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A Novel Use of Xylitol Sugar in Preventing Acute Otitis Media

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ABSTRACT. *Background.* **Xylitol, a commonly used sweetener, is effective in preventing dental caries. As it inhibits the growth of pneumococci, we evaluated whether xylitol could be effective in preventing acute otitis media (AOM).**

Design. **Altogether, 857 healthy children recruited from day care centers were randomized to one of five treatment groups to receive control syrup (n = 165), xylitol syrup (n = 159), control chewing gum (n = 178), xylitol gum (n = 179), or xylitol lozenge (n = 176). The daily dose of xylitol varied from 8.4 g (chewing gum) to 10 g (syrup). The design was a 3-month randomized, controlled trial, blinded within the chewing gum and syrup groups. The occurrence of AOM each time the child showed any symptoms of respiratory infection was the main outcome.**

Results. **Although at least one event of AOM was experienced by 68 (41%) of the 165 children who received control syrup, only 46 (29%) of the 159 children receiving xylitol syrup were affected, for a 30% decrease (95% confidence interval [CI]: 4.6%–55.4%). Likewise, the occurrence of otitis decreased by 40% compared with control subjects in the children who received xylitol chewing gum (CI: 10.0%–71.1%) and by 20% in the lozenge group (CI: −12.9%–51.4%). Thus, the occurrence of AOM during the follow-up period was significantly lower in those who received xylitol syrup or gum, and these children required antimicrobials less often than did controls. Xylitol was well tolerated.**

Conclusions. **Xylitol sugar, when given in a syrup or chewing gum, was effective in preventing AOM and decreasing the need for antimicrobials. *Pediatrics* 1998; 102:879–884; *xylitol, otitis media, prevention, syrup, chewing gum.***

ABBREVIATIONS. AOM, acute otitis media; CI, confidence interval; PYR, person years at risk; URT, upper respiratory tract.

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During 1990, an estimated 24.5 million visits were made to office-based physicians in the United States at which the principal diagnosis was otitis media, about 2.5 times more visits than in 1975.[1] Otitis media causes significant economic costs both to parents and to the health care system.[2,3] Recurrent acute otitis media (AOM) may even lead to long-term sequelae in the form of learning difficulties, especially in reading and mathematics.[4,5] Thus, for children, parents, and society in general, the prevention of recurrent AOM would be more effective than the treatment of each episode separately. Surgery, in the form of tympanostomy and adenoidectomy, is effective in preventing the recurrences.[6,7] The reported estimates of the efficacy of antimicrobial prophylactics vary.[8–10]

In addition to the question of efficacy, antimicrobial prophylactics are problematic because of the potential development of resistant bacterial strains. Prophylactic and frequent use of antimicrobials, especially in day care children, is responsible for the spread of nasopharyngeal carriage of penicillin-resistant pneumococci.[11,12] Otitis media is a separate risk factor increasing the probability carrying resistant pneumococci on the nasopharynx.[11] Medication is prescribed at ~84% of all visits for otitis media.[1] Because a decrease in the use of macrolide antibiotics resulted in a reduction in streptococcal resistance to it,[13] measures that would decrease the use of antimicrobials and the occurrence of otitis media would most probably inhibit the development and spread of antimicrobial resistant bacteria. A need exists for a simple and safe alternative approach to prevent recurrences of AOM episodes.

Xylitol is a five-carbon polyol that has been used widely as a sweetening substitute for sucrose because xylitol has preventive effect on dental caries.[14,15] This beneficial effect of xylitol is mediated by inhibiting the growth of *Streptococcus mutans*, bacteria causing dental caries.[16] We found that adding xylitol to the growth media inhibited the growth of *Streptococcus pneumoniae*.[17] This inhibition was statistically significant already when the media contained

1% xylitol and increased in the concentrations of 5% xylitol.[17] In the mouth, it is easy to achieve these concentrations using chewing gum sweetened with xylitol.

In a randomized, controlled, double-blind study comparing xylitol chewing gum with sucrose chewing gum, we observed a significant decrease in the occurrence of AOM in those who received xylitol chewing gum.[18] In that study, the participating children were older than those at greatest risk for developing AOM because they had to be able to chew gum. Thus, we decided to do a new randomized, controlled trial in which we compared xylitol syrup, xylitol chewing gum, and xylitol lozenges to control subjects who received low doses of xylitol.

