A Multicenter, Randomized Controlled Study

**OBJECTIVES:** The goals of this study were to: (1) determine if management according to a standardized clinical management pathway/algorithm (compared with usual treatment) improves clinical outcomes by 6 weeks; and (2) assess the reliability and validity of a standardized clinical management pathway for chronic cough in children.

**METHODS:** A total of 272 children (mean ± SD age: 4.5 ± 3.7 years) were enrolled in a pragmatic, multicenter, randomized controlled trial in 5 Australian centers. Children were randomly allocated to 1 of 2 arms: (1) early review and use of cough algorithm (“early-arm”); or (2) usual care until review and use of cough algorithm (“delayed-arm”). The primary outcomes were proportion of children whose cough resolved and cough-specific quality of life scores at week 6. Secondary measures included cough duration postrandomization and the algorithm’s reliability, validity, and feasibility.

**RESULTS:** Cough resolution (at week 6) was significantly more likely in the early-arm group compared with the delayed-arm group (absolute risk reduction: 24.7% [95% confidence interval: 13–35]). The difference between cough-specific quality of life scores at week 6 compared with baseline was significantly better in the early-arm group (mean difference between groups: 0.6 [95% confidence interval: 0.29–1.0]). Duration of cough postrandomization was significantly shorter in the early-arm group than in the delayed-arm group (P = .001). The cough algorithm was reliable (κ = 1 in key steps). Feasibility was demonstrated by the algorithm’s validity (93%–100%) and efficacy (99.6%). Eighty-five percent of children had etiologies easily diagnosed in primary care.

**CONCLUSIONS:** Management of children with chronic cough, in accordance with a standardized algorithm, improves clinical outcomes irrespective of when it is implemented. Further testing of this standardized clinical algorithm in different settings is recommended. *Pediatrics* 2013;131:e1576–e1583
Cough is the most common symptom presenting to primary care in many countries.1 When chronic, it causes considerable burden.1,2 Furthermore, >80% of children have had ≥5 consultations for a chronic cough3 that, if ignored, could lead to progression to a serious illness such as bronchiectasis. Although the need to improve the management of chronic cough is reflected in published international data,4–6 there are few randomized controlled trials (RCTs) in this area.6

Guidelines and clinical algorithms are increasingly used,7–9; those that improve patient outcomes and which are based on good evidence are more likely to change practice.8 Many variations of chronic cough guideline/algorithms exist, but none has been subjected to a randomized study.10 Thus, we conducted a multicenter study with a pragmatic design to test the hypothesis that the management of chronic cough in children in accordance with an evidence-based management pathway is feasible, reliable, and improves clinical outcomes. Because Indigenous Australians have higher respiratory morbidity than non-Indigenous Australians, we also sought to compare outcomes between Indigenous and non-Indigenous children.

Our main objective was to test the efficacy of the pathway. However, an RCT comparing use versus nonuse of the pathway was not possible because of the need to improve the management of chronic cough in children in accordance with an evidence-based management pathway. A pragmatic design to test the hypothesis that the management of chronic cough in children in accordance with an evidence-based management pathway is feasible, reliable, and improves clinical outcomes. Because Indigenous Australians have higher respiratory morbidity than non-Indigenous Australians, we also sought to compare outcomes between Indigenous and non-Indigenous children.

Our primary question was: among children with chronic cough (>4 weeks), does management according to a standardized clinical management pathway algorithm (compared with usual treatment) improve clinical outcomes by 6 weeks? Our secondary aims were to: (1) assess the reliability and validity of a standardized clinical management pathway for chronic cough in children; and (2) compare the outcomes of chronic cough between Indigenous and non-Indigenous Australian children.

METHODS

Because the full details of our study’s protocol12 have been published (see online Supplemental Information), we outline here a summary. Subjects were children (aged <18 years) with chronic cough (>4 weeks) newly referred to the authors practicing in the participating hospitals. Children were recruited between January 2008 and February 2011. Exclusion criteria included children with a known chronic respiratory illness previously diagnosed by a respiratory physician or confirmed on objective tests (eg, cystic fibrosis, bronchiectasis) before referral.

