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Antibiotics taken for other illnesses and spontaneous clearance of *Helicobacter pylori* infection in children

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SUMMARY

Purpose—Factors that determine persistence of untreated *Helicobacter pylori* (*H. pylori*) infection in childhood are not well understood. We estimated risk differences for the effect of incidental antibiotic exposure on the probability of a detected clearance at the next test after an initial detected *H. pylori* infection.

Methods—The Pasitos Cohort Study (1998–2005) investigated predictors of *H. pylori* infection in children from El Paso, Texas, and Juarez, Mexico. Children were screened for infection at 6-month target intervals from 6–84 months of age, using the ¹³C-urea breath test corrected for body-size-dependent variation in CO₂ production. Exposure was defined as courses of any systemic antibiotic (systemic) or those with anti-*H. pylori* action (HP-effective) reported for the interval between initial detected infection and next test. Binomial regression models included country of residence, mother's education, adequacy of prenatal care, age at infection, and interval between tests.

Results—Of 205 children with a test result and antibiotic data following a detected infection, the number of children who took ≥1 course in the interval between tests was 74 for systemic and 33 for HP-effective. The proportion testing negative at the next test was 66% for 0 courses, 72% for ≥1 systemic course, and 79% for ≥1 HP-effective course. Adjusted risk differences (95% CI) for apparent clearance, comparing ≥1 to 0 courses were 10% (1–20%) for systemic and 11% (0–21%) for HP-effective.

Conclusions—Incidental antibiotic exposure appears to influence the duration of childhood *H. pylori* infection but seems to explain only a small portion of spontaneous clearance.

Keywords

Helicobacter pylori; spontaneous clearance; antibiotics; children

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Scientific presentations

Dr. Broussard presented these findings during an oral session at the 2007 International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Quebec City, Canada, and in two poster presentations at the 2007 Society for Epidemiologic Research Annual Meeting in Boston, MA. In addition, the methods for this project were discussed as part of the 2006 Society for Epidemiologic Research Student Workshop on Epidemiologic Methods, which Dr. Broussard participated in during her doctoral candidacy.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is among the most frequent human bacterial infections worldwide.^{1–2} Chronic *H. pylori* infection is a risk factor for peptic ulcer disease and gastric cancer,^{3–5} yet there remain gaps in knowledge regarding its natural history and determinants of chronic infection.⁶ The infection is usually acquired in childhood,^{2, 7–11} but patterns of persistence and spontaneous clearance have not been well described. No longitudinal studies to date have differentiated chronic and acute infection, the latter being difficult to study due to difficulty in detecting cases at onset.⁹ Understanding the determinants of persistent infection will help inform development of needed prevention and control strategies.

Asymptomatic *H. pylori* infection is not generally detected, nor is routine treatment for asymptomatic infection currently recommended.¹² Spontaneous clearance generally refers to loss of infection in the absence of directed treatment. In the small body of literature that mentions frequency of spontaneous clearance of *H. pylori* infection, most reports describe it as uncommon in adults^{13–14}; however, this characterization is based largely on follow-up of adults with prevalent infection, most of whom would have been infected for decades. There is very little information on the natural history of acute infection in adults.

Apparent spontaneous clearance of childhood *H. pylori* infection has been observed in several studies.^{7, 15–19} It has been hypothesized that exposure to antibiotics for infections other than *H. pylori* may account for spontaneous clearance of *H. pylori* infection in children.^{19–21} Few studies have examined the association between antibiotic history and *H. pylori* infection in children under age four years,^{21–22} an age period in which antibiotics are widely used²³ and acquisition of *H. pylori* infection is relatively frequent. Of the existing literature,^{8, 15, 19, 21–22, 24} results have been mixed.

Although multiple drug regimens are typically required for successful treatment of adult *H. pylori* infection (see Table 1), there have been no studies of the number of antibiotics required to treat infections of recent onset. Our aim was to examine the hypothesis that frequent exposure to antibiotic therapy for other illnesses decreases the probability of persistent *H. pylori* infection in early childhood.

