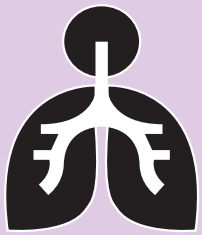
Asthma Focus

Chronic productive cough: An approach to management



Key Points

- Conditions most likely to cause chronic productive cough outlined.
- Epidemiology, clinical presentation, pathology and treatment of these conditions discussed.
- Cohort of patients with potential diagnosis of 'adult protracted bacterial bronchitis' described.
- Diagnostic algorithm for patients with chronic productive cough outlined.

A chronic 'productive' or 'wet' cough is a common presenting complaint for patients attending the adult respiratory clinic. Most reviews and guidelines suggest that the causes of a productive cough are the same as those of a non-productive cough and as such the same diagnostic pathway should be followed. Although it seems likely that all of the conditions which may present as a productive cough could present as non-productive cough, experiences suggests that some conditions are much more likely to result in productive cough than others whilst some of the common causes of dry cough such as gastroesophageal reflux disease (GERD) less commonly cause productive cough. This article is not a detailed systematic review of cough, but is intended to briefly summarise a number of conditions which are often associated with a chronic productive cough to aid decision making when encountering a patient with this often distressing symptom.

For the purposes of this review the definition of a “chronic productive cough” was considered to be a cough regularly leading to the expectoration of sputum with the same duration as the standard definition of chronic cough i.e. more than 8 weeks. Conditions causing productive cough have been listed below in an approximate order of prevalence from most to least frequent.

1. Bronchiectasis

Bronchiectasis is defined as the “irreversible abnormal dilatation of the bronchi”. It is a common cause of chronic productive cough which is diagnosed by a high resolution CT (HRCT) scan demonstrating a bronchus with an internal diameter wider than its adjacent pulmonary artery which fails to taper and bronchi visualised 1-2 cm from the pleural surface.

The prevalence of bronchiectasis is increasing in the UK and the USA, although it is unclear if this reflects a true increase in the number of cases or increased recognition of the condition due to more widespread HRCT scanning. Prevalence generally rises with age and is highest in those aged ≥70 years. The condition is more prevalent in women.

Clinical presentation: The condition usually presents as a chronic productive cough, with daily sputum production. Other factors that suggest the diagnosis include haemoptysis, systemic features of weight loss and fatigue and multiple positive sputum cultures.

Pathology: Bronchiectasis may be secondary to a multitude of other conditions (Table 1), with the most common predisposing factor thought to be post respiratory infection. However, a significant proportion of cases have no obvious discernable cause, although the number of these idiopathic cases reported differs markedly between studies.

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Table 1: Causes of Bronchiectasis in approximate order of frequency from most to least common.

Causes of Bronchiectasis
Idiopathic
Post Infectious
Immune deficiency
Alllergic Bronchopulmonary Aspergillosis
Ciliary dysfunction
Rheumatoid arthritis
Gastroeosophageal reflux disease/aspiration
Ulcerative Colitis
Cystic Fibrosis
Panbronchiolitis
Mycobacterial Infection
Congenital

It has been suggested that bronchiectasis is largely a result of dysregulation of the immune system, as it is often seen in patients with either immunodeficiency or “hyperimmune” (autoimmune) conditions such as Rheumatoid Arthritis or Inflammatory Bowel Disease. Although the initial step in the pathogenesis of the condition is not yet clear, it is broadly accepted that it progresses in a largely similar way, based on the "vicious circle' hypothesis proposed by Cole, which describes a cycle of airway inflammation, leading to structural airway damage and resultant mucous stasis, with the pooled mucus becoming colonised with bacteria, which initiate further inflammation (Fig. 1).

