Clinical Evaluation Findings

Background

Acute Otitis Media is one of the most common pediatric diseases (Marchisio *et al.*, 2004). It is also the most common reason why children are prescribed antibiotics (Wargo *et al.*, 2014). The WHO estimates that 51,000 deaths every year in children younger than 5 years are attributed to complications of acute otitis media, primarily intracranial infections and that chronic suppurative otitis is a major cause of hearing loss in many developing countries. The WHO's estimates suggest that worldwide 65 million to 330 million individuals develop chronic suppurative otitis media, 60% of whom will suffer from hearing impairment (Vergison *et al.*, 2010).

The burden of AOM can have a medical, social and economic on society as well as on the quality of life of the child and family. There is a large unmet need among pediatricians and family physicians to offer prevention strategies for AOM and in turn, reduce the amount of antibiotics consumed by a pediatric population.

What is Acute Otitis Media?

An ear infection is an inflammation of the middle ear, usually caused by bacteria, that occurs when fluid builds up behind the eardrum. Anyone can get an ear infection, but children get them more frequently than adults. An ear infection, also called otitis media, is specifically an infection of the middle ear -- the part that contains tiny bones that transmit sound from the eardrum to the inner ear. The middle ear produces secretions, which normally drain to the back of the throat through the Eustachian tube. The main reason why children get more middle ear infections is poor functioning of the drainage pathway (the Eustachian tube) that connects the middle ear to the back of the nose. This tube is the body's natural way to ventilate the ear, to allow fluid to drain when the ear is infected, and to allow air to enter the ear and keep it healthy. A child's Eustachian tube does not function as well as an adult's tube

for a variety of reasons mainly due to the fact it has not had enough time to grow and fully develop.

Just as with all other aspects of human biology, there is a broad range of Eustachian tube function in children- some children get lots of ear infections, some get none. But overall, young children are more prone to ear infections and ear fluid. This tends to improve in most children by age 4-6, when the tube matures towards the adult level of function.

In addition to problems with the Eustachain tube, young children have immature immune systems and may be exposed to other sick children in a school or day care setting. Upper respiratory tract infections (such as colds) are more common in children, and this can make the child's Eustachian tube function even worse, by causing swelling in the walls.

Allergies are common in children, but there is not much evidence to suggest that they are a cause of either ear infections or middle ear fluid. While allergies can and should be treated, this treatment does not seem to have much effect on ear disease.

However, if the fluid doesn't drain and builds up in the middle ear, it creates a warm, moist environment where bacteria and viruses grow. Invading bacteria or viruses thrive and result in the pain, crankiness, and fever that signal to parents that their child has an ear infection.

Some strategies do exist to prevent the recurrence of AOM including vaccination, breastfeeding, probiotics, complimentary medicines, homeopathy, osteopathy, chiropractics and aromatherapy, however the evidence to support these strategies vary in their effectiveness (Levi *et al.,* 2013).

Prevention

The use of xylitol for the prevention of AOM has also been explored as alternative and is supported by an number of Pediatric Associations notably, the American Academy of

Pediatrics and many pediatric association have identified xylitol as preventative for otitis media however require more clinical information (Gunasekera *et al*., 2009),.

Xylitol

Xylitol is a 5 carbon polyol that has been used widely as a sweeting substitute for sucrose because of its potential preventative effect on dental carries. Also, xylitol has been shown to inhibit the growth of *Streptococcus pneumonia* and it's use in the prevention of AOM was first described in 1970's (Wargo *et al.,* 2014).

Currently, xylitol is widely used with a large number of diverse applications; Xylitol is currently used as a sweeter for diabetics, to prevent dental carries, to prevent AOM, in respiratory disease management, parenteral nutrition, atopic dermatitis, wound repairing, gastrointestinal infections, osteoporosis, anti-aging and inflammatory process (Ferreira et al., 2015).

Studies in humans and rodents have shown that xylitol, when appropriately administered orally with adaptation, is well tolerated and safe to levels of at least 90 g/day, with no subjective or objective adverse findings.

The oral and metabolic safety of xylitol has been assessed by various international and national regulatory authorities. For example, in 1983 the Joint Expert Committee on Food Additives (JEFCA) of two United Nations agencies (FAO and WHO) allocated an "Acceptable Daily Intake" (ADI) definition "not specified" for xylitol. This indicates that no special consumption limits were needed for xylitol.

In detail, JECFA recommended:

(a) An unlimited ADI based on the safety of xylitol. This type of specification reflects the safest category this Committee can place a food additive. The specification is comparable to that of sorbitol.
(b) No additional toxicological studies were recommended.

