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Breakpoints and Drug Exposure Are Inevitably Closely Linked

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It was with great interest that we read the article by Gumbo and colleagues titled “Redefining Multidrug-Resistant Tuberculosis Based on Clinical Response to Combination Therapy” (1). The authors performed a classification and regression tree (CART) analysis showing that MIC cutoff values above which therapy failure was observed are significantly lower than current breakpoints for isoniazid (INH) and rifampin (RIF). The consequence of the finding might be that the rate of multidrug-resistant tuberculosis (MDR TB) is much higher than previously assumed (1).

The impact to revise the definition of MDR TB based on these new critical concentrations will not only be statistical. Many patients will receive a second-line treatment regimen for at least 20 months that will be accompanied by a budget impact based on direct and indirect medical costs. The clinical outcome for these “new” MDR TB patients who will be treated with a second-line treatment regimen of drugs with unclear efficacy and more toxicity (2) needs to be established.

As the authors point out correctly, the identification of breakpoints should be a pharmacokinetics-pharmacodynamics (PK/PD)-derived calculation. The CART analysis showed cutoff MIC values lower than the current breakpoint MICs. The authors choose to derive cutoff MIC values lower than the current breakpoint MICs. The authors choose to increase the doses of INH and RIF. This would have resulted in the same clinical cure rate, thereby avoiding the increase of MDR TB and subsequent prolonged and toxic treatment.

We realize that our proposed strategy will likely also have a major impact on the current first-line treatment. A randomized study would ultimately be needed to compare clinical outcomes between standard treatment and treatment with high-dose INH and RIF. The publication of Gumbo and coworkers once again showed that new dosing strategies with currently available drugs are urgently needed to turn the tide of the MDR TB epidemic. It becomes clearer every day that drug susceptibility testing was and is important to be able to select an appropriate MDR TB treatment regimen (7) and in addition tailor treatment further by optimizing drug exposure in patients (8).

REFERENCES


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