Is Antibiotic Exposure Associated With Newly Diagnosed Juvenile Idiopathic Arthritis?

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SUMMARY

In this nested case-control study in a population-representative medical records database from the United Kingdom, children with newly diagnosed juvenile idiopathic arthritis (JIA) were compared with age- and gender-matched control subjects randomly selected from general practices containing at least one case, excluding those with inflammatory bowel disease, immuno-deficiency, or other systemic rheumatic diseases. Conditional logistic regression was used to examine the association between antibacterial antibiotics (including number of antibiotic courses and timing) and JIA after adjusting for significant confounders. Any antibiotic exposure was associated with an increased rate of developing JIA [adjusted OR 2.1 (95% CI 1.2, 3.5)]. This relationship was dose dependent [adjusted OR over 5 antibiotic courses 3.0 (95% CI 1.6,5.6)], strongest for exposures within 1 year of diagnosis, and did not substantively change when adjusting for number or type of infections. In addition, antibiotic-treated upper respiratory tract infections were more strongly associated with JIA than untreated upper respiratory tract infections. The authors concluded that antibiotics were associated with newly diagnosed JIA in a dose- and time-dependent fashion. Antibiotic exposure may play a role in JIA pathogenesis, perhaps mediated through alterations in the microbiome.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Juvenile idiopathic arthritis (JIA) is globally recognized as the commonest chronic musculoskeletal disease affecting children [1]. The individual and societal impacts of this chronic condition on quality of life, productivity and health-care costs have been well documented [1,2]. Although it is well recognized as an autoimmune condition, its precise etiology and the complex interplay of factors causing and/or worsening the clinical condition are unclear. A certain degree of similarity is anticipated in the causal pathway of diverse conditions that broadly fit under the umbrella of autoimmune diseases. It is therefore not surprising that perturbations though to be involved in inflammatory bowel disease, type I diabetes mellitus, celiac disease would be explored in rheumatic conditions as well. This recent publication [3] reported a case-control study exploring the relationship between usage of antibiotics in early childhood and the subsequent diagnosis of JIA.

Critical appraisal: The case-control study design is used to study association between exposure to 'risk factors' and the occurrence of disease. Briefly, it involves recruitment of people with the outcome of interest (disease) designated as cases, and those without the outcome (disease) designated as controls; and working backwards in time to identify their exposure status. This design is especially useful to study relatively rare outcomes (diseases) particularly if the time period between exposures to outcome is long. Although it is placed relatively low on the evidence hierarchy [4] on account of high susceptibility to bias, it is an excellent design to study the effect of risk factors to which research participants cannot be ethically exposed. There are several tools available for critical appraisal of case-control studies, but in general they revolve around step-wise evaluation of three issues *viz* appraisal of validity, assessment of results and exploration of local applicability. Appraisal using such tools is summarized in ***Tables* I** and **II** [5,6].

The investigators used several methodological refinements to minimize bias and provide robust results. They also tried to distinguish the effect of antibiotics from the effect of infections, which was missing in the previous study [7]. They considered several sources of bias and confounding; and attempted to address them effectively. For these reasons, the data from this study are considered reliable. However, inexplicably ***Table* I** shows

