

# Tuberculosis in Malta: a case for sputum induction

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## Abstract

Sputum induction is a procedure used to help patients expectorate samples of sputum for laboratory analysis. It is a simple, safe and standardised procedure which may avoid the use of more invasive and potentially harmful interventions such as fiberoptic bronchoscopy. This article gives an overview of the uses in particular categories of patients, arguments for and against the procedure, and some local data.

## Keywords

Malta, tuberculosis, sputum induction

## Introduction

Sputum induction (SI) is a standardised diagnostic procedure used to provoke patients to expectorate a sample of sputum from the lower respiratory tract by means of an inhaled, nebulised, sterile, and isotonic or hypertonic saline solution. SI can be safely used in both adults and children to investigate a number of conditions including asthma, chronic obstructive pulmonary disease, cystic fibrosis, lung cancer, non-asthmatic eosinophilic bronchitis, pneumonia, sarcoidosis, and tuberculosis (TB).<sup>1,2,3</sup>

Detailed protocols on organising and conducting sputum induction safely are freely available.<sup>4,5,6</sup> Table 1 is one adaptation. The procedure may be used for patients who have no sputum to expectorate, or else are unable to cough up any sputum which may be present.<sup>6,7</sup> Sputum induction has been increasingly used for the diagnosis of TB because it produces better yields than samples collected by gastric lavage, and was better tolerated by patients.<sup>8</sup> Since the widespread introduction of fiberoptic bronchoscopy (FOB), SI was being used less often.<sup>8</sup> A modest revival has occurred because of increased awareness regarding nosocomial infection occurring during FOB, increasing drug-resistant TB, lower capital and higher running costs, patient safety, procurement of good quality sputum samples and low technological input required. SI should be promoted more and used as a safe, standardised and effective procedure in our hospitals.<sup>3,9,10,11</sup>

The most common side-effects include slight nausea, vomiting and a salty taste. The only potential adverse effect is bronchospasm in patients with asthma or COPD. Some desaturation occurs in most persons, even in healthy subjects. Patients found to be hypoxemic prior to SI require PaO<sub>2</sub> monitoring during the procedure.<sup>12</sup> This complication can be greatly reduced by routinely using an inhaled bronchodilator prior to induction, and using a normal instead of an hypertonic saline solution, although the success rate is less.<sup>10,13,14</sup> A break in the SI protocol can lead to sample cross contamination.<sup>15</sup>

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Specimens should be collected in a sputum induction booth or in an Airborne Infection Isolation room (AII room). An AII room was formerly called a negative pressure isolation room. This is a single-occupancy patient-care room used to isolate persons with suspected or confirmed infectious TB disease. Environmental factors are controlled in AII rooms to minimize the transmission of infectious agents that are spread by micro-droplet nuclei associated with coughing, sneezing or aerosolization of contaminated fluids. An AII room should have all three of these characteristics: 1) negative pressure, so air flows under the door gap into the room; 2) an air flow rate of 6 to 12 air changes per hour, and 3) direct exhaust of air from the room to the outside of the building air at least 8 meters from any inlet or recirculation of air through a high efficiency particulate filter.<sup>16</sup> The samples obtained by SI are then processed routinely for AFB smear and culture, species identification and drug sensitivities.

Sputum induction is not used in Malta in the recommended and standardised form as described in this article. An internet search which included the words *sputum induction* and *Malta* did not reveal any relevant results. No local data on the procedure has been found and the only reference to SI in the local literature is found in the National TB strategy document produced in 2012, where it was stated that its use should be considered to provide samples for investigation.

