Association Between Antibiotic Use and Primary Idiopathic Intussusception

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Background: Intussusception is the leading cause of intestinal obstruction in young children. Antibiotics are the most frequently prescribed medication in the pediatric population and have common adverse effects on the gastrointestinal tract.

Objective: To determine whether a relationship exists between primary idiopathic intussusception and antibiotic drug use.

Design: Case-control study.

Participants: Ninety-three case patients with intussusception and 353 injury controls younger than 4 years who were seen at the emergency department of the Children's Hospital of Alabama between January 1, 1996, and April 30, 2001, were included. Controls were matched to cases by quarter and year of time of diagnosis, age, and sex.

Main Outcome Measures: Odds ratios and 2-sided 95% confidence intervals were estimated using conditional logistic regression. Prevalence of antibiotic use in an age-standardized, representative sample of US children from NHANES III (Third National Health and Nutrition Examination Survey) was used for external comparisons.

Results: Antibiotic use within 48 hours of diagnosis was found in 23 cases (25%) and 33 controls (9%) (odds ratio, 4.15; 95% confidence interval, 2.17-7.92; attributable risk, 18.7%). Antibiotic use among US children according to NHANES III was 10.7%. In cases, the β-lactam class accounted for 78% of all medications used. Cephalosporin use was associated with more than a 20-fold increased risk of intussusception.

Conclusion: An association between antibiotic drug use and intussusception was identified.

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INTUSSUSCEPTION is the most common cause of intestinal obstruction in children aged 3 months to 6 years.1 John Hunter2 first described intestinal invagination in the 18th century; however, the exact mechanism is still poorly defined in this age group, and the etiology is suspected to be multifactorial. Viral pathogens such as adenovirus are known to be associated with intestinal lymphoid hyperplasia and intussusception,3 but they cannot explain all cases. Promotility medications and certain chemical substances such as cocaine, laxatives, and organophosphates have been identified as potential agents that may contribute to the development of intussusception.4,5 Inflammatory mediators such as nitric oxide, prostaglandins, and cytokines have been demonstrated to increase rates of intussusception by altering gut motility in laboratory mice.6 Antibiotics, the second most widely prescribed medication class in the United States,8 modify gut motility and intestinal flora.9 To our knowledge, no studies to date have implicated antibiotics as a potential cause of intussusception. We conducted a retrospective, hospital-based, case-control study to determine whether an association exists between antibiotic use and primary, idiopathic intussusception in children.

METHODS

DATA COLLECTION

Medical records from the emergency department (ED) at the Children’s Hospital of Alabama, University of Alabama at Birmingham, were the source of information for this study. The pediatric ED has approximately 55000 child visits per year, serving the primary, secondary, and tertiary care needs of the Birmingham Metropolitan Standard Area and the state of Alabama. This is the only pediatric ED in the Metropolitan Standard Area (US Census 2000 population aged 0-17 years: n = 231225).
A total of 111 intussusception ED cases were identified. Of these, 13 (12%) were excluded on the basis of being older than 4 years and 4 (4%) because their medical records were not found. Nine patients were excluded with lead points as a secondary diagnosis, most (8 of 9) being older than the child’s fourth birthday. Thus, 93 cases (84%) were included in the study. In 3 (5%) of 60 sets defined by the matching variables, a control-case ratio of less than 4 was obtained owing to lack of available medical records for the eligible controls. This led to the inclusion of 353 controls in the study.

Most children (n = 56) diagnosed as having intussusception were younger than 1 year (Table 1). The male-female ratio was 2.39:1. Cases and controls had similar insurance coverage (Medicaid vs private insurance). Intussusception diagnosis was primarily radiographic (n = 59), and 70 children (75%) were diagnosed as having ileocolic or ileocecal intussusception. In addition, cases and controls were similar in age (13.6 vs 13.4 months).

