Xylitol Syrup for the Prevention of Acute Otitis Media

WHAT’S KNOWN ON THIS SUBJECT: Xylitol given as a gum or syrup 5 times daily has been shown to reduce the incidence of acute otitis media in children, but this dosing schedule is unlikely to be feasible for many families.

WHAT THIS STUDY ADDS: A regimen of viscous xylitol syrup in a dose of 5 g 3 times daily was ineffective in preventing recurrences of acute otitis media in otitis-prone children.

abstract

BACKGROUND: Acute otitis media (AOM) is a common childhood illness and the leading indication for antibiotic prescriptions for US children. Xylitol, a naturally occurring sugar alcohol, can reduce AOM when given 5 times per day as a gum or syrup, but a more convenient dosing regimen is needed for widespread adoption.

METHODS: We designed a pragmatic practice-based randomized controlled trial to determine if viscous xylitol solution at a dose of 5 g 3 times per day could reduce the occurrence of clinically diagnosed AOM among otitis-prone children 6 months through 5 years of age.

RESULTS: A total of 326 subjects were enrolled, with 160 allocated to xylitol and 166 to placebo. In the primary analysis of time to first clinically diagnosed AOM episode, the hazard ratio for xylitol versus placebo recipients was 0.88 (95% confidence interval [CI] 0.61 to 1.3). In secondary analyses, the incidence of AOM was 0.53 episodes per 90 days in the xylitol group versus 0.59 in the placebo group (difference 0.06; 95% CI −0.25 to 0.13); total antibiotic use was 6.8 days per 90 days in the xylitol group versus 6.4 in the placebo group (difference 0.4; 95% CI −1.8 to 2.7). The lack of effectiveness was not explained by nonadherence to treatment, as the hazard ratio for those taking nearly all assigned xylitol compared with those taking none was 0.93 (95% CI 0.56 to 1.57).

CONCLUSIONS: Viscous xylitol solution in a dose of 5 g 3 times per day was ineffective in reducing clinically diagnosed AOM among otitis-prone children. Pediatrics 2014;133:1–7
Acute otitis media (AOM) is one of the most common illnesses in childhood, affecting 80% to 90% of children by the age of 5 years. More than 20% of US children suffer recurrent AOM, usually defined as 3 episodes within 6 months or 4 within a year. AOM results in more than 20 million office visits annually in the United States, and is the leading cause of antibiotic use among US children, accounting for ~13 million prescriptions annually, 30% of all pediatric antibiotic prescriptions. The widespread use of antibiotics for AOM has contributed to the dramatic increase in antimicrobial resistance, a major public health threat.

A promising approach for the prevention of AOM involves the use of xylitol, a 5-carbon naturally occurring sugar alcohol. Xylitol has long been known to have antibacterial properties, especially in suppressing the growth of Streptococcus mutans, a major cause of dental caries; xylitol chewing gum has been shown to prevent dental decay in children. Furthermore, in vitro studies showed that xylitol suppresses the growth of Streptococcus pneumoniae and reduces the epithelial cell adhesion of both S. pneumoniae and Haemophilus influenzae. 

The clinical use of xylitol to prevent AOM was first described by Finnish researchers in 1996. In a randomized controlled trial, Uhari et al. found that children who chewed gum containing 1.7 g of xylitol 5 times daily had significantly fewer episodes of AOM and less antibiotic use than controls. In 1998, the same researchers reported results of another randomized clinical trial, which replicated their findings among children old enough to chew gum, and also demonstrated that, among younger children, xylitol given as an oral solution in a dose of 2 g 3 times daily reduced the incidence of AOM by 30% over a 12-week study period. Despite these findings, xylitol has not entered widespread use, presumably because consistent 5 times daily treatment is not feasible for most families. The Finnish investigators who performed the original studies of xylitol for AOM prevention attempted 2 strategies aimed at more convenient use: 5 times daily dosing given only during episodes of upper respiratory illness and daily xylitol solution dosed at 3.2 g 3 times daily, both of which proved ineffective.

