Newly Diagnosed Juvenile Idiopathic Arthritis and Childhood Antibiotic Use

Hannah Niestradt
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Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most common type of arthritis in children and can be life-altering. The etiology of JIA is unknown, though current research focuses on a combination of genetic factors, immune mechanisms, and environmental triggers. Evidence has shown a genetic predisposition to JIA, but this only accounts for a portion of JIA cases. That leaves environmental triggers and immune mechanisms. One environmental trigger being investigated is childhood antibiotic exposure and has already been implicated in the pathogenesis of certain autoimmune diseases like type 1 diabetes and Crohn disease. The goal of this paper is to examine the relationship between newly diagnosed JIA and childhood antibiotic exposure.

Methods: An exhaustive search using MEDLINE-Ovid, MEDLINE-PubMed, and Web of Science was performed using the keywords: juvenile idiopathic arthritis and antibiotic exposure. The resulting studies were then screened for eligibility criteria. Once screened, the remaining studies were then thoroughly assessed and appraised for quality of evidence using The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.

Results: Two studies were included in this systematic review, meeting both inclusion and exclusion criteria. The first study was a case-control study which looked at 1298 cases and 5179 appropriate controls in Finland. Researchers found that the risk of JIA increased with the number of antibiotic purchases, with antibiotic groups lincosamides and cephalosporins showing the strongest association with JIA. Lastly, overall exposure to antibiotics before 2 years of age was associated with an increased risk of JIA. Another case-control study looked at 152 cases and 1520 appropriate controls in the UK and concluded that any antibiotic exposure was associated with an increased risk of developing JIA and was dose-dependent, with the relationship strongest within 1 year of diagnosis. These findings did not change when adjusting for the number or type of infections. In addition, antibiotic-treated upper respiratory infections (URIs) were more strongly associated with JIA than untreated URIs.

Conclusion: Clinically, this research provides utility for providers seeing younger patients receiving frequent antibiotics for infections. It could be a possible recommendation that providers screen these patients more frequently for signs and symptoms of JIA because of the association shown in the research presented in this analysis. Further research needs to be conducted in order to truly uncover the association between antibiotic exposure and JIA and the etiology of JIA and its specific categories. Future studies should also be conducted to follow patients for a longer period of time.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
juvenile idiopathic arthritis, childhood antibiotic exposure

This capstone project is available at CommonKnowledge: https://commons.pacificu.edu/pa/623
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A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 12, 2017
Faculty Advisor: Elizabeth K. Crawford, PA-C
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Biography

Hannah Niestradt is a native of Oregon where she majored in General Science with a minor in Psychology at Oregon State University. After completion of her undergraduate degree, she got her CNA license and worked at both a long-term care facility and at a hospital, both in the Portland area. She enjoys the hands-on aspect of patient care and hopes to have a career in either internal medicine, urgent care, or as part of an inpatient service.
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# Table of Contents

Newly Diagnosed Juvenile Idiopathic Arthritis and Childhood Antibiotic Exposure .......................................................... 1  
Biography ......................................................................................................................................................... 2  
Abstract .......................................................................................................................................................... 3  
Table of Contents .......................................................................................................................................... 5  
List of Tables ................................................................................................................................................ 6  
List of Abbreviations ......................................................................................................................... 6  
Newly Diagnosed Juvenile Idiopathic Arthritis and Childhood Antibiotic Exposure .............................................................. 7  
BACKGROUND ........................................................................................................................................ 7  
METHODS ............................................................................................................................................. 8  
RESULTS ............................................................................................................................................... 9  
DISCUSSION ..................................................................................................................................... 13  
CONCLUSION .................................................................................................................................... 15  
References .......................................................................................................................................... 17  
Table 1: Quality Assessment of Reviewed Articles ............................................................................. 19
List of Tables

Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

JIA   Juvenile Idiopathic Arthritis
MHC   Major Histocompatibility Complex
URI   Upper respiratory Infection
IBD   Inflammatory Bowel Disease
Newly Diagnosed Juvenile Idiopathic Arthritis and Childhood Antibiotic Exposure

BACKGROUND

Juvenile idiopathic arthritis is the most common type of arthritis in children and depending on the specific type, has the potential to be debilitating.¹ For example, for systemic type JIA, about 50% of cases develop short stature (<95th percentile) in adulthood. Overall, about 30% of people with JIA have significant functional limitations 10 or more years after onset.² The etiology of JIA is poorly understood. Current research suggests a complex interaction between genetic factors, immune mechanisms, and environmental triggers. Evidence for a genetic contribution to JIA comes from family studies³ that indicate a 15-30 times higher prevalence of JIA among siblings of JIA patients than in the general population. Most of the genetic contribution to JIA is thought to be from the major histocompatibility complex (MHC) loci, with specific alleles lending themselves to predisposing individuals to a specific type of JIA.⁴

Environmental factors contributing to JIA have been more difficult to identify, and although some genetic component is present in all types of JIA, the environmental component has shown to be stronger in some types.⁴ One of the environmental factors under
investigation is antibiotic use. There is current evidence to suggest that childhood antibiotic use creates an imbalance in the gut microbiome, setting off an immune response, which could then be responsible for the development of autoimmune diseases such as type I diabetes,\textsuperscript{5} Crohn disease,\textsuperscript{6} and JIA. This is a relatively new body of research looking at the effects of childhood antibiotic use because these subjects are part of the first generation to have frequent antibiotic exposure as infants and children, and researchers can now look at the effects of that use. In JIA specifically, it is possible this immune response results in the known pathophysiology of JIA in which invasion of the synovial tissue of joints by inflammatory cells recruited from the peripheral circulation result in the inflamed synovial tissue and subsequent joint damage.\textsuperscript{4} The goal of this paper is to examine the relationship between newly diagnosed JIA and childhood antibiotic exposure.

