MAJOR ARTICLE

Prospective Study of Sputum Induction, Gastric Washing, and Bronchoalveolar Lavage for the Diagnosis of Pulmonary Tuberculosis in Patients Who Are Unable to Expectorate

Michael Brown,[1,a] Hansa Varia,[1] Paul Bassett,[1] Robert N. Davidson,[1] Robert Wall,[2] and Geoffrey Pasvol[1,3]

[1]Department of Infection and Tropical Medicine, Lister Unit, and [2]Department of Microbiology, Northwick Park Hospital, Harrow, Middlesex, and [3]Wellcome Centre for Clinical Tropical Medicine, Imperial College London, United Kingdom

Background. Many adults with pulmonary tuberculosis are unable to expectorate. Gastric washing, sputum induction using nebulized hypertonic saline, and bronchoscopy with bronchoalveolar lavage have all been used to obtain specimens for diagnosis, but to our knowledge, the timing and volume of induced sputum have not been well studied, and these 3 methods have not been compared.

Methods. The study recruited consecutive adult inpatients with chest radiography findings suggestive of tuberculosis who were unable to expectorate. Subjects provided 3 induced sputum samples for culture on day 1 and additional samples on days 2 and 3. In addition, gastric washing specimens were collected on days 1, 2, and 3. A proportion of subjects with negative smear results underwent bronchoalveolar lavage.

Results. The study recruited 140 subjects. Among 107 subjects who provided 3 gastric washing specimens and at least 3 induced sputum specimens, 43% had cultures positive for *Mycobacterium tuberculosis*. Use of 3 induced sputum samples detected more cases than did use of 3 gastric washings (39% vs. 30%; $P = .03$). Among 79 subjects with culture results for all 5 induced sputum specimens, there was no difference in yield between samples obtained by induced sputum induction performed in a single day or that performed over 3 days (34% vs. 37%; $P = .63$). There was no association between sputum volume and positive culture results. No additional cases were diagnosed in the 21 patients who underwent bronchoscopy.

Conclusions. Use of 3 induced sputum samples was more sensitive than use of 3 gastric washings for diagnosis of tuberculosis in patients who could not expectorate spontaneously. Use of bronchoscopy with bronchoalveolar lavage did not increase diagnostic sensitivity. Samples could be collected in 1 day, allowing for faster diagnosis, faster initiation of treatment, and shorter hospital stay.

In an era of increasing drug resistance, it is important to obtain sputum specimens from patients with suspected pulmonary tuberculosis (TB) for mycobacterial culture and drug sensitivity testing. Frequently, patients have radiographic evidence of TB but are unable to expectorate sputum, and alternative methods for obtaining sputum specimens are needed. Obtainment of gastric washing (GW) specimens, sputum induction with nebulized hypertonic saline (IS), and fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) are established techniques for this indication. These methods vary in their tolerability, in their safety, and, notably, in their resource implications; bronchoscopy may not be feasible if large numbers of patients are involved, and it may not even be necessary if smear-positive specimens have been obtained by other, less invasive methods. Evidence of the relative diagnostic yield of each technique varies, although recent studies suggest that IS performs as well as BAL [1–12]. There are limited data on the number of IS samples required, the optimum volume of the sample for mycobacterial culture, and (most importantly) the timing of speci-

Received 6 November 2006; accepted 12 February 2007; electronically published 20 April 2007.

[a] Present affiliation: Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom.

Reprints or correspondence: Dr. Michael Brown, Dept. of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, United Kingdom (michael.brown@lshtm.ac.uk).

Clinical Infectious Diseases 2007; 44:1415–20

1058-4838/2007/4411-0003$15.00
DOI: 10.1086/516782

men collection—in particular, whether the specimens can be obtained in 1 day rather than over 3 days [5, 10, 11, 13].

