No Infantile Hypertrophic Pyloric Stenosis among Neonates who Received Erythromycin for Postexposure Prophylaxis against Pertussis

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INTRODUCTION

Pertussis, commonly known as whooping cough, is an infection caused by the bacterium *Bordetella pertussis*. This highly communicable disease, which affects susceptible individuals of any age, is spread by respiratory droplets and contact with recently contaminated objects. *Bordetella pertussis* causes inflammation of the larynx, trachea, and bronchi. Among neonates, the symptoms include life-threatening coughing and choking spells followed by apnea, cyanosis, bradycardia, and unresponsiveness; in this age group, the complications include pneumonia, seizures, intracranial hemorrhage, encephalopathy, and death.[1] Among children and adults, the disease is characterized by paroxysmal staccato coughing with inspiratory whoop.[1] Adults may also present atypically with prolonged repetitive cough without the inspiratory whoop; as such, pertussis may be underdiagnosed.[2]

Childhood vaccinations against pertussis do not confer lifelong immunity, and people who were vaccinated as children may become susceptible to pertussis infection as adolescents or adults because of waning immunity.[3] Adolescents and adults with untreated or unrecognized pertussis may transmit the infection to susceptible individuals, including neonates.[4] Infected adults are contagious for 3 weeks from the onset of the cough or whoop or until 5 days after initiation of treatment with appropriate antibiotics.[2] Neonates and infants up to 1 year of age who have not been vaccinated account for nearly 90% of deaths related to pertussis.[5] Three doses of pertussis vaccine are needed to protect infants and children.[6,7] Because of the significant morbidity and mortality associated with this infection, attempts to prevent pertussis are crucial.

Postexposure prophylaxis against pertussis is effective in preventing symptomatic infection among asymptomatic contacts if the prophylaxis is given within 21 days after onset of cough in the index case.[4] Macrolide antibiotics, including erythromycin, have been recommended for postexposure prophylaxis to decrease the risk of infection and its associated complications.[7] The choice of drug depends on the risks and benefits identified for the population to be treated. An additional consideration with erythromycin is the reported link between use of erythromycin and increased risk of infantile hypertrophic pyloric stenosis (IHPS).[8-10] Erythromycin induces gastrointestinal motor activity, probably through binding to motilin receptors.[11,12] The role of erythromycin in IHPS may be related to increased work of the smooth muscles leading to hypertrophy.[11] Some dose-dependent gastrointestinal effects of erythromycin have been noted, although a threshold dose associated with IHPS has not been identified.[11,12]

The cause of IHPS is unknown.[11] An incidence of 2 per 1000 live births has been reported, but the incidence has also been reported to change over time in some geographic regions.[13,14] Other factors associated with an increased risk include male sex, first-born child, white race, family history of the condition, and erythromycin use in neonates and infants less than 90 days of age.[8-10,14,15] Preterm infants typically experience IHPS symptoms later than term infants; this observation is probably related to the development of functional motilin receptors, which are usually present after 32 weeks' gestation.[10,16,17] IHPS is usually diagnosed at about 1 month of age and rarely after 3 months of age, although it has been diagnosed during the neonatal period.[13] The classical presentation of IHPS includes nonbilious projectile vomiting and irritability with feeding. In severe cases, dehydration, weight loss, and electrolyte abnormalities may occur.[13]

The objective of the case series reported here was to determine if the use of erythromycin for postexposure prophylaxis against pertussis in preterm and term neonates was associated with any cases of IHPS.

CASE SERIES

This study was approved by the Research Ethics Board of Mount Sinai Hospital in Toronto, Ontario.

In August 2004, several neonates in the Level II Neonatal Intensive Care Unit (NICU) of Mount Sinai Hospital were exposed to pertussis. The relatives of one patient in the Level II NICU visited repeatedly over a 16-day period while they were contagious with pertussis. One relative was coughing for all 16 days, although this person did not visit daily. Two other relatives who visited daily were coughing for 6 days before diagnosis. The relatives were unaware that they had pertussis until one of them was admitted to a different hospital, where pertussis was diagnosed by a positive result on polymerase chain reaction (PCR) testing of a nasopharyngeal sample.

