Transmission of isoniazid-resistant tuberculosis: letter
Borgdorff, M.W.

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Transmission of Isoniazid-Resistant Tuberculosis

To the Editor—Burgos et al. conclude that isoniazid-resistant strains are less likely than drug-susceptible strains to result in secondary cases [1]. Although Burgos et al., with the excellent database available in San Francisco, are well placed to study this subject, the method of analysis that they have used seems biased.

In the analysis, a secondary case is required to have the same RFLP pattern and the same drug-resistance pattern as does a case diagnosed previously. Although the requirement of an identical RFLP pattern does not introduce bias, the requirement of an identical drug-resistance pattern does. This is most easily explained if we consider a cluster (defined on the basis of identical RFLP patterns) with some cases of drug-susceptible tuberculosis and a single case of drug-resistant tuberculosis. That single case of drug-resistant tuberculosis may be due to (1) transmission outside the study area, (2) reactivation of an infection acquired before the study period, or (3) transmission from an individual within the cluster who had drug-susceptible tuberculosis at diagnosis but who acquired drug resistance later (e.g., because of poor compliance with prescribed treatment). If the first or second possibility applies in a drug-susceptible case, it would be considered a secondary case, leading to an overestimate of the transmission of drug-susceptible tuberculosis. If the third possibility applies, then transmission of a drug-resistant strain would be missed, leading to an underestimate of the transmission of drug-resistant tuberculosis. Both biases lead to an underestimate of the relative secondary-case rate.

Although these uncertainties cannot be avoided altogether, bias can be avoided by comparing the clustering percentages of drug-resistant and drug-susceptible cases, where clustering is defined solely on the basis of the RFLP pattern [2]. The resulting odds ratio does not suffer from the aforementioned biases.

Martien W. Borgdorff
Department of Infectious Diseases, Tropical Medicine, and AIDS, Academic Medical Center, University of Amsterdam, Amsterdam, and KNCV Tuberculosis Foundation, The Hague, The Netherlands

References

Reply

To the Editor—We appreciate Dr. Borgdorff’s comments [1] concerning our recently published article [2]. In our analysis we calculated the number of secondary cases that arose from all drug-susceptible and drug-resistant cases, by assuming that strains were transmitted to other patients if the drug-susceptibility test and genotype patterns were identical. Dr. Borgdorff points out that, although the requirement of an identical RFLP pattern does not introduce bias, the requirement of an identical drug-resistance pattern does. He suggests that bias can be avoided by comparing the clustering percentages of drug-resistant and drug-susceptible cases, instead of directly calculating the number of secondary cases produced by both phenotypes.

We have done the analysis suggested by Dr. Borgdorff, using the n = 1 method to evaluate clustering [3], and the analysis does not change our overall conclusions. Strains that were resistant to isoniazid either alone or in combination with other drug resistance were less likely to be in clusters than were drug-susceptible isolates (table 1).

Table. 1. Results of bivariate analyses of the association between initial drug-resistance phenotype and clustered (vs. unique) genotype, San Francisco, 1991–1999.

<table>
<thead>
<tr>
<th>Drug-resistance phenotype</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>0.46 (0.25–0.82)</td>
<td>.006</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4.68 (1.85–12.81)</td>
<td>.0001</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1.05 (0.60–1.78)</td>
<td>.853</td>
</tr>
<tr>
<td>Isoniazid and streptomycin</td>
<td>0.19 (0.05–0.53)</td>
<td>.0002</td>
</tr>
<tr>
<td>MDR tuberculosis</td>
<td>0.00 (0.00–0.38)</td>
<td>.0004</td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; MDR, multidrug-resistant tuberculosis (resistance to at least isoniazid and rifampin); OR, odds ratio.