Much of the recent increase in the rate of TB in the United Kingdom has involved recent migrants from countries with a high prevalence of TB [14]. Active case finding by chest radiography screening performed at ports of arrival—predominantly at London's Heathrow Airport—is one element of the TB-control effort for this group of persons [15, 16]. A large proportion of subjects who were found to have abnormal radiograph findings at Heathrow Airport were investigated in our unit. For patients such as these, who are often asymptomatic, have minimal change in radiography findings, and are unable to expectorate sputum, our practice has been to perform GW on 3 consecutive days with BAL, especially when the GW smears yield negative results [17, 18]. Confirmation of active *Mycobacterium tuberculosis* disease was achieved through GW examination alone for 42% of our patients [17]. There is good reason to believe that patients tolerate IS better than either of these techniques. Therefore, we performed a prospective study to establish whether the yield for IS culture was similar to that for GW culture in this patient group, as well as whether multiple IS samples could be collected in a single day and whether examination of BAL specimens could be used to diagnose additional cases missed by GW or IS examinations.

METHODS

Patient population. Patients with symptoms of or chest radiographs suggestive of pulmonary TB were referred to the Northwest Thames Regional Infectious Disease Unit (Lister Unit, Northwick Park Hospital; Harrow, Middlesex, United Kingdom) by primary health care practitioners, other hospital departments, and the Health Control Unit at Heathrow Airport. Many new migrants who enter the United Kingdom from countries where TB is highly endemic undergo screening by chest radiography at the port of arrival. Those with radiography findings suggestive of active pulmonary TB are referred to a hospital for further evaluation.

Study design. Ethics approval for the study was granted by Harrow Research Ethics Committee (Ethics Committee number 04/Q0405/51). Consecutive inpatients with abnormal chest radiography findings consistent with active pulmonary TB, regardless of symptoms, were encouraged to expectorate sputum for microscopic evaluation and mycobacterial culture. During the period from September 2004 through February 2006, subjects who were unable to expectorate sputum spontaneously were recruited for the study after providing signed informed consent. These subjects underwent a total of 3 GW and 5 IS procedures, in accordance with the protocol described in table 1; in brief, a GW was followed by 3 consecutive IS procedures on day 1, a GW was followed by an IS procedure on day 2, and a GW was followed by an IS procedure on day 3. BAL was performed on day 3 or later for smear-negative patients for whom it was particularly important to exclude multidrug-resistant TB. A diagnosis of TB was made, and treatment was instituted, if *M. tuberculosis* was detected in diagnostic samples or if the radiography findings were highly suggestive of TB in the absence of an alternative diagnosis or a clear past history of receipt of appropriate antituberculous chemotherapy. For the majority of subjects, initiation of treatment preceded culture confirmation of TB.

Table 1. Design of a study of the use of sputum induction with nebulized hypertonic saline (IS), gastric washing (GW), and bronchoalveolar lavage (BAL) procedures for the diagnosis of pulmonary tuberculosis in patients who are unable to expectorate.

Day of study	Specimen obtained
Day 1	GW and 3 IS specimens
Day 2	GW and IS
Day 3	GW and IS, with or without BAL

GW. GW specimens were obtained early in the morning, before breakfast. This technique involves inserting a nasogastric tube into the patient, rinsing the stomach with ~50 mL of sterile water, and aspirating the water and respiratory secretions that have been swallowed overnight. The procedure typically yielded volumes of 10–20 mL. GW specimens were transported to the microbiology laboratory within 2–4 h of collection.

Sputum induction. IS specimens were obtained in negative-pressure isolation rooms. Staff protection measures included use of appropriate respiratory protection masks, limitation of the time spent in the room during the procedure, and use of standard hospital procedures for staff exposed to TB. For each IS procedure, 30 mL of 3% hypertonic saline was administered via a mouthpiece using an ultrasonic nebulizer (Devilbiss Ultraneb 99 or Respiflo Aerodyne Omega Plus). Typically, 1–20 mL of sputum was obtained over the subsequent 1–2 h (the volume was recorded by the nurse performing IS), and the specimen was processed in accordance with standard techniques for mycobacterial examination of sputum samples. The 3 IS procedures on day 1 (hereafter, "day 1 IS") were performed ~4 h apart. The 3-day course of IS procedures (hereafter, "3-day IS") were generally performed in the morning. Patients who had severe asthma, chronic obstructive pulmonary disease, or an oxygen saturation level <94% were excluded from the study, because of the risk of exacerbation of pulmonary disease by sputum induction.