Of the numerous positive public health evaluations of xylitol one should mention the FASEB report of the year 1986. FASEB (Federation of American Societies for Experimental Biology) reports are based on comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine (Makinen, 2002).
In 1986 FASEB's expert panel completed a report on the health aspects of sugar alcohols and lactose. Based on the comprehensive body of scientific information, the FASEB report concluded that:

(a) No significant safety concerns would be expected from use of xylitol in humans, and that
(b) Xylitol appears to have the same safety profile as other sugar alcohols, such as sorbitol and D- mannitol.

Xylitol has been evaluated in the prevention of otitis media for a number of years. Many studies have even evaluated the attitudes of physicians in providing guidance on the use of xylitol as a prophylactic in children. In 2010, Danhauer *et al.,* conduct a national survey of Pediatricians in the United States to evaluate how closely they adhered to the AAP/AAFP guideline, and their knowledge and opinions about xylitol use, (Danhauer *et al.*, 2010) and eventually identify barriers to xylitol's use as a prophylaxis for AOM in the United States.
The study was a randomized, national postal survey where a 48-item questionnaire was mailed to a random sample of 506 physicians in the United States. The questionnaire assessed pediatricians' demographics, adherence to the guideline, and knowledge and opinions about and use of xylitol as a prophylaxis for AOM in children.
The questionnaire response rate was 22%. Participants were equal for gender, and almost all were in private practice for over 10 yr. Most had pediatric patients with at least one bout of AOM annually. Almost all believed that conductive hearing loss could hinder speech-

language and academic development, and AOM could reduce quality of life of children. They also believed that those under 6 months of age with AOM should receive antibacterial therapy beginning with amoxicillin but did not use complementary and alternative medicine (CAM). Only about half knew about medical uses for xylitol, but of those, most were aware of its use in chewing gum to prevent AOM but had not used it with patients. Most would use xylitol if evidence supported it and wanted information about it via reprints or electronically.

The results of the survey indicate that most of the pediatricians adhered to the AAP/AAFP guideline. They were not using complementary and alternative medicines like xylitol for preventing AOM in children but would be interested in learning more about the clinical evidence. Since the study, in 2013, the American Academy of Pediatrics updated their guidelines with the mention of xylitol to prevent otitis media and states it can have a positive impact on reducing the incident rate if used daily and throughout the respiratory illness season (AAP Guidelines, 2013).

How does Xylitol work?

In a study by Kurola *et al.,* they looked at xylitol and the capsular gene expression in *Streptococcus pneumonia* in vitro. Their findings support previous results where exposure to xylitol changed the ultrastructure of the pneumococcal capsule. The study demonstrated that xylitol significantly decreased the capsular gene expression levels in *S. pneumonia* isolates and could further explain the high clinical efficacy of xylitol in preventing acute otitis media (Kurola *et al*., 2009).

In another study, (Zabner *et al*., 2000) they examined the results when xylitol in a saline spray is administered to the airway surface liquid (ASL) in adult volunteers. Their conclusions demonstrate that xylitol delivered to the airway surface may enhance the innate antibacterial defense system. These results suggest the hypothesis that xylitol could prevent the onset of bacterial infections. The research also demonstrated that the xylitol was not

absorbed, indicating the actions were mechanical and due to the osmotic properties of the xylitol.

Xylitol and the Prevention of Otitis Media

Xylitol was first used in clinical trials to evaluate it's potential to prevent AOM in Finland in the late 1990's. Dr. Uhari was the xylitol pioneer and conducted a number of studies based on Xylitol in a day care setting. Since then, a host of other investigators have asked the question if Xylitol can be used as a prophylactic in preventing infections and since the 1970's, over 500 studies have been conducted on Xylitol and the prevention of infections.

Clinical Evidence

A number of clinical trials have investigated the use of Xylitol for the prevention of AOM.
In a Cochrane review (Azarpazhooh A *et al*., 2011), 4 studies were identified to answer the study's objective, which was to assess the efficacy and safety of xylitol to prevent AOM in children up to 12 years old. These 4 studies were conducted by Uhari and his groups in Finalnd (Uhari *et al.* 1996 & 1998, Hautalahti *et al*., 2007, Tapiainen *et al.,* 2002) The studies selected were randomized controlled trials (RTCs) or quasi- RTCs of children 12 years or younger where xylitol in supplementation was compared to placebo or no treatment to prevent AOM.

In three RCTs with a total of 1826 healthy Finnish children attending day care, there was a reduced risk of occurrence of AOM in the xylitol group (in any form) compared to the control group (RR 0.75; 95% CI 0.65 to 0.88). The fourth RCT included 1277 Finnish day care children with a respiratory infection and found no effect of xylitol on reducing the occurrence of AOM (RR 1.13; 95% CI 0.83 to 1.53).

