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Detection of *Mycobacterium tuberculosis* in Gastric Aspirates Collected From Children: Hospitalization Is Not Necessary

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ABSTRACT. *Objective.* To compare the yields of gastric aspirates collected for culture of *Mycobacterium tuberculosis* from children evaluated as outpatients versus inpatients and to determine factors associated with a positive culture.

Methods. Retrospective study of 100 children <12 years of age with tuberculosis diagnosed at a pediatric referral hospital or in one of two tuberculosis control programs in California.

Results. Of the 100 children who had tuberculosis, 80 had at least one gastric aspirate collected. *M tuberculosis* was isolated from 33 (41%) of the 80 children who had a gastric aspirate; 4 children had a positive culture from an aspirate subsequent to the first. Inpatients had a higher proportion of positive gastric aspirates than that of children who had aspirates collected as outpatients (48% vs 37%); however, this difference was not statistically significant. Resistance to isoniazid was found in three isolates (9%) of children all of whose presumptive source case had a susceptible strain of *M tuberculosis*. Characteristics that were associated with an ~50% yield from gastric aspirates were identification of a source case, age <2 years, birth in the United States, symptomatic tuberculosis, and pulmonary disease.

Conclusions. The culture of *M tuberculosis* from gastric aspirates of children in the outpatient setting has a yield comparable to aspirates collected from hospitalized children. Collection of gastric aspirates in the outpatient setting will reduce both the cost and the inconvenience of the procedure. Although the yield from gastric aspirates is relatively low, important information including drug susceptibility patterns may be obtained. *Pediatrics* 1998;102(4). URL: <http://www.pediatrics.org/cgi/content/full/102/4/e40>; tuberculosis, gastric aspirate, children.

In patients suspected of having tuberculosis, culture for *Mycobacterium tuberculosis* is important to confirm the diagnosis, guide treatment, and assess response to treatment. Among children with tuberculosis, obtaining a specimen for culture is especially important when either no source case is

identified or when the child is possibly infected with an antibiotic-resistant strain of *M tuberculosis*. Yet, in 1994, only 36% of children in California <5 years of age and reported with tuberculosis had a probable source case identified (Mark N. Lobato, unpublished data) and among children 0 to 14 years of age with tuberculosis only 37% had any specimen obtained for culture.¹ Moreover, 12 (8.4%) of the 143 culture-positive cases among children <5 years of age reported from 1993 to 1995 had a *M tuberculosis* strain resistant to isoniazid.²

Because infants and young children do not expectorate, but instead swallow their sputum, aspiration or lavage of the gastric contents is the best procedure for obtaining a specimen from which to culture *M tuberculosis*. Gastric lavage has an even higher yield for *M tuberculosis* than bronchoalveolar lavage in children with pulmonary tuberculosis.^{3,4} The standard approach to collecting gastric aspirates is to hospitalize the child and collect three aspirates on consecutive mornings before gastric emptying is stimulated either by being ambulatory or by eating. The expense of hospitalization and the variable yield from gastric aspirates discourages the routine collection of gastric aspirates from children suspected to have tuberculosis.

No alternative approach to hospitalization for the collection of gastric aspirates from hospitalized patients has been evaluated. The performance of gastric aspirates on ambulatory patients is a reasonable strategy to evaluate. To determine whether the collection of gastric aspirates on an outpatient basis is a viable alternative, we compared the yield from gastric aspirates collected from children evaluated as outpatients and as hospitalized inpatients. We also identified factors that may be associated with a higher yield for culture.

METHODS

Study Sites and Population

Three sites that evaluate children for tuberculosis participated in this study: a children's referral hospital (site A) in the San Francisco East Bay area and two health jurisdictions, one in northern California (site B) and one in southern California (site C). Children evaluated at site A were referred by local caregivers, outpatient clinics, or three tuberculosis control programs. Children at site B were referred either by public health clinics or community doctors in a single county in the Central Valley. Children at site C were referred from a single county in southern California.

The study population included all children 11 years of age and younger in whom tuberculosis was diagnosed between January

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1993 and January 1997. The study sites used the case definition for tuberculosis from the Centers for Disease Control and Prevention. The case definition specifies the laboratory and clinical criteria for a confirmed tuberculosis case.⁵ A culture-positive case was one that had *M tuberculosis* isolated from the gastric aspirate. Pulmonary tuberculosis was defined as parenchymal disease, not including isolated hilar adenopathy. The weighted average incidence of tuberculosis during the study period for the four counties from which the study population was drawn was 9.6 cases/100 000 children 0 to 4 years of age and 3.7 cases/100 000 children 5 to 14 years of age; these rates were comparable to the state average of 9.7 and 4.1, respectively.