BAL. Bronchoscopy with BAL was performed after the patient had fasted overnight; local anesthesia and sedation were administered. After the bronchial tree was inspected, 60–100 mL of normal saline was instilled and aspirated from lung segments involved in the disease process, as indicated by a chest radiograph. Typically, 20–30 mL of BAL fluid was obtained and processed in accordance with standard procedures. Sputum

produced immediately after the procedure was collected and processed in accordance with standard methods.

Microscopy and culture of mycobacteria. Samples were centrifuged at 2014 *g* for 15 min, and the supernatant was decanted. From the deposit, thin films were prepared for auramine staining. An equal volume of 4% sodium hydroxide was added to the deposit, which was then vortexed and neutralized in phosphate-buffered saline (pH, 6.8), concentrated using centrifugation, and incubated into BacT/Alert liquid culture medium (bioMérieux) for up to 8 weeks. Cultures in which mycobacteria grew were referred to the Mycobacterial Reference Laboratory of the Health Protection Agency (Dulwich, UK) for identification and antimicrobial resistance testing.

Statistical analysis. On the basis of previous evidence of a GW culture positivity rate of ~25% [18], we calculated that 100 subjects would need to be recruited in our study to show equivalence of GW and IS to within 15% (assuming a proportion with discordant results of 25% cases), with 95% power at a 10% significance level. The initial recruitment period of 12 months was extended when it became clear that, for a proportion of enrolled subjects, not all 8 samples had been obtained or prepared for culture. Statistical analysis was performed using Stata software, version 7.0 (Stata). The paired exact test was used to compare the proportion of culture-positive samples between different methods. The Mann-Whitney *U* test was used to examine the difference in IS specimen volume between subjects with positive culture results and those with negative culture results.

RESULTS

Study profile. One hundred forty consecutive subjects with chest radiograph findings consistent with pulmonary TB who were unable to expectorate sputum spontaneously were enrolled in the study (figure 1). Among these subjects, 3 were unable to tolerate GW or provided an insufficient volume of gastric aspirate for analysis; 1 was unable to tolerate IS; 7 did not complete the sampling protocol during their admission (TB was believed to be unlikely in these subjects on the basis of other available clinical information, such as an alternative diagnosis); 5 commenced a regimen of anti-TB therapy because urgent treatment was believed to be appropriate or because positive results of a microscopic evaluation of at least 2 specimens had been obtained before completion of the sampling protocol; 2 refused to complete the sampling protocol; and 19 were unable to provide all 5 IS samples, because sputum induction was unsuccessful on at least 1 occasion. At least 1 sample was missing or leaked in transit or the culture became contaminated for 24 patients. Although 79 subjects had complete data for all time points, analyses that compared IS with GW procedures included additional subjects who provided all

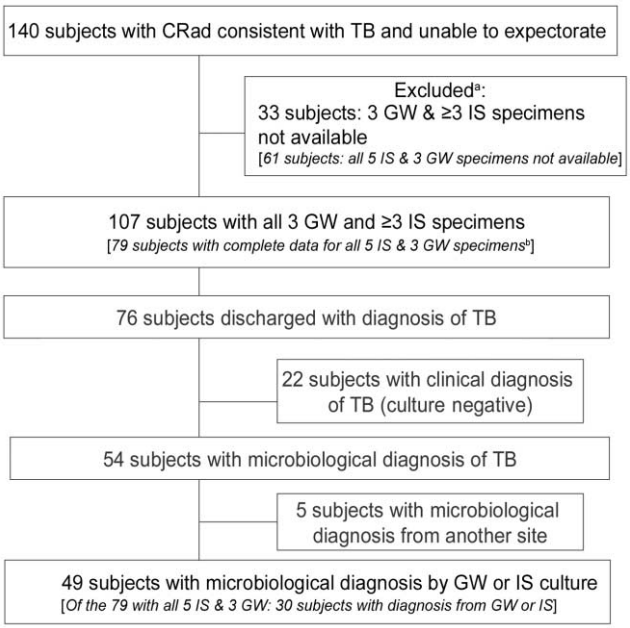

Figure 1. Study profile for 140 subjects with chest radiography (CRad) findings suggestive of tuberculosis (TB) who were unable to expectorate. GW, gastric washing; IS, sputum induction with nebulized hypertonic saline. [a]See Results for the breakdown of subjects who were unable to complete the protocol. [b]Analyses comparing day 1 with 3-day IS samples (see text) were performed on this smaller group (shown in italic font).

