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## SUSPECTED PULMONARY TUBERCULOSIS IN RURAL SOUTH AFRICA — SPUTUM INDUCTION AS A SIMPLE DIAGNOSTIC TOOL?

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**Objectives.** To assess the value of sputum induction (SI) as a diagnostic tool for patients with suspected pulmonary tuberculosis (PTB) who are unable to expectorate or who have a negative sputum smear.

**Design.** Study of an inpatient cohort undergoing SI.

**Setting.** Mseleni Hospital, a rural district hospital in northern KwaZulu-Natal.

**Subjects.** All adult patients with suspected TB seen at the hospital over a 4-month period.

**Outcome measures.** (i) Successful SI; (ii) sputum acid-fast smear result; (iii) change of admission diagnosis as a result of the induction procedure; and (iv) number of patients discharged with a diagnosis other than TB who re-presented within 4 months with TB.

**Results.** A total of 51 patients (31 female) underwent SI; of these 36 (71%) were able to produce a sputum sample. Fifteen (42%) of those were acid-fast smear-positive (29% of all patients included). The admission diagnosis was changed in 16 (44%) of the patients who were able to give an induced sputum sample as opposed to 4 (27%) who had been unable to expectorate despite an induction attempt ( $P = 0.38$ ). Three (12.5%) of the 24 patients with a discharge diagnosis other than TB (17 pneumonia, 3 old TB, 2 carcinoma of the lung, 1 bronchiectasis) turned out to have TB within the follow-up period; 2 of those had extra-pulmonary TB.

**Conclusion.** SI produced a positive smear result in 29% of patients with suspected TB who had previously been smear-negative or unable to expectorate. The method proved an aid to clinical decision making.

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The diagnosis of HIV-associated pulmonary tuberculosis (PTB) can be difficult as atypical chest radiographs and sputum smear-negative presentations in immunodepleted individuals are common.<sup>1</sup> In the absence of bacteriological confirmation the diagnosis often rests on uncertain clinical grounds.<sup>2</sup> Sputum induction (SI) with hypertonic saline is a simple, non-invasive procedure that can safely be used to aid the diagnosis of pneumocystic pneumonia (PCP) and lung cancer.<sup>3,5</sup> The inhalation of hypertonic saline in the form of a fine mist and its deposition at peripheral sites in the lung causes irritation of the airways and bronchial hypersecretion. The influx of fluid through osmosis helps to mobilise organisms, which are shifted centrally and expectorated.<sup>6</sup> Although not recommended for routine use or as a screening tool, SI can assist the diagnosis of PTB in patients with a negative sputum smear or those who are unable to expectorate.<sup>7,8</sup> Surprisingly few recent reports exist on its diagnostic value in the context of the HIV-related tuberculosis (TB) epidemic in developing countries.<sup>9,10</sup>

We used the method of SI to aid the diagnosis of PTB in patients who were sputum smear-negative or who were unable to produce sputum spontaneously. The study was carried out in a rural setting with a high HIV-associated TB burden (650/100 000 new TB cases per annum, 69% HIV co-infection in 2000).

## METHODS

Adult patients, aged 16 years or older, who were unable to expectorate or had three negative acid-fast sputum smears, but who were strongly suspected to have PTB (admission diagnosis TB) or possibly have TB (admission diagnosis non-TB — see Fig. 2) underwent oxygen-driven nebulisation with hypertonic (3.5%) saline administered through a disposable nebuliser mask (Trident Medical International, Cat T1805, USA) for 20 minutes. Manual chest physiotherapy helped in the collection of three sputum samples. A Ziehl-Neelsen stain was done within 24 hours of the procedure. Culture was not done routinely. HIV test counselling was offered to all patients in accordance with hospital policy. Patients with a positive smear were notified and received standard antituberculosis treatment. In the absence of a positive smear patients were also treated if clinical features and chest radiographs suggested the diagnosis of PTB. If the sputum smear was negative and the clinical decision was not to treat for TB, patients were advised to return for follow-up.

Outcome measures were: (i) successful sputum production for acid-fast microscopy, with adverse effects documented; (ii) microscopy result of the acid-fast smear (positive/negative); (iii) admission and discharge diagnoses and a change of original admission diagnosis as a result of a positive/negative smear (impact of procedure on clinical decision making); and (iv) number of patients who were discharged with a diagnosis

other than TB but who re-presented within 4 months with the diagnosis of TB (detection of false-negative diagnoses).

## RESULTS

A total of 51 patients (31 female) underwent SI between March and October 1999 (44 were unable to produce spontaneously, 7 had three negative acid-fast smears). Respiratory complications were not observed, but 3 patients complained of retching and vomited after the procedure.