**METHODS**

An exhaustive literature search was performed using MEDLINE-Ovid, MEDLINE-PubMed, and Web of Science. The following keywords were used in this search: “juvenile idiopathic arthritis” and “antibiotic exposure” and both inclusion and exclusion criteria were applied. Included were studies with patients diagnosed with JIA, evaluating the role of antibiotics leading up to that diagnosis. Other inclusion criteria
were studies less than 5 years old, human-only studies, and studies written in English. Exclusion criteria included studies that evaluated other immune-modulated diseases and studies evaluating other medication besides antibiotics. The quality of relevant articles was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group guidelines.

RESULTS

The initial search yielded 14 articles, and through deletion of duplicates and screening with eligibility criteria, the search was narrowed down to 2 articles. Both articles were case-control studies\textsuperscript{7,8} (See Table 1.)

Arvonen et al

The first study\textsuperscript{7} was done in 2014 in Finland. This is a case-control study whose objective was to explore whether childhood antibiotic exposure would be associated with the risk of developing JIA. To do this, researchers collected data from national registers containing all children born in Finland from 2000-2010 and diagnosed with JIA by the end of December 2012 (n=1298) and controls (n=5179) matched for age, sex, and place of birth. The diagnosis of JIA was based on information from a special reimbursement system in which patients with JIA received reimbursement for anti-rheumatic
drugs, glucocorticoids, and immunosuppressant drugs. In order to receive this special reimbursement, a patient’s condition and diagnosis has to be verified by a pediatric rheumatologist. During the time period of this study, 99% of the special reimbursement applications were approved, and the approval process took about 2 weeks. In addition to diagnosis of JIA and the reimbursement, the register also contained information regarding the presence of other chronic diseases (eg, asthma).\textsuperscript{7}

To evaluate for antibiotic exposure, researchers extracted information on all antibiotics for systemic use purchased for the study for children from birth until diagnosis of JIA (the starting date of the special reimbursement was used as the date of diagnosis). For the control children, antibiotic exposure was recorded from birth to index date of the respective JIA case.\textsuperscript{7}

In this study, purchase of one or more antibiotics from birth to index date was associated with an increased risk of JIA (OR 1.6, 95% CI 1.3-1.9). Antibiotic groups lincosamides and cephalosporins showed the strongest association with JIA (OR 6.6, 95% CI 3.7-11.7, and OR 1.6, 95% CI 1.4-1.8 respectively). This study also looked at exposure to antibiotics in different age ranges, and found that antibiotic use during the first 6 months of life was not significant, but the purchase
of one or more antibiotics in the first 12 months of life was associated with an increased risk of JIA (OR 1.2, 95% CI 1.2-1.6), and any exposure (0 vs. any) in the first 24 months was also associated with an increased risk of JIA (OR 1.4, 95% CI 1.2-1.6). There was a risk of JIA associated with the number of purchases of any antibiotics and separately for specific antibiotics.  

**Horton et al**

The second case-control study is more recent, done in 2015 in the UK. This study cites the first study in its references, and attempts to build on it. This study’s objective was to test the hypothesis that childhood antibiotic exposure was associated with newly diagnosed JIA, and to also further examine a time- and dose-dependent relationship, as well as control for infection and other variables. In order to do this, researchers used a population-representative electronic medical records database from over 550 practices of general practitioners across the UK. Data within this database were collected during patient visits and the information made anonymous for research purposes. Data included demographic characteristics, diagnoses, referrals, and outpatient prescriptions. Subjects ranged from 1-15 years of age of those registered in the database within 3 months of birth. Children with previous inflammatory bowel disease (IBD), immunodeficiency, or non-JIA systemic rheumatic diseases
were excluded. Ten control subjects without inclusion or exclusion diagnoses were matched according to the age and gender to each case subject, making a total of 1520 controls and 152 cases. Control subjects were randomly selected from practices containing at least 1 subject with JIA, to help alleviate the possibility of lack of practitioner awareness about JIA. The study period was from registration in the database to the index date (date of first JIA code).8

To evaluate for antibiotic exposure, systemic antibiotics prescribed by general practitioners were sorted according to type, date, and dose. Additional analyses were performed to examine antianaerobic vs. non-antianaerobic and specific antibiotic class. Antibiotics were also classified by the presence of enterohepatic circulation, the thinking being that these antibiotics may have a greater effect on the gut microbiome. Antiviral and antifungal agents were also analyzed for comparison with antibacterial agents. This study also evaluated the effect of timing of the first and last antibiotic exposure during the study period. To consider confounding by infection, researchers compared the risk of development of JIA with antibiotic-treated URIs and untreated URIs.8

