has had no contact with infectious diseases.

You now focus on common causes of cough. Although characteristics of the cough itself are not predictive, the history is diagnostically useful in the majority of cases (Mello, Irwin, & Curley, 1996). Evidence of etiology can be obtained by asking about postnasal drip, reflux, and asthma, exposure to environmental or occupational respiratory allergens or irritants, and systemic disease such as heart disease, tuberculosis, cancer, or acquired immune deficiency syndrome (AIDS). Although symptoms can suggest the cause of cough, absence of symptoms does not rule out most causes of cough. In particular, GERD, UACS, and asthma all can exist in ''silent'' forms (Irwin & Madison, 2000).

Alvin has no prominent systemic illness, night sweats, or weight loss; he denies aspiration of liquids or foreign bodies; he has no wheeze, nor dyspnea; his cough occurs while sleeping flat or in a chair (not orthopnea); he has no chest pain, nor heaviness; he has no hemoptysis; he cannot identify any trigger of coughing. He does not feel mucus in his throat, and has no symptoms of esophageal reflux even after spicy meals. He does not keep domestic birds or animals, but he has contact with farm animals and feedstuff, and sometimes uses crop sprays. He had no contact with persons with fever or cough and does not recall receiving recent immunization against pertussis.

Risk factors

You consider Alvin's risk for common causes of subacute cough (Irwin et al., 2006), which are summarized in Table 1. Without fever, dyspnea, hemoptysis, or pleuritic chest pain, pneumonia is unlikely. Cough worsening at night is suggestive of UACS, GERD, or congestive heart failure and these should be considered further (Cornia et al., 2007). You know that pertussis has recently re-emerged worldwide despite vaccination coverage (Bamberger & Srugo, 2008) and has been reported in your community. Sputum production is the defining feature of bronchitis, but Alvin has none. His antihypertensive medication could be an ACE inhibitor.

Table 1 Causes of subacute cough

Postinfectious	Triggered by infection	Other
Pneumonia	Upper airway cough syndrome (UACS)*	ACE inhibitors
Pertussis	Asthma	
Bronchitis	GERD	
	Bronchitis	

*Formerly called postnasal drip syndrome (PNDS)

Physical examination

Alvin looks well and is afebrile. He is moderately obese. His blood pressure is 144/96 mm Hg. His respiratory system is normal: examination is negative for cyanosis, finger clubbing, nasal polyps, sinus tenderness, postnasal drip, adventitious breath sounds, and wheeze. The cardiovascular system is normal: examination is negative for cardiac enlargement, carotid, renal and femoral bruits, jugular venous distension, and peripheral edema. S1 and S2 are audible without murmurs or rubs. There is no hypertensive retinopathy: no copper wiring, A-V nicking, flame hemorrhages, or exudates.

Summary of information so far

Alvin has a distressing, nonproductive, subacute cough that worsens at night. His history reveals no systemic illness, but is significant for cardiovascular and respiratory risk factors (hyperlipidemia, hypertension, smoking and occupational air-pollutant exposure). Physical examination was negative for cardiovascular and respiratory disease, except for inadequately controlled hypertension. There was no evidence to support a diagnosis of UACS or asthma. Abdominal obesity was the only suggestive feature of GERD.

Decision Point 2

At the end of your first visit with Alvin, you need to decide how to proceed. What diagnostic testing and/or treatment is indicated? You construct an initial management plan based on information so far and the ACCP guidelines for subacute cough (see Table 2).

Results

The chest X-ray (CXR) image is reported to show normal lung fields and no lymphadenopathy. Carcinoma either of the airways, or compressing the airways, is therefore ruled out. Sarcoid, bronchiectasis, and active tuberculosis are also unlikely. The heart shadow is not enlarged; therefore, neither left ventricular hypertrophy from hypertension, nor dilation because of heart failure is present.

Bordatella pertussis testing was negative. If cultures are positive, antimicrobial therapy is indicated to prevent the spread of infection, whatever the duration of cough. Unsuspected adult pertussis is a reservoir of infection for children and infants (Cornia et al., 2007), and infection must be reported to the health department.

