Bacterial Enteritis as a Risk Factor for Childhood Intussusception: A Retrospective Cohort Study

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Objective To assess the relationship between bacterial enteritis and intussusception.

Study design The Patient Administration Systems and Biostatistics Activity database from January 2002 to December 2005 was examined for clinic visits or hospital admission to a Department of Defense medical facility for children age 0-5 years. The study included the International Statistical Classification of Diseases and Related Health Problems diagnosis-related group (DRG) codes for infections with Yersinia enterocolitica, Escherichia coli, Shigella species, Salmonella species, and Campylobacter. Identified patients were then assessed for the intussusception DRG code for 0-180 days postinfection. The total number of children enrolled in military treatment facilities in the same age group (denominator) was obtained.

Results Bacterial enteritis significantly increased the relative risk of intussusception. An increased risk was found following infection with Salmonella, E coli, Shigella, and Campylobacter. The relative risk for intussusception following any bacterial enteritis was 40.6 (95% confidence interval = 28.6-57.5; P < .0001).

Conclusions Bacterial enteritis is a significant risk factor for the subsequent development of intussusception in children. (J Pediatr 2010;156:761-5)

Methods

A data record is maintained for every outpatient and inpatient encounter for each patient treated at a DOD medical treatment facility (MTF). These data records are maintained by the Patient Administration Systems and Biostatistics Activity (PASBA)
and include a collection of International Statistical Classification of Diseases and Related Health Problems (ICD) codes.

Using the PASBA database, the search was limited to children age birth to 5 years and dates between January 1998 and December 2005. The database was searched for all patients with a diagnosis-related group (DRG) code for the following intestinal infectious diseases: Y enterocolitica, E coli (enteropathogenic, enterotoxigenic, enteroinvasive, and enterohemorrhagic), Shigella spp (S dysenteriae, S flexneri, S boydii, and S sonnei), Salmonella gastroenteritis, and Campylobacter spp. The patients thus identified were then evaluated over the ensuing 6 months after the bacterial enteritis visit for a DRG or procedure code consistent with intussusception. Intussusception was defined as DRG code 560.0. The total number of intussusceptions was obtained as well. No other methods were used to verify the disease state of either enteritis or intussusception. Patients who were not identified with a corresponding DRG code were assumed to be disease-free.

The data examined included age at presentation, sex, date of the visit for enteritis, and the date of the visit for intussusception. Incidence rates were based on the number of children enrolled in MTF facilities during the study period. Wilford Hall Medical Center’s Institutional Review Board approved the study design. All HIPAA-protected data were encoded. The overall relative risk for developing intussusception and stratified relative risk by age were estimated using Mantel-Haenszel relative risk analysis for age and stratified relative risk by age were estimated using Mantel-Haenszel relative risk analysis for age when appropriate, were used for calculating probability. Statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, North Carolina) and R version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 387,514 children were enrolled in MTFs during the study period. A total of 293 cases of intussusception were reported, with a cumulative incidence of 7.56 cases/10,000 children. Of the 1412 cases of bacterial enteritis, intussusception ensued in 37; these cases represented 12.6% of all intussusceptions. The absolute risk of intussusception was increased from 0.075% in all patients to 2.62% in patients with bacterial enteritis: 0.075% in all children to 2.62% in children with bacterial enteritis (P < .0001). The absolute risk of intussusception following enteritis was 2.3% for the patients age <1 year and 3.3% for those age 1-5 years.

The 1412 cases of bacterial enteritis included 557 (39%) due to Salmonella, 496 (35%) due to E coli, 280 (20%) due to Shigella, 63 (5%) due to Campylobacter, and 16 (1%) due to Yersinia. Of the 37 cases of intussusception in these 1412 cases, 16 followed infection with Salmonella, 13 followed E coli, 6 followed Shigella, and 2 followed Campylobacter. No cases of intussusception followed infection with Yersinia, perhaps due to the overall low rate of Yersinia enteritis. The risk of intussusception was increased in all 4 types of bacterial enteritides, with a relative risk (95% CI) of 28.7 (7.2-113.4) for Salmonella, 25.0 (5.62-111.6) for E coli, 23.6 (3.6-156.0) for Shigella, and 32.9 (3.48-310.7) for Campylobacter (Table II).

The median (interquartile range) time between the episode of enteritis and the development of intussusception was 58 days (14-115 days). The interval between enteritis and intussusception ranged from 1 day to 175 days, with a cluster of cases in the immediate 2-3 weeks after the diagnosis of bacterial enteritis (Figure). The remaining cases were distributed evenly over the subsequent months, with cases still developing even as long as 4-6 months after enteritis. To help characterize the risk associated with the time interval after bacterial enteritis, negative binomial regression was performed with 30-day time periods while controlling for age. The relative risk (95% CI) for intussusception after bacterial enteritis, 9.5 (2.5-35.8; P < .0009), was highly significant for the first 30-day period. After the first 30 days, the risk was decreased; however, in all but one of these subsequent time periods, the risk of intussusception did not reach significance (Table II). No secondary diagnoses of enteritis were identified in the 180 days after intussusception.

