ORIGINAL ARTICLE

Induced sputum and bronchoscopy in the diagnosis of pulmonary tuberculosis

T McWilliams, A U Wells, A C Harrison, S Lindstrom, R J Cameron, E Foskin

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See end of article for authors' affiliations

Correspondence to: Dr A Harrison, Respiratory Services, Green Lane Hospital, Auckland, New Zealand; adrianh@adhb.govt.nz

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Background: Previous studies suggest that bronchoscopy and a single induced sputum sample are equally effective for diagnosing pulmonary tuberculosis.
Methods: In a prospective study of subjects with possibly active pulmonary tuberculosis, the diagnostic yield of three induced sputum tests was compared with that of bronchoscopy. Subjects either produced no sputum or (acid fast) smear negative sputum. Bronchoscopy was only performed if at least two induced sputum samples were smear negative.
Results: Of 129 subjects who completed all tests, 27 (21%) had smear negative and culture positive specimens, 14 (52%) on bronchoscopy and 26 (96%) on induced sputum ($p<0.005$). One patient was culture positive on bronchoscopy alone compared with 13 on induced sputum alone; 13 were culture positive on both tests. Induced sputum positivity was strikingly more prevalent when chest radiographic appearances showed any features of active tuberculosis (20/63, 32%) than when appearances suggested inactivity (1/44, 2%; $p<0.005$). Induced sputum costs were about one third those of bronchoscopy, and the ratio of costs of the two tests per case of tuberculosis diagnosed could be as much as 1:6.
Conclusions: In subjects investigated for possibly active or inactive tuberculosis who produce no sputum or have smear negative sputum, the most cost effective strategy is to perform three induced sputum tests without bronchoscopy. Induced sputum testing carries a high risk of nosocomial tuberculosis unless performed in respiratory isolation conditions. The cost benefits shown could be lost if risk management measures are not observed.

Bronchoscopy is commonly used for investigating patients with possible pulmonary tuberculosis (TB) when spontaneous sputum is smear negative. However, there is a wide range in the diagnostic yield from bronchoscopy in suspected TB,[1–5] and bronchoscopy is both expensive and semi-invasive. A cheaper non-invasive means of providing the same information as bronchoscopy would be advantageous.

Induced sputum testing has previously been reported to be a useful test in the diagnosis of subjects with smear negative sputum or no reliable sputum production.[6–8] Anderson *et al*[9] compared the induced sputum test and bronchoscopy in the diagnosis of TB, and reported that the diagnostic yield of a single induced sputum test was equivalent to that of bronchoscopy. Similar results were obtained from a larger study in Brazil.[10] We have compared the results of three induced sputum tests with bronchoscopy washings in 160 subjects with possibly active pulmonary tuberculosis.

METHODS

Subject population

People were referred for the investigation of pulmonary TB to the Department of Respiratory Services, a regional adult centre for tuberculosis at Green Lane Hospital in Auckland, New Zealand. Subjects who were unable to produce sputum spontaneously, or who produced smear negative sputum, were prospectively enrolled between January 1996 and December 1998. Inclusion criteria comprised: (1) clinical suspicion of active TB, and (2) clinical suspicion of inactive previous TB, where it was important, for immigration or for clinical purposes, to exclude active disease. Exclusion criteria were severe asthma or severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume in 1 second (FEV_1) <65% predicted), oral steroid treatment for either of these conditions in the previous month, or inability to give informed consent. Ethical approval was obtained from the Auckland ethics committee.

Demographic and clinical information was collected, and current and previous chest radiographs were reviewed. A Mantoux test was performed (using 5 TU PPD) if clinically indicated; HIV testing was not done routinely.

