

Primary care

Effect of recolonisation with “interfering” α streptococci on recurrences of acute and secretory otitis media in children: randomised placebo controlled trial

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BMJ 2001;322:1-4

Abstract

Objective To study the effect of recolonisation with α streptococci with the ability to inhibit the growth of otopathogens (“interfering” activity) on the recurrence of acute otitis media in susceptible children and the effect on the frequency of secretory otitis media.

Design Double blind, randomised, placebo controlled study.

Setting Ear, nose, and throat clinic with three doctors.

Participants 130 children prone to otitis media aged between 6 months and 6 years, 108 of whom were eligible and followed for 3 months.

Main outcome measures Recurrence of otitis media during follow up and a normal tympanic membrane at the last valid visit.

Interventions Children with no recurrences during the last month received phenoxymethylpenicillin (n = 22), and those with a recurrence within 1 month received amoxicillin clavulanic acid (n = 86), both twice daily for 10 days. These were followed by a streptococcal or placebo solution sprayed into the nose for a further 10 days. At day 60 the same spray was started for another 10 days.

Results At 3 months 22 children (42%) given the streptococcal spray were healthy and had a normal tympanic membrane compared with 12 (22%) of those given placebo. This difference was shown separately for recurrences of both acute otitis media and secretory otitis media.

Conclusions Selected bacteria with the ability to inhibit the growth of common otopathogens can be used to protect against recurrent acute otitis media and secretory otitis media in children.

Introduction

Acute otitis media is the most common bacterial infection in young children, and large amounts of antibiotics are prescribed, especially for those with recurrent episodes. The peak incidence of acute otitis media is at 1-2 years of age. The risk of developing another episode within one month after the onset of the primary infection is estimated at 35%.¹ About 5% of children are prone to otitis media, defined as six or more episodes, or recently as three or more episodes, during one year.^{2,3} The recent definition results in a

greater number of children who are considered prone to otitis media.

The most common bacteria associated with acute otitis media are *Streptococcus pneumoniae*, *Haemophilus influenzae* and, less often, *Moraxella catarrhalis* and group A β streptococci. These bacteria originate and spread from the nasopharynx to the middle ear cavity by way of the eustachian tube. Carlin et al showed that 75% of the bacteria associated with recurrent otitis media represented new bacterial strains.¹ The remaining 25% were from either reinfection with the same bacterial strain or treatment failures.

Secretory otitis media is the most common sequela of acute otitis media. One or more of *S pneumoniae*, *H influenzae*, or *M catarrhalis* are found in about 30% of patients with secretory otitis media.³

The importance of normal flora for protecting against infection in an anatomical site has recently been shown in the upper respiratory tract, and lack of bacteria with interfering activity (the ability to inhibit the growth of the common otopathogens), especially the α streptococci, has been associated with a higher incidence of reinfections in patients with streptococcal pharyngotonsillitis.^{4,5} Lower numbers of α streptococci have been found in the nasopharynx of children who are prone to otitis media compared with those who are not prone and in those with secretory otitis media compared with healthy children.⁶⁻⁸ α Streptococci isolated from adenoid tissue have also been shown to have less interfering activity on pathogens associated with acute otitis media than have those isolated from the opening of the eustachian tube.⁹

We aimed to study the effect of recolonisation with α streptococci with interfering activity against the common otopathogens on the recurrence rate of acute otitis media. We also aimed to determine whether the frequency of secretory otitis media was affected by this treatment.

Participants and methods

Study design—From 1996 to 1999 we performed a double blind, randomised study with two arms on 130 children aged between 6 months and 6 years. Randomisation was undertaken by a technician with no access to information on the patients or doctors. Three ear,

nose, and throat specialists at Lundby Hospital, Gothenburg, Sweden, were engaged in the study.

Patients—Children eligible for inclusion in our study were those who had had recurrent otitis media and who had been either referred by their general practitioner or a paediatrician to the open care unit of the ear, nose, and throat department at Lundby Hospital or were directly seeking medical advice for ear pain. The children had had at least two episodes of acute otitis media during the past six months or five episodes during the past year. At the next occurrence of ear pain the children were examined, and those with a red or pale, bulging, thickened tympanic membrane were included in the study. We excluded those with penicillin allergy, serious underlying disease, immunological deficiency, a valvular heart defect, major lesions in the mouth or nose, a grommet in the ear, or chronic otitis media.

