

## CORRESPONDENCE

### **Cirrhosis as a risk factor to drug-resistant tuberculosis**

*To the Editor:*

ARÉVALO *et al.* [1] are correct to be cautious in accepting as true the unexpected and apparently biologically implausible association between hepatic cirrhosis and drug-resistant tuberculosis (TB) found in their study. However, the explanations they offered for this finding are not satisfactory and merit further consideration.

If the diagnosis of cirrhosis was not made in some patients, which is quite possible because cirrhosis was not routinely investigated in this series, there is no reason to believe that individuals with drug-resistant TB received that diagnosis more often than patients without drug-resistance. The consequence of such nondifferential misclassification of exposure [2] would have been bias of the odds ratio towards the unit, *i.e.* to underestimation of the association between cirrhosis and drug-resistant TB. In other words, the true odds ratio would be higher than 104!

The hypothesis of hepatic cirrhosis being a surrogate to alcoholism, implying more opportunity of exposure to noncompliers of TB treatment, is also not totally convincing. Alcoholism was one of the variables included in the multiple logistic regression model and, therefore, the odds ratio of drug-resistant TB for cirrhotics is adjusted for it. It is possible that there were patients whose alcoholism was not registered in their charts, but this would probably happen with less severe alcoholics, as alcoholism is a well-known risk factor for TB, and would be expected to be mentioned in the medical records.

As to the possibility of a type I error, although it is theoretically possible it is certainly very unlikely that an odds ratio of 104 occurred by chance. The large 95% confidence interval around this figure does reflect the imprecision of the estimate due to the small numbers, but the point is that it is much more likely that the association between cirrhosis and drug resistant TB is due to bias than to random error.

The arguments presented above are an attempt to refute the hypotheses of ARÉVALO *et al.* [1] but do not provide an alternative explanation. One possible explanation could be related to the fact that TB, being a transmissible disease, tends to cluster in groups of persons who have close contact. If some patients included in this study were not independent of each other as to the way they acquired TB, for instance if their infection was transmitted from one to the other, or acquired from a common source, this could have led to spurious associations between drug-resistant TB and factors that were shared by these individuals. One could think, for instance, of a hypothetical scenario of a small outbreak of drug resistant TB involving cirrhotics in the hepatology outpatient clinic. Looking at table 2 in the paper by ARÉVALO *et al.* [1] one could speculate that patients Nos. 1 and 3, both with hepatic cirrhosis and streptomycin-resistant pulmonary TB, and patients Nos. 6 and 22, both with cirrhosis and isoniazid-resistant pulmonary TB, were related to each other.

ARÉVALO *et al.* [1] are in the best position to assess whether clustering of cases of drug-resistant TB could have created an artificial association with hepatic cirrhosis.

#### **References**

1. Arévalo M, Solera J, Cebrian D, Bartolomé J, Robles P. Risk factors associated with drug-resistant *Mycobacterium tuberculosis* in Castilla-la-Mancha (Spain). *Eur Respir J* 1996; 9: 274–278.
2. Rothman KJ. *Modern Epidemiology*. Boston, Little, Brown and Co., 1986; pp. 86–89.

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## REPLY

*From the authors:*

We wish to thank Dr Nishioka for his comments on our report [1]. Dr Nishioka suggests that the association between hepatic cirrhosis and drug-resistant *Mycobacterium tuberculosis* in our study could possibly be due to the fact that the group of subjects in question were in close contact with each other (*i.e.* that their infection was transmitted from one to the other, or acquired from a common source).

We checked the clinical reports and did not find any relationship between the four patients that Dr Nishioka mentions (table 2, patients Nos. 1 and 3, and patients Nos. 6 and 22). These patients were treated in two different centres of the Albacete Hospital Complex, each individual separated from the other by a distance of 3 km. Patient No. 1 was diagnosed and treated in December 1988 in the General Hospital and patient No. 3 in December 1989 in the Thorax Hospital. Patient No. 6 was diagnosed and treated in the same hospital in March 1993, while patient No. 22 was attended in the General Hospital in August 1992. Moreover, there was no parental or occupational relationship between them.

Therefore, we cannot confirm Dr Nishioka's hypothesis, and we still consider that hepatic cirrhosis may simply reflect a marker for heavy alcohol drinkers who are more likely to be noncompliant patients of the tuberculosis treatment. It should be emphasized, however, that this study did not address the association of hepatic cirrhosis and resistance to antituberculosis drugs, so our suggestion regarding this association is only speculative. It would be really interesting, if other investigators were to undertake a similar study, and so allow us to make comparisons between the results obtained.

### References

1. Arévalo M, Solera J, Cebrian D, Bartolomé J, Robles P. Risk factors associated with drug-resistant *Mycobacterium tuberculosis* in Castilla-la-Mancha (Spain). *Eur Respir J* 1996; 9: 274–278.

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## CORRESPONDENCE

### Pulmonologists and respiratory intensive care

*To the Editor:*

It is certainly true that pneumologists should become more involved in intensive care medicine. In their editorial: "Pulmonologists and respiratory intensive care", C. Roussos and A. Rossi [1] write that "In Europe in the 4 years of training needed to become a European Community (EC) certified pulmonologist, a period in the ICU is not included".

This statement needs a correction and some comment. In the programme drawn by the UEMS Specialist Section Pneumology on the training in Pneumology in the European Community (EC), which was published in 1994 and was accorded by the ERS [2], is clearly outlined that at least 4 months of training in intensive care medicine is necessary:

"6.4.1 Intensive care: All trainees must gain experience in intensive care and should spend a period of at least 4 months attached to an intensive care unit. This period can be undertaken as part of the common trunk or as part of the specialty programme".

This statement became part of the European Training Charter [3].

The European Board of Pneumology, in which members of the UEMS and ERS co-operate [4], has the task to realize the Training Charter for Pneumology and will work out the qualification for EC certified pneumologists. However, the Board is not in the position to adapt

existing training programs of the individual member countries, but can only refuse to recognize European pneumologists if their training and examination does not meet the standards.

Therefore, the Editorial of Roussos and Rossi [1] is more than welcome to persuade the national organizations to implement a training period in intensive care in the national training programmes for pneumologists, as far as this had not been realized already.

### References

1. Roussos C, Rossi A. Pulmonologists and respiratory in-tensive care (Editorial). *Eur Respir J* 1996; 9: 183.
2. Dijkman JH, Martinez Gonzales del Rio J, Loddenkemper R, Prowse K, Siafakas N. Report of the working party of the "UEMS Monospecialty Section on Pneumology" on training requirements and facilities in Europe. *Eur Respir J* 1994; 7: 1019–1022.
3. UEMS: European Training Charter for Medical Specialists. Brussels, 1995.
4. Dijkman JH. Cooperation between ESRM and UEMS (Editorial). *ERS Newsletter* March 1996.

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