Possible Preventative Effects of Childhood Antibiotics on Caries Development: An Evidence-Based Survey of the Literature

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Bryan Waxman
Mercedes Cuartero
Vipin Grover
Matthew Dang
Faisal Waseem
Sabrina Rosati

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Abstract

Prevention of caries development is one of the goals dental practitioners provide and educate their patients with. This study addressed the possible preventative effects of long-term, systemically administered antibiotics during the ages of 3 – 18 years of age on subsequent caries development. From the literature surveyed, six studies were found to be relevant to the topic in question, all of which scored fair or slightly less on the level of evidence, study design, and checklist scoring system. Five out of the six studies demonstrated significant preventative effects of childhood antibiotics to caries development, while one study showed inconclusive results. However, when considering the strength of the studies included and the risk/benefits rationale of antibiotics as a form of caries prevention, the drugs' preventative effects remains to be a possibility and is not recommended for the sole prevention of caries development.

Introduction

An antibiotic is a drug that kills or prevents the growth of bacteria. Since bacterial growth, colonization, and invasion comprise the etiological basis for caries development, it is biologically plausible that antibiotics, which targets this system, can arrest the advancement of caries.

Antibiotics are one class of antimicrobials, a larger group that also contains anti-fungal and anti-parasitic drugs. Antibiotics can be categorized based on their target specificity, broad spectrum and narrow spectrum. Broad spectrum covers a wider range of bacteria, while narrow spectrum antibiotics target specific types of bacteria. In the past, the most commonly prescribed antibiotic was penicillin, which targets the transpeptidase enzyme responsible for maintaining the cell walls of gram-positive bacteria[1]. Most articles looked at in this study date back to the past where penicillin was the most popular antibiotic used.

Childhood dental caries requires four main and several predisposing factors, which include: susceptible host (i.e. teeth and saliva), the agent (i.e. mutans streptococci and lactobacilli), the substrate (fermentable carbohydrates) and time. Other predisposing factors are: age, socioeconomic status, level of parental education, and diet. These factors are involved in caries formation. Dental caries begins with microbiota that is capable of adhering to tooth surface, leading to a dental biofilm formation. In the presence of fermentable carbohydrates, the bacteria produce acids, which result in a drop of pH to levels that may result in demineralization of the tooth. Demineralization of tooth surface may result in the formation of a cavity.

Carious lesions occur with the presence of mutans streptococci, which is a known agent in caries formation. Antibiotics may decrease the amount of mutans streptococci and this may result in a subsequent decrease in dental caries.

We reviewed the current literature to assess whether administering antibiotics in children had an effect on dental caries. This literature integrates the strongest evidence regarding the effects of childhood antibiotics on dental caries.

Methods

All studies cited were searched for, selected and appraised by employing a systematic approach.

Search Strategy

An initial search for relevant papers was performed via electronic bibliographic databases using the following key words: antibiotics and caries, antibiotics and strap mutans, and long term antibiotics and dental caries. The databases explored and their respective numbers of articles yielded were as follows: PubMed (1964 – present) with “86” articles, Medline (1964 - present) with “19” and web of science with “57”. There were 3 articles recommended by experts. The relevance of these articles was assessed using predetermined inclusion criteria. The titles of studies found in the reference lists of the “8” articles that met the criteria were then reviewed as additional potentially relevant articles. Of the “184” references surveyed, “174” were deemed irrelevant based on title, while inclusion criteria were applied to the abstracts of “10”. Ultimately “8” were selected for validity scoring.

Determination of Relevance

After elimination of “184” articles based on title, abstract, and overlap between the electronic journal database, “10” articles were read and reviewed to determine relevance.

Inclusion Criteria

The articles selected for this report had to meet the following specifications:
1. Articles had to be written in English.
2. Articles had to be published between January 1964 to present.
3. Article had to either be review articles or use case control cohort study design.
4. Articles had to examine human subjects.
6. Articles that scored more than 7 on the checklist.

Exclusion Criteria

1. Antibiotics administered to adults.
2. Antibiotics leading to dental fluorosis or any other such dental problems other than caries
3. Antibiotics administered topically.
4. Articles written in any other languages other than English.

