A Cough Algorithm for Chronic Cough in Children: A Multicenter, Randomized Controlled Study

WHAT'S KNOWN ON THIS SUBJECT: Parents of children with chronic cough have poor quality of life and often seek multiple consultations. There are few randomized controlled trials on the management of cough or on the efficacy of management algorithms outside of inpatient settings.

WHAT THIS STUDY ADDS: In a multicenter, trial, we found that the management of children with chronic cough, in accordance with a standardized algorithm, improves clinical outcomes. Earlier application of the algorithm leads to earlier cough resolution and improved parental quality of life.

abstract

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

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KEY WORDS: children, cough, guidelines, randomized controlled trial

ABBREVIATIONS: CI—confidence interval IQR—interquartile range NNT—number needed to treat PedsQL—pediatric quality of life PC-Qol—parent-proxy cough-specific quality of life RCT—randomized controlled trial

Dr Chang conceptualized and designed the study, conducted the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. Drs Robertson, van Asperen, and Glasgow contributed to the design of the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Masters contributed to recruitment of patients, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Teoh contributed to recruitment of patients, coordinated and supervised data collection at the Canberra site, reviewed and revised the manuscript, and approved the final manuscript as submitted. Drs Mellis, Landau, and Morris contributed to the design of the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. And Dr Marchant reviewed and revised the manuscript, and approved the final manuscript as submitted.

(Continued on last page)
Brief Study Protocol
The study was approved by all the institutions’ human research ethics committees. Enrolled children were randomized to the next allocated number sequentially within 2 age strata (≤6 and >6 years) and 5 site strata (Brisbane, Melbourne, Sydney, Canberra, and Darwin). The allocation sequence was concealed from all the investigators, participants, and caregivers. All enrolled children were managed according to the algorithm by the treating clinician (all except 1 were respiratory physicians) and followed up until a primary diagnosis and cough resolution were achieved (maximum: 12 months). A simplified version of the algorithm showing the initial assessment and treatment strategy is shown in Fig 1. If the child has specific cough pointers, the pathway leads to the second figure in our protocol. The main steps in the algorithm were: assessment of the presence of specific cough pointers; presence/absence of chest radiograph and/or spirometry abnormalities and wet/dry cough; discussion on expectations and tobacco smoke exposure; and a watchful waiting period when appropriate and clinical review. To assess reliability and adherence to the algorithm, a random computer-generated sample of children’s records in the 3 largest centers was examined (n = 20 each from Brisbane, Sydney, and Melbourne).

Definitions and Outcomes
Cough resolution (considered cough-free) was defined as improvement of ≥75% or total resolution according to the recorded cough score for ≥3 consecutive days. 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.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) score16 at week 6. Secondary outcomes were PC-QoL and pediatric quality of life (PedsQL)17 scores collected at the different time points.

The efficacy, reliability, and validity of our cough algorithm were defined a priori.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 κ (K) value of >0.6 was considered acceptable for clinical practice.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 (nonspecific cough or specific cough)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.12

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 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.12 We assumed that cough resolution would occur by 6 weeks in 35% of the control arm19 and 55% of the early-arm group. Our goal was to enroll 220 to 250 children, with at least 220 receiving the allocated intervention.
(n = 27) 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 ± 1.6 weeks and those in the delayed-arm group in a mean of 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 postuse of the algorithm 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 range, 0.45–0.95 [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 = 35 (14.6%); 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
TABLE 1 Baseline Data Comparing Children in the 2 Study Arms

