CME Article

Chronic cough in children

P Y Chow, D K K Ng

ABSTRACT

Chronic cough, defined as coughing for more than four weeks, is a common childhood complaint. With careful history-taking and appropriate investigations, a single cause can be found in most cases- these can be successfully treated. Although we have some understanding about the cough reflex through animal studies, the full mechanism and exact location of the responsible neurons in the human brain have not been completely elucidated. There are many causes for it but asthma, chronic rhinosinusitis and gastroesophageal reflux disease account for most of the cases. Other causes, such as dysfunctional swallowing, congenital anomalies and cigarette smoking, are also important. All children with chronic cough deserve a thorough and proper evaluation. The current review provides essential information for medical practitioners to approach this problem. An algorithm is provided to aid the diagnostic process.

Keywords: children, cough, cough reflex, chronic cough

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INTRODUCTION

Cough is a common symptom that brings a child to medical attention. The prevalence of chronic cough in Chinese children is about 6.4%[1]. In the United States, it accounts for 3% of medical consultations[2]. Girls seem to have a lower cough threshold, but the reason for this gender difference is unclear[3]. While much of acute cough is due to viral infection of the upper respiratory tract, chronic cough, defined as coughing for more than four weeks duration[4], can be caused by various conditions other than infection, some of which may be serious. A single cause can be found in up to 82% of all cases of chronic cough[4]. The majority of these can be successfully treated. Thus, it is imperative that one looks for the underlying cause and treat appropriately rather than use cough suppressants indiscriminately.

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NEURAL PATHWAY OF COUGH REFLEX

Cough is an important reflex defense mechanism for clearing the airways of inhaled noxious stimuli. The reflex begins with stimulation of the cough receptors by viruses, aeroallergens and chemicals. There are two distinct types of afferent fibres, namely: the rapidly adapting irritant receptors (RARs) and the capsaicin-sensitive unmyelinated bronchial C-fibres[5]. The former type of fibres is sensitive to mechanical and/or chemical stimuli[5]. They are present throughout the respiratory tract down to the respiratory bronchioles, especially the posterior wall of the trachea, carina and branching points of large airways. They are also present in the external auditory canals and tympanic membrane, pleura and pericardium, where they tend to respond to only mechanical stimuli[6]. The bronchial C-fibres are neuropeptide-containing nerve fibres that are sensitive to chemical stimulation rather than mechanical stimulation[7]. Stimulation of these fibres causes bronchial smooth muscle contraction, vasodilatation, plasma extravasation and mucus secretion[8]. However, the exact role of C-fibres in the human cough reflex is still unclear[7].

The afferent impulses, through the vagus, glossopharyngeal and trigeminal nerves, are relayed to the nucleus of the tractus solitarius in the brainstem before they are transmitted to the cough centres in the medulla oblongata where they are integrated. The efferent output is located in the nuclei retroambigualis and ambiguus in the brainstem, and this travels down the phrenic and other spinal motor nerves to the respiratory musculature[6]. There are also vagal efferents innervating the bronchial smooth muscle, thus causing constriction[9]. Animal studies suggest that the production of cough is a gated process. The exact location and identity of the responsible neurons in the brainstem remain unclear, but this tracheobronchial gate regulates the production, magnitude and duration of the cough[10]. The vagal afferents may also directly stimulate the airway submucosal glands, thereby causing mucus production,

which serves as another protective mechanism against noxious aeroallergens[11]. The neural pathway may undergo changes, termed plasticity of cough reflex, resulting in excessive and inappropriate responses. This may be due to an increase in receptor density or an upregulation of the receptor sensitivity, either at the periphery or central level[12].

PHYSIOLOGY OF COUGH

Cough is a rapid and ballistic movement. A typical cough starts with a deep inspiration to at least 50% of the vital capacity. This is followed by the compression phase, where the glottis closes for about 0.2 second and there is contraction of the respiratory musculature. The glottis then opens suddenly. This unleashes the high intrapleural pressure that develops during the glottic closure, creating a high expiratory flow rate and narrowing the central airways, which can be as high as 12 L/sec and reaches a peak flow of 30 to 50 msec following the start of the expiratory phase. Finally, the relaxation phase completes the act when the respiratory musculature relaxes with a reversal of the intrathoracic pressure[6,10]. Normal function of the mucociliary apparatus is critical in maintaining an effective cough, as it brings secretions from the periphery to the proximal airways where they can be cleared by coughing.