Alvin's antihypertensive drug is not an ACE inhibitor. This class of drugs causes a dry persistent cough in 5–35% of patients treated, possibly because ACE inhibition allows accumulation of pro-inflammatory substances (Dicpinigaitis, 2006b). Angiotensin receptor blockers (ARBs) have similar effects on blood pressure control, but carry less risk of cough (Matchar et al., 2008). Alvin's therapy is a diuretic, but it is inadequate and needs revision.

Alvin's fasting blood lipids are borderline high. Although it is not because of his cough, Alvin has more than one risk factor for cardiovascular disease and active lipid-lowering therapy is needed.

Pathophysiology of cough

Cough as a normal protective reflex

Cough is an essential reflex that protects the airways from irritants such as accumulated secretions, aspirated fluids, inhaled irritants, pathogens, postnasal drip, edema fluid, or inflammation of the mucosa (Canning, 2006). The clearing action depends on inhaling, closing the glottis, and generating high intrathoracic pressure to compress the airways and drive the airstream during exhalation (McCool, 2006). Those with a weak cough such as the elderly, newborns, and persons with significant neuromuscular weakness or paralysis are at risk for aspiration pneumonia.

Anatomy of the cough reflex

The vagal sensory receptors that initiate the afferent arm of the cough reflex are abundant in the mucosa of the carina, pulmonary bronchi, and pharynx. Airway reflexes can also originate in the stomach or the esophagus, or occasionally in the external ear (Canning, 2006). Cough is a reflex modification of normal breathing and is integrated in the brainstem medullary networks where generation and modulation of normal breathing occurs (Shannon, Baekey, Morris, & Nuding, 2004). The motor (efferent) arm of the reflex stimulates the muscles of respiration. The conscious brain can normally inhibit cough up to a point, but central sensitization of the reflex also occurs, perseverating cough (Canning).

Table 2 Initial management plan for cough

Feature of management	Action	Reason
Time frame	Check in 1 month	He is not acutely ill; after 1 month the cough will be resolved or chronic
Testing	CXR	With chronic cough, hypertension, and smoking, cardiovascular system changes and lung cancer must be checked
	Nasopharyngeal swab for *Bordatella pertussis* isolation	Pertussis is in your community
	Fasting blood lipid measurement	Obesity, history of hyperlipidemia
Tasks	Help Alvin to stop smoking	Cause of cough
	Find out whether hypertensive medication is ACE-inhibitor	Can cause cough
	Improve control of hypertension, but avoid {ß}-blocking agent	Can cause bronchoconstriction
	Research the pathophysiology of cough	Aids in management

Note: CXR, chest radiograph; CVS, cardiovascular system; ACE, angiotensin converting enzyme; {ß}, beta.

Mechanical and chemical stimuli of cough

Stimuli triggering airway receptors are inhaled particles, pathogens, accumulated secretions, postnasal drip, or inflammation of the respiratory mucosa. Stimuli for the pharyngeal receptors are any type of mechanical stimulation such as sharp food, postnasal drip, or even a water bolus. Stimulus of the gastroesophageal receptors occurs with reflux. Although aspiration will cause cough in GERD, pH monitoring has shown that coughing can be stimulated when refluxate enters only the lower esophagus (Canning, 2006). Some individuals become sensitized at the receptor level and cough with slight provocation.

Pathological cough

Sometimes the reflex ceases to be protective and becomes excessive, persistent, and unhelpful. Chronic cough can be triggered by multiple diseases in multiple anatomical sites and, in addition to disease of the larynx, airways, and lungs, disease of the esophagus, pharynx, sinuses, and brainstem also should be routinely considered (Irwin & Madison, 2001). The *anatomical-diagnostic* model identifies the specific anatomical site at which the reflex is triggered and the specific factors that stimulate it in each case. This model, developed 25 years ago, identified UACS, GERD, and asthma as the three diagnoses that accounted for the vast majority of chronic coughs (Irwin & Madison). The *therapeutic-diagnostic* model refers to diagnosis by complete or significant response to appropriate specific therapy (Morice & Kastelik, 2003). Response to therapy is considered the ''gold standard'' in assessing the accuracy of diagnosis (Irwin & Madison; Pratter, Brightling, Boulet, & Irwin, 2006).