3 GW specimens and at least 3 IS specimens. Twenty-one subjects underwent bronchoscopy with BAL.

Patient characteristics. Results of at least 3 IS cultures and 3 GW cultures were available for 107 patients. Among these subjects, the median age was 28 years (range, 16–76 years), and 63% were male. Forty-two subjects (39%) were referred directly from Heathrow Airport. Eighty-four subjects consented to HIV testing during their admission, and results were positive for 3 subjects. Thirteen subjects had pleural effusions. A clinical diagnosis of TB was made for 76 subjects. The organism was isolated from 54 of these subjects; in 4 subjects, the organism was only detected in pleural fluid specimens, and in 1 subject, it was detected only in an ascitic fluid sample. Nontuberculous mycobacteria were cultured from 7 subjects; in no case was this believed to be clinically relevant. Three cases of isoniazid-resistant TB and 1 case of multidrug-resistant TB were detected.

Comparison of IS with GW. Subjects with culture results for all 3 GW specimens and for at least 3 IS samples were included in the following analyses. If >3 IS culture results were available, the first 3 were used for these analyses (for 3 subjects, only the day 2 or day 3 IS cultures yielded positive results; therefore, the total number of culture-positive cases in this analysis is 46, rather than the 49 culture-confirmed cases diagnosed in total using IS or GW specimens). Table 2 illustrates the number of cases diagnosed with the use of each technique.

Table 2. Comparison of culture yield for *Mycobacterium tuberculosis* for sputum induced nebulized hypertonic saline (IS) and gastric washing (GW) specimens for 107 subjects with 3 GW and ⩾3 IS specimens.

IS culture result	No. (%) of subjects		
	Positive GW culture result[a]	Negative GW culture result[b]	Total
Positive[c]	28	14	42 (39)
Negative[d]	4	61	65 (61)
Total	32 (30)	75 (70)	107 (100)

NOTE. $P = .03$ by Fisher's exact test comparing the diagnostic yield of IS versus GW culture.

[a] Any of 3 GW cultures yielded positive results.
[b] All 3 GW cultures yielded negative results.
[c] Any of the first 3 IS specimens yielded positive culture results.
[d] All of the first 3 IS cultures yielded negative results.

Forty-two subjects (39%) had positive results for any of 3 IS cultures, compared with 32 subjects (30%) who had positive results for any of 3 daily GW cultures ($P = .03$)

The first IS sample obtained yielded positive culture results for 30% subjects. Three IS samples detected 9% (95% CI, 4%–15%) more culture-positive cases than the first IS sample alone ($P = .002$) and 6% (95% CI, 2%–11%) more cases than the first 2 IS samples ($P = .02$).

Fourteen subjects (13%) had positive smear results, as determined by direct microscopic examination; 11 of these subjects had positive smear results for both GW and IS specimens. One subject was had positive smear results only for GW specimens, and 2 had positive smear results only for IS specimens. There were no statistically significant differences between methods ($P = 1.00$). Nine of the 13 IS microscopy–positive subjects had positive results with the first IS sample; 6 of the 12 GW microscopy–positive subjects had positive results with the first GW sample.

Induced sputum volume. The median volume of IS specimen acquired was 4 mL (interquartile range, 3–5 mL). There was no association between IS specimen volume and positive culture results (the median volume for both positive and negative culture results was 4 mL, and the interquartile range for both was 3–5 mL; $P = .39$) or between IS specimen volume and direct microscopy findings ($P = .39$).

BAL. BAL was performed for 21 subjects who had negative smear results. BAL cultures for 5 patients (24%) were positive for TB, and all were positive using the day 1 IS samples. In fact, 2 subjects had positive culture results with day 1 IS specimens but negative results with BAL specimens.

Comparison of day 1 IS with 3-day IS procedures. Seventy-nine subjects had complete data for all 5 IS time points. Among these subjects, 27 (34%) had positive culture results with day 1 IS specimens, compared with 29 subjects (37%) who had positive culture results with 3-day IS procedures ($P = 1.00$). Table 3 presents the diagnosed cases according to the day of IS sampling.

