Cough in children is a normal occurrence, and identifying where treatment or referral is indicated can be challenging. Here, the authors discuss the considerations for assessing and managing childhood cough in primary care.

Cough is a common although non-specific clinical presentation of numerous different pulmonary and extra-pulmonary causes. This symptom may generate much anxiety and is often wrongly diagnosed and inappropriately treated. It is important to exclude the serious conditions that need prompt treatment or appropriate referral. Differences between childhood and adult cough suggest the need for a separate approach.

**Physiology**

Cough is one of the defensive reflexes of the respiratory tract which usually results from the stimulation of sensory nerves in the airways. The very sensitive RARs (rapidly adapting pulmonary stretch receptors) line the airways from larynx to bronchi and act as a primary mediator of cough. Mechanical, chemical and pathological conditions that stimulate these receptors (e.g. by mechanical events in the airway wall, including smooth muscle contraction, vasodilatation and oedema, mucus secretion etc.) induce cough. Blockade of these nerve fibres prevents cough.

The cough reflex (CR) has three sequential phases:

1. An inspiratory effort (inspiratory phase)
2. A forced expiratory effort against a closed glottis (compressive phase)
3. Opening of the glottis and rapid expiratory airflow (expulsive phase) associated with the characteristic sound.

This promotes clearance of mucus and material from the tracheobronchial tree and lungs.

The expiration reflex (ER) is a second defensive reflex induced by mechanical or chemical irritation of the vocal cords or of the trachea and consists of a forced expiratory effort (without preceding inspiration) with closure of the glottis, followed by opening of the glottis and an expulsive phase. The ER from the larynx will prevent the entry of material into the tracheobronchial tree and lungs. The functions of CR and ER are distinct and diametrically opposed and are well explained in a review but briefly the cough reflex (CR) will draw air into the lungs to augment the force of the subsequent expulsive phase, promoting clearance of mucus and material from the tracheobronchial tree and lungs. The ER from the larynx will prevent the entry of material into the tracheobronchial tree and lungs. The function of the ER from the trachea is less obvious. The two reflexes must have fundamentally different afferent (sensory) pathways.

**Assessment**

Generally, cough in children can be placed in one of three overlapping categories by a good history and thorough physical examination:

1. **Normal child.** This group – those currently free from upper respiratory tract infections (URTI) – can have, on average, 11 coughs each day with some experiencing more than 30 episodes per day. Cough frequency and severity increase during URTIs, especially clustered over winter. It can be difficult – and requires experience – to be sure when a child is normal in that s/he is thriving and has normal examination and no red flag signals.

2. **Specific cough.** An attempt should be made to arrive at a specific diagnosis (see Table 1)

3. **Non-specific isolated cough.** This presents as a persistent dry cough, no other respiratory symptoms, in an otherwise well child with no signs of chronic lung disease and a normal chest radiograph. It should not be thought of as a diagnosis in itself, but rather as a label. These children truly have increased cough frequency and severity; there is probably a specific but as yet unidentified cause. Although the precise diagnosis is not available, the majority are related to post-viral cough and/or increased cough receptor sensitivity and may spontaneously resolve with time. It is possible, however, that they have mild forms of one
of the specific diagnoses listed in Table 1 or very occasionally a more serious underlying condition.

Typical clinical cues recommended to be used in evaluating cough include:

- Age of symptom onset
- Quality of the cough
- Triggers, periodicity and timing of cough
- Associated features such as wheezing.

**Types of cough**

The BTS guidelines provide very helpful definitions for cough based on the duration of symptoms as well as the nature of the cough. A recent onset of cough lasting less than three weeks, mostly diagnosed as a symptom of “URTI” or “acute viral bronchitis,” is the most frequently managed acute presentation in primary care. These two diagnoses represent at least 75% of all coughs seen. Cough related to URTI resolves within 1–3 weeks in at least 90% of children. An average pre-school and primary school child has 3–8 coughs or colds per year, predominantly in the winter, with each new infection being associated with coughing that may last more than seven days.

The two key questions for acute cough assessment in children are:

- Are there symptoms or signs of a lower respiratory disease (distress, wheeze, crackles, reduced air entry, chest pain and discomfort with a catch in breath)?
- Is the child otherwise unwell (high fever, looks toxic, poorly perfused/dehydrated)?

Secondary care referral is required if after initial review and treatment there is no improvement in the above situations.