Diagnostic procedures

Induced sputum tests were performed with 3% hypertonic saline solution delivered by an ultrasonic nebuliser (Devilbiss Ultraneb 99, Sunrise Medical, Somerset, PA, USA). The inhalation continued until subjects had either produced an adequate sample of sputum or 20 minutes had elapsed. Three procedures were usually performed on consecutive days. Subjects with mild/moderate asthma or COPD received 2.5 mg salbutamol via a standard nebuliser before each induced sputum test. A nurse who was experienced with the procedure supervised all subjects.

Induced sputum tests were performed in a room with negative pressure ventilation and HEPA filtration.[11] Staff TB protection measures included wearing a respiratory protection mask[11] and standard hospital procedures for staff exposed to TB.[12] If at least two sputum test samples were smear negative, fibreoptic bronchoscopy was performed either by a respiratory physician or a training registrar. Lignocaine was the local anaesthetic agent used. Bronchial segments which were thought from the chest radiograph to be the site of active or inactive TB were washed with 40 ml normal saline.

Specimens were processed using standard methodology[13] and stained with fluorochrome. Positive smears were confirmed by Ziehl-Neelsen staining. Specimens were cultured using Bactec 12B and Lowenstein-Jensen media. Mycobacterial species were identified with nucleic acid probes (GenProbe, San Diego, CA, USA). DNA fingerprinting[14] was performed when only one specimen was culture positive per subject.

Evaluation of chest radiographs

Two respiratory physicians (ACH and AUW) evaluated chest radiographs independently without access to other information. The extent of TB disease was graded as: 0=no disease; 1=trivial disease where the total possible volume of old and/or active TB was equivalent to or less than one bronchopulmonary segment; 2=intermediate disease where the total possible TB volume was greater than one bronchopulmonary segment but less than or equal to one lobe; 3=extensive disease where the total TB volume was greater than one lobe. Parenchymal disease was categorised as unilateral or bilateral. The presence of lymphadenopathy, pleural disease, or miliary abnormalities was noted.

Lung parenchymal abnormalities were classified as "inactive" or "potentially active". A grading of "inactive disease" denoted isolated fibrotic (reticular) abnormalities or calcified and/or sharply defined tuberculomata. Abnormalities compatible with "potentially active disease" included consolidation, an impression of patchy fluffy shadowing (with or without an admixture of fibrotic changes), a miliary pattern, pleural effusion or non-calcified opacities with an indistinct border. If previous radiographs were available, serial appearances were taken into account. In cases with divergent assessments, final grades were reached by consensus.

Statistical analysis

Population data were expressed as means with standard deviations, or medians with ranges, as appropriate. Group comparisons were made using the Student's *t* test or the Wilcox rank sum test, as appropriate, using the χ^2 method. A p value of <0.05 was regarded significant. Observer variation in the evaluation of radiographs was quantified using the kappa coefficient of agreement (κ). For semi-categorical grades, a weighted kappa coefficient (κ_w) was calculated using quadratic weighting.[15]

To identify the independent determinates of, firstly, smear and culture positive induced sputum and, secondly, similarly positive induced sputum in patients with a negative bronchoscopy, stepwise logistic regression models were constructed.[16]

Cost analysis

The costs of induced sputum and bronchoscopy were compared . The costs for bronchoscopy included hospital charges, professional fees for physicians and nursing staff, and laboratory charges. These were based on medical insurance rebates for this procedure in the USA: they were averaged costs from hospitals associated with the Mayo Clinic, Boston Massachusetts, and with the University of Southern California, San Diego. The cost of three induced sputum procedures included charges for nursing time, the cost of disposable equipment and other consumables, and laboratory charges for processing three specimens.

To identify the most cost effective method of diagnosing active TB where spontaneous sputum was smear negative, we compared seven different diagnostic strategies. For each, we calculated the total cost of the investigations, the cost per case diagnosed, and the number of cases in this study that would have been missed by each strategy.

