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GUIDELINE SUMMARY

Prolonged cough in children: a summary of the Belgian primary care clinical guideline

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Summary

Prolonged cough is a frequent problem in the community. Several studies in the school setting have found that as many as 4.8% to 10.4% of children suffer from prolonged cough.

There is no consensual definition of prolonged cough. In this guideline, we define prolonged cough as a daily cough lasting for more than three weeks. The literature review did not identify any quality study on the aetiology of prolonged cough in children in primary care. A diagnostic decision-tree based on the systematic literature review and expert opinion is proposed. Doctors should seek signs of any serious underlying condition. Chronic productive purulent cough should always be investigated. A careful evaluation of the impact of cough on the quality of life of the child is necessary. In absence of signs of specific underlying illness, coughing is generally a self-limiting condition. Symptomatic treatments have not yet been proven to be effective, and many of them may cause serious side effects. Their use should therefore be limited.

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See Appendix A at www.thepcrj.org

Introduction

Prolonged cough is a frequent problem in the community. Several studies in the school setting have found that up to 10.4% of children suffer from prolonged cough.[1-5] Coughing causes insomnia and anxiety for parents, particularly since they can worry that their child might choke and die during the night.[6]

One study in the United Kingdom has shown that general practitioners (GPs) often prescribe antibiotics, bronchodilators, inhaled corticosteroids, or cromoglycate for prolonged cough.[7] These children are often labelled as asthmatic.[1,8]

There is no consensual definition of prolonged cough. In this guideline, we define prolonged cough as a daily cough lasting for more than three weeks, because of the natural evolution of cough due to an upper respiratory tract infection (URTI).[9]

Methods

The literature was searched for studies on cough in children up to the age of 18. Two researchers performed independent systematic searches of the literature in the following databases:

- The websites of the Guidelines International Network and the National Guideline Clearinghouse were searched. Furthermore, guidelines were sought from various European countries: the National Institute for Health and Clinical Excellence (NICE-UK – www.nice.org.uk); the Société Scientifique De Médicine Générale (SSMG-B – www.ssmg.be); Domus Medica (B – www.wvvh.be); the Belgian Antibiotic Policy Coordination Committee (BAPCOC – www.portal.health.fgov.be); and the Nederlands Huisartsen Genootschap (NHG-NI – www.nhg.artsennet.nl). The search was performed in June 2005. Guidelines were assessed using the Agree criteria.

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- Searches of the Cochrane Library and the website of the Center for Reviews and Dissemination were performed up to May 2007.
- A search was performed on Medline from 1990 to June 2005 and on EMBASE from 1990 to January 2005. The main MeSH terms used were cough, pediatrics, child, complications, economics, diagnosis, aetiology, epidemiology, signs, chest, predictive value, mycoplasma, whooping cough, chlamydia, RCT, dust, allergy, and prevention. The authors used the EMTREE terms coughing and child (diagnosis, aetiology and epidemiology).
- Other sources such as Clinical Evidence, Folia Pharmacotherapeutica, Prescrire, the World Health Organisation website and the Belgian Public Health Institute's website (ww.iph.fgov.be) were also reviewed.

The results of the systematic search were discussed according to the scientific guidelines of the working group of the Société Scientifique de Medicine Générale (SSMG). The preliminary version of the guideline was submitted to two respiratory paediatricians. Four groups of GPs tested the final version of the guideline. Their remarks were included in the draft. The text was finally submitted to the Belgian Center for Evidence Based Medicine, which validated the guidelines after final changes.

Level of recommendations

Level A: - systematic review of randomised controlled trials (RCTs)
- meta-analysis
- more than 2 RCTs

Level B: - one RCT, other study, guideline

Level C: - expert opinion

Results: summary of literature review on prolonged cough in children

Aetiology

The literature review did not identify any quality study on the aetiology of prolonged cough.

