Efficacy and tolerability of a polysaccharide-resin-honey based cough syrup as compared to carbocysteine syrup for children with colds: a randomized, single-blinded, multicenter study

Herman Avner Cohen, Moshe Hoshen, Shmuel Gur, Arie Bahir, Yoseph Laks, Hannah Blau
Tel-Aviv, Israel

Background: **Available pediatric treatments for acute cough are limited by lack of demonstrated efficacy. The objective of this trial is to compare the effects of a polysaccharide-resin-honey based cough syrup, and carbocysteine syrups on nocturnal and daytime cough associated with childhood upper respiratory tract infections (URIs).**

Methods: **Using a single-blind randomization design, the study recruited children from 4 general pediatric community clinics. Participants included 150 children aged 2 to 5 years with an URI, nocturnal and daytime cough and illness duration of ≤7 days. To be eligible, children had to be free of medication on the day before presentation. A survey was administered to parents on 4 consecutive days beginning from the day of presentation in clinic. Children received the study preparation on the first evening and then 3 times per day for 3 further days. Main outcome measures were cough frequency, cough severity, bothersome nature of cough, and quality of sleep for both child and parent.**

Results: **Both preparations were well tolerated and cough improved over the study period. After one night and on all survey days, there was a significantly better result for polysaccharide-resin-honey ($P<0.05$) for all the main outcome measures. The trend of improvement over the 4 days was steeper for polysaccharide-resin-honey ($P<0.05$) with regards to all cough parameters.**

Conclusions: **Both polysaccharide-resin-honey and carbocysteine cough syrups were well tolerated in children over 2 years of age. The polysaccharide-resin-honey syrup was associated with a more rapid and greater improvement in all clinical cough symptoms measured, beginning from the first night of therapy. Both nocturnal and daytime cough improved, as did sleep quality for both children and parents.**

World J Pediatr 2017;13(1):27-33

Key words: **cough;**
children;
upper respiratory tract infection

Original article

Introduction

The common cold is a syndrome of nasal congestion, sneezing, rhinorrhea and pharyngitis due to many different viruses, and generally self-limiting with a median duration of 9-10 days.[1] Nevertheless, colds lead to approximately 85 million physician visits annually in the USA.[2] An estimated 22 to 189 million school days are missed annually due to colds, and working parents miss approximately 126 million workdays, staying home to care for their children.[3]

Cough is perhaps the most troubling symptom for children suffering from upper respiratory tract infections (URIs) and their parents. It often results in discomfort to the child and loss of sleep for both children and parents.[4] In an attempt to treat cough, caregivers frequently administer over-the-counter (OTC) medications to children with little evidence of proven efficacy.[5-8] Honey administered before bedtime has been reported by parents as being preferable to dextromethorphan, diphenhydramine or placebo for

Author Affiliations: Pediatric Ambulatory Community Clinic, Petah-Tikva, Israel (Cohen HA); Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel (Cohen HA, Gur S, Bahir A, Laks Y, Blau H); Clalit Research Institute, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel (Hoshen M); Pediatric Ambulatory Community Clinic, Kefar Saba, Israel (Gur S); Pediatric Ambulatory Community Clinic, Bat Yam, Israel (Bahir A); Pediatric Ambulatory Community Clinic, Ramat Aviv, Israel (Laks Y); Pulmonary Institute, Schneider Children Medical Center of Israel, Petah Tikva, Israel (Blau H)

Corresponding Author: Herman Avner Cohen, P.O.Box 187, Yehud 56000, Israel (Tel: +972-3-9398200; Fax: +972-523-870827; Email: hermanc@post.tau.ac.il)

doi: 10.1007/s12519-016-0048-4
Online First, July 2016
©Children's Hospital, Zhejiang University School of Medicine, China and Springer-Verlag Berlin Heidelberg 2016. All rights reserved.

symptomatic relief of their child's nocturnal cough and sleeping difficulty due to URIs.[9-11]