Validity Instrument

The quality of 8 of the 10 relevant articles was assessed using a “checklist to assess evidence of efficacy of therapy or prevention” developed by Leake. Each article was scored by two independent reviewers and could receive a maximum score of sixteen. When a discrepancy in the study score of two or more points was demonstrated, a final score was determined after discussion between all six group members. All studies receiving a score of 50% and above (corresponding to 7 out of 15 for the efficacy checklist) were retained.

Checklist to Assess Evidence of Efficacy of Therapy or Prevention

1. Was the study ethical?
2. Was a strong design used to assess efficacy?
3. Were outcomes (benefits and harms) validly and reliably measured?

4. Were interventions validly and reliably measured?
5. What were the results?
   - Was the treatment effect large enough to be clinically important?
   - Was the estimate of the treatment effect beyond chance and relatively precise?
   - If the findings were "no difference" was the power of the study 80% or better and the effect difference 10% or less
6. Are the results of the study valid?
   - Was the assignment of patients to treatments randomised?
   - Were all patients who entered the trial properly accounted for and attributed at its conclusion?

   i. Was loss to follow-up less than 20% and balanced between test and controls

   ii. Were patients analysed in the groups to which they were randomised?
   - Was the study of sufficient duration?
   - Were patients, health workers, and study personnel "blind" to treatment?
   - Were the groups similar at the start of the trial?
   - Aside from the experimental intervention, were the groups treated equally?
   - Was care received outside the study identified and controlled for?
7. Will the results help in caring for your patients?
   - Were all clinically important outcomes considered?
   - Are the likely benefits of treatment worth the potential harms and costs?

Results

The search study yielded six articles to be most relevant to the question if childhood antibiotics are a risk factor for caries. Before assessing the effects of childhood antibiotics, it was important to establish the administration of the antibiotics and the type of caries measurement. Thus, this study specifically looked at the effects of antibiotics administered systemically, long-term (at least one year), and during the ages of 3 – 18 years of age on caries development measured using DMFS/dmft scores. As a result, the six articles included in this study looked at preventive effects of childhood antibiotics on caries development as opposed to risk effects.

The six studies achieved checklist scores ranging from 70.6% by Handelman and others[1] 53% by Kinirons and others[6] to, as seen in Table 1. All six studies also demonstrated levels of evidence of II-2 or III, from cohort or case-control analytic studies or cross-sectional longitudinal studies. Five out of the six studies were found to have fair evidence or a grade B recommendation for specific clinical preventive action. Only the study by Mariri and others[4] displayed a grade C or conflicting evidence, disallowing a recommendation for or against the clinical preventive action. When a multi-variable analysis was performed, Mariri and others[4] did not find a significant association between antibiotic use and caries risk after controlling for other factors, namely dietary patterns, fluoride intakes, and tooth brushing habits.

Thus, five out of the six studies clearly demonstrated significant preventive effects of childhood antibiotics on caries development. Most notably, Handelman and others[1] demonstrated an average yearly caries increment of 69% less in subjects with antibiotic usage compared to subjects in the absence of antibiotics. In addition, they also found a residual effect of 51% less than the estimated annual increase in subjects who had completed antibiotic therapy. Another strong study was by Loesche and others[3], scoring 67% on the checklist and demonstrating a 48% decrease in dmft in subjects on antibiotic therapy for three years compared to subjects who have never received antibiotic therapy.

Table 1. Studies that looked at long-term, systemically administered antibiotics during the ages of 3 – 13 years, and measured caries using DMFS/dmft scores.

