CORRESPONDENCE

Drug Resistant Tuberculosis: A Worldwide Epidemic Poses a New Challenge

by Prof. Dr. med. Dr. h. c. Robert Loddenkemper, Dr. med. Barbara Hauer, MPH
in volume 1–2/2010

Historical Background

Loddenkemper and Hauer briefly mentioned the beginnings of tuberculosis treatment. I have a few comments to add. Lehman tested para-aminosalicylic acid (PAS) in 1944, and Waksman, streptomycin. However, according to Hinshaw, the observations published in 1945 did not provide a sound basis on which to assess the efficacy. The thiosemicarbazones were developed by Bayer until 1941 under the leadership of H Domagk: TB1/698 was studied in tuberculosis of the skin in Münster-Hornheide by Moncorps and Kalkoff. At the end of the war, Bayer's development laboratories in Wuppertal were ransacked, but sufficient quantities of the substance were still stored in Hornheide. Up to 1946, cases of cure were documented there; these were reproduced under scientific conditions and published as soon as Germany's scientific journals were able to resume publication—for example, in 1947 in *Dermatologische Wochenschrift*.

US based Hinshaw and Mc Dermott visited Frankfurt and Wuppertal in order to take over the substance and scientific results. In 1969, Time magazine published an article on this "war booty." Squibb and Roche conducted further research on the substances in the US. In the meantime, as early as in 1951 Domagk presented his scientific results relating to isonicotinic acid hydrazide (isoniazid, Neoteben) in New York, Bayer, Roche, and Squibb agreed in 1952 that they had developed the substance "simultaneously" (Neoteben, Rimifon, Hydrazide). But Domagk definitely pioneered its use and achieved the kind of success that held promise for the future.

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False Economies

At last, someone has made the effort of drawing attention to the "forgotten disease" that is tuberculosis, especially to the global catastrophe of increasing drug resistance. At the district hospital in Parsberg—the only closed quarantine hospital for TB in Germany—we have been treating recalcitrant TB patients for more than 40 years; in the past 10 years we have increasingly recorded a substantial increase in the MDR/XDR (multidrug resistant/extensively drug resistant) forms of TB. Since 2008, Germany's federal states have been contributing to the treatment costs (costs of isolation treatment) because this is state responsibility under the Infection Protection Act. Since then, inpatient occupation has dropped by 50% and the number of TB cases by 70%. My question is: where are these patients being treated now (the incidence has stayed roughly the same)? Or has a penny pinching mentality spread among the health offices and states and false economies applied that would put us all to shame in view of the billions invested in saving the banks? The medical service of the health insurers also examines almost each and every case and increasingly refuses inpatient treatment for such patients (who are difficult to deal with on a personal level as well as from a medical perspective). The demise of our hospital is therefore merely a question of time. But if specialist hospitals, such as ours, with their in-depth knowledge of how to treat drug resistant TB are abolished and the public health services sacrifice their careful approach on the altar of cost savings, the global catastrophe will rapidly become a national catastrophe—albeit a self inflicted one.

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What About Existing Databases?

We agree that research into and treatment optimization of multidrug resistant tuberculosis can be successfully undertaken only by way of a joint effort.

We were surprised that the review article did not mention representative data collections of patients with MDR-TB and XDR-TB in Germany. From 2004 to 2006, the Tuberculosis Network European Trials-group (TBNET) systematically collected data from patients with MDR-TB and XDR-TB in 27 hospitals and

evaluated the therapeutic successes (1). TBNET is a European alliance of doctors in clinical practice as well as scientists; the group's remit is TB research. The network receives funding from the European Union and is closely linked to the European Respiratory Society. In a study of 4557 TB patients, 177 patients were found to have MDR-TB and 7, XDR-TB. This amounts to two thirds of all patients known to have MDR-TB or XDR-TB in Germany. The mean inpatient stay for XDR-TB is 202 days, and for MDR-TB, 123 days. The expensive inpatient care, comprehensive testing for antibiotic resistance, and the availability of all required medications have yielded excellent treatment results in 89% or 80% of the cases that were subsequently documented. In 2010, TBNET has established a database to capture MDR-TB and XDR-TB in Europe, with the aim to provide a comprehensive prospective and retrospective analysis of MDR-TB and XDR-TB. We are asking our colleagues who treat patients with MDR-TB and XDR-TB to join in the concerted effort and participate in the database project, so as to make a contribution to research into this intractable disease (information at www.tb-net.org or from gguenther@fz-borstel.de).

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In Reply:

We thank our correspondents for their contributions and for their interest in our article. The publication by Eker et al, cited by Christian Herzmann and colleagues, was cited in our review article with regard to very diverse aspects because it does indeed contain important data on MDR-TB and XDR-TB in Germany. The network's activities help close existing gaps in our knowledge and answer epidemiological and clinical questions. However, with regard to the success rates of 80% in MDR-TB and XDR-TB, as cited in the letter, it should be pointed out that this proportion relates exclusively to patients in whom treatment completion was documented (125/184). 26 patients who were lost to follow-up were not included—and in these patients, a successful treatment result is highly doubtful. 33 further patients were still undergoing treatment at the time the data were collected. The success rate according to the definition, which was used for the purpose of comparison with other studies, was 59% for the entire cohort. We used as a particular example the publication by Eker et al to point out that "the relevant percentage of patients whose therapeutic outcome is unknown, or whose treatment has not yet been completed, can substantially diminish the success rate, depending on how this rate is defined." We wish to thank our correspondents for providing us with an opportunity to explain the problems in some greater detail. For the cited study, may we remind our readers of the comparatively higher lethality due to TB for this age group (about 40 years of age), of 14 deaths among 177 patients with MDR-TB and 1 death in 7 patients with XDR-TB. If the reference variable is adjusted for the above categories of patients (14/120), then the letality for MDR-TB is almost 12%.

The relevant number of patients with complex forms of resistance described by Eker et al, whose therapeutic result is not easy to determine, gives cause for concern and is almost certainly also a manifestation of the special problems that Dr Mütterlein describes in his letter. Compulsory isolation of men with TB in Parsberg and of women with TB in Bad Lippspringe requires careful examination of each individual case. The decision was certainly not made lightly, but it should equally certainly not depend on financial factors. As drastic as compulsory isolation may seem, these institutions provide persons whose multiple and complex health problems endanger their therapeutic success with an opportunity to receive competent, individually tailored, and successful treatment for their illness. Additionally, the risk for further spread of the mostly resistant TB—and thus the risk for the patient's environment—is successfully minimized.

We thank Professor Hundeiker for providing additional historical background information and for his interesting details of the early days of anti-TB chemotherapy.

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Conflict of interest statement
The authors of all contributions declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.