Xylitol chewing gum was superior to xylitol syrup in preventing AOM among healthy children (RR 0.59; 95% CI 0.39 to 0.89) but not during respiratory infection (RR 0.68; 95% CI 0.43 to 1.07). There was no difference between xylitol lozenges and xylitol syrups in preventing AOM among healthy children (RR 0.77; 95% CI 0.53 to 1.11) or among children during respiratory infection (RR 0.74; 95% CI 0.47 to 1.14). Similarly, no difference was noted between xylitol chewing gum and xylitol lozenges in preventing AOM among healthy children (RR 0.73; 95% CI 0.47 to 1.13) or among children during respiratory infection (RR 0.92; 95% CI 0.59 to 1.46). Among the reasons for drop-outs, there were no significant differences in abdominal discomfort and rash between the xylitol and the control groups (Azarpazhooh A *et al*., 2011).

The conclusion of the Cochrane Review is that there is fair evidence that the prophylactic administration of xylitol among healthy children attending day care centers reduces the occurrence of AOM by 25%. This meta-analysis is limited since the data arise from a small number of studies, mainly from the same research group.

In 2007, (Vernacchio *et al.,* 2007) examined if xylitol, given as 2g orally five times-a-day, significantly reduced the incidence of acute otitis media (AOM) in children. The study was a 3-month randomized placebo-controlled trial of the tolerability and acceptability of oral xylitol solution in 120 children (6-36 months of age) performed in the SCOR Network.
Study withdrawals and unscheduled medical visits for gastrointestinal complaints did not differ significantly among the study groups. The proportions of subjects in the xylitol TID group who experienced excessive gas or diarrhea at months 1, 2, and 3 were 22.7%, 10.0%, and 14.3%, respectively, and in the xylitol QD group were 27.3%, 17.4%, and 14.3%, respectively, and these did not differ from the placebo groups. The proportions who accepted the study solution easily or with only minor difficulty at 1, 2, and 3 months in the xylitol TID group were 77.3%, 90.0%, and 90.5% and in the xylitol QD group, 77.3%, 82.6%, and 90.5%, respectively. The investigation team determined that oral xylitol solution at dosages of 5g TID and 7.5g QD was well-tolerated by young children and these results are encouraging given the potential for xylitol as a safe, inexpensive option for AOM prophylaxis.

The use of Xylitol in the form of a nasal spray is patented, therefore is has not been the subject of study such as lozenges, gum and syrup, mouthwash and toothpaste, however, there have been a few studies conducted of which the results will be examined below.

Vernacchio *et al.,* (2014), 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. 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 non-adherence 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). Vernacchio conclused that a viscous xylitol solution in a dose of 5 g 3 times per day was ineffective in reducing clinically diagnosed AOM among otitis-prone children.

In a pilot study (Weissman *et al.* 2011), the hypothesis was to determine the tolerability of xylitol mixed with water as a nasal irrigant and to evaluate whether xylitol nasal irrigation results in symptomatic improvement of subjects with chronic rhino sinusitis. The study was conducted in 20 adults with a previous diagnosis of sinusitis, 15 of which completed the study. The conclusion of the study was that xylitol is well tolerated and only a few subjects complained about the sweet taste. Overall, there was a small but significant improvement in SNOT-20 scores with the xylitol irrigation compared to the saline irrigation.

Recently, a team in Turkey (Cingi et al., 2014) did a study to objectively determine and compare the efficacy and effectiveness of xylitol solution (Xlear Nasal Spray®) compared with xylometazoline and physiological saline with respect to quality of like (QoL) in patients with nasal congestion. The study was a prospective, randomized study in 42 adult patients.

The study population was randomized into 3 groups according to the application of xylometazoline, physiological saline, and xylitol hyperosmolar solution.

The efficacy of treatment was evaluated objectively (4-phase rhinomanometry) and subjectively (visual analogue scale VAS.) before and after the application of the nasal solutions. QoL was evaluated by means of Rhino conjunctivitis Quality of Life Questionnaire (RQLQ).

The VAS scores and 4-phase rhinomanometry scores were better in the group treated with xylometazoline compared to those treated with xylitol or saline. The xylitol procedure yielded better results than the saline procedure, but differences were not statistically significant in both objective and subjective evaluation methods. For overall QoL, there was a significant improvement from baseline for the xylometazoline and xylitol groups. However, the improvement in the xylometazoline group was significantly greater than that obtained in the xylitol group. In conclusion, the Xlear Nasal Spray® is an effective modality in the treatment of nasal congestion and has positive effect on the QoL of patients.