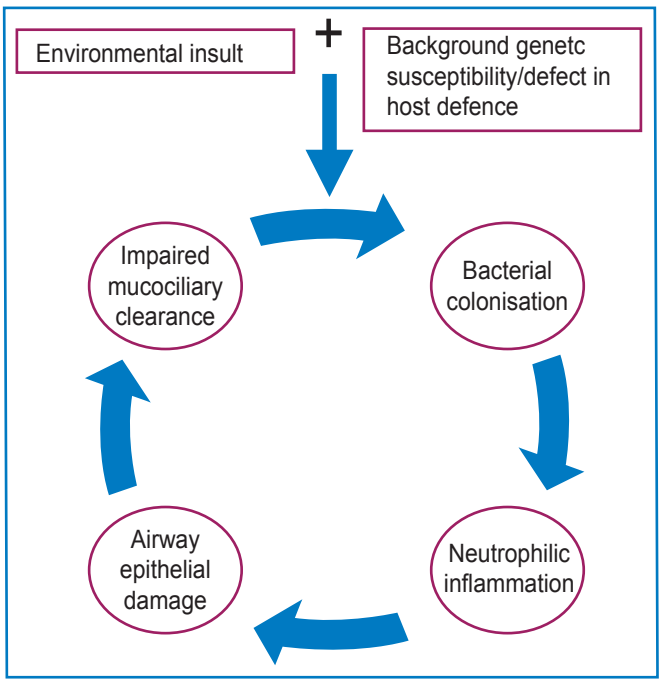

Fig. 1. The 'vicious circle' hypothesis of bronchiectasis.

The most common sputum isolates, using standard microbiological approaches, from patients with bronchiectasis are the gram negative bacteria *Haemophilus influenzae* and *Pseudomonas aerugenosa*. Colonisation of the sputum by first *H. influenzae*, and later *P. aerugenosa*, coincide with worsening of the clinical features of bronchiectasis including lung function and frequency of exacerbation.

Treatment: Broad principles in the management of the condition include treatment of the underlying cause, monitoring of disease activity using lung function and regular sputum cultures, airway clearance techniques and antibiotic treatment. These principles are further outlined in Table 2 below:

Table 2. Principles of management of bronchiectasis.

Principle of management	Specific management points
Treatment of underlying cause	e.g. Alergic Bronchopulmonary Aspergillosis (ABPA) treatment, immunoglobulin replacement, treatment of rheumatoid arthritis or inflammatory bowel disease
Monitoring of disease activity	• Lung function measured annually • Regular sputum cultures to determine colonising organisms and antibiotic resistanc
Airway clearance techniques	• Active cycle of breathing techniques • Postural drainage • Positive expiratory pressure devices • High frequency chest wall oscillation devices • Nebulised saline
Antibiotic treatment	Treatment of exacerbations • Definition of 'exacerbation' not universally agreed • No randomised controlled trials of antibiotic treatment for bronchiectasis exacerbations • Consensus opinion currently antibiotic treatment for 14 days • Antibiotic choice based on likely causative organisms and sensitivities • Sputum culture should be sent prior to treatment
	Pseudomonas eradication • If cultured for first time an attempt should be made to eradicate pseudomonas
	Regular prophylactic antibiotic therapy • Patients having ≥3 exacerbations per year requiring antibiotic therapy or those with <3 exacerbations but with significant morbidity should be considered for long term antibiotics such as macrolides

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2. Chronic bronchitis

Chronic bronchitis is defined as "the presence of a chronic productive cough for more than 3 months in 2 successive years". It is almost invariably described as a feature of Chronic Obstructive Pulmonary Disease (COPD) secondary to smoking.

The prevalence of chronic bronchitis in the general population is unclear, with many estimates ranging from 3 to 7% of adults experiencing symptoms, although higher rates of up to 22% have been reported. This uncertainty is likely owing to different definitions of the condition, variable reporting of symptoms and the inclusion of subjects in these estimates with other conditions such as bronchiectasis.

It is clear that individuals who are current or ex-smokers are more likely to have chronic bronchitis and patients with COPD have a higher prevalence of chronic bronchitis, with up to 74% affected. However, there seems to be a significant proportion of the general population experiencing these symptoms who do not have a formal respiratory diagnosis. This group may be at greater risk of morbidity/mortality than healthy subjects; a study by Guerra et al. demonstrated that subjects under the age of 50 with symptoms of chronic bronchitis were significantly more likely to develop airflow limitation with increased risk of mortality than subjects without chronic bronchitis.

Clinical presentation: Patients with chronic bronchitis present with a productive cough, although this symptom is often more unpredictable than the classic epidemiological definition of chronic bronchitis with much variation in the pattern of sputum production. Due to the large crossover of chronic bronchitis with COPD, many patients present with other features of COPD including dyspnoea and wheeze.

Pathology: Productive cough in chronic bronchitis is secondary to excessive mucus secretions in the airways. Mucus is present in excessive amounts owing to the overproduction and hypersecretion of mucus from mucus-producing goblet cells and decreased airway clearance mechanisms.