METHODS

Subject Enrollment and Assignment

This study was conducted in the Department of Pediatrics, University of Oulu, and the subjects were recruited from the day care centers in the city of Oulu between September and December 1996. The ethical committee of the Oulu Municipal Health Center approved the study protocol. Subjects were recruited from 34 typical day care centers for healthy children. We organized evening sessions in which the aims and procedures of the study were explained to the parents, and all healthy children not receiving antimicrobial prophylactics whose parents gave informed consent were recruited. Children with a congenital craniofacial malformation or a structural middle ear abnormality were excluded. No other exclusion criteria were given on the basis of the history of AOM.

History of ear infections and risk factors for AOM were obtained from the parents for each child. Before the trial began, tympanometry was performed on all children and their ear status recorded. Those with abnormal tympanography findings were examined with pneumatic otoscopy, and middle ear effusions were treated and effusion had to be cleared before the child was entered into the study.

Follow-up and Diagnostic Procedures

During the 3-month follow-up, a study nurse examined all the children with any respiratory infections with tympanometry within 3 days of the beginning of the symptoms. The follow-up examinations were performed on an outpatient basis. Tympanograms were classified according to the method described by Jerger.[19] If tympanometry was normal (A-curve), the child was reexamined weekly after the beginning of the symptoms until the end of the study. If the tympanogram was abnormal (B- or C-curves) or unsuccessful, or if the child had complained of earache, a pediatrician examined the child with pneumatic otoscopy of both ears. We had validated the tympanometry used in this trial (MicroTymp, Welch Allyn, Finland) against the weight of middle ear effusion.[20] Two devices were used.

The diagnosis of AOM required the finding of middle ear effusion in tympanometry (B- or C-curve), verified otoscopically with signs of inflammation in the tympanic membrane, and the presence of symptoms of acute respiratory infection (rhinitis, cough, conjunctivitis, sore throat, earache).[21] Otoscopy was validated against tympanocentesis and tympanometry. If the diagnosis of AOM was made after our office hours by another physician, the child was reexamined the next day and the diagnosis confirmed with tympanometry and pneumatic otoscopy. Otorrhea from a patent tympanostomy tube was counted as AOM. Children with AOM were treated with antimicrobials for 7 days and examined weekly. A new episode of AOM was recorded only after the effusion had disappeared completely.

Administration of the Preparations and Compliance

If the participating children were so young that they were unable to chew gum, they were randomized to receive either control syrup or xylitol syrup (5 mL 5 times per day after a meal). The control syrup was sweetened with xylitol in a concentration of 20 g/L, for a daily dose of 0.5 g of xylitol. The xylitol syrup consisted of xylitol 400 g/L, for a daily dose of 10 g of xylitol (Fig 1). Xylitol was used as a sweetener in the control groups as well, to avoid the possible harmful effects of sucrose, which was not done in our earlier trial and was criticized in that study.[22] The syrups were administered from a syringe in several small doses to prolong the time xylitol stayed in the mouth. Leiras Pharmaceuticals (Turku, Finland) and Orion-Farmos Pharmaceuticals (Helsinki, Finland) donated the xylitol syrups.

The children who were able to chew gum were randomized to receive either a control chewing gum sweetened with sucrose and xylitol (control group) or xylitol chewing gum sweetened with xylitol only (xylitol group) or lozenges sweetened with xylitol and maltitol (lozenge group). Two pieces of gum and three lozenges were given 5 times a day after a meal. The children chewed the gum and the lozenges for at least 5 minutes or as long as it tasted sweet. In the control chewing gum group, the daily xylitol dose was 0.5 g, and in the xylitol chewing gum group, 8.4 g. Children receiving lozenges got 10 g of xylitol per day (Fig 1). The chewing