Successful SI was achieved in 36 subjects (71%); in the remaining 15 patients (29%) no sample could be obtained.

Of the 36 sputum smear examinations, 15 (42%) were positive (2 previously negative and 13 previously unproductive) for acid-fast bacilli and 21 (58%) were negative (2 previously negative and 19 previously unproductive) as shown in Fig. 1. Sputum culture was done in 21 of the 36 samples.

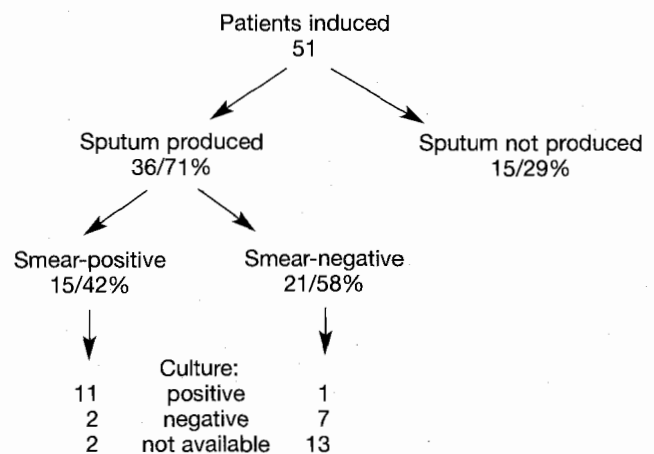


Fig. 1. Result of sputum induction.

The discharge diagnosis was TB in the 15 cases with a positive smear. A further 12 patients (5 of 21 induced sputum smear-negative, 7 of 15 unable to produce despite induction) received antituberculosis chemotherapy. The diagnoses of the remaining 24 patients were pneumonia (17), old TB (3), lung carcinoma (2) and infected bronchiectasis (1). The 2 cancer patients were transferred and diagnosed at our referral hospital in Durban (King Edward VIII), the other diagnoses were made on clinical grounds (trial of standard antibiotics and repeat chest radiograph).

A change in clinical management (admission diagnosis different from discharge diagnosis) as a result of the procedure (positive or negative smear) occurred in 16 (44%) of the 36 cases where sputum had been obtained (Fig. 2.). In comparison, in 4 (27%) of the 15 cases who were unable to expectorate despite induction the admission diagnosis was changed (chi-square test,  $P = 0.38$ ). The change of admission diagnoses



A → D	Sputum smear positive (N = 15)	Sputum smear negative (N = 21)	No sputum produced (N = 15)	
TB → TB	12 (culture positive 9, culture negative 1)	5 (culture negative 2)	6	No change of A
Non-TB → non-TB		3 (culture negative 1)	5	
Non-TB → TB	3 (culture positive 2, culture negative 1)		1	Change of A
TB → non-TB		13 (culture negative 4, culture positive 1)	3	

Fig. 2. Admission diagnosis (A) and discharge diagnosis (D) by sputum smear result. Culture result indicated where available (TB = tuberculosis; non-TB = diagnosis other than TB).

within the group of sputum producers was more likely to be from TB to non-TB than vice versa (McNemar's test,  $P = 0.025$ ). For patients without sputum this difference was not observed ( $P = 0.6$ ) and a change of diagnosis was equally likely to occur in both directions.

The value of the procedure as a confirmatory investigation was obvious; with 12 (80%) of the 15 positive smears the result confirmed the original admission diagnosis of PTB. In comparison, fewer patients (12/36, 33%) with no or negative sputum smears were still treated for TB (chi-square test,  $P = 0.003$ ). Similarly, although not significant, more patients with a negative induced sputum smear had a diagnosis other than TB (16/21, 76%) compared with those (8/15, 53%) who were unable to produce a sample despite an induction attempt ( $P = 0.28$ ).

Of the 24 patients who were discharged with diagnosis other than TB, 1 of 16 induced smear-negative patients re-presented within 2 months with nodal TB and 1 of 8 patients who had been unable to produce induced sputum returned also after 2 months with pleural TB. One further patient who was not treated (induced sputum smear-negative) and was subsequently lost to follow-up had a positive sputum culture at 8 weeks. Therefore, a combined 12.5% of patients of the 24 not treated were not correctly diagnosed (because of logistical problems only 6 of the 24 patients who were not diagnosed with TB had their sputum cultured).

HIV testing was done in 13 (48%) of the 27 patients diagnosed with TB; of these 11 (85%) were positive. In comparison, out of a cohort of all 453 adult patients seen with TB between 1999 and 2000, 69% were positive.