In this study, a pediatric cough syrup containing honey as well as specific fractions of resins, polysaccharides, saponins, flavonoids and sugars derived from *Grindelia robusta*, *Plantago lanceolata* and *Helichrysum italicum* was used as one treatment arm. This polysaccharide-resin-honey pediatric cough syrup (PRH syrup) has been shown to have a better outcome than placebo when treating nocturnal and daytime cough persisting for more than 7 days and up to 3 weeks.[12]

Cysteine derivates (carbocysteine, acetylcysteine) are mucolytic drugs that act by disrupting disulphide bridges between macromolecules and lead to reduced mucus viscosity in the respiratory tract. These derivates are widely used to treat pediatric patients with acute cough in many European and African countries.[13,14]

The objective of this trial was to compare the effects on nocturnal and daytime cough associated with URIs of PRH syrup (Grintuss®, Aboca S.p.A.) compared with carbocysteine syrup (Mucolit, CTS Ltd, Israel). Although these two medications act through different mechanisms, we wished to evaluate the outcome measures of symptomatic relief for URI in children.

Methods

Patients

Subjects were recruited from acute care visits at four general pediatric community clinics between December 2013 and April 2014. Eligible patients were those between the ages of 2 and 5 years complaining of nocturnal and day-time cough that was attributed to a URI. A URI was defined as an acute viral infection present for no more than 7 days where cough and rhinorrea were the main symptoms. Other symptoms included, but were not limited to, nasal congestion, fever, sore throat, myalgia, fatigue, malaise and headache. Patients were excluded if they had signs or symptoms of asthma, pneumonia, chronic cough, stridor or laryngotracheobronchitis, sinusitis, chronic cardiac or pulmonary condition, allergic rhinitis, or if they had used steroid treatment, antihistamines or any cough or cold medication or honey since 24 hours before presentation. Patients were not excluded when analgesic medications such as acetaminophen or ibuprofen were administered prior to presentation.

Pre-intervention study questionnaire

After attaining informed consent, all participating parents were asked to complete a 5 item questionnaire regarding their subjective assessments of the child's cough and sleep difficulty on the previous night using a Hebrew version of a previously validated questionnaire (Table 1).[11] In addition, the parents subjectively assessed their child's daytime cough on the previous day using the same questionnaire except for the two items regarding sleep parameters of the child and parents (Table 1). Survey responses were graded on a 7- point Likert scale. Minimum symptom severity was established as an inclusion criterion. Children were included if their parents rated severity as ≥3 for at least two of the three questions relating to nocturnal cough frequency, effect on the child's sleep, and effect on parental sleep, as well as for all of the questions relating to daytime cough.

Study design

A single-blinded, randomized design was used to conduct this study. Eligible children were randomized into two treatment arms: A, PRH syrup (Grintuss® pediatric syrup, Aboca S.p.A. Italy); B, carbocysteine syrup (Mucolit, CTS Ltd, Israel). The primary care physicians and the study coordinator were blinded to the study preparation dispensed.

Intervention

The syrup bottles were packed in identical white carton packs and marked with the letters A or B. The study preparations were distributed to the pediatric community clinics in blocks of four. Randomization was sequential, based on a predetermined list. After enrollment into the study, the parent went to the clinic pharmacy with a sealed envelope that included the randomization number. The envelopes containing the codes of the study preparations were stored at the pharmacy and were not opened until after the statistical analysis was completed. The pharmacist instructed the parents to give 20 ml/day of the PRH syrup, as recommended by the manufacturer for all weight and

Table 1. Cough severity assessment questionnaire scoring

Night time cough	Day time cough
How frequent was your child's coughing last night?	How frequent was your child's coughing yesterday?
How severe was your child's cough last night?	How severe was your child's cough yesterday?
How bothersome was last night's cough to your child?	How bothersome was yesterday's cough to your child?
How much did last night's cough affect your child's ability to sleep?	
How much did last night's cough affect your (parent's) ability to sleep?	