In the results of this study, any antibiotic use was associated with newly diagnosed JIA (OR 2.1 95% CI 1.2-3.5) in a dose- and
time-dependent manner. The time of the first exposure of antibiotics did not appear to have an effect, but the relationship between antibiotic exposure and incident JIA diagnosis was strongest when antibiotic exposure occurred within one year prior to diagnosis. No differences in risk were associated with specific antibiotic categories. Also, antiviral and antifungal medication exposure was not associated with an increased risk of JIA. Having multiple antibiotic-treated URIs was strongly associated with JIA while untreated URIs were not. An association with treated URIs persisted after excluding cases of acute otitis media, pharyngitis, and sinusitis.  

**DISCUSSION**

Both studies’ results support the hypothesis that antibiotic exposure is associated with an increased risk of developing JIA. In the first study, there was an upward trend in the odds ratio for more frequent purchases of antibiotics. The same phenomenon was found in the second study: a dose-dependent relationship between the number of antibiotic purchases and the risk of JIA. JIA is the most common childhood arthritis. Current incidence estimates range from 6.6-15 cases of JIA per 100 000 children. Though the risk of development of JIA with antibiotic use may not be high enough to negate the use of antibiotics in infections in the pediatric population, this relationship may be important for clinicians to screen for JIA in those children who
have repeated exposure to antibiotics and to be judicious in prescribing antibiotic therapy to only those that need it. Additionally, with the Arvonen et al study\(^7\) indicating an increased risk with the type of antibiotic prescribed (eg, lincosamides having an OR of 6.6), clinicians may be inclined to avoid those antibiotics especially in children 2 years old and younger.

Along with the evidence, there were some limitations. One limitation of the first study\(^7\) was that it did not differentiate the effects of antibiotic use from the effects of infection. It is important to distinguish these two entities when looking at the association; is the antibiotic use associated with incident diagnosis of JIA because of disruption of the microbiome or do these patients have a type of inherent abnormality of their immune system which therefore predisposes them to infection and therefore the prescription for antibiotics? Or, is there a shared susceptibility to infections and JIA, a link that has yet to be discovered? In the second study,\(^8\) though researchers did try to control for infection, other factors such as demographic variables, comorbidities, previous infections, maternal autoimmunity, and hospitalization could have been confounders.

Another issue to bring up with both studies\(^7,8\) is the presence of chronic disease and the disproportionate presence in the case
subjects. In the first study, asthma was more prevalent in the case group and children with a diagnosis of asthma had more purchases of antibiotics than those without asthma (13.4 vs. 5.3 purchases, difference 8.1, CI 7.3-8.9). In the second study, psoriasis and uveitis were more prevalent in the case subjects. Case subjects also had more history of infection, hospitalization for infection, and more infections than control subjects. Cases also had more outpatient visits and mothers of case subjects were nearly twice as likely to have autoimmune diseases.

The evidence presented in these two studies provides another avenue of exploration in the potential dangers of antibiotic use and also the etiology of JIA. But, due to the limitations of these studies, further studies need to be conducted. These should include a more representative population with a longer duration of study, an examination the specific categories of JIA, further differentiation of antibiotic use from infection and other confounders in the pathogenesis of JIA, and an evaluation of the risk of each antibiotic category.

**CONCLUSION**

Antibiotic exposure in children may play a role in the pathogenesis of JIA. If this is the case, antibiotics may be the first part of the cascade that results in JIA, and is thus a potential modifiable
risk factor in the development of the disease. Though the risk of development of JIA with antibiotic use may not be high enough to negate the use of antibiotics in infections in the pediatric population, this relationship may be important for clinicians to screen for JIA in those children who have repeated exposure to antibiotics. Given the very low quality of evidence in both studies, further clinical studies will need to be conducted in order to build upon the preliminary evidence of these two studies.
References


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# Table 1: Quality Assessment of Reviewed Articles, GRADE Profile: JIA and Childhood Antibiotic Exposure

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
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<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
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<td>Arvonen et al⁷</td>
<td>Case-Control</td>
<td>Serious&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Not Serious</td>
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<tr>
<td>Horton et al⁸</td>
<td>Case-Control</td>
<td>Serious&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Not serious</td>
<td>Not Serious</td>
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GRADE: Grading of Recommendations, Assessments, Development, and Evaluation

<sup>a</sup> Failure to adequately control confounding (infection), and differences in case and control subjects (chronic diseases)

<sup>b</sup> Overall purchases of any antibiotics from birth to diagnosis was associated with an increased risk of JIA, with an association of increased risk of JIA and the number of purchases analyzed for any antibiotics

<sup>c</sup> Differences in case and control subjects (previous autoimmunity, hx of infection, hospitalization for infection, number of outpatient visits, etc.)

<sup>d</sup> Receipt of ≥ 1 antibiotic prescription was associated with an increased risk of developing JIA, the magnitude of the association increased with additional antibiotic courses