DIFFERENTIAL CAUSES OF CHRONIC COUGH

There are many causes of chronic cough (Table I). Post-nasal drip syndrome (PND), asthma, gastroesophageal reflux disease and bronchiectasis are the most common causes of chronic cough in adults[13-16]. In children, other important causes such as congenital anomalies, foreign body aspiration and environmental exposure need to be considered[17]. The history-taking must include any neonatal problem, feeding history, history of allergies and previous infection or illness, immunisation history and any family history of tuberculosis, asthma and atopy. Information on duration and pattern of coughing, together with any specific triggers, must be sought. Enquiry about environmental history, including exposure to tobacco smoke and pets, should be made. Physical examination must include the child's growth parameters and development, as there are important indicators of disease severity.

POST-NASAL DRIP SYNDROME

The leading cause of PND, is allergic rhinitis or, more appropriately, chronic rhinosinusitis[18]. In Hong Kong, the prevalence of allergic rhinitis in children between 6 and 7 years old is 33%, and this figure increases to 52%[19] in children between 13 and 14 years old[20]. The pathogenesis of PND-induced cough is probably due to the inflammatory nature of the nasal secretion and/or direct mechanical stimulation of the cough receptors by secretions dripping from the nostrils down into the hypopharynx. Microaspiration of the secretions and nasobronchial reflex have also been suggested[17,21].

The clinical presentation of chronic rhinosinusitis, in addition to cough, commonly involves complaints of a sensation of something dripping down the throat and nasal congestion or discharge. Diagnosis of the disorder mainly depends on the history and finding of pale and swollen nasal turbinates. Radiologically, the sinuses may demonstrate air-fluid levels, opacification or mucosal thickening of greater than 6mm[22]. Computed tomography of the paranasal sinuses is considered the gold standard for diagnosis. However, paranasal sinus radiograph has a positive predictive value of 81% and a negative predictive value of 95% in predicting chronic rhinosinusitis-induced cough in those with excessive sputum production[13], though these positive and negative predictive values are only 57% and 100%, respectively, in people with chronic dry cough[16].

The mainstay of treatment of rhinosinusitis is allergen avoidance, saline nasal lavage, anti-histamines and corticosteroid nasal spray. Immunotherapy has also been shown to be effective[23]. The role of

Table I: Differential diagnoses of chronic cough (in descending order of likelihood).

Infancy	Early childhood	Late childhood
Gastroesophageal reflux	Post-viral airway hyper-responsiveness	Asthma
Infection	Asthma	Post-nasal drip
Congenital malformation	Passive smoking	Smoking
Congenital heart disease	Gastroesophageal reflux	Pulmonary tuberculosis
Passive smoking	Foreign body	Bronchiectasis
Environmental pollution	Bronchiectasis	Psychogenic cough
Asthma		

bacterial infection and use of antibiotics in chronic rhinosinusitis are controversial. An antibiotic treatment regimen of three weeks duration is suggested in some studies[4], but a shorter course of treatment of three days duration with a new generation of macrolide, azithromycin, has also been shown to be equally effective in reducing the symptoms[24].

ASTHMA

The prevalence of childhood asthma is increasing globally. In Hong Kong, the prevalence of asthma in children aged between 3 and 10 years is 6%[25]; rising to 11% in the 13- to 14-year-olds[20]. Up to 57% of asthmatics may present with only cough[26]. This is sometimes referred to as cough-variant asthma or cough-predominant asthma, which is the preferred term[27]. Asthma is a chronic airway inflammatory disease with bronchial hyper-responsiveness and reversible airway obstruction. A typical history of cough that is triggered off by viral respiratory infection or allergen exposure is worse at night, and is exacerbated by exercise, cold air or smoke. Favourable response to anti-inflammatory therapy may help one to arrive at the diagnosis[28]. Presence of other atopic features, such as allergic rhinitis, eczema, allergic conjunctivitis and urticaria, is helpful to confirm atopy and hence, supports the diagnosis of asthma. Spirometry is helpful in demonstrating airway hyper-responsiveness in children over six years of age. Other helpful investigations include skin prick test and measuring serum immunoglobulin E level.