A pragmatic real-life study design (parallel with 1:1 allocation) was used. After informed consent was received, children were randomized into 2 treatment arms: (1) early use of the cough pathway algorithm (“early-arm”); or (2) usual care until use of the cough pathway algorithm (“delayed-arm”). The delayed-arm group, which equated to usual care, was based on our usual waiting period for an appointment of 6 to 8 weeks. In the early-arm group, the children were managed in accordance with the cough algorithm within 3 weeks of randomization. During the waiting period in both treatment arms, the children’s usual care (from their referring physician [ie, either family physicians or general pediatricians]) was unaltered. For example, children assessed as not having asthma but who were still receiving asthma medications at the time of the clinical consultation (most parents had ceased giving their children their medication before seeing us) ceased their medications at that point.

Definitions and Outcomes

Cough resolution (considered cough-free) was defined as improvement of ≥75% or total resolution according to the recorded cough score14 for ≥3 consecutive days.15 The endpoint was defined as either primary diagnosis and cough resolution established, the presence of exit criteria, or at 12 months from time of enrollment (whichever occurred earliest). The exit criterion was hospitalization for a condition...
related to cough before the primary diagnosis was established. Primary diagnosis definitions and other items used in the algorithm have been published.\textsuperscript{12}

Outcomes were collected on standardized forms until the study endpoint was reached. Primary outcomes were: (1) proportion of children who were cough-free; and (2) parent-proxy cough-specific quality of life (PC-QoL) score\textsuperscript{16} at week 6. Secondary outcomes were PC-QoL and pediatric quality of life (PedsQL)\textsuperscript{17} scores collected at the different time points.

The efficacy, reliability, and validity of our cough algorithm were defined a priori.\textsuperscript{12} Efficacy of the clinical management pathway was determined by improvements in both QoL measures and the percentage of children with a primary diagnosis achieved. Reliability was determined by agreement (as assessed by the study monitor) in the implementation at key steps of the pathway in children who had their medical records re-examined. A $\kappa$ (K) value of $>0.6$ was considered acceptable for clinical practice.\textsuperscript{18} The specific key components assessed were: (1) fulfillment of entry criteria; (2) whether the appropriate protocol was followed according to the child’s cough (non-specific cough or specific cough)\textsuperscript{11,13}; (3) adherence to recommended steps if the child had nonspecific cough or isolated wet cough; and (4) adherence to diagnostic criteria. Validity of the pathway was described by using the clinical failure rate, diagnosis reached by 12 months, and misdiagnosis rates. Clinical failure was defined as the child hospitalized for a condition related to cough before the primary diagnosis was made or treatment elsewhere for cough.\textsuperscript{12}

### Statistics

Data that had a normal distribution were described by using mean ± SD values; medians and interquartile ranges (IQRs) were used otherwise. $\chi^2$ tests were used for categorical data. Unpaired Student’s $t$ test was used for 2-group comparisons of normally distributed data, and the Kruskal-Wallis analysis was used for nonparametric data. Paired data were examined by using the Wilcoxon test. A 2-tailed $P$ value of <.05 was considered significant. SPSS version 13.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) was used. Intention-to-treat analysis was used where possible; children who were lost to follow-up or did not receive allocation (ie, week 6 outcomes unavailable) were considered treatment failures. For continuous data, the missing data were omitted (ie, no data imputation was undertaken).

We planned for a relatively large sample size aimed to optimize generalizability of the results, while ensuring sufficient power (>80%) for both primary outcomes.\textsuperscript{12} We assumed that cough resolution would occur by 6 weeks in 35% of the control arm\textsuperscript{19} and 55% of the early-arm group. Our goal was to enroll 220 to 250 children, with at least 220 receiving the allocated intervention.

### RESULTS

The mean ± SD age of the 272 children randomized to treatment was 4.5 ± 3.7 years. Median duration of cough at enrollment was 16 weeks (IQR: 8–32), median PC-QoL was 3.6 (IQR: 2.6–4.8), and PedsQL was 77.5 (IQR: 65.2–86.7). The children were randomized from Brisbane ($n = 120$), Melbourne ($n = 70$), Sydney ($n = 37$), Canberra ($n = 29$), and Darwin ($n = 16$). Nineteen of the 272 children did not receive the allocated intervention because of failure to attend the scheduled appointment (Fig 2). The proportion of children who did not attend their appointment was similar among recruitment sites: Brisbane, $n = 9$ (7.5%); Melbourne, $n = 6$ (8.6%); Sydney, $n = 1$ (2.7%); Canberra, $n = 1$ (3.4%); and Darwin, $n = 2$ (12.5%). Likewise the proportion of children...
who did not have PC-QoL at week 6 was similar among sites: Brisbane, \( n = 12 \) (10%). Melbourne, \( n = 8 \) (10.8%); Sydney, \( n = 4 \) (11.4%); Canberra, \( n = 2 \) (6.9%); and Darwin, \( n = 1 \) (6.3%).