Mucus *overproduction* is caused by exposure to inflammatory stimuli such as cigarette smoke, viral or bacterial infection which lead to increased transcription of mucin genes due to activation of the epidermal growth factor receptor by inflammatory cells. Unlike in asthma, in which mucous metaplasia is known to be a result of Th2 inflammation, the corresponding inflammatory response in COPD causing mucus overproduction is not entirely clear, although it is thought to be Th17 mediated.

Continual exposure to inflammatory stimuli leads to increased numbers of goblet cells and mucin storage in the airways. As the severity of disease, i.e. extent of airway obstruction, worsens in COPD, the degree of mucous metaplasia and occlusion of the small airways by mucus tends to increase. Mucus *hypersecretion* is caused by increased goblet cell degranulation due to neutrophil elastase.

In conjunction with the increased amounts of mucus secreted into the airways, clearance of this mucus is impaired in patients with established COPD, owing to reduced ciliary function, occlusion of distal airways and respiratory muscle weakness leading to ineffective cough.

Treatment: Treatment of chronic bronchitis is largely based on treatment of the underlying COPD, as per NICE COPD guidelines. Certain treatment considerations that may particularly apply to patients with chronic bronchitis include the use of mucolytic therapy and judicious use of antibiotic therapy based on sputum colour and culture results. Another promising emerging treatment that has demonstrated efficacy in this patient group is the phosphodiesterase inhibitor roflumilast.

Mucolytic therapy: Mucolytic agents are widely prescribed to patients with chronic bronchitis in an attempt to improve their symptoms related to sputum production. The evidence for their use is mixed although a 2012 Cochrane review concluded that they may produce a small reduction in the exacerbation rate of patients with chronic bronchitis and COPD albeit with no difference in quality of life. There are some suggestions that chest physiotherapy and inhalation of nebulised saline may be beneficial in patients with patients with COPD but no randomised controlled trial data assessing the impact of these interventions.

Antibiotics: It is generally accepted that for subjects with chronic bronchitis a change in the amount or nature of sputum produced, beyond day-to-day variation, may signify an exacerbation and the production of green (purulent) sputum has been found to be highly sensitive (94.4%) and specific (77%) for the yield of a high bacterial sputum load. Guidelines therefore recommend antibiotic treatment following change in sputum quantity or quality.

Sending sputum for culture undoubtedly has a role in the management of chronic bronchitis, especially when there is a lack of response to an initial antibiotic treatment. However, potentially pathogenic micro-organisms that often permanently colonise the respiratory tract of symptomatically stable patients with COPD are frequently not isolated on standard sputum cultures. These colonising bacteria, most frequently *Haemophilus influenzae*, are associated with increased levels of airway inflammation, symptom burden and risk of exacerbation and the lack of sensitivity of standard sputum cultures to detect them has led to increasing interest in DNA-based bacterial detection techniques.

The long term use of low dose azithromycin has demonstrated efficacy in the treatment of patients with COPD with improved quality of life measures and decreased frequency of exacerbations.

Asthma Focus

Long term macrolides should be used with some caution however owing to the recognised potential side effects including QT interval prolongation, disturbance of liver function, hearing loss and development of bacterial macrolide resistance.

Roflumilast: Roflumilast is a phosphodiesterase 4 inhibitor which has anti-inflammatory effects in the airways by preventing the breakdown of intracellular cyclic AMP, a substance that when degraded leads to the release of inflammatory mediators. Two clinical trials assessing the effects of rofluminast (in addition to either salmeterol or tiotropium) vs placebo in patients with moderate to severe COPD and symptoms of chronic bronchitis both found that rofluminast significantly improved prebronchodilator FEV1 and exacerbation rate.

3. Asthma

Limited data is available regarding the prevalence of chronic productive cough (or "chronic mucus hypersecretion") in asthmatic patients, but there are reports of a significant subgroup of asthmatics in which these symptoms may be prominent. Two large scale European epidemiological studies reported the prevalence of chronic productive cough (≥3 months sputum production for 2 successive years) symptoms in populations of asthmatic non-smokers of 39% and 42%. These proportions were significantly higher for smokers with asthma, a finding replicated in a recent cross-sectional study by Thomson et al.

