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Research Article

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Mycobacterium tuberculosis Culture Yield from Three Hourly Gastric Aspirates taken in One Day

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Abstract

Tuberculosis (TB) contacts with abnormal radiographic findings are suspected to have TB disease and require further investigations. Children who are unable to spontaneously expectorate respiratory secretions have serial gastric aspirates (GA) performed for *M. tuberculosis* (MTB) studies. After overnight fasting in hospital, we utilized hourly GA sampling for MTB culture.

Objective: We aimed to determine if GA hourly sampling for MTB culture yield is comparable to the traditional method of obtaining daily specimen. We reviewed MTB culture positive results in Winnipeg Children's Hospital from 2013 to 2017.

Design: Retrospective study tabulating demographic and clinical information on the children found to have abnormal radiographic findings and underwent GA. The yield from daily sampling versus multiple samples obtained in one day were compared.

Results: MTB culture yield obtained from three daily GA specimens versus multiple samples in one day were similar.

Conclusion: Hourly GA sampling yield for MTB culture is not inferior to obtaining daily specimen. It is clinically superior with respect to: nasogastric tube insertion done only once, being able to start treatment earlier, and allowing discharge home sooner.

Keywords: Infant; Child; Early treatment

Introduction

The Pediatric Tuberculosis (TB) Service of the Children's Hospital of Winnipeg assesses 500 children each year who are identified through contact investigations to have had exposure to adults with infectious *Mycobacterium tuberculosis* (MTB) pulmonary disease. Young children are at higher risk for developing TB disease after exposure to an infectious case.

The recognition of tuberculosis (TB) disease in children is challenging. Children are less likely to have obvious symptoms of disease, so the diagnosis is based mostly on epidemiological information (contact history), immunologic evidence (tuberculin skin test) and chest radiograph (CXR) changes. The gold standard for TB diagnosis is the detection of MTB by culture or molecular methods.

Older patients can submit spontaneously expectorated sputum or liquefied airway secretions after the inhalation of hypertonic saline solution (induced sputum) [1], for laboratory studies.

Bacteriological confirmation of TB in pediatric patients is difficult because respiratory secretions for microbiological evidence are difficult to obtain (especially in young children) and pediatric disease is often paucibacillary.

When expectorated sputum cannot be obtained for suspected respiratory disease in a young child, aspirated stomach contents via gastric aspiration (GA) or gastric lavage is taken for acid fast bacilli (AFB) smear and Mycobacterium tuberculosis (MTB) culture [1]. The MTB *culture* yield from gastric aspirates ranges from 10-30% in these asymptomatic children [2].

It has been shown that multiple specimens taken in one day resulted in *smear* microscopy yield equivalent to specimen obtained over consecutive days [3].

We present our MTB *culture* results obtained from GAs done daily (2013-2015) versus multiple samples (2016-2017) obtained in one day – either at intervals more than two hours apart (MSx1) or hourly (Q1H).

Background Information

From 2001-2008, the Pediatric TB Service relied on trained Victorian Order of Nurses to perform GA for young children with suspected tuberculosis. This was done early in the morning, daily for 3 days, in their homes or in a boarding home using a standardized method for collection. Due to the dwindling number of experienced staff in 2008, it then became necessary to admit children to the hospital for 3 days to obtain early morning GA specimen. However, frequently limited in-patient bed availability forced the service to look at other options. We collaborated with the Pediatric Day Unit (PDU) of the Children's Hospital for a few years for daily out-patient morning GA. With increasing

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difficulty coordinating schedules with the PDU, we started admitting young patients to hospital to obtain GAs in early 2016. Limited bed availability, especially during respiratory syncytial virus peak season forced the service to be creative- hence the development of hourly GA sampling. This allowed us to admit the child for a fasting period overnight, obtain 3 hourly specimens in the morning, start treatment after the procedure and send the patient home soon after.

Methods

We tabulated and described demographic, epidemiologic, radiographic and mycobacteriology data obtained on the patients admitted to the Children's Hospital of Winnipeg for GA (2013-2017). We compared the rates of positive MTB cultures from samples taken daily for 3 days (ODx3), to the yield obtained from MSx1 and Q1H. Statistical analysis was performed. The University of Manitoba Health Research Ethics Board approved this study.