A specialist referral, for earlier investigations and management is warranted in the following situations:

- Where there is a characteristic recognisable cough (e.g. paroxysmal character). Unlike in adults, where cough characteristics has been shown to be of little diagnostic value, paediatricians often recognise certain cough qualities such as brassy or barking cough of croup or tracheomalacia, staccato cough in chlamydial infection and paroxysmal cough of pertussis
- Where the child has aspirated (acute history of choking/violent coughing)?
- Where the cough is not waning by the third week and is becoming more severe in frequency and intensity (“relentlessly progressive”) – a “grey” area between acute and chronic cough. If a cough is resolving, an additional period of time may be required to elapse before performing further investigations.

**Recurrent cough:**

A recurrent cough without a cold is taken as repeated cough episodes (>2/year) not associated with head colds that each last more than 7–14 days. If the periods of resolution are short, frequently recurrent cough will be difficult to distinguish from persistent chronic cough.

**Chronic cough (lasting more than eight weeks)**

It is unknown whether the primary stimulus for chronic cough in many children is identical to that for acute cough. Furthermore, it is unknown why cough associated with common acute viral URTI resolves in most people yet persists in some children. Children with chronic cough must be carefully evaluated for symptoms and signs of an underlying respiratory or systemic disease, as most of the underlying causes can result in significant morbidity and mortality if left untreated. The identification of certain red flags (Table 1) should lead to prompt referral for further evaluation.

**DEscribing cough in children**

Young children rarely expectorate sputum, even if they have airway secretions. Hence, terms such as wet/moist/chesty cough are preferable in childhood to productive/non-productive cough. Parents do not report the frequency or severity of cough accurately but parental reporting of wet versus dry cough is likely to be accurate.

A chronic moist cough is always abnormal and represents excessive airway secretions and it is the most useful clinical marker in predicting specific cough. Children with PBB have a chronic moist cough, a positive bacterial culture and a response to antibiotics, however in a small group of children natural resolution may occur.

A chronic dry cough however may represent a dry phase of an otherwise usually moist cough, or the airway secretions are too little to influence the cough quality. Chronic dry cough in the absence of specific pointers (see Table 1) in the history and examination is termed “non-specific cough” or “isolated cough”.

**Cough variant asthma**

Some children with asthma have coughing as the predominant feature, and wheezing has not been heard by a health professional. Most children with recurrent cough without other evidence of airway obstruction do not have asthma, and neither inhaled salbutamol nor beclometasone is beneficial. Natural resolution of cough in children is very common and almost the “norm”, therefore trials of asthma therapy will almost always appear to work. High dose inhaled fluticasone
for two weeks has been shown to offer a modest benefit but has side effects and is not recommended.\textsuperscript{22}

However, asthma is over-diagnosed in children with isolated cough. Only 9.6\% of children with cough lasting longer than eight weeks were found to have cough variant asthma when all children with chronic cough were evaluated according to the British Thoracic Society guidelines.\textsuperscript{23} There are problems with “trials” of inhaled corticosteroids (ICS), as it is difficult to define an endpoint. However, such trials may be helpful, especially if there are other atopic diseases (eczema, allergic rhinitis). A suggested approach regarding a trial of ICS therapy is as follows:

1. The therapy should be effectively delivered, given over a limited time frame of no more than 6-12 weeks and have objective endpoints.

2. At the end of the trial the asthma medication should be stopped. A negative response suggests the coughing is unresponsive to ICS and asthma unlikely. A positive response may indicate natural resolution of the cough or cough variant asthma.

3. If coughing recurs then the medication can be restarted. A second positive response is suggestive of cough variant asthma.\textsuperscript{24}

**Management**

**Acute cough**

There are no effective medications for the symptomatic relief of acute cough in children and a “wait, watch, review” approach is indicated.\textsuperscript{25} Clinicians should educate parents on expected illness duration, as well as the risks associated with use of over-the-counter medications as serious adverse events and accidental poisoning has been reported.\textsuperscript{26} Parental concerns should be addressed and safe and supportive care measures to alleviate the child’s discomfort advised.\textsuperscript{27}

A recent Cochrane review has concluded that honey may be better than “no treatment” and diphenhydramine in the symptomatic relief of cough, but not better than dextromethorphan.\textsuperscript{28} Randomised, placebo-controlled studies of the use of cough and cold preparations in children have not shown any meaningful differences between the active drugs and placebo.\textsuperscript{29} The safety of these products especially in younger children is also questionable. Some of the concerns stem from findings in children under six linking decongestants to cardiac arrhythmias and other cardiovascular events; antihistamines to hallucinations, and antitussives to depressed levels of consciousness and encephalopathy. In USA, a review by the Food and Drug Administration (FDA) identified 123 deaths related to the use of such products in children under six during the past several decades.\textsuperscript{30}