TABLE I CRITICAL APPRAISAL OF THE STUDY

Criteria	*Report*
Did the study address a clearly focused issue?	Yes. The investigators clearly specified their objective to examine the relationship between usage of antibiotics (E=Exposure), and subsequent confirmation of JIA (O=Outcome) in children (P=Population), compared to a matched population without exposure to antibiotics (C=Comparison).
Did the authors use an appropriate method to answer their question?	Yes. A case-control study is an acceptable way to address the research question. A comparative cohort study (comparing groups of children with and without antibiotic usage, for the development of JIA) would be superior in terms of study design (as it would allow controlling for various confounding factors thereby limiting bias), but too complex and cumbersome in terms of resources, logistics and time.
Were the cases recruited in an acceptable way?	Yes Cases were identified from a population medical record database in the UK covering about 550 general practices. In the database, JIA was defined with a code analogous to its ICD 10 code. The age range of the population of interest was 1-15 years. Efforts were made to increase the specificity of the system by examining the database for alternate definitions of the outcome of interest adding the following (singly or in combination) to JIA: prescription of NSAID or steroids during 2 months prior to one year after the diagnosis, use of any disease-modifying agents, referral to specialist rheumatology services. There were limited exclusion criteria, thereby minimizing selection bias. It is presumed that all children with JIA would be picked up through the electronic database; hence completeness of case identification is not a concern. Similarly, the system is expected to include cases of all severities hence selection bias by severity is also addressed effectively. Since data were retrieved through records, the risk of missing cases is limited unless cases with JIA were mislabeled as other disorders. Of course it is unclear if children with currently (or subsequently) diagnosed JIA could actually have other conditions mislabeled as JIA.
Were the controls recruited in an acceptable way?	Yes The investigators recruited 10 age- and gender-matched children without JIA (as described above) for each case. The controls were recruited from the same general practices as cases. As controls were identified using the electronic database and not physically recruited, bias due to non-response is absent. There is no well-defined optimal ratio of cases to controls, but in general, statistical power improves with more controls although the effect plateaus at about 4 controls per case.
Was the exposure accurately measured to minimize bias?	Yes. The electronic database was used to retrieve information about antibiotic prescriptions, including data on antibiotic name, dosage and duration. Presumably there is no other way (than prescriptions) for children to obtain antibiotics in the population studied. The electronic database precludes measurement and recall biases to exposure. The same method to assess exposure was used for cases and controls.
What confounding factors have the authors accounted for?	The investigators attempted to identify and take into account several potential confounding factors including demographic features, frequency and type of preceding infections, prevalence of auto-immune disease, maternal auto-immune disease, and frequency of hospitalization. However, the frequency and duration of breastfeeding as well as ethnicity of recruited children have not been considered. Further, personal or family history of immune-deficiency has also not been considered. The authors did include an index representing (socio-economic) deprivation, but did not describe results by this variable. Data analysis included sensitivity analysis as well as regression.
What are the results of this study? How precise are the results?	In summary, the study reported that JIA cases were more likely to be exposed to antibiotic therapy, greater number of antibiotics, more antibiotics with entero-hepatic circulation, more infections, hospitalization, auto-immune diseases, as well as maternal auto-immune disease. The following adjusted odds ratios (95% Confidence intervals) were presented: Any antibiotic prescription: 2.1 (1.2, 3.5); Any infection: 1.8 (0.4, 3.4); Auto-immune disease in the child: 30.6 (3.4, 278.0). The primary outcome result was robust even when four alternate

	case definitions were used. There was increased risk of developing JIA with greater number of antibiotic courses, higher total duration of antibiotic use, and more recent usage of antibiotics. Most of these results were robust when explored with alternate case definitions.
Do you believe the results?	The results are fairly convincing in terms of clinically significant effect, demonstration of dose dependency, and robustness with changes in case definition. The study demonstrates the fulfilment of several of the Bradford Hill criteria for causation (***Table* II**).
Can the results be applied to the local population?	Theoretically the results can be applied to any population unless strong reasons for the contrary can be unequivocally demonstrated. There are no obvious biological, genetic, social, cultural, or economic reasons to believe that if antibiotic exposure is somehow a part of the causal pathway of JIA in this UK based study, the results would be different in India. However, it is difficult to quantify the increased risk in the local population in the absence of baseline prevalence data.
Do the results of this study fit with other available evidence?	Unfortunately, there is very limited data exploring the relationship between antibiotic exposure and JIA. However, one recent case-control study [7] examining a country-wide database over 10 years in Finland with 1298 cases and 5179 age, gender and residence matched controls; identified odds ratio of developing JIA with antibiotic exposure to be 1.6 (95% CI 1.3, 1.9). They also reported that early antibiotic exposure (i.e prior to 2 years of age) increased the risk significantly. There do not appear to be animal experiments testing antibiotic exposure and the subsequent development of JIA type symptoms, or histopathology.