Results

Fifty-seven patients who were admitted to the Children's Hospital of Winnipeg for GA MTB studies between January 1, 2013 to December 31, 2019. There were 31 males and 26 females, whose ages ranged from 3-months to 16 years (mean 41 months; median 33 months). All patients had never been treated for TB in the past and all children tested negative for HIV (Figure 1).

Of the 57 children, there were 6 patients (3M: 3F) who were admitted to hospital with acute symptoms -– ataxia, emesis, dehydration, fever; headache, seizure, difficulty speaking, low energy; shortness of breath, cough; lower limb tingling sensation; pneumonia. Ages ranged from 7 months to 16 years (mean - 7 years; median - 5 years). None of these children had known exposure history or TB contact information. Only 2 of the 6 children had PPD done, both were >5mm indurated. For imaging, 1 patient had normal CXR findings, while the other 5 had abnormal CXR descriptions – 1 with miliary pattern (and R paratracheal lymphadenopathy) and 4 with pneumonia., The child with the normal CXR had significantly abnormal MRI central nervous system (CNS) imaging suggestive of tuberculosis, while the patient with military pattern on CXR had leptomeningeal enhancement and eye changes on MRI. Of the 4 with chest x-ray findings of pneumonia, 1 also had paratracheal adenopathy (and CNS imaging changes), another had mediastinal lymph nodes (and vertebral bony changes on MRI), and one had a concomitant pleural effusion (and abnormal CNS imaging).

The other 51 patients were identified through contact investigation. These patients were all relatively asymptomatic.

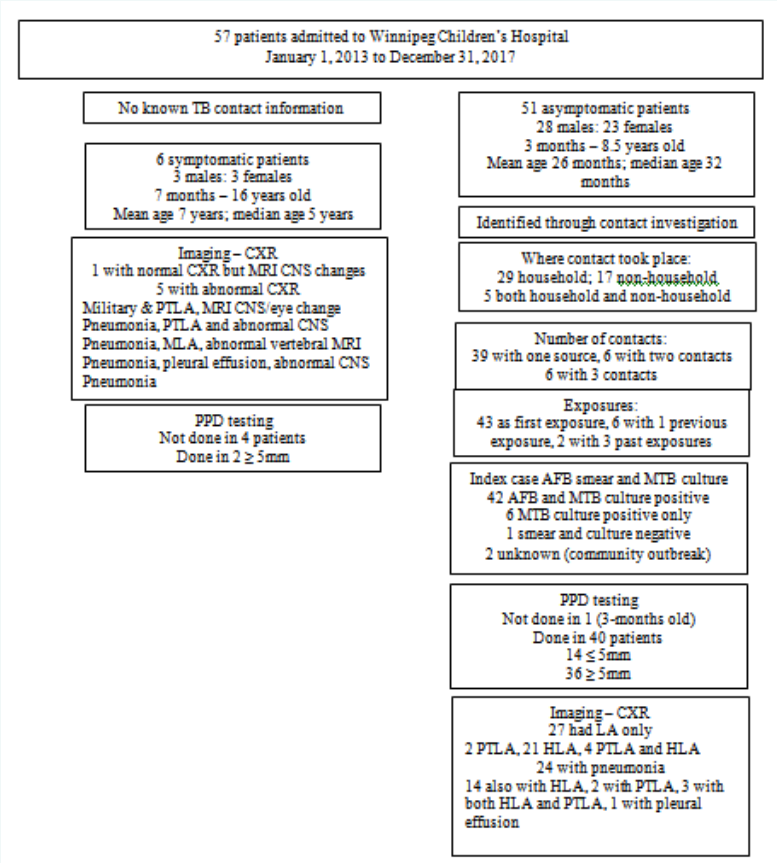

Figure 1 Patient demographics. AFB: Acid Fast Bacilli; MTB: Mycobacterium Tuberculosis; PPD: Purified Protein Derivative; CXR: Chest X Ray; MRI: Magnetic Resonance Imaging; CNS: Central Nervous System; PTLA: Paratracheal Lymphadenopathy; HLA: Hilar Lymphadenopathy..