Informed written consent was obtained from one of the parents of each eligible child. The study protocol was approved by the Medical Products Agency.

Antibiotic treatment—Those children with no recurrences during the past month but who had acute otitis media were given phenoxymethylpenicillin (Kåvepenin, AstraZeneca, Sweden) 25 mg/kg bodyweight. Those children with a recurrence within the past month were given amoxicillin clavulanic acid (Spektramox, AstraZeneca) 20 mg/kg bodyweight. Both antibiotics were given twice daily for 10 days.

Spray treatment—The streptococcal spray was made up by isolating α haemolytic streptococci from the opening of the eustachian tube of the healthy children and selecting five strains (of about 800 tested) for their superior ability to inhibit the growth of *S pneumoniae*, *H influenzae*, *M catarrhalis*, and *S pyogenes* (group A streptococci), using a method described earlier.¹⁰ The streptococci represented two strains of *S sanguis*, two strains of *S mitis*, and one strain of *S oralis* in equal proportions. They were freeze dried in skimmed milk, reconstituted in 0.9% sodium chloride immediately before use, and kept cold during the treatment period. The mixture corresponded to a suspension of 5×10^8 colony forming units per millilitre. The viable counts in the bottle at the end of treatment still exceeded 5×10^6 colony forming units per millilitre. Placebo comprised skimmed milk powder, with the same texture and colour as the spray. Parents were informed both verbally and in writing on how to give the spray, and this was demonstrated at the first visit. The bottle was given to the doctor at follow up visits to ensure that adequate amounts of spray had been given. At least five days of spray treatment (more than 50% of the suspension) had to be given for the patient to be evaluated for efficacy.

Participant flow and follow up analysis

At the first visit (day 1) the child's medical history and background data were recorded and a clinical examination was performed, including otomicroscopy (this is superior to otoscopy and allows a detailed inspection of the tympanic membrane). A nasopharyngeal swab was taken for bacteriological analysis and a 10 day course of antibiotics prescribed. Information about the study was given both in writing (signed by a parent) and verbally.

At the second visit (days 8-10) the children were examined by otomicroscopy and excluded from the study if signs or symptoms of infection were still present. The parent was given a fresh bottle of spray with instructions to give three puffs into each nostril twice a day for 10 days, starting 2-12 hours after the last dose of antibiotic. At the end of spray treatment the children returned for a third visit (days 25-30), and the children or parents, or both, were interviewed about compliance. At the fourth visit (days 55-60) a further 10 day course of spray treatment was started. The last valid visit was between days 88 and 92. At the third and fifth visits the amount of unused spray in the bottle was recorded. A clinical examination was performed at all visits, the status of the tympanic membranes checked by otomicroscopy, and the clinical response classified as cured (normal tympanic membrane), improved (major decrease in signs and symptoms—only applicable at the second visit), secretory otitis media (signs of middle ear fluid, but no signs of infection), or recurrence (new otitis media).

The children or parents, or both, were advised to seek medical help at any time during the study if there were signs and symptoms of new otitis media. If the children needed help from a doctor other than the three specialists, they took a form with them on which the doctor described the status of the ears and the treatment given. Whether a recurrence had taken place was decided on the basis of the formulary and medical records. Adverse events that were spontaneously reported and information obtained by non-leading questions were recorded at follow up visits. The local ethics committee in Gothenburg approved the study.

Statistics

We used Fisher's exact test and logistic regression, both bivariate and multivariate. We regarded a sample size of 130 patients, 65 in each group, as sufficient for an analysis of the clinical efficacy and safety of treatment. Earlier studies have shown that at least 50% of patients acquire new otitis media during the three months after an episode. We allowed for a drop out rate of 15%.