METHODS

Study design and study population

The Pasitos Cohort Study was initiated in 1998 to investigate predictors of acquisition and persistence of *H. pylori* infection in children from Hispanic families in the border region of El Paso, Texas, and Juarez, Mexico, a population disparately affected by *H. pylori* infection.²⁷ This analysis used data collected prospectively through 2005 from 608 cohort children at the baseline prenatal visit and subsequent follow-up visits, targeted at 6-month intervals. Details on the Pasitos Cohort Study have been described elsewhere.^{27–28}

H. pylori detection and classification

Because changes in *H. pylori* status are not associated with specific symptoms, they must be inferred by changes in screening test results from one follow-up exam to another. *H. pylori* infection was detected using the ¹³C-urea breath test (UBT),^{29–32} which detects bacterial urease activity by comparing the ¹³C/¹²C ratio in breath samples collected before and after ingestion of labeled ¹³C-urea. A non-dispersive isotope-selective infrared spectrometer (Infrared-¹³C-Stable Isotope Analyser (IRIS), Wagner Analysen Technik, Germany) was used for isotope-ratio measurement. Validation studies of the IRIS for ¹³C-UBT analysis in

Brazilian children aged 6 months to 6 years have estimated sensitivities and specificities of 88–93% and 96–100%, respectively, when compared to either culture alone or histologic examination coupled with a urease biopsy test.^{33–34}

Positivity was based on Klein's recommended adjustment of the ¹³C-UBT value for age-dependent variations in urea hydrolysis, using metabolic equations based on age, sex, weight, and height to estimate the urea hydrolysis rate (UHR), with values of >10μg classified as positive.²⁹ For 58 (<2%) test results, the UHR could not be calculated due to missing anthropometric data and was imputed following a procedure used in previous analyses.²⁸ Some results were excluded due to implausible values (3.5% of all samples). The frequency of plausible breath test results for the entire cohort is shown in Table 2. The mean number of plausible test results was 4.8.

Infection frequency measures

Ascertainment of *H. pylori* positivity was limited to follow-up visits where subjects were tested. Infection onsets and clearances may have been missed between tests, hence the events counted in this study are referred to as detected infection events. The measure of spontaneous clearance frequency was the risk of detected clearance in the interval between the first detected infection and the next test. Inclusion criteria were study participants with a positive UBT result (only the first positive result was used) and at least one subsequent UBT result and without missing data on antibiotic use during the interval between tests.

Ascertainment of antibiotic use

Participants' caretakers (usually mothers) documented medications taken by the child during the period between follow-up visits. At each follow-up visit, interviewers recorded medication names, dates and duration of administration, and the illnesses for which they were taken. The questionnaire also ascertained illnesses since the preceding visit, and this information was cross-checked against reported medications to facilitate recall. Photo sheets of commonly used medications were utilized during the interview to aid recall of medication types.

Medication classification

A coding algorithm was used to classify antibiotics.³⁵ Each medication's generic component drugs were identified using either the Physician's Desk Reference (for US drug names) or online drug reference resources (for both US and Mexican drug names), such as MedlinePlus Drug Information and the National Autonomous University of Mexico medical pages. Medications were classified as either systemic antibiotics (i.e., non-topical aminoglycosides, cephalosporins, fluoroquinolones, macrolides, penicillins, sulfonamides, tetracyclines, or other antibiotic classes) or other drugs (i.e., systemic antimicrobials other than antibiotics such as antivirals, topical antimicrobials, or non-antimicrobial drugs), and further classified by antibiotic class and effectiveness against *H. pylori* (those with *in vitro* bactericidal or *in vivo* eradication efficacy, listed in Table 1).

Analyses were conducted for all systemic antibiotics combined and separately for those that were *H. pylori*-effective (HP-effective). Antibiotic exposure frequency, measured as the number of treatment courses per interval, was examined as a dichotomous variable (one or more courses versus none) and as a continuous variable. The Pasitos Cohort Study did not collect data on dose, and collected information on treatment duration was insufficient due to missing data.