Cough severity assessment questionnaire scoring: 0, not at all; 1, not too much; 2, a little; 3, somewhat; 4, a lot; 5, very much; 6, extremely.

ages or 25 mg/kg/day of carbocysteine divided into three doses, as per manufacturers' instructions, for four days. The first dose was given the night of enrollment into the study and the child then received three doses per day of the study preparation for a further three days.

Post intervention study questionnaire

On each day of treatment, the parent who had completed the pre-intervention questionnaire was contacted by telephone. Trained research assistants who were blinded to the treatment arm asked the parent to complete a diary containing the same questions that had been answered in writing before the intervention, now referring to the previous evening and day. The parents were asked to return the completed diary to the clinics. No physician examination was performed on the study days unless dictated by illness progression.

Outcome measures

The primary outcome of interest was the change in night cough score between the first two nights: the pretreatment night (N_0) and the first night of treatment (N_1). The cough score change was evaluated for each of the parameters: frequency, severity, cough bother, child's and parent's sleep and the combined cough score (sum of all single items).

The secondary outcome measures were the change in the daytime and night-time cough scores from the day and night before enrollment (D_0 and N_0) to the end of the study (D_4 and N_4).

Sample size analysis

On the basis of previously published data (11), we estimated that the sample size necessary to detect an 0.75-point SD 1.3 difference between any one cough parameter between the two treatment arms (using analysis of variance) with 90% power and $P<0.05$ was 60 subjects per treatment arm. To compensate for possible dropouts and abnormal data distribution, we aimed to recruit 75 patients per arm.

Statistical analysis

Statistical comparisons of variables between treatment arms were performed by using the χ^2 test for nominal variables and analysis of variance for continuous variables. For comparisons of cough evaluation before and after treatment, a paired Student t test was used. For trends and multivariable analysis we used linear regression. $P<0.05$ was considered statistically significant throughout. All statistical analyses were performed using SPSS package for Windows (version 20, IBM, Chicago, IL, USA).

Ethics

The study was approved by the Clalit Health Services' Community Health Institutional Review Board.

Results

One hundred and fifty children with URIs were enrolled and one hundred forty one (94%) completed the study (Fig. 1). Seventy eight children received the PRH syrup and seventy two received the carbocysteine syrup. Three children dropped out from the PRH syrup and six from the carbocysteine arm.

The median age of the patients completing the study was 41.5 months (range, 24-70 months), with no significant difference in age between treatment arms. Seventy one of the children (47.3%) were boys, of which thirty seven (47.4%) in the PRH syrup arm and thirty four (47.2%) in the carbocysteine arm. The mean duration of coughing before enrollment was 3.14 days (±SD 1.53) for the PRH syrup and 3.14 (±SD 1.44) for the carbocysteine arm, with no significant difference between treatment arms (P=0.993, by ANOVA). Ninety

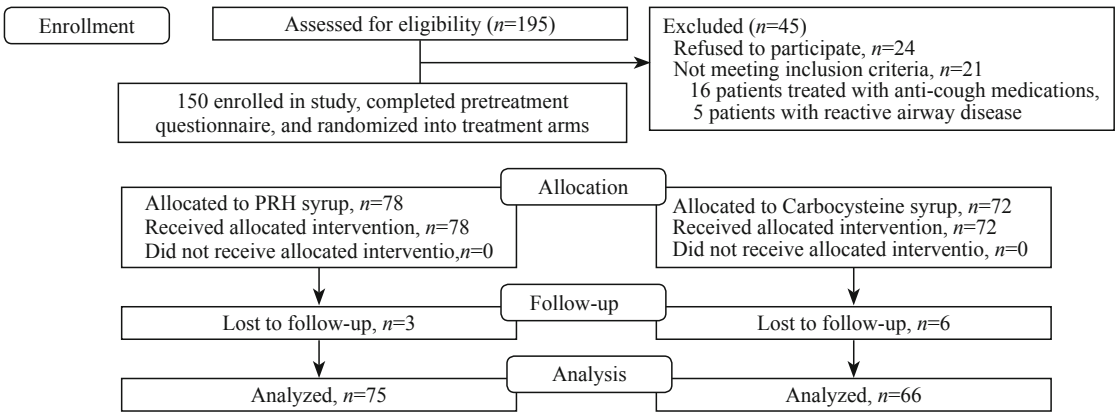

Fig. 1. Patient flow diagram. PRH: polysaccharide-resin- honey.