Discussion

The results of our retrospective cohort study show a statistically significant increase in the risk of intussusception in

<table>
<thead>
<tr>
<th>Intussusception group</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>P*</th>
<th>Total number of children</th>
<th>Total cases of bacterial enteritis</th>
<th>Intussusceptions following infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>40.56</td>
<td>28.61-57.48</td>
<td>&lt;.0001</td>
<td>387,514</td>
<td>1412</td>
<td>37</td>
</tr>
<tr>
<td>Age &lt;1</td>
<td>15.98</td>
<td>9.10-28.17</td>
<td>&lt;.0001</td>
<td>54,927</td>
<td>426</td>
<td>14</td>
</tr>
<tr>
<td>Age 1-5</td>
<td>56.24</td>
<td>36.03-87.79</td>
<td>&lt;.0001</td>
<td>332,587</td>
<td>986</td>
<td>23</td>
</tr>
</tbody>
</table>

*Probability was calculated using the χ² test.
children with a history of bacterial enteritis within the previous 6 months. The study examined the association between bacterial enteritis and intussusception. Population studies showing coinciding trends in intussusception and enteritis support our findings. Studies from Denmark, Australia, and the United States evaluating the rate of intussusception over varying periods ranging from 6 years to 21 years have consistently found a downward trend with time.26-29 This observed downward trend demonstrates a 25%-48% drop in the rate of intussusception. A US study using data from the Indian Health Survey found an 86% decrease in the rate of intussusception from 1980 to 1997.30 The authors noted that this downward trend coincided with both improvements in water sanitation and hospitalizations for diarrheal disease in the study population. A downward trend in the rates of Salmonella and Shigella enteritidies also has been reported. Between 1995 and 2005, the Centers of Disease Control found a 12% decrease in Salmonella infection and a 46% decrease in Shigella infection.31-34 Both Salmonella and Shigella are most common in children age ≤5 years old.31,33 The rate of E coli O157: H7 infection remained stable between 1996 and 2005.35,36 Although no independent conclusions can be drawn from these coinciding downward population-based trends of intussusception and bacterial enteritis, they are of interest in the context of our results. In our study population, 12.6% of all cases of intussusception followed bacterial enteritis.

Beyond the observation of an overall increased risk of intussusception after enteritis, we report several other interesting findings. First, the cases of intussusception were distributed across the 6-month follow-up period (Figure). Our analysis of the age-adjusted relative risk by 30-day time periods revealed only 2 time periods of significance, the first month and the fifth month after exposure. We note that because of the very small numbers involved, drawing a definite conclusion as to the temporal risk of intussusception after enteritis is difficult. Our data suggest a high risk of intussusception in the first 30 days after enteritis, followed by a lingering, yet lower risk of intussusception in the subsequent months. Second, the relative risk was higher in the patients in the older age group (1-5 years) than in the younger group (<1 year). This difference is put in perspective by the absolute risk of intussusception after enteritis of 2.3% in those age <1 year and 3.3% in those age 1-5 years. The higher relative risk of intussusception in the older age group may be consistent with literature reporting children age >1 year are more likely to have a pathological cause or lead point of intussusception than those age <1 year.37

The present study was not designed to look specifically at the etiology of the observed increased risk of intussusception after bacterial enteritis. One possible explanation for the increased risk is that bacterial enteritis stimulates an increased immune response, which in turn leads to bowel lymphoid hyperplasia. Any one of these lymphoid aggregates could serve as a lead point for intussusception. It also is possible that the delayed cases of intussusception may be secondary to reduced immune function. This could lead to increased susceptibility to prolonged or new infection and possibly predispose patients to prolonged hypertrophy of Peyer’s patches. Another possible explanation for the increased risk of intussusception may be related to altered bowel motility. Studies have indicated that 7%-36% of patients with acute bacterial gastroenteritis develop symptoms of irritable bowel syndrome (IBS).38-41 Two prospective