Ages ranged from 3 months to 8 years 6 months; mean of 36 months; median 32 months.

Twenty-nine children were identified as close household contacts to an adult diagnosed with respiratory TB. Seventeen were described as non-household contacts and another 5 children were exposed to both household and non-household cases.

Thirty-nine children were exposed to one known adult case, 6 were being investigated for having contact with two adult cases, and 6 had exposure to 3 index cases (from the same household).

Forty-three patients had one established contact with an MTB index case while 6 had two separate exposures and another 2 had 3 documented occasions of contact with cases.

Forty-two source cases were described as being AFB smear and MTB culture positive and 6 were culture positive only. There was 1 source case who was both smear and culture negative (referred to as a "clinical case") and for two patients no information was provided other than the children coming from an "outbreak community".

Sixteen adult contacts had cavitary findings on their CXRs and they were all AFB smear and MTB culture positive.

Fifty patients had PPD skin testing; a 3-month old infant was not PPD tested. Fourteen had skin test indurations measured <5mm and 36 were ≥ 5mm.

Lymphadenopathy on CXR was the most commonly seen radiographic finding, Of the 51 patients, lymphadenopathy was the only finding reported in 27. In 2 patients, the only abnormal CXR finding was paratracheal adenopathy, 21 patients had hilar adenopathy only, while 4 children had enlarged paratracheal and hilar lymph nodes. Densities, opacities or pneumonia were described in 24 patients, one of whom also had a pleural effusion. Nineteen of the patients with parenchymal changes on CXR also had adenopathy – 14 hilar, 2 paratracheal and 3 with both. Other imaging included MRI, CT scans, abdominal ultrasound.

Thirty-one children had daily GA done (14M: 17F), 5 MSx1 (4M: 1F) and 21 patients had QH1 (13M: 8F). A total of 169 GA procedures were performed- 93 were obtained ODx3, 13 from MSx1, and 63 by QH1 collection. Patient ages ranged from 3-months old to 14-years old, with mean of 39-months old, median 32-months old (Figure 2).

Twenty-one males and 10 females had ODx3 GA. All the 93 GA specimens obtained ODx3 were AFB smear negative; the MTB culture yield was 12%. The number of positive cultures per patient was 1 of 3 samples in 2 patients, 2 of 3 samples in 3 patients, 3 of 3 samples in 1 patient. Six patients (19%) were confirmed MTB culture positive using daily GA.

The age of the 5 patients sampled MSx1 ranged from 8 to 81-months old (mean 34 months old, median, 40 months old). There were 4 male and 1 female patients. A total of 13 GA was obtained (two patients only had 2 GA samples) and they were all AFB smear negative. There were positive MTB culture results in only 3/13 samples (23%). All the three samples that cultured positive were from the same patient.

Twenty-one patients underwent single nasogastric tube insertion for QH1 GA collection. Their ages ranged from 7-months to 16 years (mean 40-months old, median 39-months old). Three samples were obtained in each patient. None of the samples were AFB smear positive. MTB culture yield was in 19/63 samples (30%). Nine patients had culture confirmed TB (42%). The number of positive cultures per patient was 1 of 3-2 patients; 2 of 3-4 patients, 3 of 3-3 patients.

In total, 16/57 patients (28%) and 33/169 GA samples cultured positive for MTB. All culture positive samples were pan-sensitive. Non-tuberculous mycobacterium was not isolated in any of the symptomatic or asymptomatic patients.

For the symptomatic patients, GA MTB culture yield was positive in 5/6 patients (83%) and in 10/18 samples (56%). Two of the 6 patients had ODx3 GA sampling, and in both patients the sample that cultured positive was obtained on the 2nd day. None of the patients underwent MSx1 GA. Three of 4 children who had the QH1 GA procedure cultured positive. In these 3 culture positive patients, all hourly samples isolated MTB except for the first obtained sample in one patient. The MTB culture negative (patient had CNS imaging suspicious of a tuberculosis process (superior sagittal sinus and frontal cortical vein thrombosis), also did not culture positive for MTB on non-respiratory samples, and was MTB-PCR negative – so an alternative diagnosis was later considered (Figure 3).