three (62%) of the children had been coughing at least 3 days, of which forty seven (60.3%) in the PRH syrup arm and forty six (63.9%) in the carbocysteine arm, with no difference between arms (P=0.645). None of the children participating in the study were receiving antibiotic therapy. Overall, the patients in PRH syrup arm carried slightly higher scores of symptom severity at baseline for all night-time parameters (P<0.01) (Table 2).

Primary end-point

Night-time cough (night 1 versus night 0)

When symptom scores were compared for each treatment arm from the night before enrollment to the first night of treatment, significant differences between the two treatment arms were detected in the improvement reported for all the study outcome items (Table 3, Fig. 2). For cough frequency, those who received the PRH syrup had a 0.85±0.18 point (mean±SE) improvement from N_0 to N_1 compared to a 0.17±0.15 point change for those receiving carbocysteine syrup (P=0.007). Parents also noted similar improvements in the severity of their child's cough: 0.72±0.18 points with the PRH syrup *vs.* 0.06±0.14 points with carbocysteine syrup (P=0.007). Parents also felt the cough was less bothersome on N_1, where the PRH syrup provided a relief of a 0.97±0.19 point change compared with a 0.38±0.15 point change for the carbocysteine syrup arm (P=0.020). Quality of their child's sleep improved after receiving the PRH syrup by 1.36±0.19 points compared with an 0.58±0.18 point improvement following carbocysteine syrup (P=0.005). As might be expected, parental sleep improved in a fashion similar to that of their children,

Table 2. Baseline patient characteristics by treatment arm

		PRH syrup arm	Carbocysteine arm	Total
Patients enrolled, *n*		78	72	150
Age	Mean±SD, mon	42.49±12.96	43.17±14.57	42.81±13.71
	Median, mon	41.5	41	41.5
Sex	Male, *n* (%)	37 (47.4%)	34 (47.2%)	71 (47.3%)
	Female, *n* (%)	41 (52.6%)	38 (52.8%)	79 (52.7%)
Mean days of cough before enrollment, mean±SD		3.14±1.53	3.14±1.44	-
Patients coughing since ≥3 days at presentation, *n* (%)		47 (60.3%)	46 (63.9%)	93 (62.0%)
Total night score N_0, mean±SD		19.92±4.19*	17.74±3.26	18.87±3.92
Total day score D_0, mean±SD		10.56±1.98	10.08±1.75	10.33±1.88

*: P<0.01 between treatment arms. SD: standard deviation.

Table 3. Change in night cough score from N_0 to N_1 (score reduction indicates improvement in patient condition)

Parameters	Score reduction from N_0 to N_1 (±SE)		P value between arms
	PRH syrup arm n=75	Carbocysteine arm n=66	
Frequency	0.85±0.18	0.17±0.15	0.007
Severity	0.72±0.18	0.06±0.14	0.007
Cough bother	0.97±0.19	0.38±0.15	0.020
Child's sleep	1.36±0.19	0.58±0.18	0.005
Parent's sleep	1.25±0.2	0.59±0.19	0.024
Combined score	5.16±0.85	1.77±0.67	0.005

SE: standard error.