Baseline Characteristics

Because we could not collect data from the 19 children who were randomized to treatment but did not attend their appointment, we could not compare their baseline characteristics. Those 226 children who had all primary outcomes available (ie, including week 6 PC-QoL) were not significantly different from those 27 children who did not have data available. The children’s baseline characteristics were also similar in both study arms (Table 1).

Effect of Early Versus Delayed Use of the Cough Management Algorithm

Children in the early-arm group were managed in accordance with the cough algorithm in a mean of 1.94 ± 1 weeks and those in the delayed-arm group in 5.1 ± 1.8 weeks. The proportion of children who were cough-free at week 6 (primary outcome) was significantly higher in the early-arm group (54.3%) compared with the delayed-arm group (29.5%) (Table 2), irrespective of inclusion or exclusion of those who did not attend their appointment (ie, did not receive allocated intervention). The absolute risk reduction between the groups in the intention-to-treat analysis was 24.7% (95% confidence interval [CI]: 13–35); number needed to treat (NNT) for benefit at week 6 was 4 (95% CI: 3–8). In the cohort in which all primary outcomes \(( n = 226 )\) were available, the absolute risk reduction was 38% (95% CI: 27–48), and NNT was 3 (95% CI: 2–4). The beneficial effect of early use of the cough algorithm was also evident in the second primary outcome (PC-QoL at week 6) (Fig 3). Although both groups significantly improved, PC-QoL at week 6 was significantly higher in the early-arm group. The mean difference in PC-QoL (week 6 minus baseline) between groups was 0.6 (95% CI: 0.29–1.0).

There was no significant difference between groups in PedsQL at week 6 (Table 3). The mean duration of cough postrandomization was significantly shorter in the early-arm group compared with the delayed-arm group. Duration of cough postrandomization was similar between groups. The final PC-QoL between groups was similar. When Indigenous children \(( n = 15 )\) were compared with non-Indigenous children \(( n = 238 )\), there was no significant difference between groups for any of the outcomes \(( P \text{ range}, 0.45–0.95 [\text{data not shown}])\).

Assigned Diagnosis and Follow-up

Primary diagnosis was obtained in all 226 children who completed the follow-up; 80 (26.5%) children had nonspecific cough and 166 (73.5%) had specific cough.11,12 Of the children with nonspecific cough (ie, cough without any specific cough pointers), their eventual primary diagnosis was: natural resolution, \( n = 33 \) (14.8%); habit cough, \( n = 11 \) (4.9%); pertussis, \( n = 8 \) (3.5%); mycoplasma, \( n = 5 \) (2.2%); and upper airway problems, \( n = 3 \) (1.3%). The primary diagnosis in those with specific cough (ie, specific cough pointers present) were: protracted bacterial bronchitis, \( n = 94 \) (41.6%); asthma or reactive airway disease, \( n = 37 \) (16.4%); bronchiectasis, \( n = 13 \) (5.7%); aspiration lung disease, \( n = 3 \) (1.3%); tracheobronchomalacia, \( n = 16 \) (7.1%); atelectasis, \( n = 2 \) (0.9%); and cystic fibrosis, \( n = 1 \) (0.4%). Using the protocol, the algorithm identified 85% with simple etiology without any specialist investigations.

In 51 children, >1 attributed cause for their cough was found; the most common co-diagnosis was tracheobronchomalacia with protracted bacterial bronchitis \(( n = 18 )\). During follow-up, none of the children had an
additional respiratory diagnosis and none fulfilled the predetermined exit criterion. Data for PC-QoL at weeks 10, 14, 26, and 52 are not presented because there were few data available as the study endpoint was reached in most children before these time points.

**Efficacy, Reliability, and Validity of the Cough Management Algorithm**

We defined efficacy of the cough algorithm through improvements in PC-QoL and PedsQL and achievement of the primary diagnosis. Both PC-QoL and PedsQL significantly improved in the entire cohort. For PC-QoL, the median score at baseline was 3.6 (IQR: 2.7–4.9) and at the final time point, it was 6.5 (IQR: 5.2–7.3) (P = .0001); for PedsQL, it was 78.3 (IQR: 68.5–86.9) and 92.5 (IQR: 85.4–99.8) (P = .0001), respectively.