* Based on either the χ² test of proportions or Fisher’s exact test and the Cornfield approximation.
Seronegative Hepatitis C Virus Infection, Not Just RNA Detection

To the Editor—Castillo et al. are to be congratulated for their careful evaluation of hepatitis C virus (HCV) infection in individuals with persistently negative results of HCV-antibody tests [1]. The high (57%) rate of “serosilent” HCV infection in their 100 subjects with unexplained abnormal liver-enzyme values was similar to the rate (67%) that we found in 15 patients with cryptogenic liver disease with persistently abnormal results of liver tests and that we previously reported in the Journal [2]. We have identified HCV RNA in whole-blood samples from >50 individuals with persistently negative results of HCV-antibody tests [2–4], and, in some cases, have documented HCV RNA in patients for >7 years. Furthermore, viral RNA was detected by at least 2 different sets of oligonucleotide primers in reverse-transcriptase–polymerase chain reactions [2, 4], and sequence analysis demonstrated that the HCV RNA in these individuals was not due to laboratory contamination [3]. It is important to note that these high rates of seronegative HCV infection were found in people with active liver disease [1–3]—and that they may be different in healthy individuals with normal levels of liver-associated enzymes; for example, we found no cases of seronegative infection among either 342 healthy blood donors (J.T.S. and L.K., unpublished data) or 102 individuals with diabetes mellitus but without history of liver disease [4].

Castillo et al. provide clear evidence of HCV replication in seronegative people with cryptogenic liver disease by demonstrating HCV RNA sequences in liver tissue [1]. Because HCV is a hepatotropic virus, demonstration of HCV RNA—particularly the antisense (replicative intermediate) strand—in liver tissue strongly corroborates previous descriptions of seronegative HCV infection. HCV is found in lymphocytes [5], and HCV replication (i.e., detection of HCV antisense RNA) has been observed in some, but not in most, studies. The amount of virus RNA present in lymphocytes is far less than that found in hepatocytes, and most lymphocyte-associated virus is probably produced by infected hepatocytes. Nevertheless, because of both the invasive nature of liver biopsy and the technical difficulties with detection of RNA in histological specimens, it is unlikely that liver biopsy will become the standard for making the diagnosis of surreptitious HCV infection. Our previous findings suggest that a large number of these cases may be identified by using whole blood as the source of RNA for detection of HCV by nucleic acid–amplification methodologies.

The reason that whole blood is a more plentiful source of HCV RNA than is serum relates not only to the association between HCV and lymphocytes [5], but also to the proclivity of HCV to induce rheumatoid factor (RF) and cryoglobulins (CGs). We analyzed 115 HCV-positive subjects for levels of RF, CG, and HCV RNA in serum and in whole-blood samples [6]. The amount of HCV RNA was similar in whole-blood and serum samples obtained from HCV-infected individuals without CG detected in their serum; however, in people with CG, the recovery of HCV RNA from whole blood was greater than that in serum, and the increased recovery of HCV RNA from whole blood correlated directly with the concentration of CG [6]. Furthermore, we found that approximately half the viral RNA present in the whole-blood pellet was not intraacellular; presumably this viral RNA represented aggregates of immunoglobulin- or lipoprotein–HCV complexes [5]. The higher sensitivity of whole-blood HCV RNA in CG-positive patients is clinically relevant, because ~40% and ~80% of individuals with HCV infection have detectable CG and RF, respectively [6].

Other lines of evidence for seronegative HCV infection also exist; for example, transmission of HCV infection from a persistently seronegative blood donor has been described [7], and, as noted by Lerat and Hollinger (8], prolonged seronegative infection has been documented in chimpanzees experimentally infected with HCV [9]. In women exposed to contaminated immunoglobulins, HCV-specific antibody responses were not detected 18 years after infection, whereas HCV-specific helper and cytolytic T cell responses were identified [10], further supporting prior HCV infection without development of HCV antibody. Seronegative HCV infection has also been shown in up to 9% of HIV-positive individuals and has been shown to persist for >7 years in one well-documented case [4]. Although this probably represents impaired immune responses in HIV-positive individuals, this high rate of seronegative infection deserves careful attention.

Lerat and Hollinger state in their editorial that “[u]til other investigators can confirm the provocative data … we are left to speculate about the significance of
their observations” [8, p. 5]. We believe that the carefully performed study presented by Castillo et al. [1] confirms the findings of previous studies noted above, and that seronegative HCV infection—not RNA detection—warrants further recognition and investigation.

Jack T. Stapleton, Warren N. Schmidt, and Louis Katz

1Medical Service, Iowa City VA Medical Center and Department of Internal Medicine, Roy J. Carver College of Medicine, University of Iowa, Iowa City, and 2Mississippi Valley Regional Blood Center, Davenport, Iowa

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