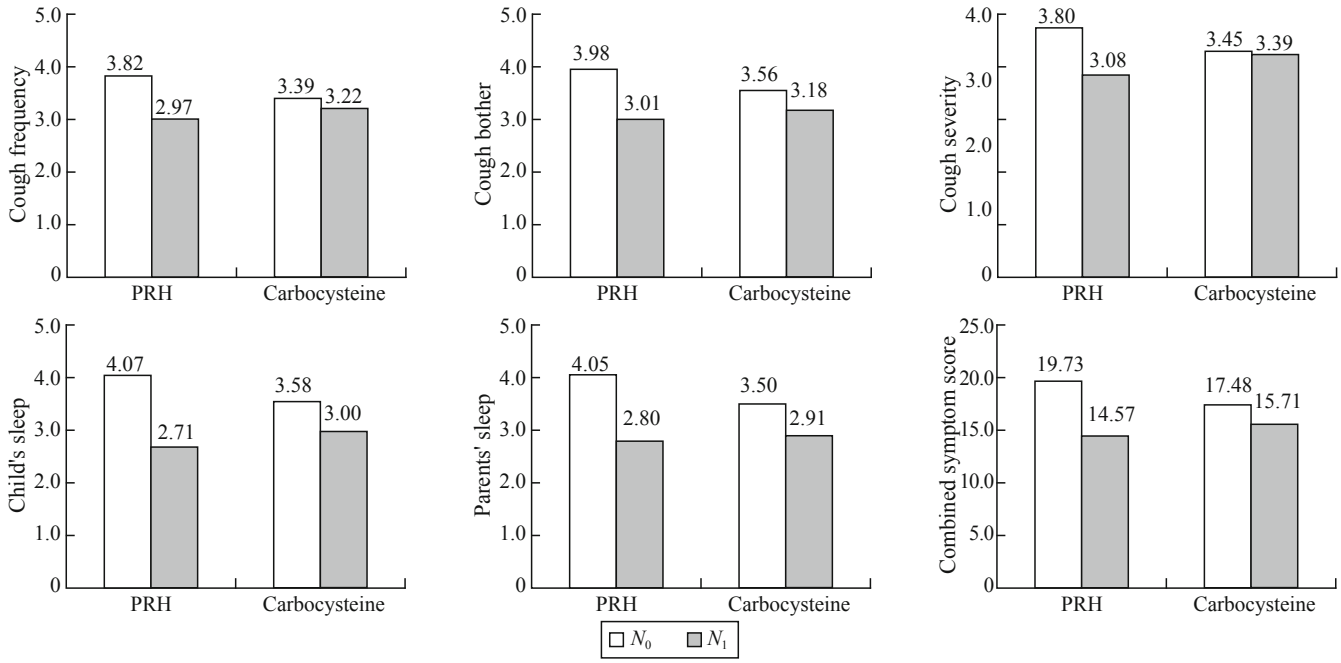

Fig. 2. The effect of PRH syrup *vs.* carbocysteine syrup on cough frequency, cough severity, cough bother, child's sleep and parents' sleep and combined symptom score, for night 0 and night 1.

with the PRH syrup treatment arm improving by a mean of 1.25±0.20 points compared to 0.59±0.19 points for the carbocysteine syrup arm (P=0.024). When the results for these outcomes were combined by adding the scores from the individual categories, the PRH syrup again proved to be the most effective treatment. The children in this arm improved by 5.16±0.85 points compared to 1.77±0.67 points for those who were treated with carbocysteine syrup (P=0.005).

Secondary end-points

Night-time cough (night 0 to night 4)