In an unpublished study, Kalanin et al., 2005 evaluated the effectiveness of regular Xlear Nasal Wash® three times daily in prevention of acute otitis media in a group of children suffering from recurrent AOM episodes. The primary objective was to prove/disprove a significant decrease of recurrent AOM in the group treated regularly with a xylitol nasal wash three times daily during a 3-month period. The secondary objective of the study was to assess a lowered incidence of other infections commonly affecting upper the airways - especially those of bacterial origin.

The trial was a multi-center, randomized, double-blind, placebo-controlled study, conducted over a 3-month period of active treatment in approximately 8-12 investigational sites.
There were 82 male and 86 female outpatients from 1 to 15 years of age with recurrent AOM. The mean age was 6,14 years.

The investigators observed 31 recurrences of AOM in a group of 80 treated with solution and in the control group of 74 subjects treated with distilled water, 67 episodes were recorded, meaning 50% more incidents of AOM in the group of subjects using the water nasal spray.

In the group treated with xylitol, 26 cases of infections were indicated for antibiotic therapy, of the 26 cases, 9 cases (12% of patients) treated. In the group treated with distilled water, 39 infectious episodes were treated by antibiotics in total (52.7% of treated), whereas AOM was the reason for antibiotics use in 26 cases – it means 35.1% frequency in this group.

In the evaluated group there were following kinds of bacteria revealed by nasal and throat smear before and after the onset of therapy (please see the table below). Interestingly, there was almost identical occurrence of Str. pneumoniae in both groups: significant reduction of pneumococcal colonization of both nasal and pharyngeal mucosae at the end of study. There are some indices that Xlear® was capable to suppress Haemofilus growth, as well as S. aureus and the other strains of Streptococci. However, numbers of bacterial occurrence were not large enough to give us significant values.

Strain	XLEAR Prior (Nose/throat)	Xlear After	CTRL Prior	CTRL After
Str.pneumoniae	10/9	0/0	9/6	0/0
S. aureus	5/0	2/0	5/2	12/8
Haemophilus spp.	2/6	0/1	2/4	2/2
H. influenzae	½	0/0	4/1	3/0
Str. betahemolyt.	2/0	0/0	2/3	0/0
S. Milleri	2/0	0/0	1/0	0/0

E. coli	0/1	0/0	0/0	0/0
Moraxella cat.	0/0	1/0	2/0	2/0
Branhamella cat.	0/0	0/1	0/0	0/3

In conclusion, there was 2.3 times lower frequency of AOM in treated group than in the control one. Secondly, antibiotic therapy was used 2.66 times more in control group in comparison with xylitol subjects, finally, the frequency of upper airways infectious episodes was 1.26 times lower in the xylitol group, therefore demonstrating that Xlear® Nasal Wash has the capacity to reduce the incidence of AOM and reduce the amount of bacterial colonization in children over the age of one.

Clinical Evaluation Findings

The conclusions and finding of this clinical evaluation demonstrate the following:

- AOM is a disease that can affect all children.
- AOM has a negative impact on the quality of life of the children and families it affects.

- AOM can have life-long lasting effects such as speech impairments and hearing loss.
- Xylitol is safe and poses no harm to infants, children or adults.
- Xylitol has been safely used in a number of diverse ways (Medical, nutritional).
- Xylitol prevents the creation of bacterial biofilms.
- Xylitol inhibits the bacterial growth in nasal passageways, notably on the air surface liquid found in the nose.
- Xylitol can reduce and prevent the incident of AOM in children and adults
- Xylitol can not be used to treat AOM
- Xylitol nasal spray is a safe alternative to prevent the incident of AOM

XLEAR: Overall Conclusion

Xlear's design features address many of the current issues raised in the published literature specifically with regard to the recommendations by a number of pediatric associations that xylitol should be used to help with the prevention of otits media.

Numerous studies have been conducted on the use of xylitol and the challenge that has constantly been addressed is the method of delivery. By developing a spray containing xylitol, the product can eliminate the barrier of delivery and provide a safe, easy and convenient way for patients to benefit from the protection of xylitol.

Given the satisfactory performance and safety record of Xlear on the market and the satisfactory performance and safety record of the other similar products currently sold in Europe, the United States and abroad, Xlear should be provided with a marketing authorization.

Future Updates

The clinical evaluation of Xlear will be updated every 2 years, with the first update and review to take place in July 2017. To ensure the safety of the product, the continued commitment to materiovigilance is very important and will be reviewed along with new clinical and published information on currently marketed nasal sprays.

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