Treatment involves the inhalation of corticosteroids, which is the cornerstone of therapy[29,30]. Maximal symptomatic benefit from the inhaled corticosteroids may take six to eight weeks to realise[31]. Nevertheless, there is concern over growth and lung maturation. However, growth is a complicated process and poorly-controlled asthma can also lead to growth failure. Recent studies have shown that children on long-term corticosteroid therapy were able to attain adult height, though there was a significant effect on growth rates in the initial 1-2 years[32-34]. Thus, the inhalation of corticosteroids is currently still the best treatment for asthma.

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux (GER) is a normal event, especially during infancy. The prevalence of GER in healthy infants is around 40% to 65%[35]. It peaks at between one to four months of age[36], and resolves spontaneously at 12 months[37]. It becomes pathological when it causes symptoms and physical complications, hence the term gastroesophageal reflux disease (GERD). The prevalence of GERD, as a cause of chronic cough, in children is estimated to be 15%[38]. In infants, the disease can lead to apnoea, bradycardia and arching of back, as well as cough. Cough as the sole manifestation of GERD, however, is uncommon in children[39]. There may be failure to thrive and developmental delay. A history of feeding difficulties or coughing and choking during feeding is highly suggestive of chronic aspiration. Symptoms mostly occur in the post-prandial period, though it may not always be the case in children.

A few mechanisms have been proposed for the reflux causing chronic cough. Dysfunction of the lower oesophageal sphincter is the major reason, but impaired oesophageal acid clearance may also play a role[40]. The reflux content may be large enough to cause gross aspiration, resulting in pulmonary aspiration syndromes or recurrent aspiration pneumonia. Microaspiration also leads to laryngeal inflammation and bronchitis[41]. Using 24-hour oesophageal pH monitoring with distal and proximal pH probes, minor reflux into the hypopharynx has been shown to occur frequently in some patients[42]. Vagally-mediated distal oesophageal-tracheobronchial reflex mechanisms have also been described in patients with chronic cough[42,43]. The 24-hour ambulatory oesophageal pH monitoring technique is the most sensitive diagnostic tool[44]. Other tools such as milk scan and oesophago-gastro-duodenoscopy can also be used.

Elevation of the head of the bed and thickening of feeds can be helpful, though the latter may promote more silent reflux because of increased viscosity of gastric fluid and delayed gastric emptying[45]. Cigarette smoke can decrease the lower oesophageal sphincter pressure. Parents should, therefore, be strongly advised to quit smoking. Prokinetic agents, including cisapride and domperidone, have been evaluated in children with GERD and chronic cough. They have been found to be equally effective in 64.5% to 100% of cases[46,47]. However, cisapride has been withdrawn from general clinical use due to its possible link to prolonged QT interval, cardiac arrhythmias, torsades de pointes and sudden death. Nevertheless, it is still used in difficult cases where the eligibility criteria have been fulfilled. H2 blockers, such as cimetidine or ranitidine, and proton pump inhibitor, such as omeprazole, are alternative medications for GERD. Medical treatment is successful in 80% of cases[48]. Anti-reflux surgery, such as fundoplication with or without pyloroplasty, is only needed in very resistant cases.

BRONCHIECTASIS

While it accounts for about 4% of all cases of chronic cough in adults[4,13], the figure for incidence of bronchiectasis in children is not available. The causes of bronchiectasis include pertussis, pulmonary tuberculosis, recurrent aspiration, primary ciliary dyskinesis, immunodeficiency, foreign body aspiration, inhalation of chemical irritants, alpha-1 antitrypsin deficiency and cystic fibrosis[4]. Helicobacter pylori infection may play a role in adult bronchiectasis[49]. However, this has not been studied in children.