Statistical analysis

Descriptive statistics are presented for antibiotic exposure and infection frequencies. We estimated the probability (risk) of spontaneous clearance within a specified follow-up interval rather than clearance rates based on person-time at risk of clearance; the inability to observe the timing within intervals of either the clearance events or the infection onset events that established the time at risk of clearance precluded reasonable estimates of person-time at risk.

Since intervals between tests varied substantially across subjects, the risk of spontaneous clearance was estimated for the interval between the first detected infection and the next test, which may or may not have occurred at the next targeted visit. Because this estimate does not correspond to a specified time interval, the distribution of interval length and the average time period of this interval are presented.

Stata 8.2 (Stata Corporation, College Station, TX) was used for statistical analyses. We estimated clearance proportions for categories of antibiotic exposure status. We used binomial regression (Stata's `binreg` command) to estimate differences in the risk of detected clearance as a linear function of the independent variables. The main exposure of interest was number of courses of antibiotics (either dichotomous or continuous) during the follow-up interval. The included covariates were age at infection onset, maternal education (0–6, 7–11, 12–17 years), country of residence (US, Mexico), and adequacy of prenatal care (inadequate, intermediate, adequate – based on a modification of the Adequacy of Prenatal Care Utilization Index³⁶); category differences in categorical variables were parameterized as having equal effects. These variables were chosen because they are factors which may be associated with both antibiotic history and infection dynamics, maternal education being an indicator of socioeconomic status and adequacy of prenatal care being a measure of health care seeking behavior. To account for varying follow-up intervals, models also included the interval length. The risk difference model, in contrast with standard logistic regression, better reflects the hypothesis that exposure boosts the probability of the body clearing the infection in the short term, provides a more intuitive quantification, and does not assume this interacts with other determinants of clearance in complex ways that would require more data to disentangle. Difference estimates provide the absolute increase or decrease in disease frequency associated with exposure. Limitations in the available data described above also made the risk difference model a better choice than models of clearance rates or time to clearance.

There was insufficient exposure to other HP-effective medications (see Table 1 footnote) in the cohort to examine effect-measure modification by these drugs.

Sensitivity analysis

We conducted a sensitivity analysis to determine how much the true association would differ from the results due to plausible levels of misclassifying medication exposure, the most important potential measurement error.

Ethics approval

The Pasitos Cohort Study was approved by institutional review boards of the University of Texas Health Science Center at Houston, the University of Texas at El Paso, the Texas Department of State Health Services, and the Mexican Social Security Institute.

RESULTS

Frequency of infection and spontaneous clearance

Of the 608 subjects who had at least one breath test, 265 (44%; equal for girls and boys) were ever infected according to positive breath test results. The majority of subjects who became infected had the first detected infection by age 2 years (see Figure 1).

Of the 265 participants who were ever infected and thus eligible to have cleared, 47 were not followed past the first infection. Of the 218 infected subjects with a subsequent test, 78% had a clearance detected at one or more subsequent visits, at ages ranging from 9 to 84 months. The greatest number of first detected clearances occurred between ages 1 and 3 years.

Antibiotic exposure in children followed past first detected *H. pylori* infection

Among the 205 children who were tested after the first detected infection and who provided data regarding antibiotic usage, 74 (36%) took at least one systemic antibiotic course during the interval between the first detected infection and the next test [45 (35%) of 129 US children, and 29 (38%) of 76 Mexican children]. Thirty-three (17%) of 197 children took at least one HP-effective antibiotic course during this interval [26 (21%) of 125 US children and 7 (10%) of 72 Mexican children]. Some subjects (10% for systemic and 2% for HP-effective) reported more than one course during this interval. Of systemic antibiotic courses for which class was reported, 61% were penicillins, and of HP-effective courses, 89% were amoxicillin.