TABLE II BRADFORD HILL CRITERIA [6] FOR ASSESSMENT OF CAUSALITY

Criteria	*Assessment*
Strength of association	The odds of developing JIA were at least two-fold higher with exposure to antibiotics, suggesting a fairly strong association.
Temporality	This study [3] was designed to identify prior antibiotic exposure in children with JIA.
Consistency	There is only one other similar study [7] showing results in a similar direction.
Theoretical plausibility.	This criterion is fulfilled as the investigators' hypothesized that antibiotics alter the gut microbiome, causing perturbations in local and perhaps systemic immunity thereby increasing risk of JIA. They observed that only anti-bacterial antibiotics increased risk of JIA whereas other types did not. However, they could not show a greater risk with antibiotics that have entero-hepatic circulation.
Coherence	It is too early to conclude that "antibiotics cause JIA" as there are several pieces of evidence missing (see below).
Specificity in the causes.	Development of JIA and other auto-immune diseases appear to be influenced by a wide variety of factors that could include genetic, ethnic, environmental, and possibly hitherto unknown exposures. This study cannot be taken to suggest specificity. The hypothetical mechanism (alteration of the gut microbiome) was not studied in this investigation.
Dose response relationship.	There appears to be a linear relationship between the amount (frequency and duration) of antibiotics used and the risk of JIA.
Experimental evidence.	There are no in vitro or animal model experiments done to prove a causal relationship between antibiotics and JIA. Prospective controlled comparative studies would be unethical.
Analogy	There are no additional analogous or anecdotal pieces of evidence in the same direction.

a total of 1672 participants (152 cases + 1520 controls) at one place but only 1662 (1280 exposed + 382 unexposed) at another place. The investigators did not consider subgroup analyses base on different types of JIA.

Overall this well-conducted study suggests that antibiotic usage in childhood is associated with a greater risk of developing JIA in later childhood. In contrast, there are three well-known pieces of information that complicate the puzzle. First, if antibiotics are responsible for causation of JIA, it follows that health-care systems where childhood antibiotic use is rampant (India is a classic example) should witness the highest incidence/prevalence of JIA. Unfortunately, there is no robust population-based prevalence data in India to support or refute this. However,

there is a single study [8] evaluating prevalence of musculoskeletal symptoms in school children (6-17 y) where one case of JIA was identified among 2059 children studied. From this, the authors calculated a population prevalence of 48.5/100,000 school children. A similar study in Oman reported a prevalence of 20 per 100,000 [9]. In contrast, the prevalence in developed countries is variably reported to range from 100-400 per 100,000 (A), although more recent estimates suggest 50-60/ 100,000 in one region of the USA [10], 90/100,000 in Sweden (L), and 33.5/100,000 in this study [3]. Of course, the limited Indian data cannot be reliably compared with other studies on account of methodological differences; however clinical experience also does not suggest an unusually high burden of JIA.

If early [7] and more recent [3] antibiotic exposure increase the risk of developing JIA, it would be expected that countries with high burden of neonatal sepsis (such as India) would have very high burden of JIA, and that too presenting at a relatively younger age.

Further, there is no data from developed or developing countries to suggest that population subgroups exposed to greater frequency and/or duration of antibiotics (such as children with primary or secondary immune deficiencies) have higher prevalence of JIA. Of course, the reverse has been noted *i.e* children with JIA (or other autoimmune conditions) have greater frequency of infections requiring antibiotics [11]. Some authors have reported co-existing JIA and primary immune deficiencies [12-15] , but it is unclear which came first, although there is a report of a small cohort of 25 primary immune-deficiency patients in Turkey who were observed to later develop (rather be diagnosed with) diverse auto-immune conditions [16].

One other issue is that most auto-immune diseases (including JIA) have a female preponderance, whereas antibiotic exposure is generally gender independent. All these points suggest that while antibiotic usage could contribute, it is unlikely to be the absolute cause of development of JIA.