**Chronic cough**\textsuperscript{24}

In otherwise healthy children with chronic dry or recurrent cough, management decisions are based on the identification of specific causes:

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**TABLE 1: RED FLAGS/CONDITIONS REQUIRING FURTHER INVESTIGATIONS AND/OR SPECIALIST REFERRAL**

*(Adapted from Chang & Glomb. Chest 2006)*

<table>
<thead>
<tr>
<th>Pointers to underlying aetiology</th>
<th>Possible underlying aetiology*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily moist or productive cough</td>
<td>Protracted bacterial bronchitis (PBB)</td>
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<tr>
<td></td>
<td>Cystic Fibrosis</td>
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<tr>
<td></td>
<td>Immune deficiencies</td>
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<tr>
<td></td>
<td>Primary ciliary disorders (PCD)</td>
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<td></td>
<td>Recurrent pulmonary aspiration</td>
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<tr>
<td></td>
<td>Retained inhaled foreign body</td>
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<tr>
<td><strong>Cough characteristics</strong> (cough with choking, cough quality, cough starting from birth)</td>
<td>Congenital airway or lung abnormalities</td>
</tr>
<tr>
<td><strong>Exertional dyspnoea</strong></td>
<td>Compromised lung function of any chronic lung or cardiac disease</td>
</tr>
<tr>
<td><strong>Chest pain</strong></td>
<td>Asthma, functional, pleuritis</td>
</tr>
<tr>
<td><strong>Symptoms of upper respiratory tract infection</strong> (may coexist or be a trigger for an underlying problem)</td>
<td>Upper airway cough syndrome (UACS), PCD</td>
</tr>
<tr>
<td><strong>Feeding difficulties</strong> (including choking/vomiting)**</td>
<td>Compromised lung function, primary aspiration</td>
</tr>
<tr>
<td><strong>Failure to thrive</strong></td>
<td>Compromised lung function, immunodeficiency, cystic fibrosis</td>
</tr>
<tr>
<td><strong>Neurodevelopmental abnormality</strong></td>
<td>Primary or secondary aspiration</td>
</tr>
<tr>
<td><strong>Abnormal findings on chest auscultation</strong> (wheeze, crackles, differential breath sounds)</td>
<td>Asthma, bronchitis, congenital lung disease, foreign body aspiration, airway abnormality</td>
</tr>
<tr>
<td><strong>Digital clubbing</strong></td>
<td>Chronic supplicative lung disease</td>
</tr>
<tr>
<td><strong>Chest wall deformity</strong></td>
<td>Any chronic lung disease</td>
</tr>
<tr>
<td><strong>Haemoptysis</strong></td>
<td>Acute or chronic infection, foreign body</td>
</tr>
<tr>
<td><strong>Recurrent pneumonia</strong></td>
<td>Immunodeficiency, congenital lung problem, airway abnormality</td>
</tr>
<tr>
<td><strong>Immune deficiency</strong></td>
<td>Atypical and typical respiratory infections</td>
</tr>
<tr>
<td><strong>Cardiac abnormalities</strong> (also think of associated airway problems, pulmonary oedema, Kartagener’s syndrome or immunodeficiency)**</td>
<td>Any cardiac illness</td>
</tr>
<tr>
<td><strong>Medications or drugs</strong> (angiotensin-converting enzyme [ACE] inhibitors, puffers, illicit drug use) – though these are rare causes of cough in children</td>
<td>A problem dry cough which stops once the ACE inhibitor is stopped.</td>
</tr>
</tbody>
</table>

* This is a non-exhaustive list; only the more common respiratory diseases are mentioned. Unlike in adults with chronic cough, asthma and asthma-like symptoms, protracted bacterial bronchitis (PBB), and upper airway cough syndrome (UACS) are the commonest reasons for chronic cough in children.\textsuperscript{19, 21, 24}
Allergic rhinitis and/or post nasal drip (upper airways cough syndrome). These children have a clearing the throat type snorting cough and should respond to allergen exclusion where possible and intranasal steroids with or without antihistamines.

Psychogenic coughs. These may be characterised by a dry repetitive “tic-like” cough after an episode of bronchitis. Other children develop bizarre honking coughs which can be very disruptive to school and family life. Typically these coughs do not upset the child; the coughing reduces when they are engrossed in some activity and when asleep. Biofeedback, distraction and suggestion psychotherapies may be required.