Follow-up

Alvin arrives for follow-up 4 weeks later. He is relieved that no evidence of cancer was found, but disappointed that his dry cough is unchanged despite stopping smoking. Dry cough is caused by immediate airway irritation from smoke (Lee, Gerhardstein, Wang, & Burki, 1993), and should improve upon removal of the irritant. However, chronic cough with sputum increases with the number of cigarettes smoked and takes several weeks to improve after smoking cessation (Pratter et al., 2006).

Alvin can now be described as a patient with a chronic dry cough who does not appear ill, is not smoking, is not taking an ACE inhibitor, has no abnormal findings on physical examination, and has a normal chest radiograph. These negative findings are not unusual in chronic cough (Pavord, 2005).

You review the causes of chronic cough (Pratter, 2006a) which are summarized in Table 3, and see that several have already been excluded by negative examination and chest X-ray. UACS, CVA, GERD, and nonasthmatic

Table 3 Causes of chronic cough

Common	Less common	Uncommon
Upper airway cough syndrome (UACS), formerly called postnasal drip syndrome	Postinfectious Chronic bronchitis	Bronchogenic carcinoma
Asthma (classical or cough-variant)	Nonasthmatic eosinophilic bronchitis (NAEB)	Left ventricular failure
Gastroesophageal reflux disease (GERD)	Bronchiectasis	Sarcoidosis
Cigarette smoking	Psychogenic cough	Tuberculosis
ACE inhibitors		

eosinophilic bronchitis (NAEB), can all exist ''silently'' except for cough, and remain to be considered. Psychogenic cough is considered only when physical causes have been excluded (Irwin & Madison, 2000).

Decision Point 3

You need to decide whether to (a) suppress the cough with a centrally acting medication (such as dextromethorphan) without discovering the specific cause, (b) arrange comprehensive imaging and functional testing of the airways and upper GI tract, or (c) follow the sequential therapeutic-diagnostic protocol in the ACCP guidelines.

You decide that long-term cure depends on determining the specific cause or causes of the cough, but you wish to spare Alvin unnecessary testing and expense. You derive a therapeutic-diagnostic plan from the ACCP guidelines (see Table 4) and explain to Alvin that response to sequential trials of treatment aids in diagnosis.

Alvin's progress in the therapeutic-diagnostic trial

Month 1: UACS refers to inflammatory conditions of the nose and sinuses that induce the cough reflex. Antihistamines reduce inflammation in part by reducing vasodilation and, for unknown reasons, first-generation H_1 receptor blockers are most effective (Pratter, 2006b). Alvin took the antihistamine and decongestant (A/D, such as chlorpheniramine and pseudoephedrine) as prescribed, but his cough is not relieved.

Month 2: The sinus CT scan is negative for sinusitis. Noticeable response to A/D therapy should have taken place within days to several weeks (Pratter et al., 2006), but after 2 months Alvin's cough persists unchanged. UACS is therefore not causing the cough and the medication is discontinued.

Month 3: Cough is the predominant or sole symptom in CVA. Alvin' spirometry testing in the office records the vital capacity (VC) and forced expiratory volume in 1 s (FEV1) predicted from his gender, height, and age. The FEV_1/VC ratio is 72%, and an increase of only 5% in the $FEV_1$15 min after inhaling a short-acting bronchodilator (salbutamol) shows there is no significant airway obstruction. These normal spirometry results do not exclude CVA as a diagnosis (Dicpinigaitis, 2006a). According to the ACCP guidelines, an empirical trial of inhaled corticosteroid and inhaled bronchodilator (ß-agonist) is indicated and a favorable response of the cough confirms the diagnosis. Improvement is expected within 1 week, although resolution may take several weeks. After 4 weeks Alvin