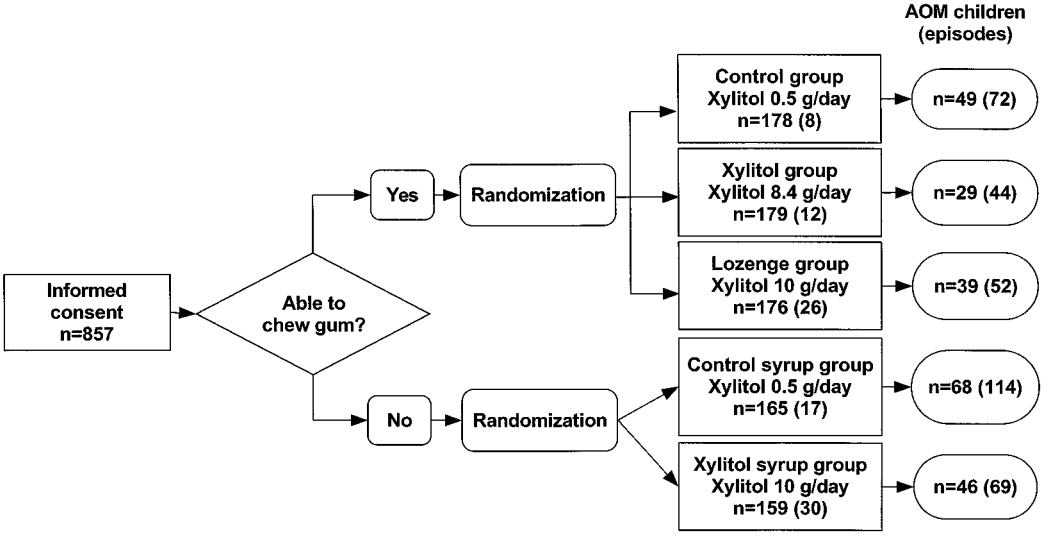

Fig 1. Trial design: Children were allocated to two groups according to their ability to chew gum and then randomized within these groups. The number of children in each group is given (rectangular boxes), along with the number of children who dropped out (parenthesis). The number of children with at least one episode of AOM and the total number of AOM episodes are indicated in the last column.

gums and lozenges were donated by Leaf-Huhtamäki (Turku, Finland).

Compliance was followed with daily symptom reports on which parents recorded the given doses. Three of the 5 daily doses were given in the day care center during working days. Unused chewing gums and lozenges were returned to us and counted.

Study Design

The study was double-blind in the syrup and chewing gum groups and open between the chewing gum and lozenge groups. The xylitol syrup was sweeter than the control syrup, but the taste of the chewing gums was quite similar regardless of the sweeteners used. Randomization was performed using tables of random numbers and using a block randomization with a block size of six.[23] We used block randomization to ensure approximately equal numbers of subjects in each study group in each day care center.

Sample Size

Sample size calculations were based on our earlier experience of the occurrence of AOM during a respiratory infection season in children in day care centers. Because we chose a power of 80%, a .05% type 1 error (*P* value), and a 30% decrease in the occurrence of AOM to be clinically significant, a group size of 150 was required.

Statistical Analysis

Analyses of the differences between the treatment groups were performed separately to those randomized to receive syrups and to those receiving chewing gum or lozenge because of the different age distributions and thus different AOM incidence density. Time at risk was summed for each group. A child who dropped out of the study contributed days at risk as long as he/she participated in the study. Incidence density analysis of AOM attacks was calculated for each group, and the rates were standardized for 365 days at risk. The occurrence of AOM episodes and courses of antimicrobials were assumed to follow a Poisson distribution, and differences in incidence rates and 95% confidence intervals (CI) were calculated accordingly.[24] Differences between proportions were tested with a standard normal deviate test and analysis of variance, and Student's *t* test was used to compare means for continuous variables with normal distributions. The Kaplan–Meier method was used to analyze the cumulative occurrence of the first AOM attack during the follow-up. The log rank test was used to test the differences between the cumulative occurrences in the control and active forms of treatment. Most of the statistical analyses were performed using SPSS version for Windows 95.

RESULTS

A total of 857 children were screened with tympanometry and allocated to receive chewing gum/lozenge or syrup on the basis of their ability to chew gum. Of the children receiving syrup, 165 were randomized to receive control syrup and 159 to receive xylitol syrup (Fig 1). Of those who received syrups, 47 did not complete the trial, primarily because the parents ended participation (Table 1). Of the children receiving gum, 178 were randomized to receive control chewing gum, 179 to receive xylitol chewing gum, and 176 to receive lozenges (Fig 1). By chance, there were more girls among those who received xylitol syrup, but fewer girls among those who received xylitol chewing gum or lozenges. Altogether, 46 children dropped out, twice as many in the lozenge group as in the chewing gum groups. The number of forgotten dosages, ~10% of all dosages, was comparable in each treatment group (Table 1). Baseline characteristics of the different treatment groups were similar (Table 1).