### Sputum induction in children

Each year, about 1 million children develop TB (11% of the global total); most (80%) occur in the 22 high-burden countries. The reported proportion of cases occurring in children in countries worldwide varies from 3 to more than 25%.<sup>17</sup>

Children, especially those less than 5 years, are more susceptible to TB; they are more easily infected, latent period is briefer, active disease is more likely to develop, dissemination more common, and there is both higher morbidity and mortality.<sup>18</sup> In addition, because of the lack of sputum production and because specimens frequently have low concentrations of mycobacteria, there are fewer positive bacteriological tests.<sup>19</sup> Thus while obtaining sputum samples in children is important it remains more problematic. Hence, the diagnosis of pulmonary TB in children is made mainly on the basis of a combination of non-specific signs and symptoms (often absent), tuberculin testing, chest radiography and a history of close contact with an adult case of infectious TB. Thus in children, the diagnosis is usually circumstantial, epidemiological, and difficult.<sup>20</sup>

A number of procedures are used to collect samples, including gastric aspiration (GA), laryngeal swab (LS), nasopharyngeal aspiration (NPA) and sputum induction, to help in diagnosis.

Gastric aspiration is considered as the method of choice

(especially in neonates); positive AFB smears

occur in approximately 15 %, and positive cultures in 50 % to 70 % of children. These results are similar when GA is performed both as an in- and out-patient procedure.<sup>21,22</sup>

Laryngeal swabs are simple and easy to perform even as an out-patients procedure. It was shown to yield 80 % positive cultures in pulmonary TB.<sup>23</sup>

Nasopharyngeal aspiration is simple, requiring much less expense and produces similar results to sputum induction in children.<sup>24</sup>

Sputum induction is useful and safe for investigating children, irrespective of HIV status.<sup>25</sup> SI effective in children of all ages (except neonates) but the procedure poses a number of safety issues for staff, due to the production of a possible infective aerosol. The provision of a separate room adequately isolated with negative ventilation, disposable equipment is essential, training of personnel is also required. The National Institute for Health and Clinical Excellence (NICE) guidelines recommend that in children unable to expectorate, induction of sputum should be considered, if it can be done safely, with gastric washings considered as the third option.<sup>17,26</sup> Studies have reported safe and successful sputum induction in children as young as 6 years, with a positive AFB smear in 10 to 14 % and positive AFB culture in 20 to 30 % of children.<sup>27,14</sup> One study showed that in children less than 5 years of age, a SI sample was equivalent to 3 gastric aspirate samples.<sup>14</sup> SI was also found to be a useful adjunct to the diagnosis of other respiratory pathogens in immunocompromised children.<sup>28</sup> A description of procedures for sputum induction in children is available.<sup>17</sup>

### Asylum seekers, tuberculosis and Malta

Increasing numbers of new entrants in recent years have resulted in a corresponding increase in those diagnosed with tuberculosis. The total number of all cases for the ten year period (2002–2011) was 304; 191 cases occurred in boat-arrivals, 32 in those foreign-born residing in Malta, while 81 occurred in the local-born population. Pulmonary TB made up 70% (212) of all cases. Both foreign TB case rate and incidence have now exceeded values found in the local population. Drug resistance was also more common where none existed before: 9.7% of all culture positive cases in boat refugees excluding streptomycin. A number of patients (10%), who were adequately or otherwise treated for TB abroad in the past, had relapsed, a proportion suffered from concomitant AIDS.<sup>29</sup> Thus for a National TB Programme, enhanced sputum collection for smear microscopy, mycobacterial culture, drug sensitivities and DNA-fingerprinting is a priority. In addition, World Health

Organization, European and National guidelines recommend the collection of sputum, and other samples, in every case of suspected TB prior to treatment.

In Malta, both active and passive case finding are practiced among boat arrivals because this group is considered to be one at high risk for developing TB. Active case finding is performed within one week of detention and again on release, usually a few months later, using radiological, followed if required, by clinical screening. Passive case finding is performed when persons with suspicious symptoms refer themselves to a doctor.<sup>29</sup>

Detention centres are usually resource-limited areas without adequate ventilated and isolation rooms, collection of sputum is thus safer and simpler when performed outdoors, of necessity in the shade as mycobacteria are quickly killed by ultra-violet rays of direct sunlight. While the services of a physiotherapist are not required,<sup>30</sup> a health-care professional should instruct, supervise and observe the collection of induced sputum, under the supervision of a physician.<sup>31</sup> As all new detainees immediately undergo a chest x-ray examination on entry, including those not symptomatic, a good number are diagnosed within a couple of days or if radiological uncertainty remains, six weeks later during repeat x-ray examination and review. Thus in many instances tuberculosis may still be in the initial stages and spontaneously expectorated sputum is often not available, the next simple alternative for sample collection should be sputum induction.