Specimen Collection

Gastric aspirates for *M tuberculosis* were collected from children who were either outpatients (not admitted overnight to hospital) or inpatients (hospitalized overnight). In general, the children had three gastric aspirates collected; however, some children had fewer aspirates if a probable source case was identified. For children who were inpatients, either a nurse or a resident physician placed a nasogastric tube to obtain gastric specimens. On three consecutive mornings the specimens were collected while the child was recumbent and before the child had any oral intake.

For outpatients, the procedure was performed by a nurse who had been previously trained in the protocol for collecting gastric aspirates; however, the protocols differed among the study sites. At all sites, a nurse placed a nasogastric tube and collected a gastric specimen with the child in a recumbent position. At site A, the parents of the child were instructed to withhold feedings after an early morning awakening, keep the child recumbent during transport, and come directly to the *day hospital* on three consecutive mornings. At site B, the children were admitted as day patients early in the morning before the child received any food or liquids. All specimens at site B were collected on the same day at ~6 hour intervals. After each gastric aspirate was collected, the child was allowed to take clear liquids ad libitum until 1 hour before the next specimen was collected. At site C, most children had the procedure performed at the public health clinic early in the morning before the child received any food or liquids on three consecutive mornings, but were not required to be recumbent before the procedure.

Specimen Processing

For the collection of gastric contents at the three sites, a silastic nasogastric tube was placed, usually without sedation, before the

child had taken anything by mouth. At least 5 mL of the patient's gastric secretions were collected by aspiration. When the initial attempt to aspirate was unsuccessful, 10 to 20 mL of sterile distilled water were instilled and aspirated. Specimens were delivered immediately to the laboratory.

Gastric specimens were processed for neutralization and digestion by standard methods.⁶ The specimen was either processed immediately or neutralized with 100 mg of sodium bicarbonate per 5 to 10 mL of aspirate or lavage and then refrigerated. Digestion-decontamination was achieved by adding freshly made *N*-acetyl-L-cysteine to equal volumes of 4% sodium hydroxide and 2.9% sodium citrate dihydrate, then vortexed until the specimen and the digestion solution were well homogenized. This solution was allowed to stand for 15 minutes and was then neutralized with ≤50 mL of phosphate buffer and centrifuged at 3000 × *g* for 20 minutes. After centrifugation, the sediment was inoculated on Middlebrook 7H-10 or Löwenstein-Jensen media and the BACTEC radiometric method.⁷ Drug susceptibility testing was performed by the BACTEC method (sites B and C) and on solid medium (all sites).

Data Management and Analysis

Information was abstracted from the medical records of the 100 children with tuberculosis. The information collected included age, sex, race, ethnicity, epidemiologic features (source case if identified), clinical features (site of disease, chest radiograph results, treatment regimen), and gastric aspirate procedure (collection time) and results (culture results, drug susceptibilities).

We compared the characteristics of children who had gastric aspirates collected as outpatients with the inpatient group using the χ^2 test for categorical variables and analysis of variance for continuous variables. We calculated the yield for *M tuberculosis* culture and odds ratios and 95% confidence intervals for factors associated with a positive culture. A *P* value of <.05 was considered significant (all tests two-tailed).

RESULTS

Characteristics of the Study Population

The demographic and clinical characteristics of the 100 children with tuberculosis reflect differences in the populations from which the patients were drawn (Table 1). Children at site A were predominantly African-American and born in the United States.

TABLE 1. Demographic and Clinical Characteristics of the 100 Children in Whom Tuberculosis Was Diagnosed

