

INDUCED SPUTUM IN HIV- INFECTED PATIENTS: DIAGNOSIS OF ACUTE PULMONARY DISEASES

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SUMMARY

OBJECTIVE. To make a narrative review of the accuracy of induced sputum for diagnosis of pulmonary disease in HIV-infected patients. Data sources: The MEDLINE, LILACS, EMBASE and the Cochrane Library were searched. reference lists, abstracts of conference proceedings and scientific meetings were hand searched.

METHODS. Study selection: Fifteen articles that specifically addressed the stated purpose were selected. Data extraction: Yield of sputum induction and fiberoptic bronchoscopy with bronchoalveolar lavage were analyzed using explicit methodologic to evaluate the quality of clinical trials.

RESULTS. Sputum induction demonstrated 55.5% sensitivity and 98.6% specificity to *Pneumocystis pneumonia*. Sensitivity of sputum induction was significantly higher with immunofluorescence than with cytochemical staining (67.1 versus 43.1%). Sputum induction for diagnosis of bacterial pneumonia demonstrated 60% sensitivity, 40% specificity, 80% positive predictive value, 20% negative predictive value and 56% accuracy. In relation to tuberculosis, sputum induction demonstrated 36% sensitivity, 100% specificity, 100% positive predictive value and 54.2% negative predictive value.

CONCLUSION. Sputum induction seems to be effective and safe for diagnosis of pulmonary diseases in HIV-infected patients.

KEY WORDS: Induced Sputum. Bronchoscopy. Bronchoalveolar Lavage. HIV. Review Literature.

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BACKGROUND

The spectrum of pulmonary manifestations in patients infected with human immunodeficiency virus (HIV) is broad, including many infectious and noninfectious complications. In the evaluation of an HIV-infected patient with diffuse pulmonary disease, a definitive diagnosis is preferred over empiric therapy in most patients. Patients, usually receive empiric treatment for community-acquired pneumonia or pneumocystosis, with nonresponders undergoing additional diagnostic testing ¹.

Pneumonia is the leading HIV-associated infection. It is estimated that 65% of the patients infected with HIV will present pulmonary involvement as their first clinical manifestation of the syndrome and that approximately 80% of these patients will present some kind of pulmonary involvement in the course of the disease ².

The spectrum of microorganisms includes bacteria, mainly *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* and *Mycobacterium tuberculosis*. In addition, fungi such as *Pneumocystis jiroveci*, *Cryptococcus*

neoformans and *Histoplasma capsulatum* are common HIV-associated pathogens. Diagnostic work-up relies on the epidemiology and immune status (CD4-lymphocytes count). Imaging techniques are always required, and the microbiological analysis of expectorations should be performed ³.

Induced sputum in HIV- infected patients

In 1958, a simple, harmless and efficient method for artificial induction of sputum was described. It was first considered as a potentially useful method for early detection of lung cancer ⁴.

This technique was logically extended to patients with pneumonia who had a nonproductive cough. In 1964, a study reported an experience applying this method to 15 patients with pneumonia who were unable to produce sputum voluntarily. In 13 (87%) of these cases, a bacteriologic diagnosis was reported ⁵.

In the mid-1980's the examination of induced sputum by inhalation of hypertonic saline solution was frequently used to diagnose pneumocystosis (PCP) in patients with acquired immunodeficiency syndrome ⁶.

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Since then, this technique has emerged as a simple and noninvasive procedure, although a rather wide variation in diagnostic accuracy has been reported.

While induced sputum may be less invasive and less expensive to perform than bronchoscopy, cost is not trivial, and has been reported to be approximately 40% the cost of bronchoscopy⁷.

Although sputum induction appears to be a safe and relatively simple method, it is important that the staff involved at all stages of this test be properly trained⁸.

Induced sputum in HIV- infected patients

Purpose

To make a narrative review, for clinicians and pneumologists, about the accuracy of sputum induction for diagnosis of pulmonary disease in HIV-infected patients.

Data sources

We searched the MEDLINE, LILACS, EMBASE.com and Cochrane Central Register of Controlled Trials (CENTRAL/CCTR), the Cochrane HIV/AIDS Group (1997 to January 2007). We also hand searched ,without language restrictions, reference lists, abstracts of conference proceedings and scientific meetings (1997 to January 2007) and bibliographic review of textbooks and review articles. Our search strategy was: MEDLINE, "AIDS-Related Opportunistic Infections"[MeSH] AND "Sputum"[MeSH] Limits: All Adult:< 19 years, published in the last 10 years, Humans; LILACS, (aids) or "infecoes oportunistas relacionadas com a AIDS" [Descritor de assunto] and (escarro induzido) or "ESCARRO" [Descritor de assunto] and not (criança) or "crianca" [Descritor de assunto]; EMBASE.com: aids/exp AND sputum/exp AND [humans]/lim AND ([adolescent]/lim OR [adult]/lim OR [aged]/lim) AND [1997-2007]; Cochrane Library: "sputum".

Induced sputum in HIV- infected patients

Study selection

Several articles were independently selected and reviewed by two reviewers. Disagreement was resolved by consensus with a third party. Only studies that evaluated the yield of induced sputum in diagnosis of pulmonary disease in HIV-infected patients were included.