Clinical Presentation: The symptom of chronic productive cough seems to be associated with an accelerated decline in FEV1 in asthmatic patients regardless of smoking status. Thomson et al. found that asthmatic smokers with chronic productive cough had worse asthma control than those without a cough and asthmatic non-smokers with a productive cough had more exacerbations than those without cough.

Pathology: The cause of chronic productive cough in asthmatic patients is not entirely clear. Possible pathologies underlying this symptom include mucus hypersecretion or chronic bacterial infection/ colonisation.

Mucus hypersecretion: Mucus hypersecretion has long been recognised as a feature of asthma with mucus plugging of the airways acknowledged as a contributing factor in cases of fatal asthma. Pathophysiological features of mucus hypersecretion in asthma include goblet cell hyperplasia and submucosal gland hypertrophy, both of which lead to increased sputum production. These changes are thought to be driven by TH2 lymphocyte release of cytokines IL-9 and IL-13 as well as mast cell infiltration of submucosal glands, with subsequent mast cell degranulation leading to increased amounts of luminal mucus.

Respiratory infections/colonisation: Certain groups of asthmatic patients have been identified with stable clinical features of disease that have sputum cultures positive for potentially pathogenic organisms.

Studies identified subgroups of 'stable' asthmatic patients with significant loads of potentially pathogenic bacteria (including *Haemophilus influenzae*) in sputum culture with high sputum neutrophil counts. All of these patients were taking high dose inhaled corticosteroids, which have been linked with increased risk of respiratory infection. Inhaled fluticasone propionate has recently been shown to increase the risk of lower respiratory tract infections in patients with COPD and also asthma and it is possible that inhaled corticosteroids lead to chronic bronchitis in some patients by reducing host defence mechanisms, contributing to chronic infection.

A more recent investigation found that 29/56 (52%) of a cohort of patients with severe but stable asthma (and bronchiectasis excluded by HRCT) had positive sputum cultures, with *H. influenzae* most commonly cultured. Of the 29 patients with positive sputum cultures 23 had repeat sputum cultures and 16 of these were again positive, with 14 having the same bacteria isolated on both occasions, suggesting these bacteria were colonising the airways. The investigators did not identify any particular distinguishing characteristics of the group with positive sputum cultures, except for a significantly longer duration of asthma and a greater number of exacerbations in the preceding year in those who were 'colonised'.

Treatment: The association between severe neutrophilic asthma and airway colonisation by potentially pathogenic bacteria may suggest a mechanism for the reduction in asthma exacerbations and LRTI in a sub group of patients with non-eosinophilic asthma treated with a prolonged course of azithromycin in the AZIZAST study, although this finding is yet to be verified. The use of antibiotics in asthmatics with sputum production as a main symptom should probably be guided by the results of sputum culture if possible, although the limitations of sputum cultures as described above should be considered.

4. Eosinophilic bronchitis

Eosinophilic bronchitis (EB) describes a group of patients with cough (which may be productive) secondary to eosinophilic airway inflammation but with no bronchial reactivity

EB is thought to account for between 10 and 30% of cases of chronic cough referred to the specialist respiratory clinic. Further data regarding incidence and prevalence are lacking as establishing the diagnosis requires the confirmation of eosinophilic inflammation either at bronchoscopy or by

ASTHMA SCOOP

Screening smokers with pneumonia may lead to early detection of lung cancer

Study says nearly 10 percent of smokers hospitalized for pneumonia are diagnosed with lung cancer within one year

In a new study published in American Journal of Medicine, researchers proposed that screening heavy smokers admitted to the hospital with community-acquired pneumonia could facilitate the early diagnosis of lung cancer and thereby reduce the incidence of mortality. Heavy smokers who are diagnosed with pneumonia are one of the highest lung cancer risk groups- and therefore should be considered for early screening by chest-computer tomography. The research was led by Daniel Shepshelovich, MD, of TAU's Sackler Faculty of Medicine and Rabin Medical Center.

An early warning system

"Lung cancer is truly aggressive," said Dr. Shepshelovich. "The only chance of recuperation is if it's caught before it begins to cause any symptoms at all. The idea is to find the tumor well in advance. Previous studies have shown that a low-dose radiation CT scan conducted once a year on heavy smokers has the potential to lower lung cancer mortality rates. But this requires huge resources, and we still don't know how it will perform in real-world conditions, outside of strictly conducted clinical trials.