The pathogenesis of bronchiectasis involves interaction between the insult and the disorder of host defenses[50]. The resulting inflammatory response impairs bronchial clearance and mucociliary transport mechanism, leading to chronic colonisation of airways by micro-organisms. There is dilatation of subsegmental bronchi or patchy destruction of the cartilage, leading to irregular bronchial contour. The small distal airway may be obliterated.

The disorder is suggested by the history, clinical findings and imaging. Cough is one of the most important symptoms[4,50]; 97% of children with bronchiectasis will present with it- singly or in combination with other symptoms, such as haemoptysis, wheezing, dyspnoea and poor weight gain. There is an excessive production of purulent sputum, recurrent chest infection and rarely, severe bronchiolitis-like syndromes. Chest radiographs may show bronchial dilatation, bronchial wall thickening and compensatory hyperinflation. High-resolution computed tomography of thorax is the preferred imaging technique, with a sensitivity and specificity approaching 100%[51].

Chest physiotherapy, postural drainage, mechanical devices, such as flutter and in-exsufflator, together with the judicious use of antibiotics in acute exacerbations, are the mainstays of treatment. Some adults may benefit from inhaled corticosteroids[52,53], but its role in children needs to be further evaluated. Nebulised antibiotics such as tobramycin is useful in cystic fibrosis[54], but again, this has not been studied in non-cystic fibrosis bronchiectasis[4]. A high caloric intake is necessary to compensate for the high energy level in these patients. Surgical resection can be contemplated if the disease is localised.

DYSFUNCTIONAL SWALLOWING

Children, especially those with neuromuscular disorders or spastic cerebral palsy, are prone to swallowing difficulties[55]. Medications, such as anticonvulsants and neuroleptics used in the treatment of epilepsy and behavioural disorders, can affect the pharyngeal musculature tone and leads to repeated aspiration and chronic cough[56]. Videofluoroscopical examination of swallowing is the gold standard in diagnosis. However, recent guidelines suggest that fibreoptic endoscopic evaluation of swallowing is safe and effective, and has the added advantage of providing visual display to help parents and patients learn various swallowing manoeuvres[57]. Referral to a speech therapist for treatment is recommended, and continuous nasogastric or gastrostomy tube feeding may be necessary.