When symptom scores were compared for each treatment arm from the night before enrollment to the end of treatment, significant differences between the two treatment arms were detected in the improvement reported for all the study outcome items. For cough frequency, those who received the PRH syrup had a mean 2.56±0.18 (mean±SE) point improvement compared with a 1.72±0.21 point change for those receiving carbocysteine syrup (P=0.003). Regarding severity of cough there was an improvement of 2.50±0.19 points with the PRH syrup and 1.73±0.22 points with the carbocysteine syrup (P=0.009). Parents also felt the cough was less bothersome on the fourth night, with a 2.83±0.19 point decrease in the PRH syrup arm compared with a 1.95±0.23 point decrease in the carbocysteine syrup arm (P=0.004). Parents rated their child's sleep as improved after receiving the PRH syrup for 4 nights by 3.01±0.20 points compared with a 2.08±0.23 point improvement for the carbocysteine syrup arm (P=0.003). As might be expected, parental sleep improved in a fashion similar to that of their children, with the PRH syrup treatment arm improving a mean of 3.00±0.20 points *vs.* 2.00±0.23 points in the carbocysteine syrup arm (P=0.001). When the results for these outcomes were combined by adding the scores from the individual categories, the PRH syrup again proved to be the most effective treatment. The children in this arm improved by an average of 13.92±0.92 points, compared with 9.48±1.08 points for those who were treated with carbocysteine syrup (P=0.002).

Daytime cough (day 0 to day 4)

When symptom scores were compared for each treatment arm from the day before enrollment to the fourth day of treatment, significant differences between the two treatment arms were detected in the improvement reported for almost all the study outcome items. For cough frequency after 4 days, those who received PRH syrup had a mean 1.94±0.15 (mean±SE) point improvement compared with a 1.43±0.19 point change for those receiving carbocysteine syrup (P=0.034). Parents also noted similar improvements in the severity of their child's cough: 1.89±0.15 points with the PRH syrup *vs.* 1.41±0.20 points with carbocysteine syrup (P=0.059). Parents felt the cough was less bothersome on the fourth day with the PRH syrup with a 2.33±0.16 point decrease compared with a 1.70±0.22 point decrease for the carbocysteine syrup arm (P=0.021). When the results for these outcomes were combined by adding the scores from the individual categories, the PRH syrup again proved to be the most effective treatment. The children in the PRH syrup arm improved by an average of 6.17±0.43 points, compared with 4.54±0.6 points for those who were treated with carbocysteine syrup (P=0.026).

Trend analysis

In reference to both nighttime (from N_0 to N_4) and daytime cough scores from day 0 to day 4, we used linear regression to model cough scores by day and treatment arm. We found that indeed cough scores decreased with time for both treatment arms. The drop was however significantly greater (P<0.005) in the PRH syrup arm for each of the night scores (five items+ combined) as well as for the day scores (P=0.027 for frequency; P=0.03 for severity; P=0.008 for cough bother and P=0.011 for the combined score).

Side effects

Stomach ache, nausea or vomiting where reported by parents of five patients in the PRH syrup arm and six in the carbocysteine arm. A rash was reported in one child of each arm. Other than this, no symptoms of hypersensitivity or allergy were reported. Two parents reported drowsiness in the carbocysteine arm. There were no reports of dryness of mouth. These side effects were mild and transient and none were ruled severe enough to justify withdrawal. The incidence was not significantly different between arms.

Discussion

This study demonstrates that nocturnal and daytime URI associated cough improved in both the PRH syrup and the carbocysteine syrup treatment arms. The PRH syrup was more effective than carbocysteine regarding all outcome measures related to nocturnal and daytime cough and quality of the child's and parent's sleep. Improvement occurred immediately (one day) after initiation of treatment and continued over the four day treatment period regarding both absolute change and slope (mean daily improvement). The improvement in child and parent sleep quality is an important benefit likely to decrease loss of work days and schooling.