Results

We excluded 5 of 137 potentially eligible patients for geographical reasons, language problems, or difficulties with follow up. Of 132 children included, 108 (82%) were eligible for analysis of efficacy (53 in the α spray group and 55 in the placebo group) and 126 (95%) for analysis of adverse events. The main reasons for not being eligible for the efficacy analysis were withdrawal from the study or refusal to start spray treatment (eight children), inadequate handling of spray (four), and antibiotic treatment being received for reasons other than acute otitis media (three). The other five patients were either lost to follow up (two), allergic to penicillin (one), or we were unable to determine whether a recurrence had occurred because they were treated by another doctor during the study (two).

The mean age of the children was 23 months. We found no significant differences between the two treatment groups for age, number of siblings, parental proneness to otitis media, allergy, duration of breast feeding, day care, or parental smoking. Recurrence was the only variable that correlated significantly with a

Cure rate in children prone to otitis either recolonised with α streptococci or given placebo. Values are numbers (percentages) unless stated otherwise

	Streptococcal (n=53)*	Placebo (n=55)†	95% CI‡	P value
Cured	22 (42)	12 (22)	0.028 to 0.372	0.02
Recurrence of otitis media during follow up (92 days)	21 (40)	28 (51)	0.065 to 0.285	0.04
Secretory otitis media at last valid visit	10	15	0.074 to 0.286	0.05

*12 treated with penicillin and 41 with amoxicillin clavulanic acid.

†10 treated with penicillin and 45 with amoxicillin clavulanic acid.

‡Difference between proportion cured with streptococcal spray and proportion cured with placebo.

parental history of recurrent acute otitis media during childhood. An age of less than two years was also associated with a higher recurrence rate, but this was not important. Children who had had six or more episodes of acute otitis media during the past year, or two or more during the past six months, were equally distributed between the two treatment groups, and there were no differences in efficacy outcome between these two groups. Only seven children visited another doctor for ear pain during the study.

Of the children receiving the spray, 27 (22 of whom could be evaluated) were given penicillin and 103 (86 of whom could be evaluated) amoxicillin clavulanic acid. These children were equally distributed between the spray and placebo groups.

At inclusion we isolated *M catarrhalis*, *S pneumoniae*, and *H influenzae* from 75 (61%), 66 (54%), and 46 (37%) of 123 children, respectively. More than one of these three species could be isolated from 66 (54%) of the children. *S pneumoniae* was the predominant bacteria in 50 (41%) children. No differences in distribution of the bacteria were found between the spray and placebo groups.

In children given the spray the rate of recurrence during the three months of follow up was significantly reduced compared with those given placebo. Overall, 22 (42%) of the children given spray experienced no acute otitis media during the study and had a normal tympanic membrane at the last valid visit compared with 12 (22%) of the children given placebo (table). Furthermore, 10 (31%) of the 32 children without recurrence who were given the spray had secretory otitis media at the last valid visit compared with 15 (56%) of the 27 children in the placebo group.

Of the 130 children included, 22 in the spray group had adverse events compared with 25 in the placebo group. One child in the placebo group got pneumonia and spray treatment was stopped, and another child in the same group stopped treatment owing to an adverse event.

Discussion

Heredity and age under 2 years are important factors in recurrent otitis media.¹¹ Passive smoking, breast feeding, number of siblings, type of day care, and allergy have also been implicated, but studies of these are not as conclusive.

We found a 50% rate of recurrence of acute otitis media within three months of an episode in children who are prone to otitis despite adequate antibiotic treatment. We also found a high frequency of secretory otitis media. Up to 78% of the children treated with antibiotics and placebo either had a recurrence or still had secretory otitis media after three months.

Antibiotic prophylaxis, either long term seasonal treatment or intermittent treatment in relation to viral infection, is used to reduce the frequency of new episodes of acute otitis media in children with recurrent otitis.^{12, 13} Such treatments have, however, been questioned because of the increasing antibiotic resistance of respiratory tract pathogens. Placement of a tympanostomy tube has been practised and seems to effectively prevent recurrent otitis media in these children.¹³ The procedure, however, carries a risk, is costly, needs to be performed under general anaesthesia, and has complications and sequelae related to the tympanic membrane.¹⁴ Vaccination against pneumococci and *H influenzae* seems to have little impact on the frequency of acute otitis media in children under 2 years.