Eight subjects had positive results of direct microscopic examinations for the samples obtained from the 3-day IS procedures. All of these subjects, in addition to 1 additional subject, had positive smear results with the day 1 IS samples ($P = 1.00$).

For the 79 subjects with all 5 IS results, the yield from each sampling time point could be compared. All GW specimens and all IS specimens had similar yields, suggesting that sputum induction had no effect on the yield of subsequent GW or IS samples. The prevalence of positive TB culture results among the first day 1 IS samples (27%) was no greater than that among the second day 1 IS samples (24%; $P = .73$), the third day 1 IS samples (27%; $P = 1.00$), the day 2 IS samples (28%; $P = 1.00$), or the day 3 IS samples (28%; $P = 1.00$). The prevalence of *M. tuberculosis*–positive cultures for day 1 GW samples (23%) was no greater than that for day 2 GW samples (20%; $P = .63$) or day 3 GW samples (23%; $P = 1.00$).

Figure 2 illustrates the cumulative yield of successive IS samples (as well as the yield of 3 GW samples and of BAL samples) for subjects with results for all 5 IS samples and all 3 GW samples. Day 2 and day 3 IS specimen collections resulted in a total of only 3 additional positive culture results, compared with the results for samples obtained on day 1 ($P = .25$ for a paired binomial exact test comparing 5 IS specimens with the first 3 IS specimens).

DISCUSSION

In patients with suspected pulmonary TB who are unable to expectorate sputum spontaneously, the diagnostic yield of 3 sputum samples induced by nebulized hypertonic saline was greater than that of GW specimens obtained on 3 consecutive

Table 3. Comparison of culture yield for *Mycobacterium tuberculosis* for day 1 versus 3-daily sputum specimens induced by nebulized hypertonic saline (IS) for 79 subjects with all 5 IS culture results.

Day 1 IS culture results	No. (%) of subjects		
	Positive results of any of 3-day IS cultures[a]	Negative results of any of 3-day IS cultures[b]	Total
Positive[c]	26	1	27 (34)
Negative[d]	3	49	52 (66)
Total (%)	29 (37)	50 (63)	79 (100)

NOTE. $P = .63$ by Fisher's exact test comparing the diagnostic yield of day 1 versus 3-day IS cultures.

[a] First day 1 IS culture or an IS culture from day 2 or 3 yielded positive results.
[b] First day 1 IS culture and IS cultures from days 2 and 3 yielded negative results.
[c] Any day 1 IS culture yielded positive results.
[d] All day 1 IS cultures yielded negative results.

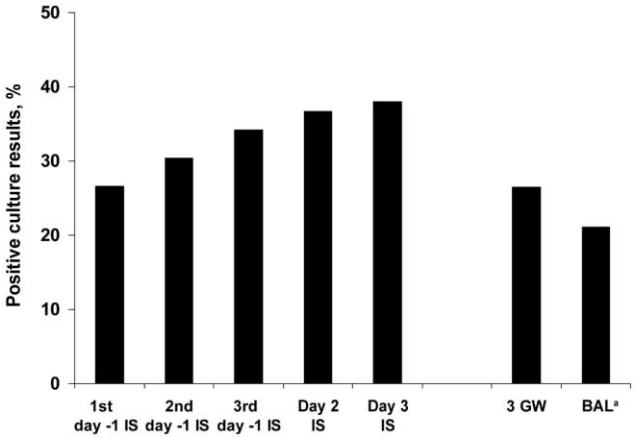

Figure 2. Proportion of subjects with cultures positive for *Mycobacterium tuberculosis,* by diagnostic technique, for 79 subjects with results for all 5 sputum samples obtained by induction with nebulized hypertonic saline (IS) and all 3 gastric washing (GW) specimens. Cumulative proportions are shown for the 5 IS samples. $P = .25$, by paired binomial probability test comparing diagnostic yield of all 5 IS samples versus 3 day 1 IS samples. [a]Bronchoalveolar lavage (BAL) culture results were available for 19 subjects.

days. Culture positivity was not associated with the volume of sputum attained or with the timing of sampling; the IS samples could be obtained in a single day, allowing for earlier diagnosis, earlier initiation of treatment, and shorter hospital stay. BAL samples were obtained from 21 patients with negative smear results but yielded no additional positive culture results—in fact, BAL cultures missed 2 cases that had been diagnosed by IS testing, suggesting that IS culture performs at least as well as (and perhaps better than) BAL culture in this specific group of patients, who are unable to expectorate [9, 10].