## Discussion

Sputum induction has been widely used abroad since the early 1990's, when the first attempts to standardise the method of induction, laboratory processing and analysis were made. SI out-performs both spontaneous and supervised sputum collection.<sup>32</sup> It is a very safe and simple procedure, well tolerated and preferred by patients, even children, and much less costly than FOB.<sup>3,10</sup> In addition, SI significantly improved the ease of expectoration on a 5-point scale.<sup>12</sup> Unfortunately it may appear less attractive and not as prestigious for physicians. Many find it difficult to believe that a simple and less invasive procedure can produce comparable and even better results than FOB, especially when SI is repeated serially.<sup>11,31</sup> Brown et al recruited adult inpatients with both chest radiograph findings suggestive of TB, and an inability to expectorate. Subjects provided gastric washing specimens and induced sputum specimens. Investigation of three induced sputum specimens detected more cases than did the use of three gastric washings in the same subjects. There was no difference in yield between serial samples obtained by SI performed in a single day or that performed over a 3-day period. No additional cases were diagnosed in the 21 patients who underwent bronchoscopy.<sup>34</sup>

While many physicians prefer fibre-optic

bronchoscopy as their first choice, performing bronchoscopy on a patient who probably has infectious TB, with the possibility of multi-drug resistant (MDR), extensively drug resistant (XDR), or even Totally Drug Resistant TB, can be both dangerous and life-threatening for the operators and nurses if nosocomial infection occurs. These infections are very expensive and difficult to treat and carry a high morbidity and mortality. In addition, regimes for the treatment of latent infection for these resistant infections are still under investigation and as yet none are recommended.<sup>35</sup>

SI has been shown to provide clinicians with adequate sputum samples for AFB smears, cultures, species identification and drug sensitivities, this is essential to monitor drug resistance and the choice of drugs prescribed to treat TB. Drug resistance (together with TB incidence, regime completion and cure rates) give a good indication of the efficacy of a National TB Programme.<sup>12</sup> One of the basic requisites of a successful National TB programme is the acquisition of samples for AFB smear and culture prior to start of treatment. It is important to secure cultures for drug sensitivities, because once treatment is initiated, any mycobacteria present quickly lose viability, in fact, by day two of treatment, nearly 90% of bacteria would have been killed and by 14-21 days this value approaches 99%.<sup>36</sup>

The diagnosis of TB is sometimes quite straight forward, but more often it is not, especially in low-incidence countries akin to Malta. Diagnosis can be difficult when radiological evidence of past unsuspected TB is present; re-activation of TB in a lung, which has suffered the past ravages of this infection, can very easily be masked and overlooked. The scars of concomitant chronic lung disease may also be present and to compound matters further, any new infiltrate may be due to a coincidental or alternative infection. Thus the diagnosis can often be delayed or even missed, thereby increasing the risk of transmission.

About 75% of all TB patients have pulmonary disease, thus the initial and easiest method of obtaining samples would be for the patient to spontaneously expectorate. Initially cough is dry but if productive any sputum present may not be expectorated due to patient-related difficulties. Obtaining sputum samples can be difficult or impossible in the early stages of pulmonary infection, patients discovered through active screening, females, children, the elderly, and in those living with HIV/AIDS.<sup>37</sup> If spontaneous expectoration is not possible, SI or FOB should be considered. Many now strongly favour SI over bronchoscopy for initial investigation of pulmonary TB, as the diagnostic yield of sputum induction has

been consistently shown to be equivalent or better than FOB in the diagnosis of smear-negative pulmonary TB.<sup>1,10,33</sup> SI is well tolerated, convenient, low-cost, and also much safer for both patient and medical staff, provided safety precautions are closely adhered to. SI is also very effective in enabling patients (97%) to expectorate sputum for analysis.<sup>33</sup> SI can easily be repeated serially even on the same day, and yield is even better.<sup>38</sup> Cross-contamination can occur both during both SI and FOB, when safety, administrative, and laboratory protocols are not adhered to.