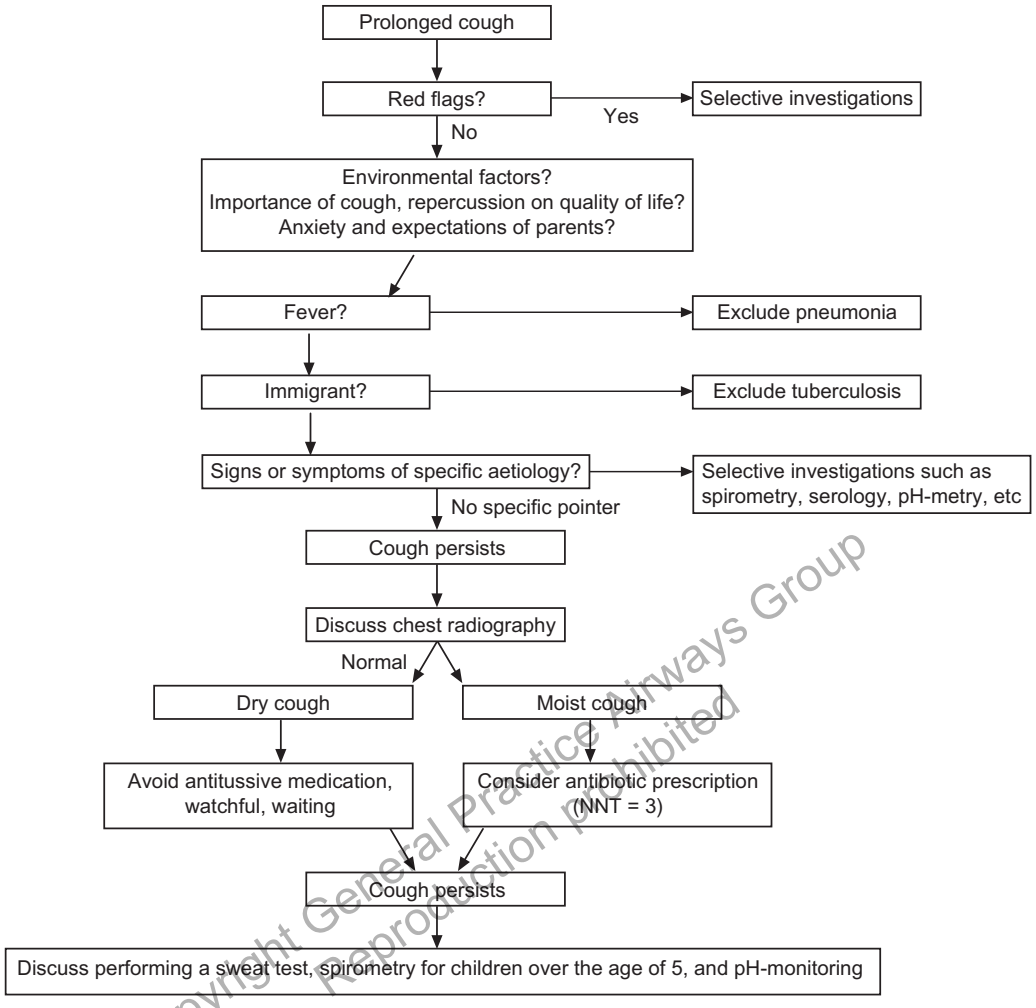
According to expert opinion and case series', the following aetiologies may be causes of prolonged cough – but they are not based on studies in primary care settings:[10]

- *Infections*
  Ten per cent of children still cough 25 days after an URTI.[11] A succession of different infections or specific causal agents such as respiratory syncytial virus, adenovirus, Mycoplasma pneumoniae, and Chlamydia pneumoniae can be involved.[12] Doctors should also bear in mind the possibility of pertussis[13-15] and tuberculosis infections.[16,17]
- *Asthma*
  Doctors should exercise caution when making the diagnosis of "cough variant asthma". Children in this category appear to have different characteristics than those with classic asthma, including a better prognosis.[1,2,18-20]
- *Postnasal drip syndrome*
- *Environmental agents*
  Several studies have shown that passive smoking increases the incidence of cough and/or sinusitis in children.[5,21-24] A relationship between factors in a child's indoor environment (nitric oxide, space heater, charcoal heater, kerosene firing, wood firing, mould) and cough has been found in observational studies.[25-28]
- *Gastro-oesophageal reflux* is often associated with chronic cough.[29,30]
- *Other causes*
  - foreign bodies
  - immunodeficiency
  - cystic fibrosis
  - psychogenic cough
  - congenital lung lesions, e.g., tracheomalacia, tracheo-oesophageal fistula
  - ciliary dyskinesia