Other potential causes. These include:

- Wax in the external ear canal has been associated with chronic coughing. This is an irritating dry cough because of stimulation of shared neural pathways
- Hypertrophied tonsillar tissue impinging on the epiglottis
- Gastrooesophageal reflux (GOR): evidence associating GORD and cough in children. In selected children a trial of anti-reflux therapy can be useful
- Children’s interstitial lung disease usually presents with breathlessness, but early evolving cases can be associated with a dry repetitive cough
- Chronic non-specific isolated dry cough: In most cases, this type of cough is not serious and will self-resolve without intervention; however non-resolution of cough despite simple management should trigger a specialist referral. Attention to parental concerns and fears must be part of the treatment process.

Children with chronic cough must be carefully evaluated for symptoms and signs of underlying disease

Other potential causes. These include:

- Management of cough in children necessitates a different approach from adult cough
- A normal child will have, on average, 11 coughs each day with some experiencing more than 30 episodes per day
- For specific coughs, it is important to arrive at a specific diagnosis
- Age of onset, cough triggers and associated features are helpful clinical cues in assessment of cough
- In contrast to adult cough, cough characteristics in children are important diagnostic features and may trigger early referral
- Children with chronic cough should be carefully evaluated for underlying disease and ‘red flags’
- Asthma is overdiagnosed in children with isolated cough. Trials of asthma therapy are of limited diagnostic value
- Parents should be warned of the potential dangers of giving children OTC medicines
- Chronic wet cough requires specific and specialist management, driven by diagnosis of underlying cause

Conditions associated with chronic wet cough require specific and specialist management (see Table 1). For PBB, a two-week course of amoxycillin clavulanate achieved cough resolution in a significant number of children with chronic wet cough. BAL data supported the diagnosis of PBB in the majority of these children. As the diagnosis of PBB is based on confirmation of bacteria on respiratory secretions (cough swab and if that is negative, bronchoalveolar lavage), generally speaking these children will require specialist referral and management; however for the first episode of a prolonged wet cough of longer than eight weeks and a positive cough swab, a two-week course of oral antibiotics could be instigated in primary care. The majority of the patients will be completely symptom free after two courses of antibiotics, but in one study up to 13% of patients required more than six courses of antibiotics. Maintenance azithromycin is increasingly used in various childhood pulmonary conditions and a recent large randomised study of once-weekly azithromycin for up to 24 months decreased pulmonary exacerbations in indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (bronchiectasis suspected clinically when HRCT scans were unavailable). However, this strategy was also accompanied by increased carriage of azithromycin-resistant bacteria, the clinical consequences of which are uncertain. Additional long-term studies are needed to identify children most likely to benefit from maintenance azithromycin, to describe how long these beneficial effects persist, to define the optimum duration of treatment, and establish the clinical significance of acquisition of azithromycin-resistant pathogens before this strategy gets implemented on a more widespread basis.

A case study relevant to this article is available on our website www.bjfm.co.uk

KEY POINTS

1. Management of cough in children necessitates a different approach from adult cough
2. A normal child will have, on average, 11 coughs each day with some experiencing more than 30 episodes per day
3. For specific coughs, it is important to arrive at a specific diagnosis
4. Age of onset, cough triggers and associated features are helpful clinical cues in assessment of cough
5. In contrast to adult cough, cough characteristics in children are important diagnostic features and may trigger early referral
6. Children with chronic cough should be carefully evaluated for underlying disease and ‘red flags’
7. Asthma is overdiagnosed in children with isolated cough. Trials of asthma therapy are of limited diagnostic value
8. Parents should be warned of the potential dangers of giving children OTC medicines
9. Chronic wet cough requires specific and specialist management, driven by diagnosis of underlying cause
Important Safety Information

Resolor® (prucalopride) is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief.

Please consult the Resolor® Summary of Product Characteristics before prescribing, particularly in relation to hypersensitivity to any of the constituents, renal impairment requiring dialysis, intestinal perforation or obstruction, obstructive ileus, severe inflammatory conditions of the intestinal tract, severe and clinically unstable concomitant diseases, especially when used in patients with arrhythmias or ischaemic cardiovascular disease.

Very common side effects associated with Resolor® are headache, nausea, diarrhoea, abdominal pain, occurring predominantly at the start of therapy and usually disappearing within a few days with continued treatment. Common side effects are dizziness, vomiting, dyspepsia, rectal haemorrhage, flatulence, abnormal bowel sounds, polialkaliuria, fatigue.

Prescribing Information
(Please refer to the full Summary of Product Characteristics before prescribing).