In the asymptomatic contacts, GA MTB culture yield for was 11/51 patients (22%) and in 23/151 samples (15%). Of the 23 positive cultures, 8 came from the 1st GA taken, 9 from the 2nd and 6 from the 3rd sample. Of the 12 GA taken daily from 4 patients, 9 cultured positive -3 from the 1st day, 4 from day 2 and 2 from day 3. MSx1 sampling – only one patient had confirmed MTB, with all 3 GA specimen culturing positive. Six of the 17 patients who had QH1 GA cultured positive-4 from the 1st aspirate, 4 from the 2nd hour GA and 3 from the last hourly specimen.

Seven of the 29 household contacts cultured for MTB on GA, only 3 of the 17 children who were non-household contacts were MTB positive, while 1 of the 5 patients with both household and non-household exposures had GA positive culture. Both children who were exposed in the community and the patient identified to have been in contact with a "clinical case" did not culture on GA for MTB.

Only 1 of the 6 children with two separate exposures at different times (mostly in the same household) was culture positive. One of the 2 patients with a history of 3 documented exposures cultured positive on GA. Of the 43 children with one identified exposure, 9/43 were positive on GA culture for MTB.

All patients who cultured on GA for MTB were exposed to smear positive cases. None of the children exposed to the smear negative, culture positive only cases or clinical cases yielded MTB on GA.

Three of the 11 children who cultured positive on GA were exposed to adults with cavitary changes on CXR.

One patient who had a <5mm PPD reaction cultured positive

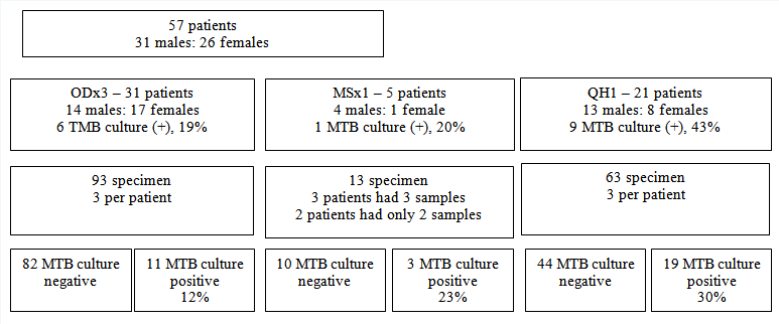

Figure 2 Gastric Aspirate results by method and culture yield. ODx3: Daily for 3 days; MSx1: Multiple Samples in one day; QH1: hourly sampling; MTB: Mycobacterium Tuberculosis; AFB: Acid Fast Bacilli.

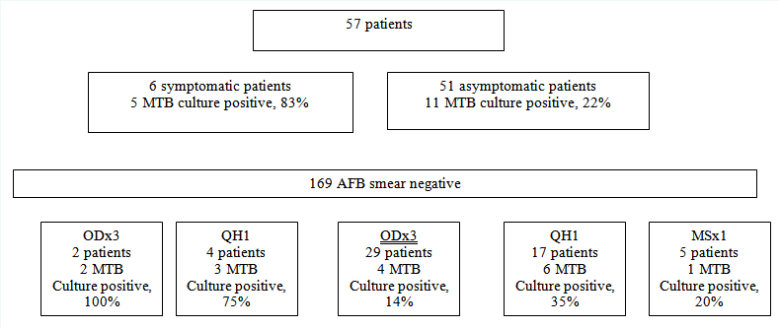

Figure 3 Gastric aspirate results by patient and culture yield. ODx3: Daily for 3 days; MSx1: Multiple Samples in one day; QH1: Hourly Sampling; MTB: Mycobacterium Tuberculosis.

on GA for MTB.