Table 4 Therapeutic-diagnostic plan for management of chronic cough

Time frame	Action	Reason
Start plan	Explain checking needed monthly	Response to therapy is diagnostic
Month 1	Presumptive diagnosis of UACS	Most common cause/contributory cause of chronic cough
	• Empirical trial of first-generation antihistamine/decongestant	Expert opinion finds it most effective
	• Call Alvin to encourage compliance	Drug causes drowsiness
	• Evaluate cough—if response inadequate proceed to month 2	
Month 2	• Order sinus imaging	Sinus infections can be clinically silent
	• Continue antihistamine/decongestant	Prolonged treatment can improve results
	• If imaging negative and response to treatment still inadequate proceed to month 3	Without evidence of sinus infection or response to specific treatment, diagnosis of UACS unlikely
Month 3	Presumptive diagnosis of CVA	Common cause of chronic cough
	• Spirometry, particularly FEV_1/VC	Asthma is characterized by airways hyperreactivity and airflow obstruction
	• Empirical trial of inhaled corticosteroid and inhaled bronchodilator	Pathophysiology of asthma includes inflammation and bronchoconstriction
	• Monitor inhalation technique	Inadequate technique reduces drug delivery to airways
	• If no significant improvement in cough or spirometry, proceed to month 4	CVA unlikely as diagnosis
Month 4	Presumptive diagnosis of GERD:	Common cause of chronic cough
	• Dietary and lifestyle changes	Designed to reduce reflux
	• Empirical trial of pharmocological antireflux and acid suppression therapy	Reduce reflux and decrease gastric acid production (increase pH)
	• Check Alvin for compliance	Lifestyle changes often not sustained

Note: UACS, upper airway cough syndrome; CVA, cough-variant asthma; FEV1, forced expiratory volume; VC, vital capacity; GERD, gastroesophageal reflux disease.

Table 5 Specialized testing for cough

Test	Procedure	Significance
Induced sputum retrieval (Irwin et al., 2006)	Nebulized hypertonic saline given after short-acting bronchodilator; safe and effective	Cells types identified; eosinophils increased in both asthma and NAEB
Bronchial provocation challenge (Irwin et al., 2006)	Inhaled methacholine induces drop of >20% baseline FEV_1 in asthma; risk of excessive bronchoconstriction	Detects airway hyperresponsiveness asthma ruled out if negative
Capsacain challenge (Irwin, 2006b)	Concentration of inhaled capsacain to induce 5 coughs	Demonstrates heightened sensitivity of cough
Fractional concentration exhaled nitric oxide (Kovesi, Kulka, & Dales, 2008)	Slow exhalation with monitoring for NO	Indicator of airway inflammation*, response to steroids
Esophageal pH monitoring (Irwin et al., 2006)	Nasoesophageal catheter and recording device placed for 24 hours	Best test for GERD available, but results subject to interpretation
Endoscopy of upper GI tract (Irwin et al., 2006)	Performed under local anesthetic	Detects esophagitis, erosions, hiatal hernia associated with GERD
High-resolution CT		Detects bronchiectasis and interstitial lung disease
Endoscopy of airways (Irwin et al., 2006)	Performed only if occult airway disease or mass suspected	Detects tumor, sarcoid, and other diseases

Note: FEV_1, forced expiratory volume; GERD, gastroesophageal reflux disease; NAEB, non-asthmatic eosinophilic bronchitis; CT, computed tomography.

reports only partial if any improvement, and the cough still disrupts his life.

Month 4: Patients who do not smoke, do not take ACE inhibitors, have a normal chest X-ray and continue to cough for more than 2 months despite adequate treatment for UACS and CVA very often have GERD. The ACCP guidelines (Irwin et al., 2006) state that testing for GERD is unwarranted at this stage and treatment should begin with lifestyle changes (resting 30 min after eating, avoiding stooping, raising the head of the bed and adding a pillow, and antireflux diet) together with a proton pump inhibitor to suppress gastric acid production. Response is variable, but failure to respond within a few weeks does not exclude GERD as a cause of the cough.

Alvin adopts the lifestyle changes and takes acid suppression therapy (such as omeprazole) as prescribed, but continues to cough. Although it should be possible to reach a diagnosis of cough in primary care through a systematic approach to response to therapy (Irwin & Madison, 2000), after 4 months and three therapies Alvin has not responded and he is becoming discouraged.