People who lack interfering α streptococci seem to have more streptococcal throat infections than those with interfering α streptococci on their tonsils.^{4, 5} Furthermore, patients with recurrent streptococcal pharyngotonsillitis have fewer recurrences after recolonisation with a mixture of four α streptococcal strains with good growth inhibiting activity of group A streptococci.^{15, 16}

Nasopharyngeal cultures from children who are prone to otitis or secretory otitis media show low numbers of α streptococci with interfering activity against common pathogens of acute otitis media. We therefore tried to recolonise children prone to recurrent acute otitis media with a mixture of five strains of interfering α streptococci. This resulted in a significantly decreased number of recurrences of acute otitis media in the treated children compared with those given placebo. This difference was also seen in the children with secretory otitis media at the last valid visit.

The results of ecological recolonisation studies, both in patients with streptococcal pharyngotonsillitis and in children with recurrent otitis media, have emphasised the importance of a normal balance between microorganisms in the upper respiratory tract. α Streptococci were used in these studies, but it has recently been shown that other bacteria such as *Prevotella* and *Peptostreptococcus* species have interfering activity on pathogens in the upper respiratory tract and could therefore be candidates for ecological interventions.⁷ Most antibiotics used to treat infections in the upper respiratory tract have an impact on the normal bacterial flora, including the dominating α streptococci. As these bacteria are part of the body's natural defence, treatment with antibiotics abates this part of the defence system and thus facilitates colonisation with pathogenic bacteria. Paradoxically, repeated courses of antibiotics might contribute to recurrent infections in children who are prone to otitis. Restoration of the normal flora would therefore be the logical way to inhibit further recurrences.

In conclusion, recolonisation with α streptococci with inhibitory activity against common pathogens of otitis media significantly diminishes the recurrence rate of this condition in susceptible children. This is also true for secretory otitis media, often arising as a complication of acute otitis media.

Although the number of failures is still high, treatment with α streptococci could be of considerable value owing to the high incidence of acute otitis media

What is already known on this topic

Lack of interfering bacteria, especially the *a* streptococci, has been associated with a high incidence of reinfection in streptococcal pharyngotonsillitis

Lower numbers of *a* streptococci have been found in the nasopharynx of children prone to otitis compared with those who are not and of children with secretory otitis media compared with healthy children

What this study adds

Recolonisation with *a* streptococci with inhibitory activity against common pathogens in the upper respiratory tract diminishes the recurrence rate of acute otitis media in susceptible children

This is also true for secretory otitis media, often seen as a complication of acute otitis media

Treatment with *a* streptococci could help reduce antibiotic consumption

and secretory otitis media in children. Such treatment would also reduce the intake of antibiotics.

Lundby Hospital supported the clinical part of the study by giving access to necessary staff. The authors of this study have been cooperating for over 15 years in the study of recurrent infections in the upper respiratory tract and the present study is a continuation of earlier studies on bacterial interference done by the authors.

Contributors: KR, EGH, and SH formulated the study hypothesis, discussed core ideas, designed the protocol, and evaluated the data. KR coordinated the study and included most of his patients in the study. SH supervised the bacteriological part of the study. EGH was responsible for the selection of interfering *a* streptococci and prepared the streptococcal suspension together with Marie Eklund. Hanna Eklöf monitored the study. Eva Lydén and Carl von Sydow included patients from Lundby Hospital. Hans Stenlund, University of Umeå, was responsible for the statistical analysis. The Medical Products Agency in Uppsala approved the design and suggested minor changes.

Funding: The study was supported by the Swedish National Board for Industrial and Technical Development and the Teknikbro Foundation and grants from Samariten Foundation, Stockholm.

Competing interests: We have been involved in the interference between potentially pathogenic bacteria and apathogens in the upper respiratory tract for many years. This has resulted in several theses at the University of Umeå and Gothenburg. This study is a continuation of ongoing scientific studies covering the upper respiratory tract. We believe that bacterial interference is of importance for the normal defence system and has a clinical impact. We hope that it might be routinely applied as an alternative, or supplement, to antibiotic treatment in the future. We have therefore applied for a patent in some countries for the bacterial strains used in the study.

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(Accepted 29 September 2000)