Two of the 11 culture positive contacts only had adenopathy on CXR, while 8 children had both parenchymal densities and adenopathy and one had radiographic changes of pneumonia.

Household exposure, smear status and culture positivity of the index case, number of patient contacts and PPD were associated with MTB culture positivity (Tables 1 and 2).

The percent of positive MTB specimen and percent of patients who cultured positive for MTB was higher in the QH1 group, as was the number of positive cultures taken from sample 2 but there was no statistical significance measured (Tables 3 and 4).

Discussion

It can never be overemphasized that the diagnosis of TB disease in a child indicates recent transmission of TB disease from an adult case. And, in order to establish disease in a child suspected to have tuberculosis, it is important to attempt collection of respiratory secretions not only to confirm the diagnosis with MTB culture but also to obtain culture sensitivity to appropriately direct pharmacologic management.

The conventional procedure for GA is to insert a nasogastric tube (NGT) in the early morning to obtain respiratory secretions that were swallowed overnight. This is done on three consecutive mornings - therefore entails repeated NGT insertion, which can be and is quite traumatic for young children. Treatment with anti-TB medications is then started only after the three specimens are obtained.

Recent studies in adults have shown non-inferior MTB culture sensitivity and specificity of hourly sputum sampling method compared to conventional daily sampling. A metaanalysis [4],

Table 1: Mean age, number contact and number of exposures by positive culture* *At least one positive culture from 3 samples. P-value calculated using t-test P<0.5 is considered as significant.

Variable	Culture (+) Mean 95%CI	Culture (-) Mean 95%CI	p-value
Age (months)	52.4 (23.4 to 81.4)	35.9 (28.6 to 43.3)	0.25
Number of contacts	0.88 (0.45 to 1.3)	1.3 (1.1 to 1.6)	0.04
Number of exposures	0.88 (0.45 to 1.3)	1.1 (1.0 to 1.3)	0.22

Table 2: Percentage of positive culture* by Patient demographics, Exposure, PPD & Chest Results.

Variables	Culture (+) n, % (95%CI), N=16	Culture (-) n, % (95%CI), N=41	p-value
Procedure ODx3 M H	 6, 37.5 (0.125-0.615) 1, 6.3 (-0.06-0.14) 9, 56.3 (0.31-0.81)	 25, 60.9 (0.46-0.76) 4, 9.8 (0.1-0.19) 12, 29.3 (0.15-0.43)	0.16
Sex Male Female	 10, 62.5 (0.38-0.87) 6, 37.5 (0.13-0.62)	 21, 51.2 (0.31-15) 20, 48.8 (0.33-0.16)	0.55
Location of exposure Household Non-Household Both Unknown	 7, 43.8 0.18-0.68) 3, 18.8 (-0.0-0.39) 1, 6.3 (-0.06-0.14) 5, 31.3 (0.08-0.54)	 22, 53.7 (0.38-0.68) 14, 34.2 (1.19-1.87) 4, 9.8 (0.1-0.19) 1, 2.4 (-0.02-0.07)	0.02
Source AFB Smear No information Negative Positive	 5, 31.3 0.08-0.54) 0 11, 68.8 (0.45-0.91)	 3, 7.3 (-0.01-0.15) 7, 17.1 0.05-0.29) 31, 75.6 (0.63-0.89)	0.02
Source MTB culture No information Negative Positive	 5, 31.3 0.08-0.54) 0 11, 68.8 (0.45-0.91)	 3, 7.3 (-0.01-0.15) 1, 2.4 (-0.02-0.07) 37, 90.2 (0.81-0.99)	0.05
Source CXR cavitary No Yes	 13, 81.3 (0.61-0.2) 3, 18.8 (-0.0-0.39)	 28, 68.3 (0.68-0.14) 13, 31.7 (0.17-0.45)	0.51
Source MTB PCR No information Positive PCR	 16, 100 (1-1) 0	 36, 87.8 (0.78-0.98) 5, 12.2 (0.12-0.22)	0.31
Patient PPD Not done <5mm >=5mm	 3, 18.8 (-0.0-0.39) 1, 6.3 (-0.06-0.14) 12, 75.0 (0.53-0.97)	 2, 4.8 (-0.02-0.12) 13, 31.7 (0.17-0.45) 26, 63.4 (0.48-0.78)	0.05
*At least one positive culture from 3 samples. P-value calculated using Fisher exact test P<0.05 is considered as significant			

Table 3: Rate of positive culture by procedure and other factors. Poison regression model; outcome: number of counts from three repeated samples. Statistical significance considered at P<0.05.