Once the diagnosis of pertussis was confirmed, a team consisting of microbiologists, infectious disease specialists, public health staff, and the health care team for the Level II NICU met to determine who required treatment and to discuss antibiotic regimens. The patient whose relatives were sick was considered at high risk of contracting pertussis. Other neonates in the Level II NICU were also considered to have been at risk of pertussis exposure, especially those residing in close proximity to the high-risk patient or near places where the relatives may have congregated and those being cared for by nurses who also cared for the high-risk patient. Admission and discharge records were reviewed to identify all neonates who might have been exposed to pertussis. Public health staff and the clinical nurse specialist for the Level II NICU contacted the physicians and parents of neonates who had been discharged to inform them of the exposure and treatment plans. The medical and nursing records of the high-risk patient were reviewed to identify other hospital staff members who had been in contact with the family or the high-risk patient. In addition, a letter describing the exposure was circulated to departments who provided support services to the Level II NICU to help identify any other potential contacts. Because the parents of neonates in the Level II NICU might have spent undocumented time with the contagious relatives, prophylaxis was provided to all of the parents and close contacts of the exposed NICU patients in an attempt to prevent subsequent infections. To minimize additional exposures in the Level II NICU, no new admissions were allowed for 5 days, and all staff, parents, and patients in the Level II NICU were monitored for 21 days for signs of infection.

Within 24 h of the confirmed exposure, the clinical nurse specialist and attending neonatologist contacted the parents and close contacts of patients, and public health staff contacted exposed staff members to explain the situation and provide prophylactic drugs (azithromycin [500 mg on day 1, then 250 mg daily for 4 days] or sulfamethoxazole-trimethoprim [one double-strength tablet twice daily for 14 days] for those with allergy to macrolides). The high-risk patient and exposed neonates were given erythromycin for 14 days according to the hospital's neonatal dosing guidelines: 10 mg/kg per dose q12h for neonates 0 to 7 days old, q8h for neonates more than 7 days old, and q6h for infants. Before erythromycin was started, nasopharyngeal swab samples for pertussis PCR testing were collected from the high-risk patient and from all neonates who were to be treated.

Approximately 3 months after the exposure, the clinical pharmacist, clinical nurse specialist, or neonatologist contacted the parents by telephone for a follow-up interview. The parents were asked if the erythromycin regimen had been completed, if anyone in the family had experienced a cough or any respiratory symptoms since the antibiotics were given, and if the parents had noted any adverse effects. The parents were also asked if the mother had been breastfeeding while she was taking azithromycin.

The clinical pharmacist (B.N.) reviewed the charts, including medical and pharmacy records, of the patients who received erythromycin prophylaxis after pertussis exposure in August 2004. The following information was collected: demographic data, the day of life on which erythromycin was started, the erythromycin regimen (including duration of treatment), breastfeeding status while the mother was taking azithromycin, any symptoms consistent with clinical pertussis, and any adverse reactions recorded in hospital.

In addition to the high-risk patient (patient A in Table 1), 20 neonates were considered to be at risk of contracting pertussis. When erythromycin was started, the 21 patients were categorized, on the basis of postmenstrual age (gestational age plus chronological age) as preterm neonates (n = 15), term-corrected neonates (n = 2), term neonates (n = 3), and infant (n = 1). Of these 21 patients, 2 neonates at risk of exposure had been discharged before the confirmed exposure and therefore received their entire course of erythromycin outside the Level II NICU. Seventeen patients completed the course of erythromycin while admitted to the Level II NICU, and 2 were discharged home during treatment.