Data extraction

Fifteen articles that specifically addressed the stated purpose were selected: two retrospective studies comparing induced and expectorated sputum^{7,20}, ten prospective studies investigating the diagnostic accuracy of sputum induction in comparison with fiberoptic bronchoscopy with BAL^{8-12,14-16,18-21}; one economic study type cost-effectiveness analysis (PCP)¹⁹; one meta-analysis of diagnostic procedures for PCP in HIV-1 infected patients¹⁷; and one evaluation of the quality of sputum from AIDS patients with pulmonary manifestations¹³.

Results of data synthesis [Table 1]

Five studies were about PCP^{7, 16- 19} three were about tuberculosis^{9, 15, 21}, four were about lung diseases^{8, 10, 11, 12}, two about bacterial community-acquired pneumonia^{14, 20}, and one was about the evaluation of the quality of sputum¹³.

Induced sputum in HIV- infected patients

Sputum induction has proven useful in the diagnosis of *Pneumocystis jiroveci* pneumonia and mycobacterial infections,

but data are scant on its use for diagnosis of community-acquired pneumonia (CAP). There was no significant difference in the sensitivity of induced and expectorated sputum for diagnosis of PCP when the direct fluorescent antibody method of staining was used⁷. When BAL was the gold standard, sputum induction in PCP demonstrated 55.5% sensitivity and 98.6% specificity. Sensitivity of sputum induction was significantly higher with immunofluorescence than with cytochemical staining (67.1 versus 43.1%). In settings of 25-60% prevalence of PCP, positive and negative predictive values ranged 86-96.7 and 66.2-89.8, respectively, with immunofluorescence, and 79-94.4 and 53-83.5% with cytochemical staining¹⁶.

In sputum induction for diagnosis of bacterial pneumonia, sensitivity was 60% and specificity 40%; the positive predictive value (PPV) was 80%, negative predictive value (NPV) 20% and accuracy 56%. In addition, sputum induction with quantitative culture can be helpful for diagnosis of bacterial pneumonia in HIV-positive patients¹⁴.

Among tuberculosis HIV-seropositive patients, agreement between acid-fast bacilli (AFB) smear and culture results for sputum induction and BAL specimens were 98% and 86%, respectively. The PPV of an AFB smear for diagnosis of pulmonary tuberculosis (PTB) was 100% and NPV 54.2% among seropositive patients undergoing sputum induction or BAL⁹. In a setting with a high prevalence of *Mycobacterium avium* complex in respiratory specimens, the predictive value of the acid-fast bacilli smear for *Mycobacterium tuberculosis* was 92% for expectorated sputum specimens, 71% for sputum induction specimens, and 71% for BAL specimens²¹.

Induced sputum in HIV- infected patients

These findings reflect the different prevalence of isolation of mycobacteria other than those of tuberculosis in respiratory specimens.

Sputum induction by hypertonic saline inhalation does not improve specimen quality as indicated by the PMNs (polymorphonuclear neutrophils) / SECs (squamous epithelial cells) ratio on Gram stain²².

DISCUSSION

We found that sputum induction is a sensitivity and specificity test to detect pulmonary disease in HIV-infected adult patients. There are several benefits of sputum induction when compared to BAL. This technique is less expensive and invasive than bronchoscopy with BAL, saves time, and is painless. Attempting induction early, preferably before starting antibiotics, may increase its diagnostic yield. Bronchoscopy is an invasive procedure and is not easily applicable on a large scale.

Induced sputum in HIV- infected patients

In PCP, sputum induction has a significant higher sensitivity with immunofluorescence staining when compared to cytochemical staining of sputum specimens¹⁶. Moreover, the decreased prevalence of PCP related to widespread use of antibiotic prophylaxis, and availability of highly active antiretroviral therapy (HAART) provide further grounds for re-evaluation of *Pneumocystis jiroveci* diagnosis¹⁶.

Pulmonary tuberculosis (TB) remains one of the most important health problems in the world. Nearly 2 billion people - about one third of the world's population - are infected with tuberculosis