Variable	Rate of culture (+) 95%CI	p-value
Procedure ODx3 (reference) MSx1 QH1	 1.7 (0.35 to 8.2) 2.5 (1.02 to 6.4)	 0.51 0.05
Sex Female (reference) Male	 1.7 (0.68 to 4.2)	 0.26
Location of exposure Unknown (reference) Household Non-household Both	 0.33 (0.13 to 0.86) 0.21 (0.06 to 0.72) 0.12 (0.01 to 1.4)	 0.02 0.01 0.09
Number of contacts	0.52 (0.27 to 1.04)	0.06
Number of exposures	0.59 (0.26 to 1.3)	0.20
AFB Smear No information (reference) Negative Positive	 - 0.44 (0.18 to 1.05)	 0.07

reported similar sensitivity and specificity of sputum microscopy for hourly same-day sampling and sampling obtained over two days. They found that hourly sampling provided the additional advantages of reducing patient drop out, and allowing faster decision making regarding respiratory isolation and discharge.

The Pediatric TB Service adopted the hourly GA method to obtain secretions for AFB/MTB studies in 2016 to facilitate timely treatment and discharge. We also aimed, in line with the Hospital's Pain Initiative ("comfort promise") to develop a policy that would offer a less frequently traumatic procedure to children, especially if the culture yield was similar or better than obtaining GA specimen over a 3-day period. GA is used also whenever a patient is unable to spontaneously expectorate and/or sputum induction is unsuccessful, hence the few patients who are older than 5 years of age.

The procedure can be used also for older children who are unable to expectorate spontaneously or have decreased levels of consciousness as was performed in our sicker patients with CNS disease.

It has been reported that up to approximately 50% MTB GA [5], culture yield from children with symptomatic TB [6], so it was not surprising to see a higher yield of MTB cultures in our symptomatic and sicker children.

Table 4: Percentage of culture positive by different procedures from three samples.

Sample	ODx3 positive n, % 95%(CI) n=31*	MSx1 positive n, % 95%(CI) n=5*, n=3**	QH1 positive % 95%(CI) n=21*	p-value***
Sample 1	3, 9.7 (3.4 to 24.9)	1, 20.0 (3.6 to 62.5)	6, 28.6 (13.8 to 50.0)	0.16
Sample 2	6, 19.4 (9.2 to 36.3)	1, 20.0 (3.6 to 62.5)	7, 33.3 (17.2 to 54.6)	0.59
Sample 3	2, 6.4 (1.8 to 20.7)	1, 33.3 (6.2 to 79.2)	6, 28.6 (13.8 to 50.0)	0.05

* n per procedure; ** n per procedure for sample 3; ***p-value calculated using Fisher exact test P<0.05 is considered as significant.

There was an improved/better MTB culture yield from our group of asymptomatic pediatric TB contact with the hourly GA procedure compared to a previously reported median GA yield of 20% [7], using the standardized daily GA technique [8]. As in previous reports [9], adenopathy and disseminated TB seemed to be clinical predictors of positive yield.

GA remains the standard of care for specimen collection prior to the initiation of anti-TB treatment [10], in pediatric paucibacillary clinical TB disease. We have shown that hourly GA sampling is a more convenient and less traumatic procedure that not only can provide comparative culture yield/confirmation of diagnosis but has the advantage of offering earlier treatment and hospital discharge of patients and families. The overnight fasting that is required may be a limitation where access to an inpatient facility is not easily accessible. Although this paper is limited by the retrospective and observational nature and the small number of patients, the results provide useful and valuable information that may lead to a change in practice for clinicians.

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