RESULTS

Subjects

One hundred and sixty subjects were enrolled. Thirty one (19.4%) did not complete three induced sputum tests and/or bronchoscopy for the reasons listed in table 1, so 129 (78 men and 51 women) participated in the study. Their median age was 38 years (range 15–85). The ethnicities of the participants included European (n=12, 9.3%), Maori (n=11, 8.5%), Polynesian (n=15, 11.6%), Asian (n= 40, 31%), African (n=26, 20%), and other (n=25, 19.4%). One hundred and four subjects were immigrants to New Zealand, 77 arriving after 1995. Of these, 64 had investigations for TB within a year of arrival. One hundred and twenty four of the 129 (96%) participants tolerated the induced sputum test without difficulty.

Table 1 Reasons why subjects did not complete the study protocol

Smear positive on induced sputum testing	11
Technical*	6
Intolerant of induced sputum testing	3
Unknown	8
Other diseases†	3
Total number of subjects	31

*Ultrasonic nebuliser broken (n=4), sample lost (n=1), inadequate specimen on sputum induction (n=1).
†Lymphangiomyomatosis, AIDS, Aspergilloma.

Table 2 Mycobacterial diagnosis

	n
(A) Subjects who completed study tests	
Active TB	**27**
Induced sputum only	13
Bronchoscopy only	1
Induced sputum and bronchoscopy	13
Active NTM	**1**
NTM (probable contaminant)	**3**
No mycobacterial disease	**98**
Subtotal (A)	**129**
(B) Excluded subjects	
Active TB	**15**
Smear (+) on induced sputum	11
Smear (–), culture positive subjects	4
No evidence of TB	**16**
Subtotal (B)	**31**
Total subjects (A+B)	**160**

NTM = non-tuberculous mycobacteria.

Diagnosis of TB

Forty two cases of TB were diagnosed from 160 subjects (table 2). Among the 31 excluded subjects, 11 had smear positive induced sputum and did not proceed to bronchoscopy. Four of the remaining 20 subjects were diagnosed with TB and were excluded from the statistical comparison of induced sputum with bronchoscopy because of failure to complete all tests. All four were smear negative and culture positive on induced sputum, and two were culture positive on bronchial washings. The smear positive pick-up rate from bronchoscopy was zero in this study.

Twenty seven of 129 subjects who completed all tests were diagnosed with smear negative, culture positive pulmonary TB. Twenty six of the 27 (96.3%) were identified by induced sputum testing and 14 (51.9%) by bronchoscopy. One case was diagnosed only by bronchoscopy, whereas induced sputum testing alone diagnosed 13. Thirteen were culture positive by both tests. Induced sputum was therefore more sensitive than bronchoscopy ($p<0.005$, McNemar χ^2 test) in diagnosing active TB in this subject group.

Of 26 subjects who were culture positive on sputum testing, six were positive on one test, seven were positive on two tests, and 13 were positive on all three samples. DNA fingerprinting was performed on the six samples from subjects who were culture positive on a single specimen. In only one subject did the induced sputum isolate have a DNA restriction fragment length polymorphism (RFLP) identical to another isolate processed in the laboratory at the same time. This subject presented with cough and sputum, and had chest radiograph abnormalities that improved with treatment.

Table 3 Chest radiograph results

Radiographic disease	Induced sputum +ve	Total
Grade of disease		
Normal (1)	5	22
Trivial (2)	9	50
Intermediate (3)	7	36
Extensive (4)	5	21
Extent of disease		
Unilateral	15	68
Bilateral	6	39
Disease activity		
Active	20	63
Inactive	1	44
Total number of subjects	26	129

Table 4 Cost of diagnostic procedures ($US)

	Cost ($US)
Bronchoscopy	
Procedure*	1100
Laboratory charges†	96
Total	1196
Induced sputum	
Laboratory charges†	289
Consumables‡	60
Nursing charge	21
Total	370

*Cost of diagnostic bronchoscopy includes hospital and doctors' fees, nursing charges, consumables, cleaning and transport costs.
†For bronchoscopy, cost of mycobacterial tests on a single specimen; for induced sputum, cost for these tests on three induced sputum specimens.
‡Includes disposable equipment (such as nebuliser bowl), cleaning, and specimen transport costs.