The maximal dose of xylitol, like that of all sugar alcohols, is limited by osmotic diarrhea. To identify the maximal tolerated dose of xylitol solution in young children, we previously conducted a clinical trial examining the effects of escalating doses of oral xylitol solution. We found that a dose of 5 g delivered 3 times daily was tolerated in infants as young as 6 months of age, thus allowing a total daily dose of 15 g, a 50% increase in the total daily dose used in the negative 3 times daily study by Uhari et al. Furthermore, after completion of our dosing study, a viscous oral xylitol solution became available that included 2 mucosal adherence agents (carboxymethylcellulose and potato starch) intended to enhance the effect of xylitol by prolonging its contact with the pharyngeal mucosa. Although previously studied xylitol solutions did not contain such agents, this strategy has been used in other medication preparations intended to work at the mucosal level. Therefore, by using the 2 strategies of dose maximization and mucosal adherence agents, we designed a pragmatic randomized controlled trial of viscous oral xylitol solution given as daily prophylaxis in a dose of 5 g 3 times daily to otitis-prone children with the goal of reducing episodes of clinically diagnosed AOM and antibiotic use.

**METHODS**

We invited physicians from 3 pediatric practice-based networks to participate: the Slone Center Office-based Research Network at Boston University, the Pediatric Physicians’ Organization at Children’s (Boston), and the North Carolina Child Health Research Network at the University of North Carolina. Participating physicians were asked to identify eligible subjects in the course of their routine clinical practice and, optionally, by reviewing medical records for children who met screening criteria. When potentially eligible subjects were identified and if the parent/guardian (hereafter, “parent”) agreed, parent contact information was faxed or mailed to the study coordinating center. Study staff then telephoned the parent of each referred child to confirm eligibility and obtain informed consent. Inclusion criteria consisted of the following: age 6 to 71 months, history of at least 3 clinically diagnosed episodes of AOM in the previous 12 months with at least 1 in the previous 6 months, general good health (defined as a lack of chronic medical conditions requiring ongoing pharmacologic treatment with the exception of acid suppression therapy for gastroesophageal reflux disease and treatment of asthma/reactive airways disease), and English or Spanish speaking. Potential subjects were excluded if they had a history of tympanostomy tubes or had diabetes mellitus or inborn errors of metabolism (because of uncertain effects of sugar alcohols in these conditions).

Once informed consent was obtained, subjects were randomized in a 1:1 ratio to xylitol or placebo solution. The randomization was stratified by referring practice and arranged in randomly permuted blocks of 2 and 4. The xylitol solution (Xylarex; Arbor Pharmaceuticals, Atlanta, GA) consisted of a 66.7% aqueous xylitol solution with the addition of...
carboxymethylcellulose and potato starch as mucosal adherence agents and natural flavoring. The placebo consisted of a 30% sorbitol solution with identical additives that was indistinguishable in appearance and taste from the active treatment; studies have demonstrated that sorbitol, although similar in appearance and taste to xylitol, does not share its antibacterial properties. The dose of each syrup was 7.5 mL 3 times daily for 12 weeks (ie, 5 g xylitol per dose in the active treatment group or 2.25 g sorbitol per dose in the placebo group). After randomization, study materials, including the blinded study syrup, appropriate oral syringes, and a study calendar, were shipped to the subject’s home. A telephone interview was conducted within 3 days of shipment delivery to ensure receipt of the study materials and to review the study protocol. Three follow-up telephone interviews were conducted at ∼1, 2, and 3 months after enrollment. In each interview, the parent was asked whether the subject had had any unscheduled visits to a health care provider since the previous contact and, if so, for what reasons; a list of possible reasons for such visits, including “ear infection” among other common pediatric illnesses, was then read to the parent to ensure that all visits were reported. Adherence was assessed by asking the parent at each interview how much of the recommended syrup the subject had taken since the last interview (“All or nearly all of the doses,” “More than half of the doses, but not all,” “Less than half of the doses,” and “None or nearly none of the doses”). At the end of the study, medical records from each subject’s primary care physician and from any other health care provider whom the parent identified as having treated the subject during the study period were obtained and reviewed by the principal investigator (L.V.) in a blinded fashion.