Extendibility: The study setting, population characteristics (ethnicity, genetic background, environmental exposures, etc) and health-care system are very different from our country. However, the conclusion that antibiotic usage could be linked to JIA appears extendible to India also. Unfortunately, the contrary pieces of evidence complicate the picture, making it difficult to draw a firm conclusion. Nevertheless, it goes without saying that unnecessary antibiotic use must be restricted to the maximum extent possible. Further, all antibiotic therapy must be well documented in terms of indication, drugs used, dosage and duration.

Conclusions: This well-designed case-control study suggests that antibiotic use in early childhood could have a dose-dependent impact on subsequent development of JIA.

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JOSEPH L MATHEW
Department of Pediatrics,
PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

Pediatric Rheumatologist's Viewpoint

In this paper, Horton, *et al*. make a compelling case for implicating antimicrobials with evolution of juvenile idiopathic arthritis (JIA). A recent study from another center also showed an association, albeit indirect, with JIA [1]. JIA remains the commonest rheumatic disease of childhood and is associated with significant morbidity.

There is no gainsaying the fact that antimicrobials are frequently misused in children. It is also known that use of antimicrobials in early childhood significantly alters the human microbiome and may predispose to long-term and, seemingly unrelated, consequences. These include, amongst others, inflammatory bowel disease and obesity [2-4].

In this study, authors suggest that use of antimicrobials in children may have some role to play in the pathogenesis of JIA. Their conclusion is based on a nested case-control study from the United Kingdom conducted on an apparently 'population-representative medical records database'. The data, however, need to be interpreted with some caution. JIA is a complex clinical entity [5,6]. Its etiology remains unknown and the pathogenesis poorly understood. It must also be understood that JIA is by no means a single disease entity but a conglomerate of disparate clinical conditions having chronic arthritis as the common denominator. Further, each of these conditions may have a different etiology [5,6]. At least two types of JIA are considered to be rather distinctive in their clinical presentation and pathogenesis. For instance, it is now well known that systemic JIA (sJIA) is more of an autoinflammatory rather than an autoimmune disorder [7]. Similarly the clinical phenotype of enthesitis related arthritis (ERA) is very different from, say, polyarticular or oligoarticular JIA. ERA has a distinct association with preceding gastrointestinal or genito-urinary infections while the other types of JIA do not [8,9]. Horton, *et al*. do not specify how many of their patients had sJIA or ERA. It is difficult to interpret the data in absence of this information. It may perhaps have been more prudent to exclude these two categories of JIA from final analysis.

Nevertheless paediatricians, and especially paediatric rheumatologists, would do well to keep the results of this study in mind the next time they see a child with JIA, and the next time they consider prescribing an antimicrobial to a child!

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SURJIT SINGH
Department of Pediatrics,
PGIMER, Chandigarh, India.
surjitsinghpgi@rediffmail.com

Infectious Disease Specialist's Viewpoint

Investigators have used the Health Improvement Network, a population-based medical records database in the United Kingdom that contains comprehensive diagnostic and outpatient prescription data, to identify people younger than 16 years of age who were newly

diagnosed with arthritis. The 152 children with juvenile arthritis were matched, for age and sex, with 1520 control subjects from general practices in the United Kingdom. They looked for antibiotic prescriptions in these 152 children in the last one year. The risk of developing arthritis was found to increase as exposure to antibiotics increased. However, there was no association between the development of arthritis and exposure to nonbacterial antimicrobial agents, including antifungal and antiviral drugs. After adjustment for the number and type of infections children had, the associations did not change significantly. The age at which children were exposed to antibiotics also had no significant effect on the associations.

Authors suggest that alterations in the human microbiome might be implicated in the development of autoimmune diseaases; and that includes inflammatory bowel disease and rheumatoid arthritis and perhaps psoriatic arthritis; all of which have some common features with juvenile arthritis. If the association between antibiotics and juvenile arthritis is true, judicious use of antibiotics might be one of the few ways we have to prevent JIA and other autoimmune diseases.

JANANI SANKAR
Department of Pediatrics,
Kanchi Kamakoti CHILDS Trust Hospital,
Chennai, India.
janani.sankar@yahoo.com