Risk of first detected clearance

The mean time interval between first detected infection and next test was 9 months (see Figure 3), with 168 (77%) of 218 next tests occurring at the next targeted visit. Of the 218 subjects who were tested after the first detected infection, 148 (68%; 95% CI: 61–74%) were negative on the next test (119 of which occurred at the next targeted visit). The estimated risk of first detected clearance was 71% (95% CI: 63–80%) among boys, 65% (95% CI: 56–73%) among girls, 77% (95% CI: 70–84%) among US children, and 53% (95% CI: 42–64%) among Mexican children.

Effect of antibiotic exposure on risk of first detected clearance

Among the 205 children with breath test and antibiotic data past the first detected infection, 140 (68%) were negative on the next test. This proportion was the same among children with breath test and HP-effective antibiotic data past the first detected infection [133 (68%) of 197]. The proportion testing negative at the next test was 66% for 0 antibiotic courses, 72% for ≥ 1 systemic course, and 79% for ≥ 1 HP-effective course.

Table 3 presents clearance proportions and crude and adjusted risk differences for the effect of each antibiotic exposure on the risk of first detected clearance. The multivariable models included all prespecified covariates as well as age at first detected infection and interval between first detected infection and next test.

After adjustment, risk differences for nearly all antibiotic exposures increased, and the corresponding confidence intervals became narrower and excluded negative values. For systemic antibiotic exposure, the risk difference comparing 0 to ≥ 1 course increased after adjustment from 5 to 10 percentage points (95% CI: 1–20 percentage points). The risk difference for the continuous model of each additional course of systemic antibiotic increased to 7 percentage points (95% CI: 3–12 percentage points). This positive trend was supported by estimates for the categorical form of systemic exposure, with a risk difference

of 4 percentage points comparing 0 to 1 course, and a much higher difference of 20 percentage points comparing 0 to 2–4 courses. However, the confidence interval for the middle category included both negative and positive values. The point estimates for dichotomous and continuous forms of HP-effective antibiotic exposure were each one percentage point higher than the corresponding forms of systemic antibiotic exposure.

Sensitivity analysis

A sensitivity analysis was performed to determine whether the estimated risk differences for the effect of antibiotic exposure on first detected clearance were sensitive to changes in exposure classification resulting from hypothetical scenarios for missing exposure data due to unclassified medications. Only five subjects were exposed to ≥ 1 unidentified medication course in the interval immediately preceding the next test after the first detected infection. Since including these additional subjects only adds a few observations, only two hypothetical scenarios were considered – all subjects with missing antibiotic status were exposed to systemic antibiotics or no subjects with missing status were exposed; each scenario produced little change in the unadjusted risk differences and confidence intervals (results not shown).

DISCUSSION

In the Pasitos Cohort Study, children who took antibiotics between the first detected infection and the next test had an increased probability (~ 10 percentage points) of a detected clearance; the risk difference was negligibly higher for HP-effective exposure. Thus, incidental antibiotic exposure appears to influence the duration of childhood *H. pylori* infection; however, this seems to explain only a small portion of spontaneous clearance given high clearance frequencies observed in children without antibiotic exposure.

Previous studies that estimated antibiotic effects on *H. pylori* infection mainly utilized cross-sectional designs. A few studies reported an inverse association between antibiotic exposure and *H. pylori* infection prevalence^{8,21–22} but only one specifically examined the effect on spontaneous clearance.¹⁵ In a prospective study, Rothenbacher, Bode, & Brenner found that antibiotic classes containing HP-effective antibiotics were more associated with clearance in children (measured by stool antigen test) than were other antibiotic classes.¹⁵ The current study found that HP-effective antibiotics, which were almost exclusively amoxicillin, were associated with a slightly higher risk of detected clearance compared to all systemic antibiotics, which were also predominantly penicillins.