TB disease is divided into two main forms according to site; pulmonary and extra-pulmonary TB. Pulmonary TB is considered as infectious, further differentiation is made on the basis of smear status for acid fast bacilli; either positive or negative. Smear positive pulmonary TB is about 5 to 6 times more infectious than the smear negative form. Extra-pulmonary not considered as infectious. Regarding the diagnosis of pleural TB, which is considered as an extra-pulmonary site, this can be misleading because previously it was widely assumed that pleural TB was not infectious, because lung parenchyma was not usually seen to be involved.<sup>13</sup> However, contrary to this belief, a sample of sputum obtained by SI can often reveal mycobacteria.<sup>13</sup> Conde and colleagues have shown that SI can yield AFB smear-positive results in 11% and in those with normal lung parenchyma (apart from the effusion), and a high yield of positive cultures in 52 % of patients.<sup>13</sup> In addition, computed tomography can show parenchymal involvement obscured by an effusion when none is apparent on standard chest x-ray. Pleural biopsy may further provide histological and bacteriologic confirmation in 60–80% of patients.<sup>13</sup>

Among persons living with HIV/AIDS, tuberculosis often creates further diagnostic difficulties and delay due to atypical presentations and manifestations. These features depend upon the patient's immune status, and the decline in CD4 cell count. When these counts are near normal, presentation is usually pulmonary, including cavitation. As the CD4 count falls, extra-pulmonary disease occurs more often, and with the lowest CD4 counts disseminated, miliary, and meningeal disease increasingly occur. Loss of Type IV cellular immunity, results in non-cavitary disease with a decrease in sputum volume, and a decrease in AFB smear positivity. Tuberculosis in those living with HIV may frequently show chest x-ray changes that are atypical, or none at all (25%). Sputum may also be smear-positive for *M.tb* even in the total absence of symptoms. Thus in those suspected of HIV, high-risk aerosol-generating procedures, should be carried out in an appropriately engineered and ventilated area. Such procedures may include bronchoscopy, sputum induction, nebulized treatment, autopsy and processing in the mycobacteriology lab. As regards the wards, patients on

an HIV ward, regardless of whether a diagnosis of TB has been considered or not, and patients in whom TB is considered a possible diagnosis, should all use the AII room during high risk procedures.<sup>26</sup>

In HIV, *Pneumocystis carinii* pneumonia (PCP), can be diagnosed from a sample obtained using SI which has a sensitivity of 94.7% and a negative predictive value of 96%, compared with bronchoalveolar lavage. Spontaneously expectorated sputum has very low sensitivity and should not be submitted for diagnosis.<sup>39</sup> SI can provide the physician with much better samples for investigation hence improving diagnostic yield with the advantage of avoiding invasive bronchoscopy. Sputum induction is the quickest and least-invasive method for definitively diagnosing PCP.<sup>39</sup> While oxygen desaturation can occur it is not predictable from baseline oxygen levels or a chest x-ray. Therefore oxygen saturation should be continuously monitored during the procedure. Although SI causes significant falls in oxygen saturation and FEV<sub>1</sub>, it provides a safe and sensitive alternative to bronchoscopy for diagnosing PCP.<sup>40</sup> The diagnosis of PCP or tuberculosis in persons living with HIV/AIDS using bronchoscopy carries an avoidable morbidity and mortality risk.