Diagnosis (see Figure 1)

- Doctors should seek signs of any serious underlying condition:
  - Neonatal onset of the cough
  - Family history of lung disease
  - Serious upper respiratory tract infections
  - Important vomiting
  - Dysphagia
  - Abnormal voice or crying
  - Focal thoracic abnormality
  - Failure to thrive
  - Clubbing
  - Inspiratory stridor
- History:
  Doctors should assess the importance of the symptom, its place in, and the repercussions on, the life of the child. Doctors should also inquire about the parents' anxieties and expectations. History taking should include asking about signs and symptoms of the most frequent aetiologies: postnasal drip syndrome, asthma, respiratory tract infections and gastro-oesophageal reflux. Environmental factors such as passive smoking exposure and the epidemic context should be noted.
- Clinical examination should include:[31,32]
  - respiratory rate
  - signs of dyspnoea
  - signs of atopy
  - height, weight
  - temperature
  - ear, nose and throat examination
  - chest auscultation

Figure 1. Decision-tree based on the systematic literature review and expert opinion.



- Investigations:
  Doctors should order tests depending on their clinical hypotheses.

Suspicion of infection:

Serology for Mycoplasma pneumoniae and serology plus PCR for Bordetella pertussis could be useful,[14,33] (*EBM level B*). According to expert opinion, if there is a suspicion of pneumonia, a chest X-ray should be performed, (*EBM level C*).

There is no evidence of the usefulness of determining the CRP concentration or leukocyte count in chronic cough.

Suspicion of asthma:

- *Spirometry* with reversibility should be done if the child is older than 5 years, (*EBM level B*).
- *Peak flow* monitoring is useful in order to diagnose or exclude asthma if the spirometry results are normal. Peak flow monitoring is also useful for the follow-up of asthma.[32] A single value is not enough: the variability of the peak flow should be assessed,[34] (*EBM level B*).
- *Diagnostic trial:* some authors and guidelines recommend trying inhaled β-agonists or inhaled corticosteroids (ICS) and assessing responsiveness.[18,31,34-36] Such trials are particularly useful in young children when spirometry is not available. However, there is not sufficient evidence to recommend diagnostic trials systematically: responsiveness is not specific for asthma.

Suspicion of sinusitis:

- Sinus radiography:
  - before the age of six years, radiography is unnecessary (88% of X-rays are positive if there is a clinical history of sinusitis).
  - after the age of six, radiography can sometimes be useful to exclude sinusitis,[37] (*EBM level B*).
- Sinus scanning is only necessary in rare cases when a complication is suspected or if surgery is warranted.[38]

Suspicion of gastro-oesophageal reflux:

pH-monitoring is the most useful test to assess the temporal

association between reflux and cough,[39] (EBM level B).

Chest radiography:

There is not sufficient evidence to recommend chest radiography in all cases. It can be useful when specific lung pathology is suspected or in unclear cases which do not improve, (*EBM level C*).

Treatment

A. No specific aetiology

At present, no treatment has proven efficacy for the treatment of cough in children when there is no known aetiology (see Appendix A, available online at www.thepcrj.org). Several studies have shown that placebos are effective.[40-42] Doctors should explain to the parents that the cough is very likely to resolve spontaneously. No treatment is required unless the cough is painful, interferes with sleep, or causes insomnia, vomiting or fatigue.[43,44]

The first recommendation is to avoid passive smoking and any other irritant. If the doctor still decides to prescribe medication, consideration should be given to the contraindications and potential side effects of the medication. Combination products should be avoided.