For the primary outcome of clinical diagnoses of AOM, the medical record was considered the gold standard. For those cases in which the medical record was not available, the parent’s report of AOM diagnoses was used. Our previous research has demonstrated that parents’ recall of recent episodes of AOM is highly accurate. We calculated that 408 evaluable subjects would be needed to provide 90% power to detect a 35% decrease in the hazard rate for AOM. Such a decrease would reduce the 3-month cumulative incidence of AOM from the anticipated 60% in the placebo group (our a priori estimate) to 45% in treated subjects. A total of 304 evaluable subjects would provide 80% power for the same effect. All analyses were based on the intention-to-treat principle. For the primary analysis, we compared the time to first clinically diagnosed AOM episode after randomization in the 2 study groups using a proportional hazards model. For secondary analyses, we compared the proportion of subjects in each group with no AOM episodes and no antibiotic use by Fisher exact test, as well as the incidence of AOM episodes per 90 days and antibiotic use per 90 days between groups by 2-tailed t test. For the comparison of incidence, rates were calculated individually (events divided by days of enrollment), assuming a zero rate for the 12 subjects with no follow-up. The t test was weighted by duration of enrollment. The results were corroborated by Poisson regression comparing event counts using length of enrollment as an offset variable.

This project was approved by the institutional review boards of Boston Children’s Hospital, Boston University Medical Center, and the University of North Carolina, Chapel Hill, and was performed under Food and Drug Administration Investigational New Drug application number 107246. The study was registered at www.clinicaltrials.gov (NCT01044030). There were no financial incentives paid to parents/subjects or to enrolling practices, except a nominal reimbursement for staff time involved in referring potentially eligible patents.

RESULTS

A total of 142 practices agreed to participate in the study and 97 of them referred 1 or more patients during the recruitment period from March 2010 through March 2012. Study enrollment and follow-up is summarized in Fig 1. Overall, 778 children were referred to the study for eligibility review; 452 were not enrolled. The remaining 326 were randomized with 160 allocated to xylitol and 166 to placebo. Two subjects in the xylitol group and 3 in the placebo group declined further participation. Four subjects in the xylitol group and 3 in the placebo group were lost to follow-up without any outcome information. Medical records to identify clinically diagnosed AOM episodes during the 12-week study period were obtained for 312 subjects (95.7% of those enrolled).

Baseline characteristics comparing subjects in the xylitol and placebo groups are shown in Table 1. The 2 groups were comparable with respect to demographics and known AOM risk factors.

In the primary analysis of time to first clinically diagnosed AOM episode, the hazard ratio for subjects in the xylitol group versus the placebo group was 0.88 (95% confidence interval [CI] 0.61 to 1.27; Fig 2). As a secondary analysis, we examined the incidence of clinically diagnosed AOM episodes and antibiotic use (Table 2). There were 107 subjects (66.9%) in the xylitol group and 105 subjects (63.3%) in the placebo group who had no episodes of AOM during their study participation (difference 3.6%; 95% CI –6.7% to 14.0%) and the
incidence of clinically diagnosed AOM was 0.53 episodes per 90 days in the xylitol group versus 0.59 in the placebo group, for an absolute difference of 0.06 fewer episodes per subject per 90 days in the xylitol group (95% CI for the difference –0.25 to 0.13). Ninety-seven subjects (60.6%) in the xylitol group versus 93 (56.0%) in the placebo group had no antibiotic use during their study participation (P = .4). Total antibiotic use was 6.8 days per subject per 90 days in the xylitol group versus 6.4 in the placebo group for an absolute difference of 0.4 more days of antibiotic use per subject per 90 days in the xylitol group (95% CI for the difference –1.8 to 2.7). Of all antibiotics taken during the study period, 1439 (78.2%) of 1841 days of use were for AOM. The incidence of AOM-related antibiotic use was 5.2 days per subject per 90 days in

