Very Early Exposure to Erythromycin and Infantile Hypertrophic Pyloric Stenosis

William O. Cooper, MD, MPH; Marie R. Griffin, MD, MPH; Patrick Arbogast, PhD; Gerald B. Hickson, MD; Shiva Gautam, PhD; Wayne A. Ray, PhD

Objective: To assess the link between very early erythromycin exposure and pyloric stenosis in young infants.

Design: Retrospective cohort study.

Participants and Methods: Medicaid or TennCare (Tennessee’s program for Medicaid enrollees and uninsured individuals) births in Tennessee from 1985 to 1997. Cases of infants with a hospital discharge diagnosis of pyloric stenosis and an associated surgical procedure code were used. Erythromycin exposure and other antibiotic exposure between 3 and 90 days of life were identified from prescription files.

Main Outcome Measures: Hospital discharge diagnosis of pyloric stenosis, and an associated surgical procedure code.

Results: Of 933,239 births in Tennessee during the study period, 314,029 were enrolled in Medicaid. Among these infants, 804 (2.6/1000 infants) met the criteria for pyloric stenosis. Very early exposure to erythromycin (between 3 and 13 days of life) was associated with a nearly 8-fold increased risk of pyloric stenosis (adjusted incident rate ratio, 7.88; 95% confidence interval, 1.97-31.57). No increased risk of pyloric stenosis was seen in infants exposed to erythromycin after 13 days of life or in infants exposed to antibiotics other than erythromycin.

Conclusions: The significant increase in pyloric stenosis in children with very early exposure to erythromycin is consistent with reports of other investigators. The risks and benefits of erythromycin should be weighed carefully prior to initiating such therapy in young infants.

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Infantile hypertrophic pyloric stenosis (IHPS) is a condition of infancy in which hypertrophy of the pylorus results in gastric outlet obstruction.1-3 The onset of symptoms, including projectile vomiting, usually occurs in the first 3 to 5 weeks of life.2 Morbidity from IHPS includes dehydration, weight loss, and electrolyte abnormalities, with death occurring rarely.2 While the etiology of IHPS is unknown, previous reports suggest a link between early erythromycin exposure and IHPS.4-7 It has been hypothesized that erythromycin interacts with motilin receptors, inducing strong gastric and pyloric bulb contractions and resulting in pylorus hypertrophy.8-10 Recently, Honein et al4 reported a cluster of 7 cases of pyloric stenosis attributable to very early erythromycin prophylaxis of infants potentially exposed to pertussis in a single newborn nursery.4 This represented a nearly 7-fold increased risk of pyloric stenosis. In the Honein et al study and in a recent study from a single urban hospital where infant use of erythromycin was associated with increased risk of IHPS,7 exposure to erythromycin occurred in the first 2 weeks of life, which is much earlier than typical clinical uses of erythromycin. We performed a large population-based study among infants enrolled in the Tennessee Medicaid population to assess the link between very early exposure to erythromycin and IHPS.

Results: Of 933,239 births in Tennessee during the study period, 314,029 were enrolled in Medicaid. Among these infants, 804 (2.6/1000 infants) met the criteria for pyloric stenosis. Very early exposure to erythromycin (between 3 and 13 days of life) was associated with a nearly 8-fold increased risk of pyloric stenosis (adjusted incident rate ratio, 7.88; 95% confidence interval, 1.97-31.57). No increased risk of pyloric stenosis was seen in infants exposed to erythromycin after 13 days of life or in infants exposed to antibiotics other than erythromycin.

Conclusions: The significant increase in pyloric stenosis in children with very early exposure to erythromycin is consistent with reports of other investigators. The risks and benefits of erythromycin should be weighed carefully prior to initiating such therapy in young infants.