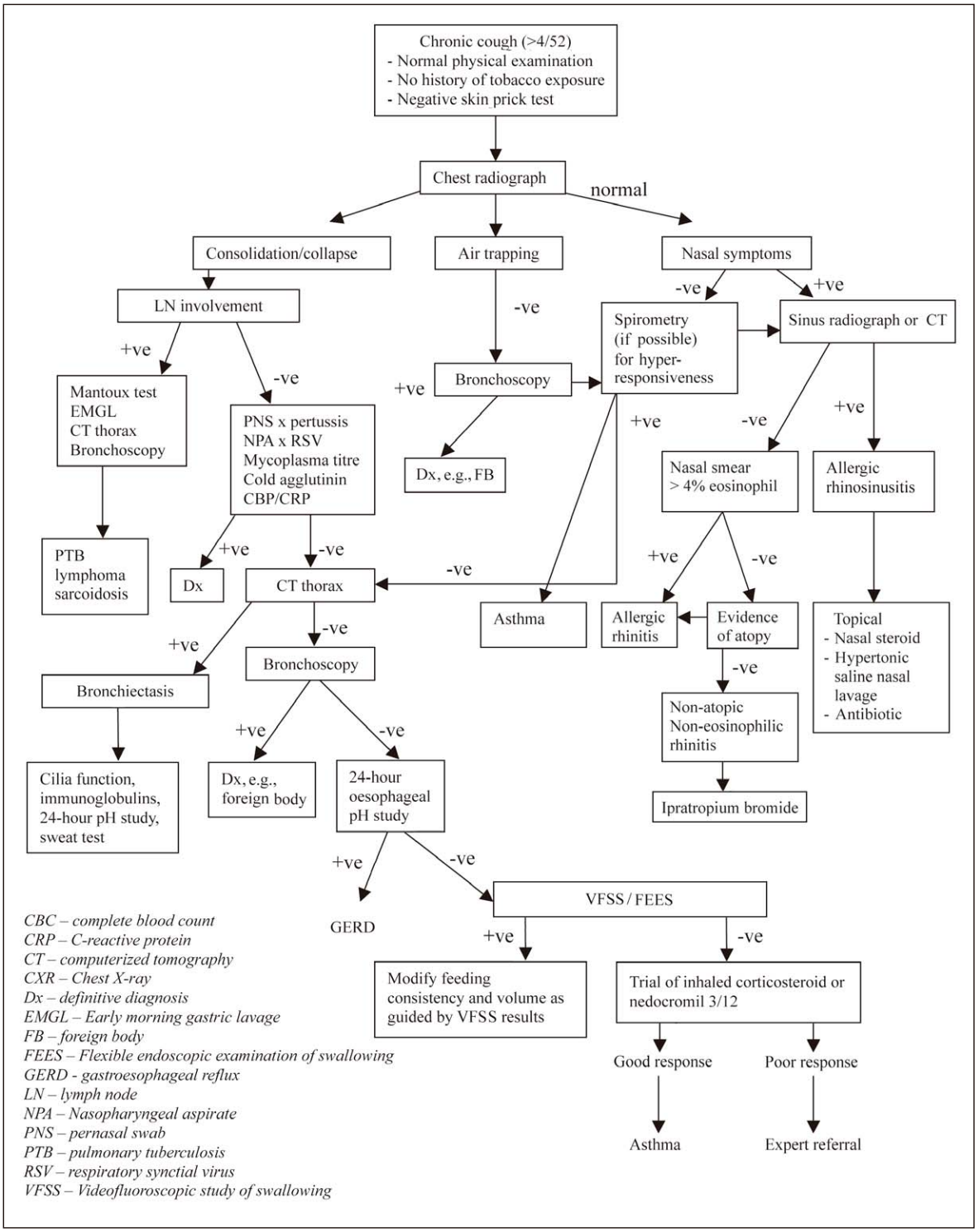
POST-INFECTIOUS/VIRAL COUGH

This is a clinical diagnosis by exclusion. However, it is frequently misdiagnosed and treated as asthma[58]. It is a recognised entity in most European studies on chronic cough[59]. The specific infection causing the chronic cough is unknown in most cases but respiratory viruses, especially respiratory syncytial virus and parainfluenza virus, Mycoplasma pneumoniae, Chlamydia pneumoniae and Bordetella pertussis, have all been implicated. The exact mechanism is probably due to persistent airway inflammation with transient airway hyper-responsiveness after infection[60]. The induced sputum shows a lack of eosinophils, which is not typical of untreated asthma[61]. The disease is self-limited and will resolve without any treatment. Inhaled corticosteroids may be tried, but no randomised study has been performed to date. Ipratropium can also be useful[62]. A brief course of oral steroid may be necessary in some protracted cases[4].

PSYCHOGENIC AND HABITUAL COUGH

This is another diagnosis by exclusion. It is common in adolescence and accounts for 10% of chronic cough in one study[38]. The cough usually sounds like throat clearing in a nervous and self-conscious patient. Some patients may show "la belle indifference" or a relative lack of concern over the symptoms, whereas others may give an elaborate and exaggerated history[63]. This can be seen as a tic[64]. Others consider it part of the Tourette's syndrome and obsessive-compulsive disorder[65]. One important diagnostic clue is that the cough tends to be worse under stress, and ceases at night or during pleasurable activities. Underlying psychosocial issues should be explored tactfully as offering a psychological attribution may provoke much anger and affect the doctor-patient relationship. Psychological therapy, including relaxation and mental imagery/self-hypnosis, with or without the use of bio-feedback, is the mainstay of therapy[66].

Fig. 1 An algorithm for evaluating children with chronic cough.



DRUG-INDUCED COUGH

This is rarely seen in children who are taking angiotensin-converting enzyme inhibitors. It is thought to be related to bradykinin, prostaglandins and possibly substance P.[67] The cough tends to be dry and hacking. The definitive treatment is to substitute the medication, or switch to angiotensin-II receptor blockers which do not have this side effect.

SMOKING

Passive smoking is another important cause of chronic cough in children[68]. Children can be exposed to the various constituents of smoke in-utero, through breast milk and through direct inhalation[69]. It had been shown that children exposed to passive smoking have a higher risk of developing chest infection and had poorer pulmonary function[70].