Non-tuberculous mycobacteria were cultured from induced sputum in four subjects. Single cultures of *Mycobacterium gordonae* (n=2) and *M triviale* (n=1) were assumed to be contaminants. In one subject *M avium intracellulare* complex was cultured from all three induced sputum samples, but bronchial washings were culture negative.

Symptoms of TB

Fifty four of 129 subjects (42%) had a recent history of respiratory symptoms (n=45) or systemic symptoms (n=32), including 23 who had both respiratory and systemic symptoms. The prevalence of culture positivity on induced sputum was marginally higher in symptomatic subjects (15/54, 28%) than in those without symptoms (11/75, 15%), p=0.07. Culture positivity on induced sputum was more frequent in those with respiratory symptoms (14/45, 31% *v* 12/84, 14%; p=0.02), but only marginally more frequent in those with systemic symptoms (10/32, 31% *v* 16/97, 16%; p=0.07).

Chest radiograph analysis

The chest radiographic appearance and its relationship with induced sputum results is shown in table 3. Interobserver agreement was good-to-excellent for the assessment of extent of disease (κ_w=0.83), categorisation of disease as unilateral or bilateral (κ_w=0.77), and grading of abnormalities as inactive or potentially active (κ_w=0.67).

In order to determine whether induced sputum positivity was associated with the characteristic radiographic appearances of TB, the 22 subjects with a normal chest radiograph were excluded from further analysis. In the remaining 107 patients the yield from induced sputum was unrelated to disease extent: nine of 50 (18%) with grade 1 disease, seven of 36 (19%) with grade 2 disease, and five of 21 (24%) with grade 3 disease had positive induced sputum tests. Similarly, the prevalence of induced sputum positivity did not differ significantly between subjects with unilateral disease (15/68 (22%) had positive induced sputum tests) and those with bilateral disease (6/39 (15%) had positive induced sputum tests). By contrast, subjects in whom radiographic abnormalities suggested possibly active TB had a strikingly higher yield from induced sputum (20/63 positive, 32%) than patients with inactive appearances (1/44 positive, 2%), p<0.0005.

On logistic regression, culture positivity of induced sputum was associated with radiographic appearances of possibly active disease (odds ratio (OR) 23.4, 95% CI 2.9 to 189.3; p=0.003) independent of the radiographic extent of disease, the presence of unilateral (as opposed to bilateral) disease, and the presence of respiratory or systemic symptoms. None of these other variables was independently linked to induced sputum positivity.

Cost analysis

The cost of each diagnostic procedure is detailed in table 4. Despite three tests being performed and processed, the costs of induced sputum tests were about one third those of bronchoscopy. The calculations shown in tables 4 and 5 were based on the assumption that only one bronchial washing specimen was tested for mycobacteria per bronchoscopy. When the seven different diagnostic strategies are compared (table 5), only three—numbered 3, 4, and 7—would have

Table 5 Costs of diagnostic strategies ($US)*

	Diagnostic strategy	Cases diagnosed	Cost of investigations	Cost per case diagnosed	Cases missed
1	Bronchoscopy only	14	154284	11020	13
2	Induced sputum tests (3) only	26	47730	1836	1
3	Bronchoscopy, then induced sputum if bronchial wash smear –ve	27	202014	7482	0
4	Induced sputum, then bronchoscopy if induced sputum smear –ve	27	202014	7482	0
5	Bronchoscopy only for those with any features of active TB on chest radiograph†	11	75361	6851	16
6	Induced sputum only for those with any features of active TB on chest radiograph†	20	23310	1165	7
7	Induced sputum; if those specimens smear –ve, bronchoscopy then for those with any features of active TB on chest radiograph†	27	123078	4558	0