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PARTICIPANTS AND METHODS

Children were included in the base population if they were born in Tennessee between 1985 and 1997 and had complete information in the Tennessee birth certificate files. Study years were selected based on the earliest available data in the Tennessee Medicaid or TennCare (Tennessee’s program for Medicaid enrollees and uninsured individuals) database and to avoid including the cases described in the Honein study, which was performed in a Tennessee community shortly after the end of the study period. Children with prolonged neonatal intensive care unit stays would be unable to have an outpatient prescription filled. Therefore, the base population included only infants who were discharged from a birth hospital by 3 days of life and who were enrolled in Medicaid by 3 days of life. To ensure complete ascertainment of erythromycin exposure and study outcomes, infants who had any lapes in Medicaid enrollment or who died in the first 3 months of life were excluded from the base population.

Cases were identified from infants in the base population as defined above (N = 314029). Medicaid encounter files were searched to identify infants having IHPS hospitalizations between 3 and 90 days of life. Initial screening included the specific International Classification of Diseases, Ninth Revision (ICD-9) code for IHPS (750.5) and ICD-9 codes for other diagnoses that could be coded for IHPS (ie, acquired pyloric stenosis [537.0] and pylorospasm [537.81]). Current Procedural Terminology (CPT) codes from physician and hospital claims were searched to identify codes for pyloromyotomy, the definitive surgical procedure for IHPS (CPT, 43520; ICD-9, 433). Cases were defined as infants with a discharge diagnosis code for IHPS along with a procedure code for pyloromyotomy.

Outpatient prescription files for all children in the cohort were searched to identify prescriptions occurring between 3 days of life and the date of admission for pyloric stenosis (cases) or 90 days of life (controls). Antibiotics included oral erythromycin and other oral antibiotics previously described as being used in children during the first months of life. Other oral antibiotics included cephalosporins, penicillins, and sulfa medications. In addition, the databases were searched for nonerythromycin macrolides (lincomycin hydrochloride, clindamycin hydrochloride, clarithromycin, azithromycin, and dirithromycin). Restricting prescriptions to those occurring from 3 days of life allowed for differences in length of hospitalization following births that occurred during the study period. Age exposure categories were developed a priori based on age of exposure to erythromycin in previous reports, with particular interest in exposure during the first 2 weeks of life, as seen in the Honein et al study. Antibiotic age exposure categories included 3 to 13 days of life, 14 to 27 days of life, 28 to 90 days of life, or no exposure during the study period.

Outpatient encounters and physician claims occurring within 14 days of the erythromycin prescription were searched to identify a possible indication for antibiotic use among infants with very early exposure to antibiotics. The encounter occurring closest to the date of the prescription was considered to represent the visit resulting in the prescription. Thus, the primary diagnosis from that encounter was used to determine a possible indication. Encounters were grouped into conjunctivitis, respiratory infections, otitis media, chlamydial infections, skin infections, vomiting, and other diagnoses not typically treated with erythromycin.

Comparisons were made between infants who had erythromycin prescriptions filled and infants who did not, using \( \chi^2 \) analysis. Age-adjusted incidence rates for each category of antibiotic exposure (any, 3-13 days of life, 14-27 days of life, and 28-90 days of life) were calculated. Poisson regression models were constructed using factors shown in previous literature to influence the development of pyloric stenosis. Variables contributing significantly were retained in final models (SAS statistical software 8.2; SAS Institute Inc, Cary, NC).

The study protocol was approved by the institutional review boards of Vanderbilt University (Nashville, Tenn) and the state of Tennessee.

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**Table 1. Characteristics of Children With Filled Erythromycin Prescriptions: Medicaid/TennCare Infants Born in Tennessee, 1985-1997**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Use of Erythromycin (N = 306,891)</th>
<th>Any Use of Erythromycin (N = 7138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up, d</td>
<td>86.9</td>
<td>86.9</td>
</tr>
<tr>
<td>Infant characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight &lt;2500 g†</td>
<td>23,916 (7.8)</td>
<td>483 (6.8)</td>
</tr>
<tr>
<td>No older siblings†</td>
<td>135,852 (44.3)</td>
<td>2983 (41.9)</td>
</tr>
<tr>
<td>Male, sex†</td>
<td>156,087 (50.9)</td>
<td>3937 (55.2)</td>
</tr>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age &lt;18 y†</td>
<td>37,003 (12.1)</td>
<td>902 (12.6)</td>
</tr>
<tr>
<td>Maternal race, black†</td>
<td>115,611 (37.7)</td>
<td>1837 (25.7)</td>
</tr>
<tr>
<td>Education &lt;12 y†</td>
<td>131,727 (43.0)</td>
<td>3648 (51.1)</td>
</tr>
<tr>
<td>Residence, rural county†</td>
<td>102,011 (33.2)</td>
<td>3489 (48.9)</td>
</tr>
</tbody>
</table>