Previous studies examined suboptimal definitions of antibiotic exposure, such as lifetime³⁷ or 5-year history.³⁸ The current analysis investigated exposures more proximal to the measurement of the clearance outcome, restricted to the interval immediately preceding the visit at which clearance status was measured. Although optimal UBT timing following antibiotic discontinuation is not clear from previous studies,³⁹ a previous analysis of Pasitos Cohort UBT results showed that children who took antibiotics within either 7 or 28 days prior to the UBT did not have a pattern of results that differed from that of those who did not take antibiotics during those time periods beyond what would be expected from random variation.⁴⁰ Timing of antibiotic use was not specifically examined in the current analysis due to considerable missing data on precise dates of exposure.

The large proportion of *H. pylori* infections with apparent spontaneous clearance (68%) among Pasitos Cohort children is inconsistent with frequent claims that *H. pylori* infection is usually persistent.^{13–14} Past criticism of Pasitos Cohort Study results have focused on the concern that infection onsets were overestimated (due to alleged poor specificity of detection methods).⁴¹ The uncertain validity of the ¹³C-UBT as a detection method in

young children has been addressed in Pasitos publications.^{28,42} If false positive results are indeed more frequent in younger children, then estimates of clearance risk might be biased upward. However, when plausible levels of measurement error are taken into account, Pasitos Cohort data patterns are most consistent with frequent transient infection.⁴³ Furthermore, the observation that clearance proportions were higher in children exposed to antibiotics suggests that much of the observed clearance was not an artifact of false positivity because it is not plausible that antibiotic exposure (not directed at *H. pylori* infection) would be associated with previous false positive UBT results.

While every effort was made to maximize antibiotic recall in the Pasitos Cohort Study, some medication details were missing due to either insufficient or incorrect recall. The resulting misclassification would be non-differential if the level of error were comparable in both *H. pylori*-positive and -negative children and independent of misclassification of other study variables; such non-differential misclassification may underestimate the magnitude of associations between antibiotic exposure and *H. pylori* spontaneous clearance. On the other hand, differential exposure misclassification could result if, for instance, mothers with more education were more likely to accurately report their children's antibiotic use, and their children also had a higher clearance frequency, which could lead to overestimation of the association between antibiotics and clearance. In the current analysis, however, mother's education had an unexpected inverse association with risk of clearance, so the preceding hypothesis was not borne out.

Although the Pasitos Cohort Study is among the largest prospective studies of *H. pylori* infection in children, with an unusually large amount of follow-up data for a hard-to-follow population, the sample size for estimating spontaneous clearance was considerably smaller than that available for estimating prevalence or incidence. Furthermore, loss to follow-up is an unavoidable limitation of cohort studies. Disease frequency estimates could have been biased if children who were lost to follow-up had different disease frequencies than those who were not lost to follow-up. The extent to which this is the case in this cohort is uncertain, but it is possible that lost children had higher infection incidence rates given previous analyses showing that children with selected *H. pylori* risk factors were less likely to return for follow-up.²⁸ Such differential loss to follow-up would bias the estimates of the effect of antibiotics on clearance if, in addition to different clearance probabilities, lost subjects had different antibiotic exposure than those who were not lost to follow-up. Factors associated with antibiotic exposure in this cohort were country of residence and maternal education. Whereas overall systemic antibiotic use from birth through age 7 years was more frequent in Mexico, HP-effective antibiotic use was more frequent in the US.⁴⁴ Children of mothers with more education had higher prevalence of both systemic and HP-effective antibiotic use. The impact of differential loss to follow-up on the effect of antibiotics on observed spontaneous clearance is hard to predict, given scant literature on determinants of spontaneous clearance.

CONCLUSION

Among Pasitos Cohort children, the frequency of apparent spontaneous clearance of *H. pylori* infection was considerably high in the absence of antibiotic exposure. Children with antibiotic exposure had an even higher clearance frequency. Incidental antibiotic exposure appears to influence the duration of childhood *H. pylori* infection; however, given that many unexposed children cleared the infection, antibiotic exposure seems to explain only a small portion of detected clearance events. This investigation of *H. pylori* clearance patterns can inform future research design, data interpretation, and therapeutic strategies involving children. In particular, studies of the effects of exposures on *H. pylori* infection frequencies should consider confounding by antibiotic history. In light of evidence from this study that

H. pylori infection clears frequently in the absence of antibiotic use, treatment guidelines should consider the distinction between persistent and transient infections, and such consideration should not be restricted to cases where incidental treatment might have caused clearance.