*Costs based on those for the 129 subjects who completed all tests (table 2).
†Sixty three subjects had some features suggestive of active TB on chest radiograph (table 3).

diagnosed all 27 cases. Strategies 3 and 4 are time consuming and costly. In strategy 7, sputum testing would be performed first, followed by bronchoscopy only if the sputum specimens were smear negative and the chest radiograph showed features suggestive of possibly active TB. However, the most cost effective strategy is strategy 2 in which all sputum smear negative cases of possible pulmonary TB are investigated with three induced sputum tests: bronchoscopy is not performed. The cost per case of tuberculosis with this strategy was $US1836. Although this strategy missed one of the 27 cases of active TB (3.7%), in the next most cost effective strategy (number 7) the costs are 2.5 times higher as a result of adding bronchoscopy for those subjects with any features of active TB on the chest radiograph. Not included in this analysis are the 11 subjects (7%) who were identified with smear positive TB on induced sputum tests. As a result of the study design, bronchoscopy was avoided in these subjects. Also not factored into the analysis are increased indirect costs—for example, for accommodation and travel—associated with subjects having to attend on three separate days for induced sputum tests.

DISCUSSION

This study has shown that induced sputum testing is more sensitive than bronchoscopy for detecting active pulmonary TB in subjects whose spontaneous sputum is smear negative or who cannot produce spontaneous sputum. These results differ from those of Anderson[9] and Conde[10] which suggest that a single induced sputum test and bronchoscopy have similar diagnostic ability. In the study by Anderson there were 101 subjects, of whom 20/26 (77%) were culture positive on sputum testing and 19/20 (95%) had culture positive bronchial washings. The report by Conde *et al* describes kappa values for agreement between induced sputum and bronchoalveolar lavage results of 0.92 for acid fast bacilli smears and 0.78 for mycobacterial cultures. In the present study, induced sputum provided a diagnosis of smear negative, culture positive TB in 26/27 subjects (96.3%). This result was considerably better than bronchoscopy, which gave the diagnosis in only 14/27 cases (51.9%). This comparison does not include the 11 subjects whose sputum was smear positive or the four TB cases who did not complete the protocol (table 2). The exclusion from sputum tests of subjects with asthma or COPD with FEV_1 <65% may have been overly cautious.[17 18]

There may be several reasons for the discrepancy between the results of the present study and those of Anderson and Conde. In Anderson's study bronchoscopy was performed by only two "board certified pulmonologists". Conde does not state who undertook this procedure. In the present study bronchoscopies were performed by respiratory physicians or training registrars under supervision. It is possible that the use of less trained bronchoscopists for some procedures may have led to underdiagnosis of TB in our study. Lignocaine is known to inhibit the growth of *M tuberculosis* in vitro.[19] If more lignocaine was used in the present study by less skilled bronchoscopists in some TB cases, this might explain the apparent false negative rate of bronchoscopy.

Another explanation may lie in the volume of bronchial lavage fluid used. Approximately 40 ml was lavaged per segment in our study compared with 50–60 ml by Anderson *et al* (R Menzies, personal communication). "Bronchoalveolar lavage", as referenced by Conde, suggests that a substantially larger volume was used in that study. The same type of ultrasonic nebuliser and the same tonicity of saline were used in all three studies.

However, rather than bronchoscopy underdiagnosing TB in our study, we believe that the induced sputum procedure gave an underestimate of TB in the two other studies. With three induced sputum procedures the diagnosis was made in 13 subjects (50%) with all three induced sputum specimens, in seven (27%) with two specimens, and in six (23%) with only one specimen. Clearly, there is considerable potential for false negative results if only a single induced sputum test is performed. The present study confirms the results of Al-Zahrani *et al*[20] who showed that multiple tests improve the diagnostic yield of induced sputum testing. In that study, the cumulative yield from smear and culture was 64% and 70%, respectively, for one test, 81% and 91% for two, 91% and 99% for three, and 98% and 100% for four induced samples from 44 culture confirmed pulmonary TB cases.