Total episodes of any respiratory infection varied from 12.2 episodes per person years at risk (PYR) in children receiving xylitol syrup to 10.0 episodes/PYR in children receiving lozenges. Differences in the treatment groups were not significant (Tables 2, 3). The number of children who remained healthy throughout the follow-up did not differ in the groups (Tables 2, 3).

At least one episode of AOM occurred in 68 of the children receiving control syrup (41%) and 46 children (29%) receiving xylitol syrup; the difference was statistically significant and implied a 30% decrease on receiving xylitol (CI: 4.6%–55.4%; $P = .028$).

TABLE 1. Baseline Characteristics of Subjects, Forgotten Dosages, and Reasons for Dropping Out by Study Group Characteristics

	Syrup		Chewing Gum		Lozenge
	Control (n = 165)	Xylitol (n = 159)	Control (n = 178)	Xylitol (n = 179)	Xylitol (n = 176)
Number of girls	66	79	100	77	73
Mean age (y) ± SD	2.2 ± 1.1	2.2 ± 1.0	4.6 ± 1.3	4.6 ± 1.4	4.7 ± 1.3
Range (y)	0.64 to 6.4	0.8 to 6.6	1.8 to 6.9	1.5 to 6.7	1.9 to 6.7
Breast feeding at least 6 months (%)	94.0	95.1	93.8	94.4	94.4
Current use of pacifier (%)	32.0	28.6	3.5	5.2	1.8
Mean duration of day care (mo) ± SD	8.3 ± 10.4	10.5 ± 12.2	22.1 ± 18.2	23.7 ± 17.7	25.0 ± 17.2
History of AOM (%)					
0 Attacks	19.1	18.6	10.7	12.0	12.3
1–5 Attacks	56.1	50.0	47.9	47.3	42.9
>5 Attacks	24.8	31.4	41.4	40.7	44.8
Adenoidectomy performed (%)	21.8	22.6	28.1	29.6	33.5
Tympanostomy tubes (%)	16.4	13.2	16.3	16.8	21.6
Mother or father smokes (%)	40.6	37.1	41.0	46.9	40.9
Effusion at first check-up (%)	22 (13.3)	19 (11.9)	3 (1.7)	6 (3.4)	10 (5.7)
Mean number of forgotten dosages (%)	49 (11)	49 (11)	35 (8)	39 (9)	49 (11)
Reasons for dropping out and number					
Unwilling to continue taking the product	9	14	7	8	14
Left the area	0	2	0	2	1
Abdominal discomfort	5	8	0	1	7
Reason unknown	3	6	1	1	4
Total (%)	17 (10.3)	30 (18.9)*	8 (4.5)	12 (6.7)	26 (14.8)**

* Statistically significant difference compared with the control group ($P = .029$).
** Statistically significant difference compared with the control group ($P = .001$).

TABLE 2. Incidence Rate of AOM and Courses of Antimicrobials Given During the 3-Month Follow-up in the Children Who Received Control Syrup or Xylitol Syrup

	Syrup		Difference	95% CI*	*P* Value
	Control	Xylitol			
PYR	37.65	34.41			
Number of children who remained healthy	39	30			NS
Incidence rate of URT (upper respiratory tract) infections/PYR	11.0	12.2			
Total number of AOM episodes	114	69			
Incidence rate of AOM/PYR	3.03	2.01	1.02	0.29–1.75	.006
Antimicrobials prescribed (courses)	163	110			
Incidence rate of prescriptions/PYR	4.33	3.20	1.13	0.25–2.01	.012
Number of days on antimicrobials/PYR	31.7	25.0	6.7	4.4–9.2	<.0001

* 95% CI of the difference.