B. Cough linked to a specific aetiology

Cough linked to asthma

Guidelines[31,34] recommend treating the cough with a ß-agonist and/or ICS. The maximal effect of symptomatic treatment with ICS is after six to eight weeks of treatment.[36]

Cough associated with gastro-oesophageal reflux

There are no studies on the management of cough associated with gastro-oesophageal reflux in children.[39] There is no evidence of the efficacy of proton pump inhibitors on cough linked to gastro-oesophageal reflux.[45]

Cough due to pertussis

Salbutamol, dexamethasone, specific immunoglobulin and diphenhydramine proved to have no efficacy in the symptomatic treatment of whooping cough.[46] However, expert opinion recommends that β-agonists are effective in infections such as pertussis with bronchial hyperreactivity.

C. Risks and contraindications of antitussive drugs

Formal contraindications

Before the age of one year, no antitussive medicine should be prescribed. Between the ages of one and two years, antitussive use should be exceptional, and requires prior medical evaluation. Dextromethorphan, noscapine, and phenothiazine derivatives are contraindicated. Between two and six years of age, any prescription should be limited.

Because of possible neurological side effects, camphor must be avoided, and eucalyptus and menthol should be used with caution.[47]

We did not find any RCTs studying the efficacy of camphor, menthol, eucalyptus, clobutinol or dimethoxane and chloral hydrate for cough in children.

D. Surveillance

If a treatment is prescribed, a follow-up evaluation is necessary to avoid unnecessary prolonged use of medications. If bronchodilators are prescribed, the doctor should see the patient after 15 days. Inhaled steroids may take as long as six weeks to be fully effective.

Discussion

In summary, in the absence of signs of specific underlying illness, coughing is generally a self-limiting condition. Symptomatic treatments have not yet been proven to be effective, and many of them may cause serious side effects. Their use should therefore be limited.

Our review showed a paucity of evidence-based literature on this topic. Two guidelines were published in 2006.[48,49] Their recommendations are often based on expert opinions and on studies done in tertiary care settings. There are no epidemiologic studies of the aetiology of prolonged cough in children in primary care, and serious diseases are probably less frequent in primary care than in secondary or tertiary settings.

These guidelines recommend at least chest radiography and spirometry if the patient's age is appropriate. There is no evidence that these tests are always necessary for patients with prolonged cough in primary care. This guideline has also asserted that chronic productive purulent cough should always be investigated to document the presence or absence of bronchiectasis and to identify underlying and treatable causes such as cystic fibrosis and immune deficiency. However, there is no strong evidence in the literature that post-nasal drip syndrome might cause cough, even though it could represent a common cause of productive cough in primary care.

Invasive investigations could probably therefore be avoided in the absence of specific 'red flags' or in the absence of improvement. Primary care physicians have to keep in mind the subjectivity of the complaint of cough when prescribing investigations. The same description may cover coughs with a wide range of frequency and intensity.

No treatment for non-specific cough has proved to have any efficacy. A careful evaluation of the impact of cough on the quality of life of the child is necessary. Doctors should also explore the expectations and anxieties of parents about their child's cough. In such cases, reassurance and watchful waiting is the best approach. If the doctor still decides to prescribe a medication, a simple sweet syrup can be a safe solution.

This literature review showed the lack of studies on prolonged cough in primary care, and the fact that more studies are needed. Firstly, prospective morbidity studies and aetiological studies should be conducted in primary care settings to determine the frequency of cough and the probable aetiologies. A study of morbidity and aetiology is

currently underway in our department. Secondly, studies on the natural evolution of prolonged cough of different aetiologies would help doctors to better inform and manage their patients. Further research could also evaluate the effectiveness and usefulness of therapeutic trials in the diagnostic work-up. Thirdly, research on the treatment of non-specific cough with valid outcome measures is especially warranted. The challenge for all therapeutic research on cough is the validation of automated measurement instruments. We are currently validating a cough counter that measures cough frequency.