The exposed patients in the Level II NICU consisted of 14 boys and 7 girls. Sixteen of the patients were first-born children, and 14 were considered white as identified by health care providers and confirmed by parents. The mean gestational age (and standard deviation [SD]) was 33 ± 4.3 weeks, the mean birth weight was 1996 ± 1029 g, and the mean age at initiation of erythromycin was 20.8 ± 31.1 days of life (median age 8 days, range 1 to 115 days). Erythromycin was started after 100 days of age for 2 patients, between

Table 1. Characteristics of 21 Infants Who Received a 14-Day Course of Erythromycin*
for Postexposure Prophylaxis against Pertussis

| Patient | Birth Weight (g) | Gestational Age† (wk) | Sex | First child | White | Erythromycin Start Date | | Breast-feeding¶ |
						Chronological Age‡ (days)	Postmenstrual Age§ (wk)	
A	610	32.71	M	Y	Y	101	47.71	Y
B	1080	26.00	M	N	Y	41	31.86	N
C	1610	31.29	F	Y	N	12	33.14	Y
D	1040	28.71	M	N	N	15	30.86	Y
E	2610	35.86	M	N	N	4	36.43	Y
F	1900	35.00	F	Y	N	1	35.14	Y
G	1420	29.43	M	Y	Y	12	31.14	Y
H	870	30.00	M	N	Y	24	33.43	Y
I	1610	34.71	F	N	Y	20	37.57	Y
J	1430	30.86	M	Y	Y	39	36.43	Y
K	3835	40.14	M	Y	Y	5	40.86	Y
L	3830	40.57	M	Y	N	8	41.71	Y
M	2150	33.00	F	Y	Y	8	34.14	Y
N	1810	34.57	F	Y	Y	2	34.86	Y
O	2510	34.57	M	Y	Y	2	34.86	N
P	3320	35.14	M	Y	Y	4	35.71	N
Q	3080	35.14	F	Y	Y	4	35.71	Y
R	1070	28.71	M	Y	N	7	29.71	Y
S	640	24.14	M	Y	N	115	40.57	Y
T	3480	38.71	M	Y	Y	5	39.43	Y
U	2020	34.57	F	Y	Y	7	35.57	Y

*For all but patient K, the duration of erythromycin therapy was 14 days; for patient K, the duration of therapy was 12 days.
†Gestational age = time elapsed between the first day of the last menstrual period and birth.
‡Chronological age = time elapsed after birth.
§Postmenstrual age = gestational age plus chronological age.
¶Breastfeeding while mother was taking azithromycin.

14 and 90 days of age for 5 patients, and at less than 14 days of age for 14 patients. Eighteen of the patients were breastfeeding while the mother was taking azithromycin.

No secondary cases of pertussis were identified. All nasopharyngeal swabs were negative for *Bordetella pertussis*. None of the neonates experienced symptoms consistent with pertussis, as reported by their parents or observed in the Level II NICU. Two patients experienced projectile vomiting possibly related to erythromycin treatment. Patient A had projectile vomiting 4 weeks after erythromycin therapy and underwent investigation for IHPS, including abdominal ultrasonography, the method of choice for diagnosis and exclusion of IHPS. The ultrasound results were reported as normal, confirming that the patient did not have IHPS. Patient K also experienced projectile vomiting during treatment and was taken to the emergency department; the erythromycin was discontinued on day 12 of the 14-day course, and the vomiting resolved. The parents and staff of the Level II NICU did not report any other adverse events for the other treated neonates or their parents.

DISCUSSION

In this small case series, erythromycin for post-exposure prophylaxis against pertussis was given to 15 preterm neonates, 2 term-corrected neonates, 3 term neonates, and 1 infant. Eighteen of the patients had additional exposure to macrolide through breast milk. Adverse effects during or after erythromycin prophylaxis were reported for 2 patients, but no cases of IHPS were identified 3 months after treatment with erythromycin.

