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CORRESPONDENCE

Development of multidrug resistance during treatment of isoniazid-resistant tuberculosis

To the Editors:

Several treatment regimens have been recommended for the treatment of isoniazid-resistant tuberculosis (TB). However, an optimal regimen and duration for this treatment remains a matter of some controversy. Here, we would like to share our experience in a case of pulmonary TB with acquired multidrug resistance, during a 12-month treatment of isoniazid-resistant TB with rifampin and ethambutol, with pyrazinamide administered during the initial 2 months.

A 55-yr-old male visited the outpatient chest clinic for the evaluation of a chronic cough. The patient had diabetes mellitus, which had been controlled with oral hypoglycaemic agents. The patient had no history of TB. His chest radiography revealed cavitary consolidation in the left upper lobe. Several sputum samples revealed a host of acid-fast bacilli. Daily anti-TB therapy was initiated with isoniazid, rifampin, ethambutol and pyrazinamide. After 2 months of this treatment, the regimen was changed to isoniazid, rifampin and ethambutol, at which time cultured isolates of *Mycobacterium tuberculosis* were processed for drug susceptibility testing. After 3 months of therapy, the results of drug susceptibility tests indicated high-grade resistance to isoniazid. Isoniazid was discontinued and rifampin and ethambutol were continuously administered on a daily basis. Monthly monitored sputum cultures for acid-fast bacilli converted to negative after 2 months of treatment. The total treatment duration was initially scheduled for a full 12 months. After 10 months of therapy, however, an additional sputum culture revealed the growth of 20 colonies of *M. tuberculosis*. A drug-susceptibility test revealed the development of resistance to both isoniazid and rifampin, as well as susceptibility to other drugs. After this, a sputum smear for acid-fast bacilli was, once again, positive.

Previous studies have suggested that standard 6-month, four-drug regimens may be effective in the treatment of isoniazid-resistant TB [1]. In recent years, however, many published guidelines for the treatment of TB have stated that it would be more prudent either to administer pyrazinamide continuously throughout the 6 months, or to prolong the duration of treatment [2–4].

If drug-susceptibility test results are available before the end of the 2 month initial phase of treatment, isoniazid should be discontinued and pyrazinamide should be continued for the entire 6-month duration of therapy (6REZ) [2, 3]. If isoniazid resistance is documented during the 9-month regimen without pyrazinamide, or in the 6-month regimen during the continuation phase of treatment, treatment with rifampin and ethambutol should be continued for a minimum of 12 months (12RE or 2REZ/10RE) [2, 4].

The effectiveness of these recommended regimens has not, until now, been well evaluated. One retrospective study has revealed that a 6-month daily regimen involving the administration of isoniazid, rifampin, ethambutol and pyrazinamide (6HREZ) proved highly effective [5]. However, the effectiveness of the 12-month regimen of rifampin and ethambutol, with or without pyrazinamide during the initial 2 months, has not been evaluated until now.

In patients with isoniazid-resistant tuberculosis, who also have manifested extensive bilateral disease or cavitation on chest radiographs, the development of acquired rifampin resistance could be possible during treatment with rifampin and ethambutol. Our report underlines the seriousness of the concerns regarding the development of multidrug-resistant tuberculosis in patients infected with a *Mycobacterium tuberculosis* strain with primary isoniazid resistance during treatment with rifampin and ethambutol for 12 months, especially in the cases in which the patient exhibits cavitary pulmonary tuberculosis.

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Should we use spirometry in the early detection of COPD?

To the Editors:

ENRIGHT *et al*. [1] in the *European Respiratory Monograph*, promote office spirometry as the way forward in the routine assessment of asthma and chronic obstructive pulmonary disease (COPD), and in the early detection of COPD. They define office spirometry as 'spirometry performed in the primary care setting'. There is an unwelcome ambiguity in their paper when it comes to both of these subjects, and the evidence they use to support their arguments is far from decisive. In the case of the early detection of COPD, the evidence seems to oppose their position.

My first concern is about their use of the term office spirometry, which seems to imply spirometry carried out by the consulting clinician. They say that spirometry with electronic spirometers is now faster than it was with traditional bellows spirometers. This latter suggestion is untrue, even using the 6 s manoeuvre, since the spirometry manoeuvre is independent of the type of spirometer used, the learning curve for the patient is the same and the instruction given by the operator is also identical. They believe that the main problem with office spirometry is in the quality of the instruction and supervision of the test by the clinician. I agree and think that this must be one of the main objections to spirometry being conducted by clinicians during routine consultations. They quote a primary care Dutch study in which the quality of the spirometry was unacceptably variable [2]. Furthermore, they recommend certification for nurses and technologists carrying out spirometry in primary care. This hardly encourages the routine office use of spirometry by clinicians in their consultations.