Of the 253 children in whom the algorithm was applied, eventual diagnosis was attained in 252 (99.6%) children. Although 20 children dropped out, diagnosis data were eventually available from routine clinic follow-up (as opposed to research follow-up with strict criteria applied). For example, the child who was nonadherent to treatment had bronchiectasis (according to results of a high-resolution computed tomography [HRCT] scan).

Validity of the cough algorithm was assessed by using clinical failure rate, diagnosis reached by 12 months, and rates of misdiagnosis. None of the children was hospitalized for the aforementioned reasons. Conservatively, assuming that lost to follow-up equates to treatment eventually sought elsewhere, the clinical failure rate was, at most, 6.7% (17 of 253). Arguably, however, given that primary diagnosis was obtained in all but 1 child, the clinical failure rate was 0.4%. Because there was no misdiagnosis within the 6-month follow-up period, this component of validity was 100%.

Our a priori definition of reliability was the agreement in the implementation of key steps in the cough management algorithm of children who had their medical records re-examined. Of the 60 medical records reviewed, 2 were of children who dropped out. Of the remaining 58, the steps undertaken were in accordance with the algorithm in all 58 (100%); interrater κ was 1.0 for all criteria.

**DISCUSSION**

To the best of our knowledge, this is the first report of an RCT assessing the use of a chronic cough management algorithm. Our multicenter study involving 272 children in a nonacute setting found that those who were managed according to the algorithm early had significantly better clinical outcomes (PC-QoL and being cough-free earlier) compared with children allocated to using it later. For cough resolution, the NNT (benefit at week 6) was 4. Once the cough algorithm was implemented, outcomes were similar. We also found that the algorithm was efficacious (significantly improved PedsQL and PC-QoL in all children with primary
diagnosis obtained in 99.6%), valid (very low clinical failure rate), and reliable (intrarater κ = 1.0 for key steps). Clinical implications of using our algorithm include achieving cough resolution within a short period (~4 weeks) that improves PC-QoL and PedsQL (Fig 3), irrespective of when the algorithm was implemented. Our study is important because it provides high-level evidence that explicit standardized management leads to better clinical outcomes by 6 weeks. Further strengths of our study include the use of validated cough outcomes and definitions and a priori defined time points for cure (or success). Some studies used any reduction in scores as evidence of efficacy; arguably, this method is insufficient because a small reduction in a cough score may not translate to patient-important outcomes. Thus, we used a previously applied definition, and this is supported by significant improvement in PC-QoL. The difference between groups for PC-QoL at week 6 (0.6) is at the upper limit of the minimal important difference range determined by using the distribution method (0.22–0.62) but less than that from the anchor method (0.9).

TABLE 3 Secondary Outcome Measures and Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early-Arm Group</th>
<th>Delayed-Arm Group</th>
<th>P</th>
<th>Difference Between Groups (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PedsQL at week 6, median (IQR)</td>
<td>92.5 (81 to 96.5)</td>
<td>87 (76 to 96.3)</td>
<td>.134</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Duration of cough postrandomization,</td>
<td>6.4 ± 5.1</td>
<td>9.1 ± 6.6</td>
<td>.001</td>
<td>−2.7 (−4.3 to −1.1)</td>
</tr>
<tr>
<td>mean ± SD, wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of cough posture of the</td>
<td>4.4 ± 5.2</td>
<td>4.2 ± 6.2</td>
<td>.732</td>
<td>0.2 (~1.3 to 1.7)</td>
</tr>
<tr>
<td>cough pathway, mean ± SD, wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC-QoL final, median (IQR)</td>
<td>6.5 (5.6 to 7)</td>
<td>6.9 (6.3 to 6.9)</td>
<td>.201</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

* Calculated when data were normally distributed.

We used a pragmatic design to align the study, as far as possible, to a real-life situation. Although a strict adherence to a time point (2 vs 6 weeks) would be arguably ideal, this design was not practical in real-life clinical settings. The waiting time for medical consultations is determined by the local health care system, and this study was not designed to examine its effect. Also, it is important to emphasize that a “watch, wait, and review” approach for children who do not have specific cough pointers, is part of the algorithm flow. We did not find any difference between Indigenous and non-Indigenous children, but the sample size for this was too small.

The algorithm used is based on current evidence derived from available studies that were largely non-RCTs, as described in the protocol. Thus, the level of evidence is mostly low because the majority of Cochrane studies in this area have yielded no suitable RCTs.