Decision Point 4

You consult with Alvin to decide how management should now proceed. Option (a) is that you could persist in diagnostic testing, increasing the duration and dose of medications or trying two therapies concurrently, since often more than one cause of cough is present (Pratter et al., 2006). Option (b) is that a centrally acting cough suppressant could be tried, without reaching a diagnosis. Option (c) is that you could refer him to a pulmonary specialist.

Response to treatment is the ultimate diagnostic tool and you know that more aggressive treatments can be prescribed: for example leukotriene receptor antagonists and oral steroids as additional anti-inflammatory therapies in asthma, or metaclopramide as a prokinetic therapy in GERD (Irwin et al., 2006). Before increasing the duration or types of medication, you would like some supporting evidence from additional testing. However, invasive testing (summarized in Table 5) is not supported by your practice. Since Alvin is still anxious to know the reason for his cough, you refer him to a specialist cough clinic.

Report from the specialist respiratory clinic

You receive a report from the specialist cough clinic that Alvin has NAEB, a condition first defined in 1989. It is characterized by a steroid-responsive cough with sputum eosinopils, heightened cough sensitivity, and normal tests of variable airflow obstruction and airway responsiveness. Diagnostic criteria include a cough for more than 2 months, a sputum eosinophil count greater than 3%, normal FEV_1(>80% predicted) and FEV1/VC ratio (>70% predicted), with increase of less than 15% in FEV_1 20 mins after 200 μg salbutamol, and stable peak flow readings.

Before Alvin's next visit you discuss this unfamiliar condition at a practice meeting and research pertinent journals to compare NAEB with asthma and CVA as a cause of chronic dry cough (see Table 6).

Table 6 Comparison of NAEB with classical and cough-variant asthma

	Asthma	CVA	NAEB
Symptoms	Cough, wheeze, dyspnea	Cough	Cough
Sensitized cough reflex	Maybe	Maybe	Yes
Atopy common	Yes	Yes	No
Bronchoconstriction	Yes, variable	Maybe	No
Spirometry normal	Maybe between attacks	Maybe	Yes
Bronchial hyperresponsiveness	Yes	Yes	No
Responds to bronchodilators	Yes	Yes	No
Site of inflammation	Mucosa and smooth muscle	Mucosa and smooth muscle	Mucosa
Response to steroids	Yes	Yes	Yes
Sputum eosinophils	Yes	Yes	Yes

Note: CVA, cough-variant asthma; NAEB, non-asthmatic eosinophilic bronchitis.

Significance for your practice

NAEB is diagnosed in 10–30% of patients seen at a specialist cough clinic (either alone or concurrent with another cause of cough) but in a much lower number of patients in primary care. Looking at the diagnostic criteria for NAEB you note that although you found Alvin's spirometry results negative for bronchial hyperresponsiveness, this alone is not a diagnosis and induced sputum analysis for eosinophilia was also necessary.

Symptoms and sputum eosinophilia in NAEB usually respond to anti-inflammatory treatment with inhaled corticosteroids (such as budesonide) for at least 4 weeks, but occasionally more aggressive anti-inflammatory therapy with oral steroids is needed (Irwin et al., 2006), and this was the case with Alvin. The inhaled steroid you prescribed in the third month of the diagnostic therapy trial was inadequate to gain control of the established inflammation and cough hypersensitivity, and a short course of oral steroids was necessary. Eventually Alvin's cough is effectively controlled by steroid inhaler alone and he is very relieved.

Significance for Alvin

NAEB usually neither progresses nor completely resolves, but remains unchanged (Berry et al., 2005) and Alvin will need long-term treatment and follow up. Additionally, NAEB has been linked to a variety of occupations involving airborne allergens or irritants (DiStefano, Di Giampaolo, Verna, & Di Giocchino, 2007; Krakowiak, Dudek, Ruta, & Palczynski, 2007). Although Alvin had a negative response to testing with plant and animal allergens, he should avoid irritants such as farm chemicals which may contribute to his airways inflammation.

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Conflict of interest disclosure statement

No relationship that might represent a conflict of interest exists between either of the authors and any product mentioned in this article. No inducements have been made by any commercial entity to submit the manuscript for publication.