### TABLE 1 Baseline Comparison of Study Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Xylitol, n = 160</th>
<th>Placebo, n = 166</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo, mean (SD)</td>
<td>22.3 (13.7)</td>
<td>21.5 (13.7)</td>
<td>.6</td>
</tr>
<tr>
<td>Girls, n (%)</td>
<td>67 (41.9)</td>
<td>73 (44.0)</td>
<td>.7</td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td></td>
<td></td>
<td>.9</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>110 (68.8)</td>
<td>114 (68.7)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>25 (15.6)</td>
<td>22 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>7 (4.4)</td>
<td>8 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown/refused</td>
<td>18 (11.3)</td>
<td>22 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Out-of-home day care, n (%)</td>
<td>73 (45.6)</td>
<td>78 (47.0)</td>
<td>.7</td>
</tr>
<tr>
<td>No. additional children in home, n (%)</td>
<td></td>
<td></td>
<td>.6</td>
</tr>
<tr>
<td>0</td>
<td>44 (27.5)</td>
<td>52 (31.3)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>70 (43.8)</td>
<td>58 (34.9)</td>
<td></td>
</tr>
<tr>
<td>2 or more</td>
<td>37 (23.1)</td>
<td>43 (25.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (5.6)</td>
<td>13 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Currently breastfeeding, n (%)</td>
<td>12 (7.5)</td>
<td>15 (9.0)</td>
<td>.8</td>
</tr>
<tr>
<td>Ever breastfed, n (%)</td>
<td>119 (74.4)</td>
<td>110 (66.3)</td>
<td>.3</td>
</tr>
<tr>
<td>Tobacco smoking in home, n (%)</td>
<td>28 (17.5)</td>
<td>28 (15.7)</td>
<td>.7</td>
</tr>
<tr>
<td>Daily pacifier use, n (%)</td>
<td>44 (27.5)</td>
<td>48 (28.9)</td>
<td>.7</td>
</tr>
<tr>
<td>Enrollment season, n (%)</td>
<td></td>
<td></td>
<td>.97</td>
</tr>
<tr>
<td>Winter</td>
<td>43 (26.9)</td>
<td>45 (27.1)</td>
<td></td>
</tr>
<tr>
<td>Spring</td>
<td>77 (48.1)</td>
<td>81 (48.8)</td>
<td></td>
</tr>
<tr>
<td>Summer</td>
<td>23 (14.4)</td>
<td>25 (15.1)</td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>17 (10.6)</td>
<td>15 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Time from most recent AOM, d, mean (SD)</td>
<td>53.1 (38.8)</td>
<td>48.1 (35.3)</td>
<td>.2</td>
</tr>
</tbody>
</table>
the xylitol group versus 5.1 in the placebo group (absolute difference 0.1 days; 95% CI for difference –1.9 to 2.2).

In terms of adherence to the assigned treatment, among subjects for whom follow-up information was available, 43 (27.9%) of 154 subjects in the xylitol group and 38 (23.8%) of 160 subjects in the placebo group discontinued treatment before the end of the study period or the occurrence of the primary outcome. The most common reasons were gastrointestinal side effects (18 in the xylitol group and 11 in the placebo group), the subject refusing to take the solution (8 in each group), and the parent becoming too busy or finding the treatment too difficult to administer (8 xylitol, 5 placebo). To determine whether adherence to therapy had an effect on the primary outcome, we analyzed the time to first AOM episode in those subjects reported to have taken all or nearly all of the assigned xylitol syrup throughout the study period (n = 60) compared with those taking no xylitol (ie, placebo group plus subjects assigned xylitol who took no study syrup, n = 183). The hazard ratio for those taking all assigned xylitol syrup compared with this control group was 0.93 (95% CI 0.56 to 1.57).