TABLE 3. Incidence Rate of AOM and Courses of Antimicrobials Given During the 3-Month Follow-up in the Children Who Received Control or Xylitol Chewing Gum or Xylitol Lozenge

Variable	Chewing Gum		Difference*	95% CI**	*P* Value	Lozenge		95% CI**	*P* Value
	Control	Xylitol				Xylitol	Difference*		
PYR	42.50	42.12				39.2			
Number of children who remained healthy	61	63				68			NS
Incidence rate of URT infections/PYR	11.8	10.6				10.0			
Total number of AOM episodes	72	44				52			
Incidence rate of AOM/PYR	1.69	1.04	0.65	0.14–1.16	.012	1.33	0.36	−0.17–0.89	.18
Antimicrobials prescribed (courses)	96	70				73			
Incidence rate of prescriptions/PYR	2.26	1.66	0.60	0.01–1.12	.046	1.86	0.40	−0.23–1.03	.211
Number of days on antimicrobials/PYR	17.8	11.8	6.0	4.3–7.6	<.0001	13.8	4.0	2.3–5.7	<.0001

* Compared with control chewing gum group.
** 95% CI of the differences.

When plotted against the follow-up time, the patterns of occurrence in the treatment groups differed significantly ($P = .035$, log rank test) (Fig 2). AOM episodes totaled 114 in the control syrup group and 69 in the xylitol syrup group, which was a significant difference (Table 2).

At least one episode of AOM occurred in 49 children (28%) receiving control chewing gum, in 29 receiving xylitol gum (16%), and in 39 receiving lozenges (22%). The difference in occurrence between the control and xylitol chewing gum groups was statistically significant and implied a 40% decrease (CI: 10.0%–71.1%; $P = .025$). The occurrence of AOM was lower in the lozenge group than in the control chewing gum group, but the difference was not statistically significant, implying a 20% decrease (CI: −12.9%–51.4%; $P = .30$). When plotted against the follow-up time, the patterns of AOM occurrence differed significantly among the treatment groups ($P = .031$, log rank test), the occurrence being significantly lower in the xylitol chewing gum group than in the control chewing gum group ($P = .009$, log rank test) (Fig 3), whereas the lozenge group did not differ statistically from the control group ($P = .42$, log rank test). AOM episodes totaled 72 in the control chewing gum group, 44 in the xylitol chewing gum, and 52 in the lozenge group. The difference between the

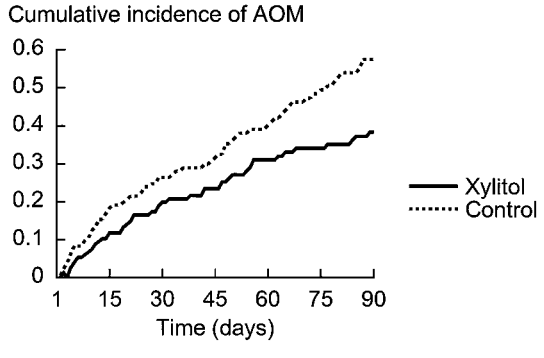

Fig 2. Cumulative occurrence of first attack of AOM during 3-month monitoring period in children who received control syrup or xylitol syrup. The difference between groups is significant ($P = .035$, log rank test).

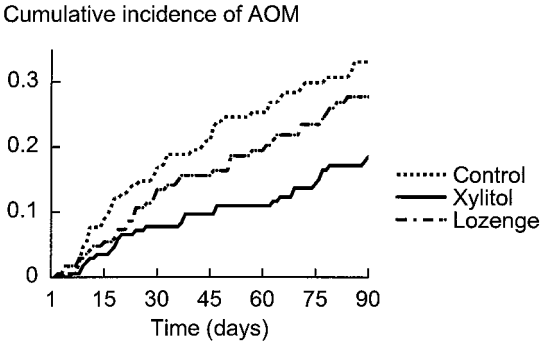

Fig 3. Cumulative occurrence of first attack of AOM during 3-month monitoring period in children who received control chewing gum, xylitol chewing gum, or xylitol lozenge. The overall difference among groups is significant ($P = .031$, overall log rank test), as is that between the control and xylitol chewing gum groups ($P = .0085$, log rank test), but not that between the control chewing gum and xylitol lozenge groups ($P = .42$, log rank test).

control and xylitol chewing groups was significant, but the difference between the control chewing gum and lozenge groups was not (Table 3).

The use of antimicrobials was significantly lower in the xylitol syrup group than in the control group (Table 2). Similarly, prescriptions for antimicrobials decreased significantly in the xylitol chewing gum group compared with the control chewing gum group, but not in the lozenge group (Table 3). The number of days on antimicrobials was significantly lower in each treatment group compared with controls (Table 2, 3).