The inevitable lack of blinding is a major limitation. A cluster-RCT design was not feasible because we have similar hospital-based practices. However, our practice is substantially different from that in the general community, which constitutes usual care in our RCT, and thus we used an early versus delayed use of the cough algorithm. Nevertheless, we believe that the potential bias is minimal because there was no significant difference between groups for PedsQL (a generic quality of life tool and the least sensitive outcome measure) and the duration of cough postuse of the cough algorithm. We did not find any difference between Indigenous and non-Indigenous children, but the sample size for this was too small.

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(Table 3), it is possible that the extra attention paid to these children and families presents a bias. Although we used robust cough outcomes\textsuperscript{14,16,22} that were validated against objective measures, absence of an objective measure is a limitation, as previously discussed.\textsuperscript{12}

There were more dropouts in the delayed-arm group (29 of 132) than in the early-arm group (17 of 140). However, we do not believe this affects our study’s validity because: (1) the difference between groups of dropouts was not statistically significant; (2) the results from the available data analysis were similar; and (3) using our pre-specified intention-to-treat analysis, all the dropouts were included in our main primary outcome.

The children in our study were seen by respiratory specialists. However, the majority of children (85%) had diagnoses that would be very easily made and managed in primary care. The rest (15%) had serious underlying disorders usually managed by respiratory specialists. Lastly, determination of adherence to protocol was limited to the key points. Because children were seen by specialists who are well aware of cough assessment and quality, extrapolation of adherence and interpretation of the protocol to the primary care setting cannot be made without ensuring that appropriate training and education are available. The reliability of key symptoms and signs used in this algorithm, such as presence of chest crackles and wheeze, are poor in primary care (\( \kappa = 0.3 \) and 0.29, respectively).\textsuperscript{25} In contrast, the reliability in tertiary care is excellent (\( \kappa = 0.79 \) and 0.77, respectively).\textsuperscript{24} Thus, before implementation of the algorithm in primary care, a large cohort study in primary care assessing epidemiology and diagnostic value of clinical features used in the algorithm is required.

**CONCLUSIONS**

Our pragmatic study is the first RCT to evaluate a cough algorithm/pathway, and it provides important RCT evidence on the management of a relatively common condition in which there is a dearth of high-quality data.\textsuperscript{5,20,25} We concluded that the management of children with chronic cough, in accordance with a standardized clinical management pathway (compared with usual treatment by community physicians), improves clinical outcomes. An evidence-based cough algorithm can be feasibly used in the outpatient setting, where it has been shown to be efficacious, valid, and reliable. Further testing of this standardized clinical algorithm in different settings is recommended.

**ACKNOWLEDGMENTS**

We thank the research nurses and coordinators for facilitating the study. H. Petsky, Emily Bailey, Sophie Anderson-James, Johanna Kappers, Merdith Larkins, Dr Karen McKay, Tracey Gonzalez, Amber Revell, Kobi Shhulz. We also thank Carol Willis for maintaining the database, and Drs Dore, Francis, and Buntain for their assistance in recruiting the children into the study. We are also grateful to the parents and children who kindly participated in the study.

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This trial has been registered at Australian New Zealand Clinical Trial Registry (ACTRN12607000526471).

The views expressed in this publication are those of the authors and do not reflect the views of the Australian National Health and Medical Research Council. www.pediatrics.org/cgi/doi/10.1542/peds.2012-3318
doi:10.1542/peds.2012-3318

Accepted for publication Jan 5, 2013

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Chang received institutional funding from GlaxoSmithKline (GSK) for an investigator-led clinical study in NTHi infections in children. Dr Morris received institutional funding from GSK and Pfizer in an investigator-led epidemiologic project of otitis media in Australian Aboriginal children. Dr Morris had also participated in an advisory board for GSK on a vaccine product and a chronic ear disease study. Neither company manufactures products that are related to the current study. The other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by an Australian National Health and Medical Research Council (NHMRC) project grant (490321) and supported by an NHMRC Centre for Research Excellence in Lung Health of Aboriginal and Torres Strait Islander Children (grant 1040830). Dr Chang is supported by an NHMRC fellowship (545216).
A Cough Algorithm for Chronic Cough in Children: A Multicenter, Randomized Controlled Study

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*Pediatrics* 2013;131;e1576

DOI: 10.1542/peds.2012-3318 originally published online April 22, 2013;
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