No study-related serious adverse events occurred in either study group. To estimate the frequency of side effects that might be attributable to the use of xylitol, we examined the rates of parent-reported diarrhea, flatulence, and abdominal pain. As shown in Table 3, the proportion of subjects experiencing these adverse events and the incidence of each did not differ between study groups.

**DISCUSSION**

In this pragmatic practice-based clinical trial, we found that viscous xylitol syrup given in a dose of 5 g 3 times daily did not appreciably reduce the time to first clinically diagnosed AOM episode, the incidence of AOM, or overall antibiotic use. Our primary result, a 12% reduction in the AOM hazard rate among the xylitol group, was not significantly significant, with the 95% CI ranging from a 39% decrease to a 27% increase.

What are the most likely reasons that xylitol treatment was not effective in our study when it was found to be effective in 2 previous clinical trials? One possible explanation is that, in contrast to the positive studies of Uhari et al., we enrolled only otitis-prone children who had already suffered at least 3 episodes of AOM in the previous year and who may have had middle ear effusions at the time of enrollment. Both positive Finnish studies enrolled children with a range of AOM history, from no episodes to more than 5, and the second study (involving children of a comparable age to our sample) only enrolled children who were free of middle ear effusion at the time of enrollment. We chose to enroll children with a history of recurrent AOM and not to exclude children with middle ear effusions both to mimic what we would expect to occur in real-world clinical practice and because we think it is highly unlikely that parents of children without a history of AOM would choose to give their children a daily preventive treatment. However, children with a history of recurrent AOM are likely already to be heavily colonized with...
AOM-causing bacteria and thus may not respond as well to xylitol as those with no or only light colonization. This hypothesis deserves further study. Another possibility is that, despite a substantial increase in the amount of xylitol per dose and per day over previous studies and despite the addition of mucosal adherence agents to the xylitol solution, 3 times daily dosing is still insufficiently frequent to achieve a measurable reduction in AOM incidence. However, if 5 (or even 4) doses per day are required for a beneficial effect, xylitol treatment may not be practical given the poor adherence known to occur with chronic medication dosing of 4 times a day or more. An additional possibility to explain our finding may relate to the definition of the primary study outcome. Our study compared the incidence of clinically diagnosed AOM episodes between the study groups. AOM diagnoses were made by a wide range of clinicians and were not otherwise verified. We chose this method of assessing the primary outcome to mimic what we would expect to occur in real-world clinical practice. However, the diagnosis of AOM by practicing clinicians is thought to be inexact and assuming that AOM diagnoses were equally inaccurate in both study groups, the overall effect would be to bias the study toward a null result. Yet, we believe that if the effectiveness of xylitol as used in this study is inadequate to reduce clinical AOM diagnoses and subsequent antibiotic use, then it has limited utility in real-world practice. Finally, lack of adherence to the intervention may be a reason for the lack of observed effect. In the previous clinical trials in which xylitol was found effective, at least 3 of the 5 daily doses were administered in a controlled day care setting, whereas all of our doses were administered by parents or other routine caregivers. In our study, approximately two-thirds of subjects completed the course of therapy through the primary end point. This adherence rate is similar to what is known about adherence to chronic medication treatment and reflects the level of treatment likely to be achieved in clinical practice. To evaluate whether adherence was the main reason for our lack of observed effect, we performed a secondary analysis comparing those with high adherence to the xylitol treatment to those with no xylitol consumption; this analysis did not demonstrate a more protective effect of treatment than the primary analysis, suggesting that lack of adherence was not the reason for our overall negative result.

An important limitation of our study was that its power was somewhat lower than planned. We anticipated having 90% power to detect a 35% decrease in the AOM hazard rate but a post hoc power calculation demonstrated that our study had ~80% power to detect a 40% decrease in the hazard rate. Our relative lack of power was due to 2 factors. First, the rate of AOM episodes in the control group was lower than expected with only 38% of subjects experiencing an AOM episode during the study period compared with the expected 60%. Second, a smaller proportion of subjects referred to the study by their primary care providers were successfully enrolled. The 778 patients referred to the study exceeded our prestudy expectations, but we were able to enroll only 326 of them, lower than the number anticipated. Despite this limitation, we believe our study provides a clinically relevant negative result in that treatment with xylitol resulted in only an additional 3.6% of children remaining AOM-free throughout their study participation, with an upper 95% confidence limit for this estimate of 14%. We feel this result excludes a benefit sufficiently large for most parents and clinicians to accept the burdens of 3 times daily prophylactic treatment.