DISCUSSION

We found a significant reduction in the occurrence of AOM and, consequently, in prescriptions of antimicrobials among the children at day care centers who regularly received xylitol syrup or xylitol chewing gum. All forms of xylitol preparations were effective in decreasing the number of days on antimicrobials. In our previous trial comparing xylitol and sugar chewing gums, we found a similar, significant reduction in the occurrence of AOM in those who received xylitol.[18] Because no other product was included in the comparison, it was claimed that the difference between the groups could be attributable to an increased occurrence of AOM in the sucrose chewing gum group rather than to a decrease in the xylitol group. In the present trial, the decrease in the occurrence of AOM was clearly related to xylitol, which also significantly reduced the need for antimicrobials, as could be expected because AOM is the most common indication for prescribing antimicrobials for young children.

One mechanism of action of xylitol in preventing AOM is its ability to inhibit the growth of pneumococci,[17] although xylitol appears to be so effective that it probably affects other otopathogens as well. We have found xylitol to have antiadhesive properties affecting both pneumococci and *Haemophilus influenzae*.[25] On the other hand, although it can act as a receptor analog inhibiting the adhesion of bacteria to nasopharyngeal cells, it seemed to have no effect on the nasopharyngeal carriage of pneumococci in our previous trial.[18] Thus at present, the preventive effect of xylitol is best explained by its local inhibitory effects on the growth of pneumococci and the inhibition of the adhesion of both pneumococci and *H influenzae* in the nasopharynx.

Whenever they had symptoms of respiratory infections, the children were examined by staff who were unaware of the preparation the child received, although only the two groups receiving chewing gum and the two receiving syrup were mutually blinded. The chewing gums were indistinguishable because even the taste of the gums was very similar. We used tympanometry, in addition to pneumatic otoscopy, to detect middle ear fluid, having found tympanometry to be both sensitive and specific.[20]

AOM is the most common indication for antimicrobial treatment in children. Bacterial resistance to antimicrobial agents is a rapidly growing problem worldwide and is associated with their increased use,[12,13] with young children attending day care centers in particular contributing to the spread of resistant bacteria.[11] Xylitol, a commonly used food sweetener, seems to offer the possibility of preventing AOM in children and reducing the need for antimicrobials. The dose of xylitol used in our trials is significantly higher than that shown to be effective in preventing dental caries.[15] We administered it 5 times a day, but we do not know whether a less frequent dosage would be as effective.

Most children with AOM are younger than age 2 years and thus are unable to chew gum. In this age group, xylitol administered in syrup form was effective in preventing AOM. However, chewing gum appeared to be the most efficient form of dosage in our trial. The lozenges we used were rather large and hard and the children had to take three of them 5 times per day, thus many children tired of sucking them regularly. In any case, xylitol given in lozenge form seems not to be effective enough to prevent the development of AOM.

Xylitol is absorbed slowly by the gut wall and causes osmotic diarrhea when ingested in large amounts; however, children can tolerate daily doses up to 45 g without significant gastrointestinal symptoms.[26] The children who received syrup and lozenges had more abdominal discomfort than those who received chewing gums. It may be that syrup and lozenges are swallowed too fast, causing high concentrations of xylitol in the gut; the same also may explain the ineffectiveness of the lozenges.

We recruited the children from day care centers because they are at greatest risk of developing AOM and because preventive trials are easy to organize there because children and parents can be contacted with less effort. We believe, however, that our results are applicable to all children regardless of their place of care. Many of the children participating in our trial had had several AOM episodes in their history and in several, adenoidectomy had been performed. Adenoidectomy is recommended and actively used in Finland to reduce recurrences of AOM.[21]

With the increasing appearance of antimicrobial resistance, alternatives are needed to prevent bacterial diseases. We found xylitol to be a promising new product, effective in syrup and chewing gums, for preventing AOM in children.

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ON DEVELOPMENTAL MILESTONES

During a recent visit for a facial eruption, an 8-year-old girl was noted to have early lesions of acne. During questioning to uncover evidence of precocious puberty, the mother was asked if the girl had developed any other signs of puberty. The mother answered "No," to which the girl quickly responded, "But Mom, you told me I've developed an attitude!"

Submitted by Robert Haber, MD

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