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**Idiopathic Pulmonary Fibrosis in Transplantation**

To the Editor:

The recent observation by Nathan et al. in the May 2003 issue of CHEST of a high rate of pulmonary embolism in patients with idiopathic pulmonary fibrosis (IPF) after lung transplantation is intriguing. A recent report by Magro et al. of 19 patients with IPF with histologic evidence at open-lung biopsy of microvascular injury along with corresponding immunologic evidence of antiphospholipid antibodies and antiendothelial cell antibodies is of note in light of the findings of Nathan et al. In the series of Magro et al., 4 of the 19 patients had “1 or more episodes of venous thrombosis.” All 4 of these patients had a positive lupus anticoagulant; 18 of the 19 patients had evidence of antiphospholipid antibodies. Of interest would be whether any of the patients of Magro et al. were tested for antiphospholipid antibodies. Both of these series suggest the possibility that IPF is a thrombophilic state. As noted by Nathan et al., past studies have also suggested an abnormally high rate of pulmonary embolism in IPF, and the rates in these studies likely were underestimates given the difficulty of diagnosis of pulmonary embolism. Endothelial injury is hypothesized to occur as part of the pathogenesis of IPF. While the primary vascular bed injured in IPF may be the pulmonary bed, leading to local damage resulting in lung fibrosis, this does not exclude the possibility of more generalized endothelial injury occurring in this disease. If damage to the endothelium in, for example, the deep venous system were also to occur, mediated by the circulating factors discovered in the patients of Magro et al., this would help explain a predisposition to thrombosis in this disease. Endothelial injury and hypercoagulability, as denoted by the presence of antiphospholipid antibodies, would be present, constituting two of the essential components of Virchow’s triad of thrombosis.

More research into the question of thrombophilia in IPF is needed; particular areas to be addressed would be confirmation of a high prevalence of antiphospholipid antibodies in these patients and whether a subgroup of these patients at particular risk for venous thromboembolic events can be identified. Such studies would point to a group of patients that would potentially benefit from anticoagulation in the pretransplant and posttransplant settings.

Matthew D. Jankowich, MD
Beth Israel Deaconess Medical Center
Boston, MA

References


To the Editor:

We thank the author for his comments, and for bringing to our attention the findings of Magro and associates, which were published after our article had been accepted. The article by Magro et al. describes a finding that provides biological plausibility for our report and is therefore supportive of the fact that the findings of our study were not due to a type I error. This apparent thrombophilic state is more likely a consequence of idiopathic pulmonary fibrosis (IPF) rather than the initiating factor, since the latter would not fit the current hypothesis that IPF is due to recurrent epithelial injury. We agree that the findings of Magro et al. need to be verified prospectively by other groups and the presence of antiphospholipid antibodies stratified by disease severity. Along these lines, although we did not test any of the patients in our reported series, we have started testing all of our new IPF patients prospectively for the presence of this class of antibodies. Depending on the results of such future studies, it may become evident that all patients with suspected IPF should be so tested, not only to stratify them for risk of thromboembolic events, but also as a potential disease marker. If the high prevalence found in the series by Magro et al. is substantiated, then a case may even be made for empirically administering anticoagulation therapy to all IPF patients.

Steven D. Nathan, MD
Scott D. Barnett, PhD
INOVA Fairfax Hospital
Fairfax, VA

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Correspondence to: Steven D. Nathan, MD, Inova Fairfax Hospital, 3300 Gallows Rd, Falls Church, VA 22042-3300
Urine Color Testing and Isoniazid Monitoring

To the Editor:

We read the article by Eidlitz-Markus et al (March 2003)1 and the accompanying editorial2 with great interest. We agree about the importance of improving patient adherence to antituberculous therapy and acknowledge the potential benefits of using the Arkansas method for monitoring compliance by testing a urine sample for breakdown products of isoniazid. However, we have severe reservations about this method, especially if used by a family physician. The method used involves using prepared stock solutions, including that of potassium cyanide, and adding varying numbers of drops of these reagents to a urine sample.3 The risks involved in handling and storing such reagents in physicians’ surgeries and other extralaboratory environments is very significant.

We therefore took these reagents and enclosed them inside a patented plastic testing device (SafeTube; University of Birmingham; Birmingham, UK), which safely contains the toxin reagents before use and seals the urine and reactants after use, with the testing kit disposed of in a “sharps” bin. This also reduces the likelihood of exposure to urine samples, which may be infected with viruses such as HIV. The testing device contains a 2-mL syringe for measuring a specific volume of urine, which is then added to tabletted reagents and mixed, with a sample positive for isoniazid metabolites turning dark blue in a matter of seconds and a stable result present at 5 min.

We have evaluated this test in a busy hospital tuberculosis outpatient clinic, recruiting patients who were receiving daily therapy with isoniazid, and the vast majority (97%) receiving it in combination with rifampicin. In a cross-sectional study to compare this new test with the visual appraisal of the presence of orange staining of the urine from rifampicin, we collected urine samples from 131 patients. Of these, only 48% had orange-stained urine. The time interval from the last reported dose varied from 40 min to 23 h. Positive test results for isoniazid were obtained from 94.6% of patients, with the remaining seven patients (3.4%) producing a color change indicating partial or noncompliance, so indicating failure to abide by treatment instructions.4

This figure is much lower than the 28.5% nonadherence found by Eidlitz-Markus et al.,1 but his patients were all being treated for latent tuberculosis infection, whereas our patients were largely being treated for active tuberculosis disease. We therefore welcome the problem of nonadherence being highlighted, but we think we have a much more convenient, more safe, and less technically demanding method than the assay using wet chemistry. Our studies indicated that the new test was a useful guide for patients who required extra monitoring and further education as to the importance of taking their drugs every day, or those who required directly observed treatment.

Graham F. Cope, PhD
University of Birmingham
Birmingham, UK
Ruth Whitfield, MD
Mayday University Hospital
Thornton Heath, UK

REFERENCES

4 Whitfield RJ. Cope GF. An audit of adherence to antituberculous drugs using a new, rapid, point of care test for isoniazid metabolites. Eur Respir J 2002; 20(suppl 38):566s

To the Editor:

We read with great interest the letter of Drs. Whitfield and Cope about their method to check metabolites of isoniazid in urine in a patented plastic testing device (Safe Tube; University of Birmingham; Birmingham, UK). We agree that although the cost of the Arkansas method1 is very cheap ($0.06),2 some of its reagents may be dangerous to sick children or debilitating old patients. If safety precautions to prevent the contact of patients with these reagents cannot be taken, the new method should be considered. We did not receive information whether the new test was empirically checked and compared to the original Arkansas method, and how long after the last dose received by the patient the test was done.

A double-controlled study, comparing the two methods with the same urine samples, should be done. If the new test will be found to be as informative as the Arkansas method, it has a safety superiority over the Arkansas method.

The cost is an important factor, as tuberculosis is increasing all over the world, especially among low-income patients with HIV.3 The cost of the new test is higher and should be considered. The two described methods are part solutions to increase adherence and improve the medical education of patients with tuberculosis infection.

Tal Eidlitz–Markus, MD
Jacob Amir, MD
Schneider Children’s Medical Center of Israel
Petah Tiqwa, Israel

REFERENCES