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This article is a summary of a Belgian primary care guideline on prolonged cough in children. This guideline was elaborated in conjunction with the scientific society of general practice and has been validated by the Belgian Center for Evidence Based Medicine in June 2007.

Conflict of interest declaration

None to declare.

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Appendix A. Summary of systematic reviews and RCTs of effects of medications on cough in children.

Reference		Medication	Nos of studies	Population studied	Outcome	Results
Schroeder 2004[50]	Systematic review	1. Dextromethorphan 1.5 mg/5 ml for children under 7 years and 10 ml three times daily for older children in one arm, and dextromethorphan with salbutamol 0.2 mg/5 ml before 7 years, and 10 ml for older children in the other arm. 2. Dextromethorphan 15 mg/5 ml	2:1/ n=50 2/ n=57	1. Children, mean age 3.8 years with acute cough 2. Children aged between 18 months and 12 years with nocturnal cough due to URTI	1. Scales from 0 to 3 for cough frequency and severity 2. Cough scores of 0 to 4	No difference between groups 2. A mean reduction in cough score of 2.1 versus 2.2 in placebo group; p=0.97
Paul 2004[51]	RCT	Dextromethorphan	n=100	Children aged between 2 and 18 years, with URTI	Subjective parental assessment of cough and sleep difficulty	No statistically significant difference of improvement on night cough scores between active and placebo groups
Schroeder 2004[50]	Systematic review	Codeine (10 mg/5 ml)	1, n=57	Children aged between 18 months and 12 years with nocturnal cough due to URTI	Cough scores of 0 to 4	Mean reduction in cough score in codeine group 2.2, versus placebo group 2.2, p = 0.52
Schroeder 2004[50]	Systematic review	Mucolytic (Letosteine, 25 mg three times daily)	1, but low quality (n=40)	Age range 2 to 12 years with acute febrile bronchitis	Cough score from 0 to 3	Difference between groups ranging from 0.1 to 0.3 in favour of treatment between days 4 and 10 (p<0.01)
Schroeder 2004[50]	Systematic review	Expectorant	No studies			
Chang 2006[52]	Systematic review	Anti-histamines 1. Pimethixene 2. Cetirizine 3. Ketotifen	3 RCTs, with heterogeneity: 1. n=49 2. n=20 3. n=113	1. Children aged between 3 and 17 years with hay fever 2. Children with cough associated with allergic rhinoconjunctivitis 3. Children aged between 6 and 36 months with prolonged cough or wheeze	- Parental questionnaire - Cough diary score	2 studies with no effect, 1 study in favour of Cetirizine, which reduces cough intensity (p<0.05) and frequency (p<0.01).
Schroeder 2004[50]	Systematic review	Anti-histamines. Clemastine fumarate versus Chlorpheniramine maleate syrup	1 study, n=143	Age range 1.5 to 60 months with common cold Symptom score	Cough improved in	39.6% in the treatment group compared with 27.6 % in the placebo group; p=0.2

Appendix A. Summary of systematic reviews and RCTs of effects of medications on cough in children continued