*All data are number (percentage) of children. \( \dagger \) \( P < .001 \); \( \chi^2 \) analysis.
After adjusting for the child’s age, sex, and race, exposure to erythromycin before 90 days of life was associated with a 2-fold increased risk of pyloric stenosis (adjusted rate ratio, 2.05; 95% confidence interval, 1.06-3.97) (Table 2). Very early exposure to erythromycin between 3 and 13 days of life was associated with a nearly 8-fold increased risk of IHPS (adjusted rate ratio, 7.88; 95% confidence interval, 1.97-31.57). The risk of IHPS was not increased in children receiving erythromycin after 14 days of life. The use of other antibiotics was more common in early infancy, accounting for 4140 child years of follow-up, but such use was not associated with an increased risk of IHPS. There were only 12 children with nonerythromycin macrolide prescriptions in the cohort. None had prescriptions filled before 14 days of life, and none developed pyloric stenosis.

Encounter claims for children having erythromycin prescriptions filled were reviewed to identify a possible indication for the prescription. Of the 2 cases with early erythromycin exposure and IHPS, 1 filled an erythromycin prescription on the sixth day of life, with a temporally associated encounter for conjunctivitis; the IHPS admission occurred 3 days later. The other patient with very early exposure had no temporally associated claim, received erythromycin beginning on the 10th day of life, and then was admitted 3 days later. Among the 70 children with very early exposure to erythromycin and no pyloric stenosis, the most common possible indications included conjunctivitis (n=23, 32.9%), respiratory infections (including upper respiratory infections [n=10, 14.9%], nonspecific respiratory infections [n=3, 4.3%], and pneumonia [n=1, 1.4%]), otitis media (n=4, 5.7%), chlamydia infection (n=2, 2.9%), impetigo or cellulitis (n=3, 4.3%), vomiting (n=2, 2.9%), and other diagnoses typically not treated with erythromycin (n=12, 17.1%); 9 infants (12.9%) did not have a temporally linked diagnosis.

The data from this retrospective cohort study representing exposure in more than 74000 child-years of follow-up are consistent with the hypothesis that early erythromycin exposure can cause IHPS. Exposure to oral erythromycin prior to 14 days of life was rare in this population, but such use increased the risk of IHPS nearly 8-fold. These findings must be viewed in the context of prior studies. In 1976, SanFilippo reported 6 cases of pyloric stenosis among 963 infants born at a single military hospital during 1 year. Five of these 6 infants received erythromycin between 8 and 17 days of life, had onset of symptoms of pyloric stenosis shortly thereafter, and had surgery between 17 and 27 days of life. In 1986, Stang reported that 6 of 122 children (5%) with pyloric stenosis who were operated on at a single children’s hospital throughout 5 years had received erythromycin prior to symptom onset. An investigation of a 6-fold increase in pyloric stenosis (7 cases) at a single community hospital in February 1999 revealed that all 7 infants had received erythromycin prophylaxis between day 2 and day 17 of life because of a nursery outbreak of pertussis. This cluster was remarkably similar to that of SanFilippo in that children received erythromycin very early in life, had symptoms shortly thereafter, and also had relatively early onset of pyloric stenosis. In a more recent study of 14876 infants born in a single urban hospital, erythromycin exposure in the first 2 weeks of life was found to represent the highest risk for IHPS as compared with exposure at later ages. The temporal relationship between erythromycin exposure and hospitalization for pyloric stenosis seen in the current study parallels the temporal relationship described in previous reports.