### Key points

- Sputum induction is not practised as a routine and standard investigation in local hospitals. Increasing numbers of new entrants, has resulted in a dramatic increase in tuberculosis. Drug resistance is higher in this population.
- A properly functioning National TB Programme mandates that appropriate samples for investigation are obtained in all cases prior to starting anti-TB treatment.
- Patient and staff safety remain of primary importance.
- Sputum induction is better than both spontaneous and supervised sputum production, and is just as effective as that obtained by fiberoptic bronchoscopy.

### Recommendations

1. Reconsider use of fibreoptic bronchoscopy in favour of sputum induction to obtain samples solely for AFB smear and culture.
2. Introduction of a sputum induction service using standardised safety protocols to improve sputum collection prior to starting anti-tuberculous drug treatment.

Recommendations	Rationale	Notes
Detailed information and detailed instructions given to patient beforehand	High degree of cooperation from patient	Improving results and safer
Bronchodilator pretreatment	Use a short acting beta2-agonist as the standard procedure in order to prevent excessive bronchoconstriction	A single dose of nebulized salbutamol 200 mg is recommended, with measurement of FEV <sub>1</sub> before and after 10 min.
Quiet environment	Separate from other routine activities	Improving results
Conducted by an experienced technician	Under supervision of an experienced physician.	Severe bronchospasm may occur
Full resuscitation equipment and trained personnel	Severe bronchoconstriction can occur.	1. As recommended for bronchial challenge procedures 2. Death in asthmatic subject with a distilled water challenge test has been reported
Rescue bronchodilator medication	To be immediately available	Together with any other emergency drugs
Spirometry	1. For baseline and to avoid excess bronchoconstriction 2. More sensitive than peak flow meters to readings of FEV <sub>1</sub>	1. Spirometry is more sensitive 2. First reading within 1 <sup>st</sup> min of nebulisation to detect those hypersensitive. 3. FEV <sub>1</sub> should be monitored at end of each induction, stop SI if FEV <sub>1</sub> falls by $\geq 20\%$
Use ultrasonic nebulisers	Ultrasonic nebuliser with a sufficient and measured output; (output 1 mL per min)	Other nebulisers do not usually exhibit sufficient output of saline aerosol.
Pulse oximetry	Monitor oxygen saturation	Subject may desaturate
Supplemental oxygen availability	May desaturation	Especially COPD subjects
Infection control procedures in place	For the protection of personnel and patients	Must be carried out according to local anti-infection policy.
Start with 0.9% saline solution	Use least concentration to avoid severe	Reaction with 0.9% perform SI at ½, 1, 5 min..if fails use 3% saline, SI at ½, 1, 5 min..if fails use 4.5% SI at ½, 1, 2, 4, 8 min.
Sterile hypertonic saline solution are reportedly more effective than normal saline	1. should be prepared freshly. 2. a severe asthma exacerbation can occur 3. normal saline should be considered in patients at greater risk of bronchospasm	Causes bronchoconstriction in asthmatic subjects
Subjects asked to stop inhalation at regular intervals	In order to cough up sputum (e.g. every 5 min), or to stop only when they feel the urge to cough. should cough spontaneously if not ask pt. to cough after 4 and 8 minutes.	Should spit out any saliva in a separate container beforehand.
Duration of 15–20 min	Appear to have similar success rates to longer inhalation times (30 min)	
An interval of 2 days between inductions	Reduce carry over effect	Act safely
For a particular study standard protocol must be followed closely in all patients	For standardization purposes, as measured parameters may vary	Proper standardisation
On completion of SI, patients should be given an inhaled short-acting b2-agonist,	Particularly if there has been a fall in FEV <sub>1</sub> of >10% from baseline value.	Patients should remain until their FEV <sub>1</sub> or PEF <sub>R</sub> has returned to within 5% of baseline.

**Table 1:** Summary of recommendations for performing safe sputum induction.\*

\* Adapted from 1. Sputum Induction *Eur Respir J* 2002; Suppl. 37, 3s-8s. REPORT OF WORKING GROUP 1.  
2. Safety of Sputum Induction. *Eur Respir J* 2002; 20: Suppl. 37, 9s-18s. REPORT OF WORKING GROUP 2.

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