### MEDICATION ANALYSES

Table 2 describes the association between intussusception and use and type of medications. Antibiotics, antipyretics and analgesics, asthma medications, GI medications, immunizations, over-the-counter cold and cough medications, and seizure medications accounted for 97% of the medications listed for cases and 99% for controls. A total of 60 antibiotics were used by 23 cases (25%) and 33 controls (9%) (adjusted OR, 4.13; 95% CI, 2.17-7.92). Amoxicillin was the most commonly used medication.
(9 cases and 16 controls), followed by ceftriaxone sodium (4 cases and 1 control) and trimethoprim-sulfamethoxazole (2 cases and 3 controls). Gastrointestinal medications were the second most common medications in cases (adjusted OR, 9.51; 95% CI, 3.91-23.12). There were 25 children (16 cases and 9 controls) taking a total of 31 GI medications at the time of ED presentation. Ranitidine (3 cases and 5 controls), prokinetics, and antipyretics and analgesics, asthma medications, over-the-counter cold and cough medicines, and seizure medications all had ORs that were lower after adjustment and that were not statistically significant. Most antibiotic use for cases (21 of 23) and controls (31 of 33) was recorded as occurring at the time of ED presentation. Each group had 2 patients not currently taking antibiotics, having discontinued using these medications within 48 hours of ED visitation. Therefore, neither group had discontinued any listed antibiotics more than 48 hours before ED presentation.

Table 3 represents the relation between intussusception and use of antibiotics by class using adjusted ORs. Classes were not mutually exclusive owing to combination products. Classes are not mutually exclusive owing to combination products. Children who did not use antibiotics during the 2 weeks preceding the emergency department admission are the reference category. Odds ratio adjusted for use of gastrointestinal medications.

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between antibiotic use and intussusception varied little regarding indication, with similar ORs for otitis media, upper respiratory tract infection, and other indications. Other indications listed were fever (1 case), urinary tract reflux (1 case), postlaceration repair (1 case), sickle cell prophylaxis (1 control), and stomach virus (1 control). For GI indications, emesis (10 cases) and gastroesophageal reflux (2 cases and 8 controls) each accounted for 40% of all indication types. Diarrhea (1 case and 1 control) accounted for 8% of all GI indications, and “other” (3 cases) accounted for the remaining 12%.

For the group of children younger than 4 years presenting to the ED with primary idiopathic intussusception, the risk attributable to antibiotic use was 18.7%. This estimate was based on a RR of 4.15 and a proportion of antibiotic users of 0.247 (23/92). From NHANES III, antibiotic use among American children during the 2 weeks before interview was approximately 10.7%, which is similar to that of the study control group. Use of β-lactam antibiotics from the NHANES III external analysis was 8.3%. Therefore, use of antibiotics in our series of intussusception cases was 2.3 times higher compared with the age-standardized NHANES III data.

Previous case series have evaluated the descriptive epidemiologic characteristics of intussusception. The findings of the intussusception cases in our study are similar to those of previous studies with respect to age and sex. Although some studies have reported little seasonal variation, most have reported peaks during the spring and early summer, which is consistent with our data showing a slight increase in the second quarter (April-June). We noted no significant differences between cases and controls regarding chronic underlying conditions, immunization status, insurance type, history of prematurity, allergies to medications, or mean age (in months).

This study found an independent association of intussusception with antibiotic use. The association of antibiotics with intussusception became somewhat stronger when the OR was adjusted for use of GI medications, indicating that the association cannot be explained by confounding by use of GI medications. The strong association of GI medications with intussusception was expected, considering the presenting clinical symptoms of abdominal pain and emesis that occur with significant frequency before proper diagnosis. We also directly analyzed the indication for antibiotic use before ED admission as it was abstracted from the medical records. No indications for antibiotic use were for GI symptoms or diagnosis; in fact, most were otitis media and upper respiratory tract infection related. These results provide further evidence that antibiotic use preceded intussusception and are consistent with national data indicating that acute otitis media and upper respiratory tract infections are the principal diagnoses for US physician visits.

Of the various antibiotic classes, the β-lactams were found in this study to be significantly associated with intussusception. Users of cephalosporins had more than a 20-fold increased risk of intussusception (OR, 22.49; 95% CI, 5.32-95.00), and use of penicillins also was associated with a significantly higher OR (OR, 3.14; 95% CI, 1.35-7.26). The use of antibiotics has been described previously to cause small-bowel disturbances. Caron et al demonstrated in humans that amoxicillin–clavulanate potassium increases the amplitude and duration of duodenal–jejunal contractions. β-Lactams interact directly with the postsynaptic γ-aminobutyric acid receptors in the central nervous system, with such receptors additionally found in the mesenteric plexus. A potential mechanism of β-lactam small intestine dysmotility may then be γ-aminobutyric acid, induced either directly or indirectly with administration of this drug class. Erythromycin, a macrolide class antibiotic, is a known motilin receptor agonist and inducer of the migrating motor complex in the human GI tract, which as a promotility agent is a potential mechanism to induce intussusception. Our hypothetical model, therefore, suggests antibiotic dysmotility as a variable factor in the development of intussusception. The exposure window of all antibiotics recorded was taken currently or within 48 hours of ED presentation. As the half-life of the various antibiotics in our series ranges from 30 minutes to 68 hours, it is possible that the antibiotic dysmotility effects may have lasted from hours to days depending on the specific antibiotic used.