A further explanation for the better result with induced sputum and the poorer result with bronchoscopy in the present study may be that different groups of subjects were investigated in the three studies. Many of our subjects had minor disease on the chest radiograph. We estimate that about 50% were tested to exclude active TB rather than to prove active disease. One might postulate that the number of reproducing organisms in a group comprising cases of "suspected inactive TB" may be significantly less than in a group with mainly "suspected active TB". Previous studies probably minimised the benefit of induced sputum by only doing one induced sputum test, and also by studying subjects with predominantly "suspected active TB".

Like bronchoscopy, induced sputum testing has some disadvantages. Firstly, there is the risk of transmission of TB to staff who supervise the tests—a concern which has recently been emphasised.[21] However, if appropriate protection measures are applied,[11 12] we suspect the risk of transmission may be less with induced sputum than with bronchoscopy: a doctor and an assistant are required to be in attendance throughout bronchoscopy while sputum induction involves only one staff member who does not need to be present throughout each test. In the present study bronchoscopy was avoided in 11 subjects who had smear positive induced sputum. A key safety measure with sputum testing is that it should only be performed using an induced sputum booth in a separate room, or is performed in a room that meets ventilation requirements for TB isolation.[11]

In our study the subjects had one induced sputum test each day for 3 days. Whether improved convenience and reduced indirect costs could be achieved by performing the three tests over 1–2 days, without reducing the diagnostic yield, remains untested. Positive induced sputum cultures for non-tuberculous mycobacteria in four of 160 subjects (2.5%) shows that, like bronchoscopy,[22–29] induced sputum carries a low risk of false positive mycobacterial cultures. Despite these potential problems, we believe the advantages of induced sputum outweigh the disadvantages. Bronchoscopy is a semi-invasive procedure. Replacing it with induced sputum testing removes the need for sedation and the risk from bronchoscopy, albeit low, of nosocomial infection.

Although three different strategies would have identified all 27 cases of culture positive pulmonary TB (table 5), the most cost effective was strategy 2, and this is the one that we recommend. This strategy comprised three induced sputum tests and it detected all but one case (3.7%) of active TB. Bronchoscopy is not required using this strategy. The total cost of diagnostic tests with strategy 2 was $US47 730, and the cost per case of TB diagnosed was $1836. By comparison, the cost per case diagnosed of bronchoscopy alone would have been sixfold greater, with failure to make the diagnosis in 48% of cases. The cost advantage would be reduced if inpatient stay was prolonged solely to enable sputum testing to be done on separate days.

The costs of bronchoscopy and induced sputum tests are not uniform within or between countries.[30] In New Zealand, during the study period the fee for bronchoscopy was approximately $NZ800–1500, equivalent to $US360–675. Assuming an average cost of $US500 and applying the same calculation methods as used in table 5, the total bronchoscopy costs in NZ for the 129 subjects would have been $US64 500. The NZ cost per case diagnosed with bronchoscopy only (strategy 1) would

have been $US4607, and that for induced sputum only (strategy 2) would have been unchanged at US$1836. Thus, the ratio of these costs per case diagnosed would have been 2.5:1 in NZ compared with 6:1 in the USA.

In summary, we have shown a significantly greater diagnostic yield for TB with induced sputum testing than with bronchoscopy. These results and the cost analysis lead us to recommend that three induced sputum tests (with appropriate precautions) should replace bronchoscopy in the investigation of possibly active, sputum smear negative, pulmonary TB. Bronchoscopy will still be required if TB is excluded and tumour or other pathology is included in the differential diagnosis.

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Authors' affiliations

T McWilliams, A U Wells, A C Harrison, S Lindstrom, R J Cameron, E Foskin, Respiratory Services, Green Lane Hospital, Auckland, New Zealand

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