### CONCLUSIONS

Viscous xylitol syrup in a dose of 5 g 3 times daily was ineffective in reducing the occurrence of clinically diagnosed AOM among otitis-prone children.

### ACKNOWLEDGMENTS

We greatly appreciate the contributions of Fiona Rice (study coordinator), Michael Bairos (information systems), Katherine Mooney and Rachel Burns (research assistants/subject interviewers), Kathleen Grellmann and Maryellen McDonough (research nurses), and Qiaoli (Lily) Chen (generation of randomization assignments). We also would like to thank the many pediatricians who took time from their busy practices to refer their patients to the study.

---

**TABLE 3** Gastrointestinal-related Adverse Events According to Study Group

<table>
<thead>
<tr>
<th>Event</th>
<th>Xylitol, n = 160</th>
<th>Placebo, n = 166</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with ≥1 episode, n (%)</td>
<td>80 (50.0)</td>
<td>84 (50.6)</td>
<td>−0.6 (−11.5 to 10.5)</td>
<td>.9</td>
</tr>
<tr>
<td>Episodes per subject per 90 d, mean (SE)</td>
<td>0.85 (0.08)</td>
<td>0.77 (0.07)</td>
<td>0.08 (−0.13 to 0.28)</td>
<td>.5</td>
</tr>
<tr>
<td><strong>Flatulence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with ≥1 episode, n (%)</td>
<td>32 (20.0)</td>
<td>35 (21.1)</td>
<td>−1.1 (−9.9 to 7.7)</td>
<td>.9</td>
</tr>
<tr>
<td>Episodes per subject per 90 d, mean (SE)</td>
<td>0.26 (0.04)</td>
<td>0.26 (0.04)</td>
<td>0.00 (−0.12 to 0.12)</td>
<td>.99</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with ≥1 episode</td>
<td>15 (9.4)</td>
<td>8 (4.8)</td>
<td>4.6 (−1.0 to 10.1)</td>
<td>.1</td>
</tr>
<tr>
<td>Episodes per subject per 90 d</td>
<td>0.14 (0.04)</td>
<td>0.06 (0.02)</td>
<td>0.07 (−0.01 to 0.16)</td>
<td>.08</td>
</tr>
</tbody>
</table>
REFERENCES


FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Primarily funded under grant RC1CO101068 from the National Institute on Deafness and Other Communication Disorders. The xylitol and placebo solutions and supplemental funding were provided by Arbor Pharmaceuticals, Atlanta, GA. A portion of Dr Feldman’s time was supported through the Harvard Catalyst and Translational Science Center under grant UL1 RR-025758 from the National Institutes of Health. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

PEDIATRICS Volume 133, Number 2, February 2014
Xylitol Syrup for the Prevention of Acute Otitis Media
Louis Vernacchio, Michael J. Corwin, Richard M. Vezina, Steven I. Pelton, Henry A. Feldman, Tamera Coyne-Beasley and Allen A. Mitchell
Pediatrics; originally published online January 6, 2014;
DOI: 10.1542/peds.2013-2373

Updated Information & Services
including high resolution figures, can be found at:
/content/early/2014/01/01/peds.2013-2373

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Xylitol Syrup for the Prevention of Acute Otitis Media
Louis Vernacchio, Michael J. Corwin, Richard M. Vezina, Steven I. Pelton, Henry A. Feldman, Tamera Coyne-Beasley and Allen A. Mitchell
Pediatrics; originally published online January 6, 2014;
DOI: 10.1542/peds.2013-2373

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/early/2014/01/01/peds.2013-2373