Reference		Medication	Nos of studies	Population studied	Outcome	Results
Paul 2004[51]	RCT	Diphenhydramine	n=100	Acute night cough due to URTI in children aged between 2 and 18 years	Subjective parental assessment of cough and sleep difficulty	No statistical difference of improvement between active and placebo groups
Schroeder 2004[50]	Systematic review	Antihistamine–decongestant 1. Brompheniramine maleate 2 mg/5 ml and Phenylpropanol-amine hydrochloride 12.5 mg/5 ml every 4 hours 2. Brompheniramine maleate 4 mg/5 ml, Phenylephrine 5 mg/5 ml, Propanolamine 5 mg/5 ml, three times daily	2 studies, n=155	Preschool children (6 months to 5 years) with URTI	Cough score	No effect 1/ mean cough score 4.67 (active treatment) versus 4.57(placebo); p=0.53. More children were asleep in the treatment group. 2. Improvement of 67% in the active treatment group, 58% in the placebo group and 70% in the no treatment group (p=0.5 and 0.8, respectively)
Chang 2004[53]	Systematic review	Inhaled anticholinergics	No RCT for children			
Chang 2003[54]	Systematic review	Inhaled cromones	1 non-randomised trial			
Smucny 2004[55]	Systematic review	β2-agonists (Albuterol syrup 0.1 mg/kg every 8 hours or Salbutamol 1 mg every 8 hours before the age of 7 and 2 mg every 8 hours for older children)	2 trials, n=109	Acute cough in children aged between 1 and 10 years	Cough score	Standardised mean difference of cough score = 0.35 (–0.05, 0.76). RR of side effects 6.76 with 95% CI: 0.86 – 53.12)
Tomerak 2005[56]	Systematic review	β2-agonists (Salbutamol 200 µg twice a day)	1 trial, n=43	Children aged between 6 and 17 years with chronic non-specific cough	Cough frequency (cough meter) and subjective cough score	No effect, but the confidence intervals are wide. Weighted mean difference in cough frequency/24h = –11 (95% CI: 150.22–128.82)
Tomerak 2005[57]	Systematic review	Inhaled steroids	2 RCTs (see below)	Children		
Davies 1999[42]	RCT	Fluticasone 1 mg twice daily for 3 days and 500 µg twice daily for 11 days	n=50	Children aged between 1 and 10 years with persistent night time cough	Cough frequency assessed by video or audio system	Significant reduction in treatment group More than 75% improvement at days 15–18, OR =4,55 (95% CI 1.33–15.57)

Appendix A. Summary of systematic reviews and RCTs of effects of medications on cough in children continued

Reference		Medication	Nos of studies	Population studied	Outcome	Results
Chang 1998[58]	RCT	Beclomethasone 200 µg twice daily	n=45	Children with non-specific recurrent cough	Cough frequency (cough meter) and subjective cough score	No significant difference between the 2 groups. Weighted mean difference for 24 h cough frequency= –27 (95% CI: –83, 29,07)
Chang 2006[59]	Systematic review	Leukotriene receptor antagonist	No RCTs included	Children with non-specific cough		
Chang 2005[60]	Systematic review	Methylxanthines	No RCTs, 1 non-randomised trial	Children with non-specific cough		
Marchant 2005[61]	Systematic review, meta-analysis	Antibiotics (erythromycin 50 mg/kg/day versus placebo or amoxicillin/ clavulanic acid 20 mg/kg/day versus placebo)	2 RCTs, but low quality (n=140)	Children with persistent moist cough	Proportion of children not cured at follow up Proportion of children who required further antibiotics	More children are cured with antibiotics: OR 0.13 (95% CI: 0.06 to 0.32), NNT = 3 (95% CI 2–4) More children required further antibiotics in the placebo group OR: 0.10 (95% CI: 0.03–0.34), NNT = 4 (95% CI: 3–5)
Altunaiji 2005[62]	Systematic review	Antibiotics (azithromycin 3 days or clarythromycin 7 days or erythromycin 7 days versus 10 to 14 days erythromycin	13 RCTs (n=2197)	Whooping cough	Bordetella pertussis eradication from the nasopharynx	No difference between short and long treatment for eradication of Bordetella pertussis RR = 1.02 (95% CI: 0.98–1.05) but fewer side effects with short treatment RR=0.66 (95% CI: 0.52–0.83).
Gavranich 2005[63]	Systematic review	Macrolide or other antibiotic	6 RCTs (n=1352)	LRTI in children aged between 1 and 10 years	Clinical response	No difference between macrolide and other antibiotics
Donnelly 2006[64]	Systematic review	Indoor air modification intervention	No RCTs	Prolonged cough in children		
Chang 2005[45]	Systematic review	Gastro-oesophageal reflux treatment	3 studies in children but no studies that can be included	Prolonged non-specific cough in children		