Author and date	Population (Age, sex, location representative of ?)	Intervention, or Test treatment (Number studied))	Control treatment (Number studied)	Outcome	Critical appraisal comments/Strength of study/ Conclusions
Handelman and others[1], 1966	Age= 6-19yrs Sex= 217m 176f Location-Maryland	N= 249 - continuous, long term Ab therapy for Rh Fever (175) or chronic respiratory disease (74)	n= 144 (untreated siblings)	69% less yearly caries for those during Ab therapy; 51% less for those once Ab therapy was stopped (residual effect)	II-2, Grade B Checklist: 12/16 = 75% Fair internal validity Not sex-matched or age matched
Littleton and others[2], 1964	Age= 6-13 Sex- unknown Location - Lancaster County	N= 73 - receiving penicillin daily, hospital outpatients	n= 362 (public school children)	Tx: DMFT: 2.29 DMFS: 3.55 Control: DMFT: 2.79 DMFS: 4.84	II-2, Grade B Checklist: 11/16 = 69% Poor internal validity Examiner knew whether child was hospital or control group
Loesche and others[3], 1989	**Retrospective** Age= 6-7 Sex= Unknown Loc= Coldwater, Michigan	N= 365 Received antibiotics: Groups: A)3x/year B)1x or 2x/year c) Less than 1x/year D)Never	N= 25 (Never group)	Antibiotic Use (mean DF score) Never 2.9 < 1/yr 2.3 1-2/yr 2.4 >3/yr 1.5 *Never and >3/yr statistically significant	III, Grade B Checklist: 11/16 =69% Long-term recall was involved = increased chance of bias
Mariri and others[4], 2003	Age= 4-7 Sex= unknown Loc= Iowa Fluoride Study	N= 39 26 female, 13 male Long term antibiotic therapy (amoxicillin, penicillin, sulfa, erythromycin, cephalosporin, pediazole, augmentin, nystatin) Illness listed: ear	N= 39 26 female, 13 male	Bivariate analysis yielded statistically significant relationship between antibiotic use at 12-16 months and dental caries at 4-7 years Mulivariable analysis did not find antibiotics to be associated with caries.	II-2,Grade C Checklist: 10/16 = 62.5% Antibiotic exposure not accurately reflected due to recall bias, misunderstanding by parents, estimates of number of days of antibiotic use. All data was self reported, and not

		infection, pneumonia, strep throat, bladder/kidney infection, skin infection			directly validated.
Fukuda and others[5], 2005	Age= 3 –12 Loc =Boston	N=60 -all subjects diagnosed with sickle cell anaemia (SCA) prior to age of 3 months and placed immediately on daily oral penicillin <u>Group 1</u>: 30 SCA (ages 3-6 years) -receiving 250mg of penicillin 2x a day <u>Group 2</u>: 30 SCA (ages 6-11) -stopped penicillin at age 6 years old	N=60 -matched with healthy child of similar age, race and socioeconomic status	<u>Group 1</u> SCA: 0% interproximal caries Control: 47% interproximal caries SCA: 0.21 DMFS/dmfs Control: 5.1 DMFS/dmfs <u>Group 2</u> SCA: 30% interproximal caries Control: 70% interproximal caries SCA: 3.89 DMFS/dmfs Control: 5.78 DMFS/dmfs	III, Grade B Checklist score= 10/16 = 62.5% - small sample size - recall bias from questionnaires answered by parents (i.e. dental history, home oral hygiene practices, fluoride history, diet history, compliance with antibiotics) - dental examiners were not calibrated before the study's onset
Kinirons and others[6], 1992	Age: 4-18 y.o. Loc=Northern Ireland	N = 164 - cystic fibrosis patients - 3 antibiotic subgroups were formed, expressed as a percentage of months of the child's life since the age of 6 years they were on antibiotics (high 70-91%, medium 50-69%, low 30-49%)	N = 164 - 0% antibiotic use - matched with healthy control from 10 randomly selected schools of similar age, sex, and social class	- DMFT scores for patients aged 8-18 High (DMFT ± SD) CF: 1.6±1.41 Ctrl: 3.9±2.73 Difference: 2.3±2.91 Medium (DMFT± SD) CF: 3.4±2.71 Ctrl: 4.7±3.15 Difference: 1.3±1.84 Low (DMFT± SD) CF: 4.9±3.44 Ctrl: 5.4±4.28 Difference: 0.5±0.71	III, Grade B Checklist score = 10/16 = 62.5% - ethics was not addressed - controls were not examined at the same clinic as their CF counterparts - study was unable to assess if other factors played a role in caries experience, such as differences in the composition or properties of saliva between CF patients

Discussion

Overall, fair evidence showed that the most commonly prescribed childhood antibiotics had a weak preventive effect on the development of caries, such as antibiotics from the penicillin family and erythromycin. This is consistent with a plausible biological relationship between antibiotics and caries reduction. The studies used DMFS/dmfs scores to assess presence or absence of caries, a reliable and valid indicator of caries experience[3]. Studies by Handelman et al.[1], Littleton et al.[2], Loesche et al.[3], Fukuda et al.[5], and Kinirons et al. [6] showed a significant decrease in caries by a reduction in DMFS scores between treatment versus control groups.