Mechanisms proposed to explain the induction of cough by URI include infection-associated airways effects such as enhanced release of cytokines, neurotransmitters and leukotrienes; increased neural receptor levels; reduced activity of neutral endopeptidases, transient modulation of afferent neural activity and mucus hypersecretion.[15-18] Recent studies evaluating urge-to-cough (UTC), the sensation of irritation preceding the motor act of coughing, have demonstrated that URI induces a transient enhancement of the UTC sensation.[17-20]

The available treatments for acute cough are limited by lack of efficacy or, as in the case of opiates, intolerable side effects at antitussive doses.[7,8]

A Cochrane review[14] reported that acetylcysteine and carbocysteine seem to have some benefit and appear to be safe in children over two years of age. The mechanisms of action appear to include breaking of disulphide bridges between macromolecules, leading to a reduction in mucus viscosity. In infants under two years of age, paradoxical bronchial congestion was reported with a warning not to use this drug for this age group.[13,14]

A different treatment approach has been proposed by Canciani et al.[12] The PRH syrup may have a protective effect on the mucosa of the upper respiratory tract, generating a local mechanical barrier on the oropharynx and decreasing the urge to cough and irritation of neural receptors and exposed nerve endings.[12] Resins have adhesive properties, while polysaccharides have shown to have both adhesive and emollient properties.[21-23] Together, they can create a mechanical barrier that may limit the contact between irritants or micro-organisms and the upper respiratory tract mucosa.

An additional effect of the PRH syrup may be to enhance mucus clearance. Polysaccharides attract water and hydrate mucus making it less viscous and easier to be expelled or ingested.[22] Nosalova reported that the use of aqueous extracts of polysaccharide rich plants for cough was related to the bioadhesive properties of polysaccharides on the epithelial mucosa, leading to the formation of a polysaccharide layer on the upper airway mucous membrane.[23]

Finally, the ingredient honey is a complex natural liquid with well-established antioxidant and antimicrobial effects.[24-26] Paul et al[9] and Cohen et al[11] reported that honey products may have a beneficial effect for symptomatic relief of nocturnal cough associated with URIs. Shadkam et al[10] also reported that honey was superior to dextromethorphan and diphenhydramine in alleviating cough. In a Cochrane review, Oduwole et al[27] concluded that honey may be better than "no treatment" and diphenhydramine in the symptomatic relief of cough but not better than dextromethorphan. Study limitations: we were unable to follow a double blind protocol for this study due to the different dosing schedules for each preparation. We did not include a placebo arm because the intent of the study was to evaluate the risk/benefit ratio of a protective cough syrup (PRH syrup) with respect to a treatment currently available in clinical practice. Assessment of adherence was limited to the diary cards filled by the parents and did not include return of study medication bottles to the clinics.

In conclusion, polysaccharide-resin-honey based cough syrup and carbocysteine syrup are both effective treatments in children over 2 years of age with a good safety profile. The polysaccharide-resin-honey cough syrup appears to allow significantly faster (first night) and more effective response (over four days of treatment) as to all clinical day and night cough symptoms, including sleep for both child and parents. We observe that a syrup containing honey and specific polysaccharide and resin extracts that create a mechanical barrier between irritants and the oropharyngeal mucosa could be regarded as a valid instrument for cough management, especially in younger children with URIs.

Funding: No funding was secured for this study.

Ethical approval: The study was approved by the Clalit Health Services' Community Health Institutional Review Board, Israel, and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its latter amendments, as revised in 2000.

Competing interest: The authors declare no conflict of interest.

Contributors: Cohen HA conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Hoshen M carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. Gur S conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Bahir A conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Laks Y conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Blau H reviewed, revised the manuscript, and provided expertise related to pediatric pulmonology.

References

1 Kesson AM. Respiratory virus infections. Paediatr Respir Rev 2007;8:240-248.
2 Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. Clin Infect Dis 2001;33:757-762.
3 Fendrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of non-influenza-related viral respiratory tract infection in the United States. Arch Intern Med 2003;163:487-494.
4 De Blasio F, Dicpinigaitis PV, Rubin BK, De Danieli G, Lanata L, Zanasi A. An observational study on cough in children:

epidemiology, impact on quality of sleep and treatment outcome. Cough 2012;8:1.
5 Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev 2012;8:CD001831.
6 Paul IM. Therapeutic options for acute cough due to upper respiratory infections in children. Lung 2012;190:41-44.
7 Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics 2004;114:e85-e90.
8 Yoder KE, Shaffer ML, La Tournous SJ, Paul IM. Child assessment of dextromethorphan, diphenhydramine, and placebo for nocturnal cough due to upper respiratory infection. Clin Pediatr (Phila) 2006;45:633-640.
9 Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med 2007;161:1140-1146.
10 Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextromethorphan, and diphenhydramine on nightly cough and sleep quality in children and their parents. J Altern Complement Med 2010;16:787-793.
11 Cohen HA, Rozen J, Kristal H, Laks Y, Berkovitch M, Uziel Y, et al. Effect of honey on nocturnal cough and sleep quality: a double-blind, randomized, placebo-controlled study. Pediatrics 2012;130:465-471.
12 Canciani M, Murgia V, Caimmi D, Anapurapu S, Licari A, Marseglia GL. Efficacy of Grintuss® pediatric syrup in treating cough in children: a randomized, multicenter, double-blind, placebo-controlled clinical study. Ital J Pediatr 2014;40:56.
13 Mallet P, Mourdi N, Dubus JC, Bavoux F, Boyer-Gervoise MJ, Jean-Pastor MJ, et al. Respiratory paradoxical adverse drug reactions associated with acetylcysteine and carbocysteine systemic use in paediatric patients: a national survey. PloS One 2011;6:e22792.
14 Chalumeau M, Duijvestijn YC. Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic-pulmonary disease. Cochrane Database Syst Rev 2013;5:CD003124.
15 Footitt J, Johnston SL. Cough and viruses in airway disease: mechanisms. Pulm Pharmacol Ther 2009;22:108-113.
16 Dicpinigaitis PV. Effect of viral upper respiratory tract infection on cough reflex sensitivity. J Thorac Dis 2014;6:S708-S711.
17 Morice AH. The cough hypersensitivity syndrome: a novel paradigm for understanding cough. Lung 2010;188:S87-S90.
18 Morice AH, McGarvey LP, Dicpinigaitis PV. Cough hypersensitivity syndrome is an important clinical concept: a pro/con debate. Lung 2012;190:3-9.
19 Davenport PW. Urge-to-cough: what can it teach us about cough? Lung 2008;186:S107-S111.
20 Dicpinigaitis PV, Bhat R, Rhoton WA, Tibb AS, Negassa A. Effect of viral upper respiratory tract infection on the urge-to-cough sensation. Respir Med 2011;105:615-618.
21 Wegener T, Kraft K. Plantain (Plantago lanceolata L.): anti-inflammatory action in upper respiratory tract infections. Wien Med Wochenschr 1999;149:211-216.[In German]
22 Franz G. Polysaccharides in pharmacy: current applications and future concepts. Planta Med 1989;55:493-497.
23 Nosalova G, Fleskova D, Jurecek L, Sadlonova V, Ray B. Herbal polysaccharides and cough reflex. Respir Physiol Neurobiol 2013;187:47-51.
24 Israili ZH. Antimicrobial properties of honey. Am J Ther 2014;21:304-323.
25 White JW. Composition of honey. In: Crabe E, eds. Honey: A comprehensive survey. New York, NY: Crane, Russak Company, 1975: 157-206.
26 Gheldof N, Engeseth NJ. Antioxidant capacity of honeys from various floral sources based on the determination of oxygen radical absorbance capacity and inhibition of in vitro lipoprotein oxidation in human serum samples. J Agric Food Chem 2002;50:3050-3055.
27 Oduwole O, Meremikwu MM, Oyo-Ita A, Udoh EE. Cochrane in context: Honey for acute cough in children. Evid Based Child Health 2014;9:401-444.
28 Warren MD, Pont SJ, Barkin SL, Callahan ST, Caples TL, Carroll KN, et al. The effect of honey on nocturnal cough and sleep quality for children and their parents. Arch Pediatr Adolesc Med 2007;161:1149-1153.

Received October 26, 2015
Accepted after revision February 15, 2016