"We want to develop a more realistic and cost-effective strategy targeting a particularly high-risk population," he said.

Dr. Shepshelovich and his team examined the files of 381 admissions of heavy smokers with community-acquired pneumonia- a form of pneumonia contracted by a person with little contact with the health care system- at Rabin Medical Center between 2007-2011. They reviewed every patient's medical file for patient demographics, smoking history, lung cancer risk factors and the anatomical location of the pneumonia. The data was then crosschecked with the National Cancer Registry for new diagnoses of cancer.

The researchers found that out of 381 admissions of heavy smokers with pneumonia, 31(9%), a figure that surprised the researchers- were diagnosed with lung cancer within a year of being hospitalized. Lung cancer incidence was found to be significantly higher in patients admitted with upper lobe pneumonia (23.8%). They also found that the lung cancer was located in the lobe affected by pneumonia in 75.8% of cases.

"We discovered that smokers hospitalized with pneumonia are diagnosed with cancer after the infection because often the cancer masquerades as pneumonia, physically obstructing the airway and creating such an infection," said Dr. Shepshelovich. "Considering that only 0.5-1% of smokers without pneumonia have a chance of being diagnosed with lung cancer every year, the fact that 9% of our study group developed lung cancer is alarming."

Extending the lives of cancer patients

"The current diagnostic methods in place- chest X-rays, sputum cytology- sometimes find the cancerous tumors, but they do not change mortality rates," Dr. Shepshelovich said. "In other words, people are aware that they have cancer for longer periods of time, but do not recover. This is not a solution.

"Smokers admitted to the hospital with pneumonia should be considered for chest-computer tomography," he continued. "Only 15 percent of lung cancer cases are detected at an early stage. We want to increase that number in order to reduce mortality or, at the very least, extend lives."

The researchers are currently considering a larger nationwide retrospective study on the subject.

Source : Science Daily, 7 January 2016

Asthma Focus

sputum differential cell count which is primarily a research investigation only available at a limited number of specialist centres.

Clinical Presentation: Diagnosis of the condition is made in patients with an appropriate clinical history, negative bronchial challenge and significant sputum eosinophilia, usually accepted as being a proportion of the total sputum cell count of ≥3%.

Pathology: EB shares many similar pathological features to asthma with equivalent levels of eosinophilic inflammation and sputum eosinophilia, airway remodelling and basement membrane thickening. It has been suggested that the key difference in pathogenesis and hence clinical features of the two conditions is the localisation of activated mast cells. Bronchial brushings from patients with eosinophilic bronchitis contained increased numbers of mast cells in comparison to those from asthma patients, suggesting activated mast cells are more abundant in superficial layers of bronchial epithelium in EB than in asthma. By contrast, asthmatic patients demonstrate increased numbers of activated mast cells in airway smooth muscle compared to subjects with EB. This difference in location of mast cells and increased IL-13 release observed in asthma compared to EB may help to explain the features of airway hyperresponsiveness and airflow obstruction observed in asthma which are not features of EB.

Treatment: The first line treatment for eosinophilic bronchitis is inhaled steroids which usually lead to a marked symptomatic improvement and decrease in sputum eosinophil count. A recent randomised controlled trial suggests that the leukotriene receptor antagonist montelukast may provide some additional benefit to inhaled corticosteroid therapy in improving quality of life measures and markers of eosinophilic inflammation. In a few cases intermittent oral corticosteroids may be required to control symptoms.

5. Immunodeficiency

A small group of patients presenting with recurrent lower respiratory tract infections are shown to have immunodeficiencies, including IgG/IgA deficiency or Combined Variable Immunodeficiency (CVID). These patients may present with recurrent but discrete episodes of infection punctuated by periods of recovery, but over time are at risk of developing bronchiectasis.

The natural history of the clinical, pathological and radiological features displayed by these patients is unclear. Previous studies have reported significant rates of bronchitis symptoms in patients with primary immunodeficiencies, but it is uncertain if these patients have symptoms secondary to established bronchiectasis or if they progress through a state of 'pre bronchiectasis' with bacterial airway colonisation and persistent cough but no significant bronchiectasis on HRCT scan.