In 1999, Honein and others[10] suggested a causal role for erythromycin in a cluster of IHPS cases among term neonates following pertussis prophylaxis; that report raised concern about erythromycin use in neonates and led to increased surveillance. Subsequently, Mahon and others[9] in 2001 and Cooper and others[8] in 2002 published reports identifying early use of systemic erythromycin, especially within the first 2 weeks of life, as increasing the risk of IHPS relative to untreated patients. Cooper and others[8] associated erythromycin exposure at less than 14 days of age with an increase by nearly 8-fold in the risk of IHPS and exposure at less than 90 days of age with a 2-fold increase in the risk of IHPS compared with patients

who did not use erythromycin. Inclusion criteria for that review included discharge from the birth hospital by 3 days of age, so it is unlikely that there were any preterm neonates in that sample.[8] Mahon and others[9] stated that 42 patients would have to be treated with erythromycin in the first 2 weeks of life to cause one additional case of IHPS. The gestational age of the patients with IHPS was 35 to 39 weeks.[9] In the case series reported here, 19 of the patients were started on systemic erythromycin before 90 days of age, and 14 of them started the drug within 14 days of age. No cases of IHPS were identified, although the sample size was small and 15 of the patients were preterm when erythromycin was started. Pyloric stenosis is reportedly rare among preterm neonates.[18] Because the proposed mechanism of erythromycin-induced pyloric stenosis involves motilin receptors, which are functionally present after 32 weeks gestational age, preterm neonates probably have a lower risk of IHPS than term neonates.[11,12,16]

The actual exposure risk for neonates in the Level II NICU and their families was unknown. Patient A was considered at high risk because of repeated direct contact with contagious relatives. After pertussis exposure the only preventive measure available for neonates and young infants who are too young to have received any protection through vaccination is to treat the primary cases and provide prompt prophylaxis for all close contacts.[6] To prevent subsequent infections and thereby minimize serious complications (including death) in neonates, it was decided to provide prophylaxis for all at-risk neonates, their parents, and exposed staff. The recommended antibiotics for prophylaxis and treatment of pertussis are erythromycin, azithromycin, clarithromycin, and sulfamethoxazole-trimethoprim.[4,7] Clarithromycin has been used effectively in infants and children 1 month to 16 years of age.[19] Azithromycin has been recommended for postexposure prophylaxis in neonates because it has not been associated with IHPS, despite a lack of effectiveness data for the treatment of pertussis.[4] Preterm neonates have limited options because of a relative contraindication to administration of sulfamethoxazole-trimethoprim related to concerns with bilirubin displacement and development of acute bilirubin encephalopathy. In addition, the team at Mount Sinai Hospital felt that erythromycin was the only suitable treatment option for these patients because of a lack of experience with azithromycin and clarithromycin in preterm neonates at the institution and limited literature available for this patient population. The hospital did not have specific dosing guidelines for preterm neonates exposed to pertussis, but its erythromycin treatment and prophylaxis regimens were the same; therefore, the NICU dosing guidelines for erythromycin treatment were used.

Prevention of pertussis by vaccination in infancy and childhood remains an important strategy to limit pertussis-related death.[4,6] The prevention of pertussis in adolescents and adults is also desirable to reduce transmission to unimmunized neonates and young infants, who have the highest risk of serious complications. To address waning of immunity in adolescents and adults, a booster dose of dTap (diphtheria-tetanus-acellular pertussis vaccine) is recommended by the National Advisory Committee on Immunizations.[3] Because the duration of protection from the acellular vaccine is not known, current recommendations specify only a single booster dose.[3]

CONCLUSIONS

In summary, in this small case series no cases of IHPS were identified 3 months after erythromycin postexposure prophylaxis against pertussis in preterm and term neonates. The risk of pertussis infection and its complications was felt to outweigh the relatively small increased risk of IHPS associated with erythromycin identified by other authors.[8-10] Additional reports of erythromycin use in preterm and term neonates are required to better define the role of erythromycin in IHPS.

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