Table 1. List for the reporting of studies of diagnostic accuracy

Author/Date/ Design	Participants	Test results	Comments
Metersky 1998 Retrospective review	<i>Pneumocystis jiroveci</i> pneumonia (n = 45)	Diagnostic yield of first sample was 10/18 (56%) for induced sputum, and 14/27 (52%) for expectorated sputum ($p > 0.05$)	No difference in the sensitivity of induced and expectorated sputum
Ortona 1997 Retrospective	HIV-infected patients respiratory illness (n = 125)	PCR-SHELA technique had a 100% sensitivity and 98% specificity in 59 bronchoalveolar lavage and 66 induced sputum samples (<i>Pneumocystis jiroveci</i>)	A new PCR-solution hybridization enzyme-linked assay (PCR-SHELA) was assessed
da Silva 2006 Cross sectional study	HIV-positive patients pulmonary disease (n = 25)	Considering induced sputum for the diagnosis of bacterial pneumonia, sensitivity was 60%, specificity 40%, the positive predictive value was 80%, negative predictive value 20% and accuracy 56%	Bronchoalveolar lavage and transbronchial lung biopsy were considered the gold standards
Conde 2000 Prospective	Suspected pulmonary tuberculosis (n = 207 HIV negative and n = 44 HIV positive)	Acid-fast bacilli (AFB) smear and mycobacterial culture results - induced (IS) and bronchoalveolar lavage (BAL) - were in agreement in 97% (202/207) and 90% (186/207). The agreements between AFB smear and culture results for SI and BAL were 98% (43 of 44) and 86% (38 of 44)	There were no significant differences in yields of AFB smears or cultures whether obtained by IS or BAL
Yajko 1994 Retrospective	Smears and results of cultures (3-year period at a hospital)	The predictive value of the acid-fast bacilli smear for <i>Mycobacterium tuberculosis</i> was 71% for induced sputum specimens	Setting with a high prevalence of <i>Mycobacterium avium</i> complex
Chuard 2001 Laboratory-blinded, randomized study	Patients with respiratory tract infection productive cough	Patients were in the induced (n = 58) and spontaneous (n = 62) sputum groups. Quality was assessed by evaluating the ratio between polymorphonuclear neutrophils and squamous epithelial cells on Gram-stained specimens	Sputum induction by hypertonic saline inhalation does not improve specimen quality

bacteria^{23,24}. Each year, Nearly 9 million people develop active tuberculosis, the infectious form of the disease, every year, and 2 million people experience TB-related deaths each year²⁵.

In Brazil, with an estimated annual prevalence of 129,000 new cases of TB, approximately 22% of adult patients with suspected pulmonary tuberculosis do not produce sputum spontaneously⁹. Sputum induction is a safe procedure with high diagnostic yield and good agreement with results from fiberoptic bronchoscopy⁹. Thus, sputum induction is a valuable tool for diagnosing pulmonary tuberculosis.

Use of HAART in a region with a high incidence of TB may reduce the risk of this disease among HIV-infected patients. The use of HAART was associated with an 81% reduction in risk of TB²⁶. Free access to HAART may contribute to reduce the incidence

of TB in populations with a low socioeconomic level and high prevalence of coinfection with HIV and *M. tuberculosis*²⁶.

Induced sputum in HIV- infected patients

Although a reduction in the risk of tuberculosis was not initially apparent, recent reports from large observational studies performed in Europe, have suggested that antiretroviral therapy has a protective effect²⁷. If the prevalence of TB with HAART is reduced, we do not know whether sputum induction would have the same diagnostic accuracy.

Patients who underwent sputum induction experienced side effects in a way similar to patients who had bronchoscopy with BAL⁹. It is recommended that sputum be processed as soon as possible or within two hours, in order to ensure optimum cell

counting and staining²³. If the specimen of sputum induction is negative, then bronchoscopy with BAL should be performed. Transbronchoscopic surgical lung biopsy is seldom needed.

CONCLUSION

Sputum induction is effective to obtain sputum in HIV-infected patients who fail to expectorate. For these patients sputum induction may be a technique that is safe and easily performed, with a good diagnostic yield.

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Conflict of interest: none

RESUMO

ESCARRO INDUZIDO NOS PACIENTES INFECTADOS PELO HIV: DIAGNÓSTICO DAS DOENÇAS PULMONARES AGUDAS

OBJETIVO. Realizar uma revisão narrativa sobre a acurácia do escarro induzido no diagnóstico da doença pulmonar nos pacientes infectados pelo HIV. Fontes de dados: pesquisamos na MEDLINE, LILACS, EMBASE e Cochrane Library. Foi realizada busca manual nas listas de referências e em resumos de anais e conferências em congressos.

MÉTODOS. Seleção dos estudos: foram selecionados 15 artigos que se relacionavam ao objetivo proposto. Extração dos dados: analisamos o rendimento do escarro induzido e da broncofibroscopia com lavado broncoalveolar, empregando critérios metodológicos na avaliação da qualidade dos ensaios clínicos.

RESULTADOS. O escarro induzido mostrou uma sensibilidade de 55,5% e especificidade de 98,6% no diagnóstico da pneumocistose; a sensibilidade do escarro induzido foi significativamente maior com a imunofluorescência do que com a coloração citoquímica (67,1 vs. 43,1%). O escarro induzido para o diagnóstico de pneumonia bacteriana mostrou uma sensibilidade de 60%, um valor preditivo positivo de 80%, um valor preditivo negativo de 20% e uma acurácia de 56%. Com relação à tuberculose, o escarro induzido mostrou uma sensibilidade de 36%, uma especificidade de 100%, um valor preditivo positivo de 100% e um valor preditivo negativo de 54,2%.

CONCLUSÃO. O escarro induzido parece ser efetivo e seguro no diagnóstico das pneumopatias nos pacientes infectados pelo HIV. [Rev Assoc Med Bras 2009; 55(5): 617-20]

UNITERMOS: Escarro induzido. Broncoscopia. Lavado broncoalveolar. HIV. Literatura de revisão.

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