The major limitation of this study is the retrospective nature of medical record analysis. Handwritten medical record information is potentially not accurate, poorly interpretable, or noninclusive. Emergency department records reviewed during the study were noncomputerized and were not dictated. The data abstractor was not masked to the study design or hypothesis. To improve the accuracy of results and minimize inconsistencies of record review, the following procedures were used: the abstractor was trained before study inception; explicit protocols were used to describe the criteria for case selection and exclusion; standardized abstraction forms for cases and controls were applied; periodic meetings were held during study abstraction to review and monitor coding protocols; and a second reviewer was used to randomly reabstract 10% of all medical records and data entries to determine interrater reliability for each abstraction step. Interrater variability was low (6.1% for medical record abstraction and 0.4% for data entry). Another potential bias may be the differing nature of information obtained between cases and controls. Intussusception records may have been more complete with respect to recording antibiotic use compared with injury control records, as many of these children were preoperative during the ED course. In addition, all recorded medication use was abstracted with standardized ED records for cases and controls, which may minimize this potential bias.

Outpatient injuries were selected as controls particularly to determine the prevalence of antibiotic use in the general population at the time of matched case diagnosis. We believe that outpatient injuries are the hospital-based series that best represents the general population of children in our area. In addition, potential confounders such as insurance type and chronic conditions were tested in multiple logistic regression models but were found not to affect the association between in-
tussusception and antibiotic use. A second strength was the use of NHANES III data as an external comparison group. Although the NHANES III analysis pertains to a different period (1988-1994 vs 1996-2001) and population (United States vs Alabama), and estimates of use of medication in NHANES III was based on a calculated use during the 2 weeks before interview compared with current use in our study subjects, the concordance of antibiotic use between NHANES III data and our control series provides external validation to our results.

Intussusception as an entity diagnosis has many etiologies. In older children and adults, a pathologic, well-defined lead point is usually discovered, such as lymphoma, Meckel's diverticulum, or intestinal polyposis. In the infant and toddler age groups, multiple viral infections have been implicated as these agents have been recovered from intestinal lymphoid tissue at the site of intussusception. Adenovirus has been found in up to 50% of intussusception appendices, significantly higher than in control populations. Lymphoid hyperplasia may be responsible for the actual lead point in primary idiopathic intussusception, but this does not explain why some infants develop the condition and others do not despite exposure to similar environmental conditions, including potentially causative viral agents. In addition, it has been suggested that anatomic or genetic predisposition may play an important role, as siblings of patients with intussusception have a reported 15- to 20-fold increase in incidence compared with the general population.

Prompted by a frequent history of mild upper respiratory tract symptoms preceding the development of intussusception, physicians suggested a potential role for infection decades before the identification of adenovirus. In the United States, pediatricians and family physicians commonly prescribe antibiotics for viral conditions in children despite consistent evidence that antimicrobial therapy has no role in their treatment. Therefore, one explanation for the antibiotic-intussusception association that we found may not be causality but confounding by viral infection. Conversely, antibiotics are known to alter gut motility, and, under certain conditions, these drug-induced changes may contribute to the development of intussusception. Antibiotics have been implicated in other GI pathophysiologic states, such as hemolytic uremic syndrome, as well as irritable bowel syndrome, and a more recently described relationship between infantile hypertrophic pyloric stenosis and erythromycin therapy.

We hypothesize that intussusception is a multivariant process that, in young children, may involve a complex interdependent progression of lymphoid hyperplasia combined with dysmotility, induced by the viral agent itself, the use of antibiotics, or other as yet unidentified factors, all or some of which may include the release of local inflammatory mediators. According to a mouse model for intussusception developed by Nissan et al, intraperitoneal injections of lipopolysaccharides may interact with other potent inflammatory mediators such as nitric oxide, ultimately increasing rates of intussusception above baseline. Therefore, the process of intussusception development is most likely a dynamic entity and may involve a series of cellular and intracellular events for intestinal invagination to occur, with an increased likelihood in individuals with an anatomic or familial predisposition. Although the exact cellular and biochemical mechanisms are not clearly defined, antibiotic therapy, viral processes, or both may contribute individually or by additive effect to induce intussusception. Although this study found an independent association between antibiotic use and intussusception, further research is necessary to determine causality.

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