Automated pharmacy records have been shown to be an excellent, unbiased source of prescription drug information. However, there are some limitations of these data that could cause misclassification of exposure. The Medicaid pharmacy files only contain claims for outpatient prescriptions. Therefore, the study was unable to detect inpatient prescribing of erythromycin. To partially address misclassification of antibiotic exposure, the current study included infants who were discharged from a birth hospital before 3 days of life, as it would not be possible for infants with prolonged hospital stays to have outpatient prescriptions filled. It is possible that some chil-

| Table 2. Antibiotic Use in the First 3 Months of Life and the Development of Infantile Hypertrophic Pyloric Stenosis Among Infants With Medicaid or TennCare Born in Tennessee Between 1985 and 1997* |
|------------------|----------|-----------------|-----------------|-----------------|
| Erythromycin     | No use of erythromycin | 74163 | 795 | 1.06 | ... | ... |
|                  | Any use of erythromycin | 576  | 9  | 1.57 | 2.05 | 1.06-3.97 |
|                  | 3-13 Days of life‡ | 16   | 2  | 12.81 | 7.88 | 1.97-31.57 |
|                  | 14-27 Days of life‡ | 70   | 1  | 1.42 | 0.92 | 0.13-6.57 |
|                  | 28-90 Days of life§ | 490  | 6  | 1.24 | 1.95 | 0.87-4.38 |
| Other antibiotics† | No use of other antibiotics | 68878 | 758 | 1.10 | ... | ... |
|                  | Any use of other antibiotics | 4140 | 37 | 0.88 | 1.16 | 0.83-1.63 |
|                  | 3-13 Days of life‡ | 102  | 1  | 0.99 | 0.63 | 0.09-4.44 |
|                  | 14-27 Days of life‡ | 520  | 9  | 1.72 | 1.12 | 0.58-2.17 |
|                  | 28-90 Days of life§ | 3518 | 27 | 0.77 | 1.22 | 0.82-1.81 |

*CI indicates confidence interval. Incidence rates are per year. Rate ratios are adjusted using Poisson regression with model including child’s age, sex, and race.
†Analysis excluded children exposed to erythromycin at any time.
‡Child years of exposure begin at 14 days of life.
§Child years of exposure begin at 28 days of life.
Previous reports have described an association between early erythromycin exposure in infants and the development of infantile hypertrophic pyloric stenosis. No large population-based studies have been performed to confirm the findings of these earlier reports. Drawing from 314,029 births (representing 74,739 child-years of follow-up) to mothers in Tennessee who were enrolled in Medicaid or TennCare, this study identified 804 cases of pyloric stenosis. Compared with infants not exposed to erythromycin, children with filled prescriptions for erythromycin in the first 2 weeks of life were at an 8-fold increased risk for pyloric stenosis. Taken in context with previous reports, this study suggests that erythromycin should be avoided in young (younger than 2 weeks) infants when possible.

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Corresponding author and reprints: William O. Cooper, MD, MPH, Division of General Pediatrics, Department of Pediatrics, Vanderbilt University School of Medicine, Suite 5028 MCE, Nashville, TN 37232-8535 (e-mail: william.cooper@mcmail.vanderbilt.edu).

What This Study Adds

Children in the study received erythromycin while still in the hospital. In addition, measuring filled prescriptions is an indirect measure of antibiotic exposure, since infants may not actually receive a medication, even though a prescription is filled. In addition, the study methodology is unable to account for variable dosage or length of antibiotic use.

The data from the current study and previous reports provide support for the hypothesis that the increased risk of IHPS among infants with very early exposure to erythromycin is high. Alternatives to erythromycin include other macrolide antibiotics, although they may not have proven efficacy for pertussis prophylaxis, and it is relatively contraindicated in this age range because of concern of bilirubin displacement and kernicterus. Thus, there is no clear best alternative for young infants at risk for pertussis. However, the risk of pyloric stenosis is sufficiently high (approximately 1%), suggesting that the risks and benefits of erythromycin in very young infants should be carefully weighed and discussed with parents prior to the initiation of therapy.

REFERENCES