RESOLOR® (prucalopride)
Selective serotonin (5-HT4) receptor agonist, enterokinetik agonist, available as 1 mg and 2 mg film-coated tablets for oral administration, once daily, with or without food, at any time of the day. INDICATION: Resolor is indicated for symptomatic treatment of chronic constipation in women in whom laxatives fail to provide adequate relief. DOSE: Women: 2 mg once daily, early (>45 years) Start with 1 mg once daily and increase to 2 mg once daily if necessary. Patients with severe renal impairment (GFR <30 mL/min/1.73 m2): 1 mg once daily. Patients with severe hepatic impairment (Child-Pugh class C) start with 1 mg once daily which may be increased to 2 mg if required to improve efficacy and if the dose is well-tolerated. No dose adjustment required in patients with mild to moderate renal or hepatic impairment. Men, children and adolescents <18 years: not recommended until further data become available. CONTRAINDICATIONS: Hypersensitivity to prucalopride or any of the excipients. Renal impairment requiring dialysis, intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract, such as Crohn's disease, ulcerative colitis and colonic and ileocolic toxic and malignant megacolon. PRECAUTIONS: Caution should be exercised when prescribing to patients with severe hepatic impairment (Child-Pugh class C) due to limited data in patients with severe hepatic impairment. The safety, efficacy and tolerability of Resolor for patients with severe and clinically unmanageable concomitant disease (e.g. cardiovascular or lung disease, neurological or psychiatric disorders, cancer or AIDS) and other endocrine disorders have not been established in controlled clinical trials. Caution should be exercised when prescribing Resolor to patients with these conditions especially when used in patients with a history of arrhythmias or ischaemic cardiovascular disease. In case of severe diarrhoea, the efficacy of oral contraceptives may be reduced. An additional contraceptive method is recommended. Contains lactose monohydrate. Patients with galactose intolerance, Lactase deficiency or glucose-galactose malabsorption must not take Resolor. INTERACTIONS: Prucalopride has a low pharmacokinetic interaction potential. Studies in healthy subjects did not show a clinically relevant effect of prucalopride on the pharmacokinetics of warfarin, digoxin, alcohol, paroxetine or oral contraceptives. A 30% increase in plasma concentrations of erythromycin was found in prucalopride co-administered subjects. The mechanism for this interaction was not clear. Ketoconazole increased the systemic exposure to prucalopride by 40%. This effect is too small to be clinically relevant. Therapeutic doses of probenecid, cimetidine, erythromycin and paroxetine did not affect the pharmacokinetics of prucalopride. PREGNANCY: Animal studies did not indicate harm. Experience of Resolor during human pregnancy is limited. Cases of spontaneous abortion have been observed in human clinical studies although in the presence of other risk factors, the relationship to Resolor is unknown. Resolor is not recommended during breastfeeding. EFFICACY TO DRIVE AND USE MACHINES: No studies have been performed. Resolor has been associated with dizziness and fatigue, particularly on the first day of treatment, which may affect driving or using machines. SIDE EFFECTS: The most commonly reported side effects in Resolor clinical trials were gastrointestinal and gastrostestinal symptoms (abdominal pain, nausea, diarrhoea) occurring in about 20% of patients each. These events occur mostly at the start of therapy and usually disappear within a few days whilst continuing Resolor. Other common adverse events in controlled trials included dizziness, vomiting, dyspepsia, rectal haemorrhage, flatulence, abnormal bowel sounds, polialkaliuria and fatigue. Uncommon adverse events included anorexia, tremors, palpitations, fever and malaise. The first day of treatment the most common adverse events were reported with similar frequency for Resolor and placebo except nausea which was reported more often on Resolor, these remained higher but the difference between Resolor and placebo was smaller (1 to 3%). Palpitations were reported in 0.7% of placebo patients, 0.9% of 1 mg Resolor patients and 0.7% of 2 mg Resolor patients. As with any new symptom, patients are advised to discuss new onset pain with their physician. PACK SIZE AND BASIC NHS PRICES: 28 tablets (4 blisters with 7 tablets) EU/109/581/001 (1 mg) £38.69, EU/109/581/002 (2 mg) £59.12. LEGAL CATEGORY: POM. MARKETING AUTHORISATION HOLDER: Shire Pharmaceuticals Ireland Limited, 5 Riverwalk, Cayanore, Portlaoise, Co. Laois, Ireland, Dublin 24, Ireland. DATE OF PREPARATION: September 2013. Further information is available on request from: Shire plc, Unity Place, Hampshire International Business Park, Chineham, Basingstoke, Hampshire RG24 8EP.

Reference:

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