Characteristic	All Sites (<i>n</i> = 100)	Site A (<i>n</i> = 51)	Site B (<i>n</i> = 27)	Site C (<i>n</i> = 22)
Median age (range, months)	34 (1–143)	35 (2–143)	32 (7–106)	29 (1–119)
Sex, female	56 (56)	N (%) 28 (55)	13 (48)	15 (68)
Race/ethnicity				
Hispanic	29 (29)	7 (14)	7 (26)	15 (68)
Black, non-Hispanic	41 (41)	36 (71)	3 (11)	2 (9)
Asian	25 (25)	8 (16)	15 (56)	2 (9)
White, non-Hispanic	5 (5)	0 (0)	2 (8)	3 (14)
Place of birth				
United States	77 (77)	46 (90)	17 (63)	14 (64)
Outside United States	23 (23)	5 (10)	10 (37)	8 (36)
Source case found				
Yes	51 (51)	31 (60)	14 (52)	6 (27)
No	49 (49)	20 (40)	13 (49)	16 (73)
Reason for evaluation				
Screening*	33 (33)	11 (22)	9 (33)	13 (62)
Contact investigation	37 (37)	21 (41)	12 (44)	4 (19)
Illness	30 (30)	19 (37)	6 (22)	5 (23)
Health status at diagnosis				
Symptomatic	61 (61)	38 (75)	15 (56)	8 (36)
Asymptomatic	39 (39)	13 (25)	12 (44)	14 (64)
Site of disease				
Pulmonary	75 (75)	39 (76)	19 (70)	17 (81)
Extrapulmonary	25 (25)	12 (24)	8 (30)	5 (19)

* Twenty-nine had a known reason (12 physical examination, 11 school entry, and 6 immigration).

TABLE 2. Culture Results of the 80 Children Who Had a Gastric Aspirate Collected as an Outpatient or as an Inpatient

Culture Results	All Sites <i>n</i> (%)	Site A <i>n</i> (%)	Site B <i>n</i> (%)	Site C <i>n</i> (%)
Culture-positive	33/80 (41)	21/46 (46)	9/21 (43)	3/13 (23)
Outpatient	18/49 (37)	11/28 (39)	5/15 (33)	2/6 (33)
Inpatient	15/31 (48)	10/18 (56)	4/6 (67)	1/7 (14)

Children at site B and site C were in the majority Asian and Hispanic, respectively, and foreign-born. The frequency with which source cases were identified varied considerably among sites; more source cases were identified at site A and site B than at site C.

In their majority, the children were from racial and ethnic minorities (95%), 5 years of age or younger (90%), born in the United States (77%), and had pulmonary disease (75%). The characteristics studied did not differ among children who had ($n = 80$) and did not have ($n = 20$) a gastric aspirate collected. Of the 23 foreign-born children, 15 had recorded their date of arrival in the United States. The median time from arrival to the collection of the gastric aspirate was 4 months (range, 1 to 64 months). The mean induration of the tuberculin skin test was 15 millimeters. Among 44 presumptive source cases with tuberculosis (91% were adults related to the child), 82% were smear-positive, and 98% were culture-positive for *M tuberculosis*. All of the culture-positive source cases had drug-susceptible strains. For the most part, the children were close contacts of the source cases; 63% of the source cases lived in the same household as the child.

Culture Results

M tuberculosis was isolated from 33 (41%) of the 80 children who had a gastric aspirate collected. The proportion of inpatients who had a positive culture (48%) was higher than the proportion of outpatients who had a positive culture (37%); however, this difference was not significantly different ($P = .42$) (Table 2). Children admitted to the hospital were more likely to be symptomatic (63% vs 26%, $P = .003$). Three children (9%) had isolates that were resistant to isoniazid (one strain was resistant to multiple drugs).

Several characteristics were associated with an increased yield for *M tuberculosis* from the gastric aspirates (Table 3). Approximately one-half of the children who were 4 years of age or younger, had

TABLE 3. Culture Results From Gastric Aspirates by the Child's Age and Site of Disease

Factor	No. Patients	Outpatient No. Positive/ No. Cultured <i>n</i> (%)	Inpatient No. Positive/ No. Cultured <i>n</i> (%)
Age, y			
<2	35	5/10 (50)	10/19 (53)
2-4	39	10/26 (38)	4/8 (50)
>4	26	4/13 (31)	0/4 (0)
Single disease site			
Pulmonary	75	16/39 (41)	12/21 (57)
Hilar adenopathy	15	2/7 (29)	1/6 (17)
Miliary	2	None	2/2 (100)

pulmonary or miliary tuberculosis, or were symptomatic at the time of the diagnosis of tuberculosis had *M tuberculosis* isolated. In this study, the only factor significantly associated with a positive culture was having a source case identified (Table 4).

In addition to the 29 children whose first gastric aspirate was culture-positive, 4 other children had *M tuberculosis* isolated only from a subsequent gastric aspirate. For the first gastric aspirate 36% (29 of 80) were positive, for the second 27% (17 of 60) were positive, and for the third 23% (8 of 35) were positive. The trend for a lower yield on sequential aspirates was not significant. Twenty-one children (26%) had one gastric aspirate collected; 18 of the 21 children were at site A (17/18 had a source case identified).