5.1. IgA deficiency: Diagnosis of IgA deficiency has been defined by international consensus as "an IgA level of 0.07 g/l after the age of 4 years in the absence of IgG and IgM deficiency". Selective IgA deficiency is the most common primary immunodeficiency with a prevalence in Caucasians of 1/300 to 1/1200. Respiratory tract infections are usually caused by bacteria including *H. influenzae* and *Streptococcus pneumoniae*. Some patients go on to develop bronchiectasis presumably secondary to recurrent infection causing airway damage and scarring.

Treatment: In general, IgA antibody replacement therapy is not indicated in patients with IgA deficiency, and such therapy may in fact be harmful. However a subgroup of patients with IgA deficiency and recurrent sinopulmonary infections may benefit from extended courses of prophylactic antibiotics or sometimes intravenous gamma globulin (IVGG) therapy if they have other associated antibody deficiencies.

5.2 Combined variable immunodeficiency: Combined Variable Immunodeficiency (CVID) is a disease defined by the defective production of immunoglobulins. Diagnosis of CVID can be made using internationally agreed diagnostic criteria, of which 1 of the 3 parts required for diagnosis states there should be "hypogammaglobulinaemia with IgG levels two standard deviations below the mean". The epidemiology of the condition is unclear but the prevalence is thought to be around 1:30000 in Northern European populations.

Clinical presentations: Clinically the disease manifests with recurrent respiratory tract infections/pneumonias, progressing later in life to bronchiectasis. Patients with CVID may also experience repeated infections of other sites of the body including the skin, soft tissues, nervous system and gastrointestinal tract. There is some evidence that asthmatics may be at greater risk of CVID than non-asthmatics, and this has been suggested as a potential reason for the increased risk of respiratory infection noted in asthmatic patients. Respiratory infections are usually caused by encapsulated bacteria, especially *H. influenzae, S. pneumoniae* and *Staphlococcus* sp, due to the inability of the immune system to produce IgG antibodies against these pathogens. Usually, the cumulative effect of these repeated infections leads to complications such as empyema, lung abscesses or, most commonly bronchiectasis. However, despite the prominent burden of symptoms this condition can cause the sufferer, there may often be delays in the diagnosis and treatment of the condition due to either a lack of awareness of its existence or the misperception that the condition only presents in childhood, when in fact the average age of presentation is thought to be around 30 years.

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Treatment: The management of pulmonary complications of CVID usually consists of regular immunoglobulin replacement and suppressive antimicrobial treatment, although there are no RCT data to support these measures. Several other interventions to maintain or improve lung function in patients with CVID have also shown some efficacy including the maintenance of higher IgG trough levels, chest physiotherapy techniques including postural drainage, azithromycin and nebulised antibiotics for eradication of Pseudomonas