Laboratory studies have demonstrated that both RARs and C-fibres are more excitable after exposure to cigarette smoke[71,72]. This correlates well with clinical findings that children of smoking mothers who are smokers tend to have a higher incidence of airway hyper-reactivity[73]. The incidence of teenage smoking is also increasing globally. In Hong Kong, the prevalence of smoking in the 8- to 12-year-olds was estimated to be 5.5%[1]. Therefore, cigarette smoking must be enquired during evaluation of chronic cough.

CONGENITAL DISORDERS

Patients with congenital tracheobronchomalacia, congenital mediastinal tumour, pulmonary sequestration, bronchogenic cyst and congenital anomalies of the major blood vessels can also present with chronic cough. Flexible bronchoscopy and radiological imaging will delineate the problem. Non-invasive positive airway pressure ventilatory support can be useful in congenital airway collapse, but surgical correction is usually needed in most of the other problems.

CONCLUSION

Careful history-taking and physical examination, together with appropriate investigations, enable the correct diagnoses to be made for most cases of chronic cough within a reasonable time frame. The diagnostic approach is summarised in Fig. 1. Most cases can be dealt with using this algorithm. For the rare cases that elude diagnosis, referral to a specialist in paediatric respiratory medicine is warranted.

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

Multiple Choice Questions (Code SMJ 200410B)

	True	False
Question 1. Differential diagnoses of chronic cough in children include:		
(a) Gastroesophageal reflux.	❑	❑
(b) Post-nasal drip due to allergic rhinitis.	❑	❑
(c) Passive smoking.	❑	❑
(d) Asthma.	❑	❑
Question 2. The following statements about dysfunctional swallowing are true:		
(a) It is more likely to affect children with neuromuscular disorders.	❑	❑
(b) The investigation of choice is 24-hour oesophageal pH study.	❑	❑
(c) It could be caused by anticonvulsants.	❑	❑
(d) Motilium is the treatment of choice.	❑	❑
Question 3. The following statements about bronchiectasis are true:		
(a) It accounts for less than 10% of chronic cough in adults.	❑	❑
(b) High-resolution computed tomography of thorax is the investigation of choice.	❑	❑
(c) Flutter is an effective treatment tool.	❑	❑
(d) Oral acetylcysteine is effective.	❑	❑
Question 4. The following statements about asthma are true:		
(a) Cough-predominant asthma occurs in nearly one-half of asthmatic children.	❑	❑
(b) Demonstration of airway hyper-responsiveness by spirometry is an important feature.	❑	❑
(c) Regular short-acting bronchodilator is the treatment of choice.	❑	❑
(d) The final adult height is impaired in children on regular inhaled low-dose corticosteroids.	❑	❑
Question 5. The first line investigations in children with chronic cough include:		
(a) 24-hour oesophageal pH study.	❑	❑
(b) Chest radiograph.	❑	❑
(c) Skin prick test for common aeroallergens.	❑	❑
(d) Sinus radiographs in those with persistent nasal symptoms.	❑	❑

Doctor's particulars:

Name in full: _____

MCR number: _____ Specialty: _____

Email address: _____

Submission instructions:

A. Using this answer form

1. Photocopy this answer form.
2. Indicate your responses by marking the "True" or "False" box ☑
3. Fill in your professional particulars.
4. Either post the answer form to the SMJ at 2 College Road, Singapore 169850 OR fax to SMJ at (65) 6224 7827.

B. Electronic submission

1. Log on at the SMJ website: URL http://www.sma.org.sg/cme/smj
2. Either download the answer form and submit to smj.cme@sma.org.sg OR download and print out the answer form for this article and follow steps A. 2-4 (above) OR complete and submit the answer form online.

Deadline for submission: (October 2004 SMJ 3B CME programme): 25 November 2004

Results:

1. Answers will be published in the SMJ December 2004 issue.
2. The MCR numbers of successful candidates will be posted online at http://www.sma.org.sg/cme/smj by 20 December 2004.
3. Passing mark is 60%. No mark will be deducted for incorrect answers.
4. The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.