predicted that RZ would be the most effective and the least expensive option for immigrants from Vietnam, Haiti, and the Philippines.2

This issue may be even more cogent in Europe, given the massive migratory flows from low-income countries and considering that, unlike the United States, HIV-positive legal immigrants, who are at higher risk for active tuberculosis, are not expelled. The European framework for tuberculosis control and elimination, including the recommendation of using INH for LTB treatment in specific groups, has been recently published.3 Nevertheless, in different European countries the origin of the immigrants' population may vary, and consequently the level of INH resistance too. For instance, in a multicenter study4 in Italy, in 2000 primary INH resistance in immigrants was reported to be 9.4%. In a survey of patients referred to the General Hospital of Verona from January 2000 to June 2003, among 231 isolates of Mycobacterium tuberculosis, 28 of 41 of strains (68.3%) resistant to at least one antituberculosis drug were from immigrants (23.9% of cases in this category of patients). Overall resistance to INH was detected in 23 strains (9.9%); 60.8% of these were isolated in immigrants from the African continent (mainly Senegal, Ghana, Ivory Coast, and Nigeria) who were infected by INH-resistant strains in 22.2% of cases. These data highlight that in the area of Verona, the INH resistance rate among immigrants is much higher compared to the national level. Therefore, the use of INH as LTB treatment could be inadequate in nearly one of four African immigrants. We believe that it is essential to evaluate the origin of immigrants in a specific area while preparing national and local guidelines for LTB treatment because of the possibility of different resistance patterns. Considering the high level of INH resistance in some endemic areas, regimens including rifampin should be recommended. Nevertheless, following the recent withdrawal of the RZ regimen in the United States, new options for LTB treatment are urgently needed. In the meantime, based on a cost-effectiveness evaluation, we would suggest that in young immigrants from high tuberculosis prevalence countries with known high INH resistance, especially if at increased risk, such as HIV-positive subjects, RZ could be still considered in absence of any hepatopathy.

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Care of Flexible Bronchoscopes

To the Editor

We experienced an unusual complication with two flexible bronchoscopes within a week. The following letter is meant to alert others, and is intended for both education and cost savings.

The flexible A-rubber sheath on the distal portion of the bronchoscope “ballooned,” and in one bronchoscope ruptured, during the sterilization process. As the repairs cost roughly $1,000 (Canadian dollars) per bronchoscope and this had never happened in our institution before, we set out to uncover the problem.

The following two simultaneous conditions were believed to be responsible: a failing check valve in the sterilizer; and the fact that the bronchoscopes had been placed into the sterilizer with a slight positive internal pressure following leak testing. A failing check valve can add as much as 6 to 7.6 lb per square inch of vacuum to the exterior surface of the bronchoscope. Any positive pressure that is left in the bronchoscope from the leak test procedure could add as much as 3.5 lb per square inch of pressure. Together, the additional pressure could cause dilation and/or rupture of the rubber sheath.

To prevent a repeat, we have emphasized the need for maintenance on any sterilizing equipment at least twice per year. As part of our own ongoing quality assurance efforts, a check step to the leak test procedure has been added to ensure that no positive pressure remains prior to sterilization. By briefly installing a venting cap onto the bronchoscope following leak testing, all remaining positive pressure is removed. To facilitate this, an ethylene oxide cap was chained to the leak tester.

Although not a common problem, the cost of repair mandates an extra effort. We think that this simple step, which requires minimal time, no extra training, and the negligible cost of a venting cap, will prevent future damage. We encourage readers to consider their own bronchoscope-venting procedures.

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Withdrawal From and Study Design of the ISOLDE Trial

To the Editor:

In a recent article, Calverley et al.1 provide us with further very interesting data from the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) trial. In their article, the authors insist on the fact that the decline of both FEV1 and health status was more rapid in patients who withdrew from follow-up. They also argue that the loss of these patients reduced the power of the ISOLDE study to show a difference for various outcome measures.

The authors did not provide a statistical analysis comparing the fluticasone- and the placebo-treated groups in both completers and withdrawals. It is, however, quite clear from the data that much of the differences observed between the placebo and the fluticasone groups in the intention-to-treat analysis published earlier2 came from withdrawals.

In this context, two points are critical for a proper understanding of the intention-to-treat analysis of the ISOLDE trial: the statistical handling of withdrawals, and the potential influence of the study design on early withdrawals.

The issue of withdrawals in long-term trials including patients with COPD is certainly difficult to deal with, and makes these studies difficult to perform. Undoubtedly, these withdrawals must be included in the analysis. How they are statistically handled is important, and is not always clearly explained in the methodology of various trials. The random coefficients hierarchical model used in the ISOLDE trial is not familiar to most of us.

More details on this particular statistical analysis was provided in another article by the same group,3 in which they stated that patients withdrawn contributed less weight in the statistical model. But what the exact relative weight of withdrawals was in the intention-to-treat analysis remains unclear.

One might argue that this is irrelevant, since a lesser weight—whatever its extent—certainly lowers the power of the study to find a statistical difference. Nevertheless, the design of the study had the potential to influence early withdrawals. Indeed, patients received oral prednisolone, 0.6 mg/kg/d, for 14 days in the run-in phase of the trial. One might suspect that after this oral prednisolone treatment, patients randomized to the placebo group had a more rapid decline in FEV1 during the first weeks of the treatment phase. One might suspect that after this oral prednisolone test could have favored—and more so in the placebo group—the occurrence of early exacerbations, of an early and rapid decline of health status, and of early withdrawals. This is critical since the raw contribution of these early withdrawals to the annualized decline of FEV1 and health status as well as to the annualized exacerbation rate could be very important.

Accordingly, it would be useful to know to what extent the fluticasone- and the placebo-treated groups differed in terms of early withdrawals due to respiratory causes (at 3 months, 6 months, and 12 months), and the exact weight attributed to withdrawals in the statistical model. Interestingly, the only two studies2,4 (lasting ≥ 1 year) that showed a statistically significant effect of inhaled steroids on health-related quality of life in COPD included a run-in with oral steroids.

In their discussion, Calverley et al.1 state that avoiding premature withdrawals is a difficult problem. However, in previous trials,2,4,5 some early withdrawals were probably due to the design of the study itself. One could argue that further studies in COPD should avoid oral steroids run-in, and that when needed inhaled steroids should be withdrawn for at least 4 weeks before the treatment phase.

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