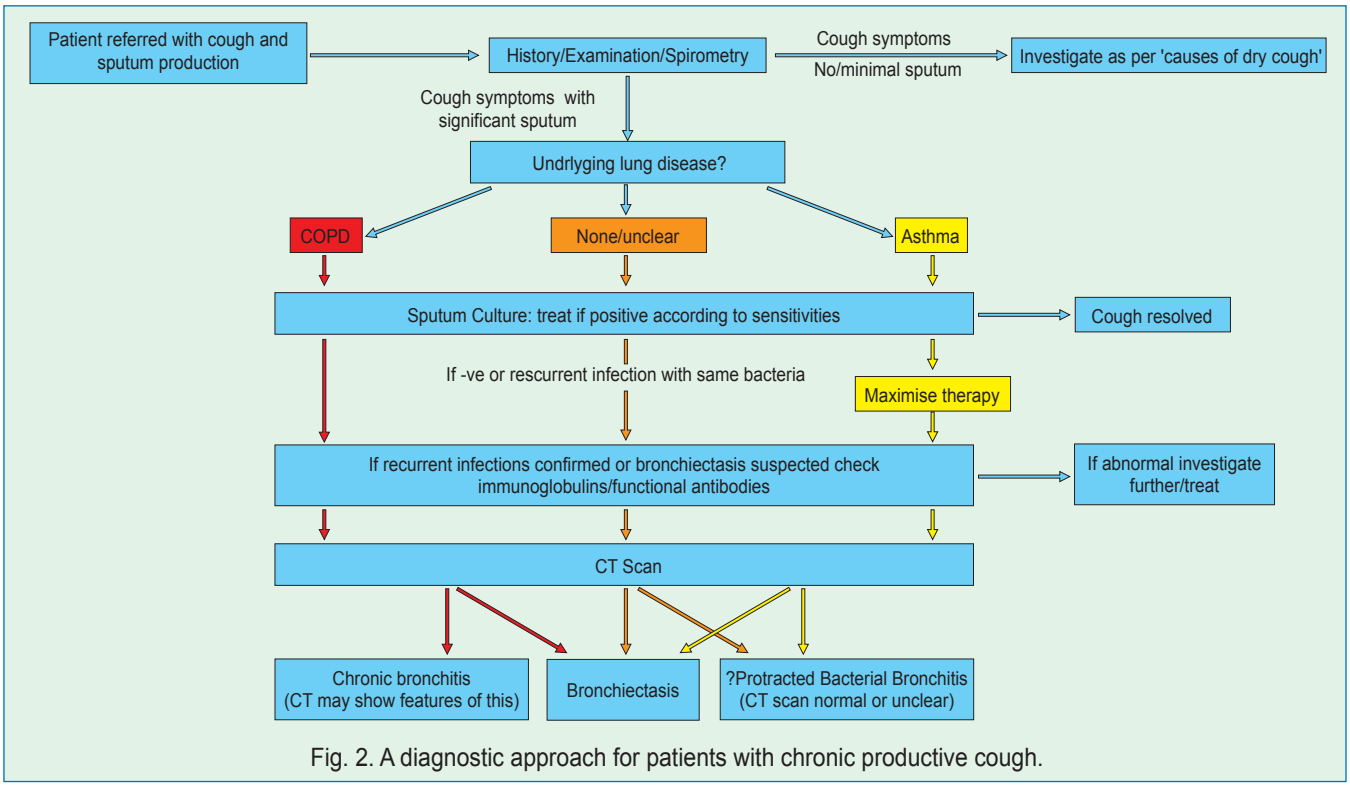

Fig. 2. A diagnostic approach for patients with chronic productive cough.

6. Idiopathic chronic productive cough

Studies observed a cohort of adult patients with chronic productive cough which improves with antibiotic treatment but quickly relapses. Many have suspected poorly controlled asthma but investigations including spirometry, bronchial challenges, chest X-ray, screen for immunodeficiency and HRCT scan are normal. Sputum culture is often positive for *Haemophilus influenzae*, and less commonly *S. pneumoniae* and *Moraxella catarrhalis* on more than one occasion. Prolonged treatment with low dose azithromycin was found to be highly effective when standard antibiotic therapy has failed.

Idiopathic chronic productive cough have many similar features in common with the paediatric diagnosis of protracted bacterial bronchitis (PBB). PBB is a common diagnosis in children and is thought to account for up to 40% of cases of paediatric chronic cough. It has been clinically defined as the presence of an isolated chronic 'wet' cough, in the absence of an alternative cause, which resolves with a prolonged course of antibiotic treatment. Children with the condition do not usually respond to bronchodilator therapy, but like our patients are often misdiagnosed as having asthma. The pathogenesis of PBB is as yet unclear, but the main finding on investigation of the condition is persistent infection of the airways with bacteria including *H. influenzae, S. pneumoniae* and *M. catarrhalis* and neutrophilic airway inflammation. It is thought that bacteria may colonise the airways from the upper respiratory tract following a period of impaired mucociliary clearance, as may occur following a viral respiratory tract infection. Once present in sufficient numbers in the conducting airways, bacteria (especially non typeable *H. influenzae*) may form biofilms as a means of defence against airway clearance mechanisms and antibiotics.

PBB is suspected to be a potential precursor to the development of bronchiectasis in adulthood and some authors have suggested the condition be renamed 'pre-bronchiectasis'. In retrospective studies the majority of adult patients with idiopathic bronchiectasis give a history of persistent wet cough from childhood. There are very few, if any, descriptions of PBB in adults, although one previous study identified 15 adult subjects with chronic productive cough secondary to 'unsuspected bacterial suppurative disease of the airways' and grossly normal HRCT scans.

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The Winners of Asthma Focus Quiz Competition

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Editorial Note

Dear Doctor,

We are happy to present you the 1st issue of "Asthma Focus" Newsletter, 2016. In this issue we have concentrated 'Chronic productive cough: An approach to management'. We hope you will enjoy reading the publication!

We appreciate your comments and queries.

Please participate in Quiz competition & win prizes.

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