<table>
<thead>
<tr>
<th>Variable at Baseline</th>
<th>Early-Arm Group (n = 132)</th>
<th>Delayed-Arm Group (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>4.8 ± 3.8</td>
<td>4.8 ± 3.7</td>
</tr>
<tr>
<td>Gender (female:male)</td>
<td>55:77</td>
<td>56:65</td>
</tr>
<tr>
<td>PC-QoL16 (median, IQR)</td>
<td>3.7 (2.7–4.9)</td>
<td>3.5 (2.5–4.7)</td>
</tr>
<tr>
<td>PedsQL4.017 (median, IQR)</td>
<td>77.3 (64.3–85.5)</td>
<td>77.8 (68–87.8)</td>
</tr>
<tr>
<td>Cough duration at enrollment (median, IQR), wk</td>
<td>16 (6–28)</td>
<td>18 (10–42)</td>
</tr>
<tr>
<td>Cough score14 at enrollment, mean ± SD</td>
<td>2.7 ± 1.1</td>
<td>2.9 ± 1.1</td>
</tr>
<tr>
<td>No. of physician visits</td>
<td></td>
<td></td>
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<tr>
<td>&lt;5</td>
<td>35</td>
<td>27</td>
</tr>
<tr>
<td>5–10</td>
<td>46</td>
<td>39</td>
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<tr>
<td>10–15</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>15–20</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>&gt;20</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Data not filled</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Household tobacco smoke exposure, n (%)</td>
<td>35 (26.5)</td>
<td>33 (27.3)</td>
</tr>
<tr>
<td>No. of children in household, mean ± SD</td>
<td>2.3 ± 1.2</td>
<td>2.3 ± 1.3</td>
</tr>
<tr>
<td>Wet cough present, n (%)</td>
<td>91 (68.9)</td>
<td>76 (62.8)</td>
</tr>
<tr>
<td>No. treated with asthma medications (β2 agonist corticosteroids, or montelukast), n (%)</td>
<td>93 (70.5)</td>
<td>91 (75.2)</td>
</tr>
<tr>
<td>Indigenous, n (%)</td>
<td>10 (7.6)</td>
<td>5 (4.1)</td>
</tr>
</tbody>
</table>

TABLE 2 Primary Outcome: Comparison of Proportion of Children Who Were Cough-Free at Week 6

<table>
<thead>
<tr>
<th>Cough-Free at Week 6</th>
<th>Early-Arm Group</th>
<th>Delayed-Arm Group</th>
<th>P (χ²)</th>
<th>Difference in Proportions Between Groups (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Children</td>
<td>Cough-Free/n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis by intention-to-treat (n = 272)</td>
<td>76/140 (54.3)</td>
<td>39/132 (29.5)</td>
<td>.0001</td>
<td>0.247 (0.134–0.361)</td>
</tr>
<tr>
<td>Analysis by received allocated intervention (n = 253)</td>
<td>76/132 (57.6)</td>
<td>39/121 (32.2)</td>
<td>.0001</td>
<td>0.253 (0.135–0.372)</td>
</tr>
<tr>
<td>Analysis by cohort with PC-QoL data at week 6 (n = 226)</td>
<td>76/123 (61.8)</td>
<td>39/103 (37.3)</td>
<td>.0001</td>
<td>0.239 (0.112–0.366)</td>
</tr>
</tbody>
</table>

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: 5.2–7.0) (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 an 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%.

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 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.
diagnosis obtained in 99.6%), valid (very low clinical failure rate), and reliable (inter-rater \( \kappa = 1.0 \) 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\(^20\); 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,\(^15,19\) 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).\(^21\)

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.\(^12\) 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.\(^11\) 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\(^17\) (a generic quality of life tool and the least sensitive outcome measure) and the duration of cough postuse of the cough algorithm was also similar between groups. If parent/subject-associated bias had been clinically important, we would have expected that the PedsQL and/or duration of cough postuse of the algorithm between groups would also have been significantly different. For the duration of cough postuse of the algorithm (\(~4\) weeks in both groups)

**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)(^a)</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, mean ± SD, wk</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>Duration of cough postuse of the cough pathway, mean ± SD, wk</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>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>

\(^a\) Calculated when data were normally distributed.
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). In contrast, the reliability in tertiary care is excellent ($\kappa = 0.79$ and 0.77, respectively). 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. 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.

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(Continued from first page)

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

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