DISCUSSION

This study demonstrates that the yield of *M tuberculosis* from gastric aspirates collected from children in the outpatient setting is comparable to the yield from aspirates collected from hospitalized children (37% vs 48%). The increased rate of hospitalization of children who had symptomatic tuberculosis, and likely an increased bacillary load, explains in large part the difference in the yields for gastric aspirates from the outpatients and inpatients. In earlier studies, gastric aspirates from hospitalized children yielded positive cultures in 20% to 52% of the cases.^{3,8-16} In this study, the yield from gastric aspirates collected from children in the outpatient setting was comparable to the yield in contemporary studies of children with pulmonary tuberculosis.^{3,8,9,14}

We identified several groups of children in whom the gastric aspirate had a yield of nearly 50%. Gastric aspirates from children 2 years of age or younger, children who have pulmonary tuberculosis, or children who had a source case identified had the highest culture yield for *M tuberculosis*. The differences among the three sites in the proportion of children evaluated because of symptoms and in the proportion of source cases identified may have influenced the gastric aspirate yields. For example, more children at site A (46% culture-positive) were symptomatic and had a source identified. In contrast, at site C (23% culture-positive) most children were identified

TABLE 4. Factors Associated With a Positive Culture From the 80 Children Who Had a Gastric Aspirate Collected

Factor	<i>n</i>	Positive, %	Relative Risk*	95% Confidence Interval
Source identified	44	55	2.2	1.2-4.1
Symptomatic	54	48	1.8	0.9-3.6
US-born	64	47	2.5	0.9-7.2
Pulmonary tuberculosis	60	47	1.7	0.8-3.7

* Compared with children who do not have this characteristic.

through screening and few source cases were found. Children with tuberculosis who are evaluated because of symptoms, rather than through screening, may have more advanced disease and a larger bacillary load explaining the higher yield from gastric aspirates.

This study did not have sufficient power to identify conclusively the factors that predict a higher yield of positive cultures from gastric aspirates. Only identification of a presumptive source case was significantly associated with a positive culture. Factors previously identified as predicting a higher yield from gastric aspirates include younger age,^{8,11,17} pulmonary and meningitic tuberculosis,^{10,18} the prevalence of tuberculosis in the child's community,¹⁹ and the number of gastric aspirates collected.¹¹ Site A, which evaluated twice the number of children with tuberculosis than either of the other sites and routinely performed gastric aspirates, had a higher yield for positive cultures than either site B or site C. This observation suggests that the experience of the staff may increase yield and that children should be referred to centers that have experience in collecting gastric aspirates.¹⁵

Surveillance data from the California tuberculosis registry indicates that gastric aspirates are an underused procedure in the assessment of children suspected of having tuberculosis. For example, among 2778 children <5 years of age reported to have tuberculosis in California from 1985 to 1995, <30% had a gastric aspirate collected (California Tuberculosis Control Branch, unpublished data). Collection of gastric aspirates in the outpatient setting may improve the diagnosis of tuberculosis in children and will reduce the cost and the inconvenience of the procedure compared with collection in the hospitalized patient.

We recommend that clinicians strongly consider collection of a gastric aspirate for mycobacterium culture in any child suspected to have tuberculosis who cannot produce an expectorated sputum suitable for culture. The collection of gastric aspirates for culture is particularly important from young children in whom a resistant strain of *M tuberculosis* is suspected or from children living in areas where isoniazid resistance exceeds 4%. These children will require a modified treatment regimen.^{20,21} In this study, 3 children had drug-resistant *M tuberculosis* cultured. The presumptive adult source cases identified by the health departments had drug-susceptible strains cultured, thus other, unidentified source cases, were responsible for the child's disease. Although drug-susceptibility patterns remain useful for both guiding treatment and epidemiologic investigations,²² molecular epidemiologic techniques are useful adjuncts to traditional contact investigations by health departments. Restriction fragment length polymorphism analyses of isolates from individuals not suspected of exposure to a source case may help to explain the patterns of disease in complex transmission networks.^{23,24} Other children who should have gastric aspirate collected are those for whom a definitive source case has not been identified, those who are ill, those who are immunocompromised,

children with disseminated disease, and children who are failing to respond to a treatment regimen.^{25,26}

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