The study was sufficiently powered to show equivalence between GW and IS examination. In comparison with our conservative estimate, the study revealed a higher rate of positive culture results and a lower proportion of discordant results (i.e., subjects who had positive results with one technique and negative results with another). Although only 56% of enrolled subjects had results for all 5 IS specimens, this sample size was sufficient to detect equivalence to within <15% between day 1 IS and 3-day IS.

The technique of sputum induction with hypertonic saline was introduced >40 years ago [1]. Early studies demonstrated evidence of enhanced performance relative to the GW procedure; however, recent outbreaks of multidrug-resistant TB associated with its use in infectious diseases units have discouraged some clinicians from using this method [19, 20]. Bronchoscopy has been regarded as an effective alternative method, but should not be necessary if smear-positive specimens can be safely obtained by IS. Bronchoscopy has limited availability in resource-poor settings, is invasive, is not without risk to both patient and staff, and, unlike IS, obtains samples from only one portion of the lungs [21–23]. This might explain why, in our study, 2 subjects with negative smear results and positive culture results with day 1 IS specimens had negative BAL culture results. A small proportion of patients (10 of 140) were unable to produce at least 3 sputum samples, even with induction; for these subjects, GW and bronchoscopy remain useful methods.

There was no evidence that IS affected subsequent GW (or IS) yield: the prevalence of culture positivity was similar for all time points. This accords with an earlier study demonstrating no effect of IS on subsequent GWs, although in that study, rates of positive culture results were lower, and a different IS technique was used [5]. There was no evidence that repeated sputum induction reduced the yield of subsequent IS sampling. Indeed, additional samples revealed more culture-positive cases. However, although the greater the number of samples collected, the greater the number of positive culture results, the additional yield contributed by fourth and fifth IS samples was small. Among subjects with all 5 IS culture results, the addition of day 2 and day 3 IS samples contributed only 3 extra culture-positive cases (10% total), compared with the 3 day-1 cases. Similar results were obtained by Al-Zahrani et al. [13] using larger saline volumes in a patient cohort with lower rates of positive culture results. For most subjects, therefore, a total of 3 IS samples collected in a single day is sufficient. Obtainment of additional samples may be justified for subjects who are at high risk of developing drug-resistant disease.

Conde et al. [24] found a high yield for IS specimens among subjects with tuberculous pleural effusions; for this reason, we included such subjects in our study. We detected TB in IS samples obtained from 3 subjects (23%) with pleural effusions; however, in all of these subjects, *M. tuberculosis* was also isolated from the pleural space. Exclusion of subjects with pleural effusions did not alter the findings (41% had positive culture results with the first 3 IS specimens, and 32% had positive culture results with the 3-daily GW specimens; $P = .04$). A larger study would be needed to confirm the finding of Conde et al. [24] of an additional benefit of IS over pleural aspirate and biopsy.

A sizeable proportion of subjects were enrolled in this study after being referred by the health control facility at Heathrow Airport. The majority of these new migrants were asymptomatic and had only minimal changes noted on radiographs. Nearly one-half had cultures positive for TB (data not shown). The demonstrated adequacy of rapid collection of 3 IS samples for TB diagnosis allows for shorter and less invasive hospital admissions for vulnerable people, such as these new migrants. Patients and nursing staff find IS to be a much better tolerated procedure. As a result of the study, we have now removed GW from our protocol for investigation of patients with suspected

TB who are unable to expectorate. Three IS samples are collected on day 1 of hospitalization, and BAL procedures are reserved for special circumstances (e.g., if adequate samples cannot be obtained by IS or GW procedures); this is followed by administration of anti-TB treatment and prompt discharge. This strategy of obtainment of 3 IS specimens on 1 day is also being extended to outpatient investigation and management of TB.

Acknowledgments

We are grateful to the Lister Unit nursing staff and the Microbiology laboratory staff at Northwick Park Hospital for collecting and processing specimens.

Potential conflicts of interest. All authors: no conflicts.

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