## DISCUSSION

As predicted by the World Health Organisation (WHO) in 1993, TB is increasingly overburdening already stretched health

care facilities in the developing world.<sup>11</sup> More in-depth, time-consuming investigations of the frequent atypical clinical presentations of HIV-associated TB are often not available. We showed that the simple method of SI can aid the diagnosis in a selected group of adult PTB suspects, the majority of whom were HIV co-infected. Sputum was successfully induced in 71% of patients; of these 42% (or 29% of all included individuals) had a positive acid-fast smear. Surprisingly, only two other reports on the use of sputum induction in a similar environment have been published. In Malawi, Parry *et al.*<sup>9</sup> reported 22% sputum positivity following SI, and in a larger field study

in China<sup>10</sup> 34% of suspected TB cases who had previously been smear-negative or who were unable to expectorate had a positive acid-fast smear.

In patients in whom SI was successful (71%) the procedure proved to be a guiding tool to the clinician, particularly in refuting rather than confirming the diagnosis of TB ( $P = 0.025$ ). A change in clinical management as a result of a positive or negative induced smear occurred in 44% of cases. However, although the numbers were small, a change of diagnosis also occurred in 27% of patients where no sputum could be obtained. Even in the absence of a confirmatory positive induced sputum, some patients may still be treated (12 patients in our study) for PTB on clinical grounds. Parry *et al.*<sup>9</sup> showed that clinical judgement can be relied on as all their smear-negative but culture-positive patients had been started on antituberculosis treatment by the clinician before the culture result was available.

To assess the impact of the results of the induced sputum procedure on the detection of smear-positive cases in that year we calculated that without the procedure sputum positivity of all 453 adult PTB patients would have dropped from 78% to 72%.

It is not clear why some patients are unable to produce sputum or have a negative smear. The importance of the patient's immune status and the presence of pulmonary cavitation have been discussed.<sup>12</sup> Other factors such as timing of the sputum collection, patient's wakefulness and activity level and physical fitness may be implicated.

Similarly intriguing is whether it may be helpful for clinical and surveillance purposes to distinguish between patients who simply cannot produce sputum and those who are able to produce sputum but have a negative smear. As far as successful SI and smear results were concerned, we found no difference between the two groups. However, Parry *et al.*<sup>9</sup>



reported a marginal difference of induced sputum positivity (28% of previously unproductive v. 19% of previously smear-negative).

It must be pointed out that the case detection rate of smear-positive TB depends, among a multitude of factors, very much on a well-performing TB control programme. Large-scale use of SI as done in the Chinese study,<sup>10</sup> where the case detection rate before introduction of the SI procedure had only been 18% and therefore well below the target of 70% set by the WHO, seems unjustified. It has been established that SI offers no advantage over conventional expectorated sputum or gastric lavage when used for routine diagnosis of TB,<sup>7</sup> and should therefore be reserved for selected patients only.

We did not assess costs, but they must have been negligible. In the Chinese field trial<sup>10</sup> the direct cost per induction was US\$0.37. Serious side-effects as previously reported by Nelson *et al.*<sup>13</sup> were not encountered and most patients tolerated the procedure well. Obviously, the induction procedure requires the implementation of safeguards as previously described to prevent in-hospital spread of TB.<sup>14</sup>

The shortcomings of our study should not be overlooked. To assess the impact of the obtained sputum results on clinical decision making a control cohort would have been desirable. Also, sputum culture of negative samples was only obtained in 6 out of 21 cases, 1 of which turned out to be positive at 8 weeks. The other 2 patients who were wrongly diagnosed as not having TB re-presented with extra-pulmonary manifestations for which sputum examination is not the adequate diagnostic procedure. Still, these figures may represent an underestimate as we introduced some bias by only recording when a patient returned with TB. Active follow-up would have also detected those who relapsed but failed to return.

HIV test results were recorded, where available, only for patients who were diagnosed with TB as these were part of the TB cohort in that year. HIV prevalence was 85% which is higher than the average 69% recorded for the TB cohort, which included all pulmonary and extra-pulmonary notifications. Again, our numbers were too small to be conclusive, but patients with no sputum or a negative smear seem to be more likely to carry HIV.<sup>12</sup>

## CONCLUSION

This study showed the usefulness of the SI method for patients with suspected TB who were labelled as sputum smear-negative using conventional diagnostic methods. Just under one-third (29%) of all patients included had a positive induced sputum smear and 55% of patients who were diagnosed with PTB could be labelled as sputum smear-positive. Affordability and availability of this safe and simple procedure makes it an attractive diagnostic facility for the developing world where

the HIV-associated TB burden is high. Wider use should be considered in selected cases in the context of an otherwise well-functioning TB control programme.

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