### Table II. Summary results from age-adjusted negative binomial regression for specific enteritidies and time periods

<table>
<thead>
<tr>
<th>Intussusception group</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>( P )</th>
<th>Total cases of bacterial enteritis at risk in category</th>
<th>Intussusceptions following infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella spp, 0-180 days postinfection</td>
<td>28.65</td>
<td>7.24-113.41</td>
<td>&lt;.0001</td>
<td>557</td>
<td>16</td>
</tr>
<tr>
<td>E coli, 0-180 days postinfection</td>
<td>25.03</td>
<td>5.62-111.55</td>
<td>&lt;.0001</td>
<td>496</td>
<td>13</td>
</tr>
<tr>
<td>Shigella spp, 0-180 days postinfection</td>
<td>23.61</td>
<td>3.56-156.02</td>
<td>.0011</td>
<td>280</td>
<td>6</td>
</tr>
<tr>
<td>Campylobacter, 0-180 days postinfection</td>
<td>32.89</td>
<td>3.48-310.69</td>
<td>.0023</td>
<td>63</td>
<td>2</td>
</tr>
<tr>
<td>All infections, 0-30 days postinfection</td>
<td>9.48</td>
<td>2.51-35.79</td>
<td>&lt;.0009</td>
<td>1412</td>
<td>13</td>
</tr>
<tr>
<td>All infections, 31-60 days postinfection</td>
<td>2.13</td>
<td>0.34-13.28</td>
<td>.42</td>
<td>1399</td>
<td>3</td>
</tr>
<tr>
<td>All infections, 61-90 days postinfection</td>
<td>2.71</td>
<td>0.48-15.30</td>
<td>.26</td>
<td>1396</td>
<td>4</td>
</tr>
<tr>
<td>All infections, 91-120 days postinfection</td>
<td>3.60</td>
<td>0.73-17.76</td>
<td>.12</td>
<td>1392</td>
<td>5</td>
</tr>
<tr>
<td>All infections, 121-150 days postinfection</td>
<td>5.46</td>
<td>1.22-24.43</td>
<td>.03</td>
<td>1387</td>
<td>8</td>
</tr>
<tr>
<td>All infections, 151-180 days postinfection</td>
<td>2.74</td>
<td>0.48-15.48</td>
<td>.25</td>
<td>1375</td>
<td>4</td>
</tr>
</tbody>
</table>

![Figure](Figure.png) **Figure.** Graph of the number of cases of intussusception by days following bacterial enteritis.
studies of adults and one pediatric study have identified bacterial gastroenteritis as a risk factor for developing IBS.\textsuperscript{40-43} Specifically, IBS has been associated with \textit{Campylobacter} and \textit{Salmonella} enteritis.\textsuperscript{44-46} Patients with IBS also have been shown to have small bowel and colonic dysmotility, both increased bowel contraction pressures and increased bowel contraction frequency.\textsuperscript{47-49} It is reasonable to speculate that children may develop altered bowel motility after infectious enteritis, leading to an increased risk of bowel invagination and intussusception.

One major strength of this study is its use of the PASBA database, which allows evaluation of a large population cohort. The PASBA database has been used for previous pediatric epidemiologic research; its best-known application may be in the studies of Wiswell et al.\textsuperscript{50-52} investigating the risk and benefits of circumcision. These data played a particular role in updating the American Academy of Pediatrics’ circumcision policy statement.\textsuperscript{53} The PASBA database continues to be used for epidemiologic research,\textsuperscript{54,55} however, a weakness of this database is its dependence on ICD coding data. As in all studies that use diagnostic codes, the accuracy of coding is a concern. The diagnostic methods for enteritis or intussusception were not available for evaluation. Of the 37 children who developed intussusception after bacterial enteritis, 24 were males (65%); this higher proportion of males is consistent with previous reports.\textsuperscript{2,27,29,30} We were unable to statistically evaluate sex as a risk factor, because we did not obtain sufficient sex data in the enteritis and total population groups. Studies from Switzerland, Denmark, Australia, and the United States report yearly rates of intussusception ranging from 3.5 to 12/10 000.\textsuperscript{2,26,27,29,30} Comparing these rates with our cumulative incidence of 7.5/10 000 over 5 years suggests that our database may not have captured all cases of intussusception in our study population. The PASBA database only captured children cared for within a DOD facility, but most MTFs maintained by the DOD are smaller hospitals, which may not have the necessary equipment or personnel to diagnose and treat children with intussusception. Therefore, we may have missed cases of intussusception within our study population because of referrals to larger hospitals, which could elevate the calculated relative risk. Another potential source of error is that the total enrollment data for MTFs commonly underrepresents the actual number of patients seen. This inaccuracy may be accentuated for infants, who often are treated and cared for within an MTF without enrollment because of delays in obtaining the birth documentation required for official enrollment. This type of error would tend to decrease the calculated relative risk.

In summary, the risk for intussusception is increased following bacterial enteritis in children. Educating both parents and physicians about this increased risk can lead to earlier detection and treatment of subsequent intussusception, resulting in decreased morbidity and mortality. The high risk of intussusception associated with bacterial enteritis detected in our study warrants future prospective studies in such areas as identifying additional risk factors, such as sex, nutritional status, type or duration of antibiotic therapy, and the duration, severity, and course of the enteritis.

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References