Although there was a significant decrease in DMFS/dmfs scores in the treatment groups, caution should be exercised when accepting these results and applying them to clinical situations. With respect to patient variables, all studies when examining the use of antibiotics formed treatment groups based on children already receiving typical childhood antibiotics for their current disease or condition. It is highly questionable as to whether the results gathered from these ill patients are generalizable to a healthy population. Further, it presents a possible confound in that other than the treatment and control groups differing in the measured variable (i.e. the administration or non-administration of antibiotics), the groups also differed in the presence or absence of a disease or condition. To further complicate matters, the illnesses were not consistent between studies, such as the study by Kinirons and others[6], who measured controls versus children receiving antibiotics for cystic fibrosis. Cystic fibrosis patients have been shown to have different saliva compositions or properties compared to healthy people, which may affect caries development. Studies were also inconsistent in the type of antibiotics administered to their treatment groups as well as the administration schedules of these antibiotics. The ages of children in the treatment groups were not matched among studies and ranged from 4-18 years. This presents another possible confound in that it is well-known that primary teeth compared to permanent teeth have different enamel and mineral compositions, and are different with respect to caries susceptibility and caries progression itself. This age range also did not take into consideration total primary teeth measurement in young children versus the mixed dentition stage nor total permanent dentition stage.

In addition to patient factors, there were also inadequacies among studies with respect to design and methodology. Sample sizes of these studies ranged from 78 to 435 subjects. Even the largest sample size was still too small, raising questions as to the applicability of these results in generalizing to an entire population. In all studies, the examiners were also not blind as to whether the child was in the treatment or control group leading to possible bias of examiners. Caries detection methods in these studies were also not standardized in that Littleton et al.[2], and Handleman et al.[1] used only explorer with dental mirror for a single examiner, leading to variability in caries diagnoses among examiners. It is also noted that radiographs were not used to complete or verify the diagnoses or absence of caries. Again, both the reliability and validity of these study results are questioned. In Fukuda et al.[5], Mariri et al.[4], and Loesche et al.[3], in attempt to gather matching criteria, relied upon self-reported long-term recall data from patients to determine factors such as antibiotics used, duration of therapy, maternal education level, medical history, dental history, oral hygiene practices, fluoride history, and diet history. This data poses risk of being flawed by the inherent recall bias from patients. Further, the weak preventive effect of antibiotics found in the studies was further compromised by the unavoidable weak study designs. The use of a randomized controlled study was impossible due to ethical reasons, such as the unnecessary administration of antibiotics to healthy subjects or halting the administration of antibiotics to ill patients.

The original question of "Are early childhood antibiotics a risk for caries?" was not addressed in this paper due to the lack of literature. Most studies have shown that early childhood antibiotics have a preventive effect. The study by Hong and others[7], which addressed and initiated this issue of antibiotics being a risk factor for caries, did not meet our inclusion criteria because it measured caries *indirectly* by examining enamel dysplasia. Most evidence from studies gathered was level II-2 or III, which are weak study designs for the assessment of efficacy of therapy or prevention. The strict inclusion criteria limited the number of acceptable articles. Articles had to study children from the ages of 4-18 years of age (which excludes adults), the antibiotics had to be administered for at least a year, studies which indirectly looked at caries by measuring etiological factors such as enamel demineralization, fluorosis, bacterial counts, and salivary flow rates were excluded, and studies had to measure systemically administered (which excludes topical applications). The strongest evidence found was at level II-2, which addresses the need to have stronger evidence in order to obtain a sound conclusion about antibiotics and their effect on caries reduction.

Future research should include better study designs such as double-blinded RCTs that do not sacrifice ethics, studies with large sample sizes, studies with specific dentitions, and studies that measure topical administration.

Conclusion

The use of antibiotics for the prevention of caries has risks and benefits, where risks include an increase in resistance, high cost to the individual and healthcare system, and increased adverse effects such as staining, fluorosis[8], hypersensitivity, GI upset, renal disease, and skin rashes. As well, stronger evidence from strong study designs is needed to help provide support for a clinical decision. Therefore, antibiotics for caries reduction for the general population are not recommended.

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