Take home messages

- Despite frequent claims that *H. pylori* infection is usually persistent, results from this cohort suggest that spontaneous clearance occurs frequently in young children.
- Children with incidental antibiotic exposure experienced an even higher spontaneous clearance frequency.
- Exposure to antibiotics taken for other illnesses seems to explain only a small portion of all detected spontaneous clearance events.

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Figure 1.

Distribution (counts) of age at first visit with positive result

N=265; mean=28 months (range: 3 to 84)

Each bar of the histogram represents a 6-month range of values, with the exception of the first bar, which only ranges from ages 3 to 6 months.

Figure 2.
Flow diagram of study participants included in the analysis.

Figure 3.
Distribution (counts) of the interval between first detected infection and next test.
N=218; mean=9 months (range: 3 to 52)

Table 1

Classes and names of *H. pylori*-effective antibiotics considered in this analysis.

Penicillins	Macrolides	Others	Tetracyclines (only recommended for ages 12 years and over) ¹²
amoxicillin	clarithromycin	metronidazole tinidazole furazolidone	tetracycline oxytetracycline

Note: For treatment aimed at eliminating *H. pylori*, gastric acid inhibitors such as proton pump inhibitors and histamine2-blockers, and bismuth compounds are often used in combination with one or more of these antibiotics, usually in triple or quadruple treatment regimens.^{25–26}

Table 2

Distribution of the number of plausible test results* per subject.

<i>Total number of valid test results</i>	<i>Participants N=608</i>	
	<i>n</i>	<i>%</i>
1	112	18
2	77	13
3	65	11
4	76	13
5	50	8
6	45	7
7	43	7
8	38	6
9	34	6
10	27	4
11	25	4
12	14	2
13	2	<1

* Test results were classified as plausible or implausible after data cleaning of extreme values, imputation of UHR status for children who were missing anthropometric data necessary for calculating a UHR value, and decisions regarding mismatches among 20 and 30 minute results.

Table 3

Comparison of unadjusted and adjusted effects* of antibiotic exposure variables on the risk of first detected clearance of *H. pylori* infection among 205 subjects with breath test and antibiotic exposure data past the first detected infection.

<i>Exposure/Covariate</i>	<i>No. + of subjects</i>	<i>No. of apparent clearances</i>	<i>% with apparent clearance</i>	<i>Risk difference (unadjusted)</i>	<i>95% CI</i>	<i>Risk Difference (adjusted)</i>	<i>95% CI</i>
<u>Systemic exposure</u>							
Systemic dichotomous							
0 courses	131	87	0.66	0	(referent)	0	(referent)
≥ 1 course	74	53	0.72	0.05	-0.08, 0.18	0.10	0.01, 0.20
Systemic 3 categories							
0 courses	131	87	0.66	0	(referent)	0	(referent)
1 course	54	37	0.69	0.02	-0.13, 0.17	0.04	-0.09, 0.18
2-4 courses	20	16	0.80	0.14	-0.06, 0.33	0.20	0.10, 0.29
Systemic continuous							
per course (range: 0-4)	205	140		0.04	-0.03, 0.12	0.07	0.03, 0.12
<u>HP-effective exposure</u>							
HP-effective dichotomous (197)							
0 courses	164	107	0.65	0	(referent)	0	(referent)
≥ 1 course	33	26	0.79	0.14	-0.02, 0.29	0.11	0.00, 0.21
HP-effective continuous (197)							
per course (range: 0-3)	197	133		0.07	-0.06, 0.19	0.08	-0.04, 0.19

No.=Number, CI=Confidence Interval

⁺For variables with missing data, numbers in parentheses indicate the number of subjects with data.

* Each exposure model adjusted for country of residence, mother's education (categorical), adequacy of prenatal care, age at first detected infection, and interval between tests.