The main argument put forward by ENRIGHT *et al*. [1] is for the use of spirometry in the early detection of COPD. They say that spirometry fulfils all the standard criteria for application of a medical test for screening. A fundamental criterion for any screening programme is the availability of a useful intervention for the patient who screens positive [3]. The main reason to detect COPD in its early stages is to intervene with smoking cessation. ENRIGHT *et al*. [1] quote three papers in support of the role of early diagnosis of COPD in smoking cessation. None of these actually support their assertion.

The first by RISSER *et al*. [4] is a trial of a complex intervention comparing education and a motivational intervention with education alone, in which spirometry was a just component of the motivational intervention. In the second paper SEGNAN *et al*. [5] actually conclude, ''In no treatment group was the outcome significantly different from that for one-time counselling at the ($p<0.05$) level.'' In the third paper, GORECKA *et al*. [6] demonstrated that the diagnosis of airflow limitation had no effect in improving smoking cessation overall, and only in a subanalysis could they show that it leads to an improvement in smoking cessation in those who have moderate or severe airflow limitation. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines acknowledge the uncertainty surrounding the benefits of community screening of COPD [7]. While there is no argument that smokers should be sought and helped to quit smoking, there is no evidence that early diagnosis of COPD improves smoking cessation.

The promotion of early diagnosis of COPD has been gathering momentum despite the lack of evidence to justify it. Many papers are appearing which report the efforts of clinicians to diagnose COPD early. In the Differential Diagnosis between Asthma and COPD study, BUFFELS *et al*. [8] report that spirometry-based screening for COPD in primary care doubles the rate of diagnosis of COPD.

The impact on patients and services of a policy to diagnose chronic obstructive pulmonary disease early, which doubles the number of cases in the system, is likely to be expensive and will dilute the resources available for the management of symptomatic chronic obstructive pulmonary disease. It should not even be considered until there is at least some evidence to support it.

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From the authors:

Pulmonary specialists welcome increased communication and collaborative work with general practitioners in an attempt to find the most effective evidence-based methods to decrease the substantial morbidity and mortality of asthma and chronic obstructive disorder (COPD). In this issue of the *European Respiratory Journal*, P. White has highlighted one of the gaps in the evidence base for recommending increased utilisation of spirometry by primary care practitioners. The evidence is indeed weak, in that adding spirometry testing to methods already demonstrated to improve smoking cessation rates (such as counselling, nicotine replacement therapy and bupropion) will further improve the success rates. The published studies were either inadequately designed or had inadequate statistical power to answer this important question. However, several medications to halt the progression of COPD will probably become available in the next few years [1], so we should prepare for them by working to make office spirometry more effective in the primary care setting.

I admit that there are few studies which decisively prove that the addition of spirometry, to the history and physical examination of patients with respiratory symptoms, improves the ability of general practitioners to substantially improve patient-centred outcomes [2]. However, 20 yrs ago, the same could have been said of blood pressure measurements, or blood glucose and haemoglobin-A1c measurements for obese and diabetic patients, respectively. I characterise the tone of our chapter in the *European Respiratory Monograph* [3] as suggesting ''cautious optimism.'' A major goal of our recommendations is to minimise spirometry misclassification rates, which leads to the many caveats in our recommendations.

When using forced expiratory volume in six seconds reference equations, the average spirometry test session (with a range of 3–8 manoeuvres) is indeed shorter, because the end-of-test criterion for an acceptable manoeuvre is much easier to meet (for children and patients with airway obstruction). Therefore, fewer manoeuvres are needed to meet the goal of three acceptable (including two repeatable) manoeuvres.

In our opinion, whoever coaches the patient to perform spirometry tests needs training and performance-based certification. In the UK, this person is usually the general practitioner (a physician), but in the USA, nurses or technologists often perform the testing. Sometimes a nurse practitioner, physician's assistant, or chronic disease manager uses the results to diagnose or manage the patient.

In Tucson, Arizona, USA, I have seen bumper stickers which say ''If I had known that I'd live this long, I would have taken better care of myself.'' You have probably seen hundreds of patients dying from end-stage COPD, first diagnosed when their forced expiratory volume in one second was <1 L [4]. How many of them have wondered, ''Since my lung disease was apparently slowly progressing for decades before I was finally diagnosed, why didn't anyone tell me about it many years ago? I would have tried much harder to quit smoking.'' I believe that our time and our limited smoking cessation resources should be preferentially targeted towards patients with the highest risks for smoking-related disease.

In conclusion, epidemiological studies have decisively demonstrated that airway obstruction is the second or third most important risk factor for morbidity and mortality in smoking adults.

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