Reply to Srivastava et al., “pH Conditions under Which Pyrazinamide Works in Humans”

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We appreciate the interest and comments from Srivastava et al. regarding our findings of an acidic milieu in patients with chronic pulmonary tuberculosis undergoing surgical resection (1). Measuring the lung tissue pH of resected lesions was a secondary aim of our study, and based on prior human and more-recent animal data, we did not expect samples to have an acidic pH (2, 3). The presence of an extracellular acidic environment as mentioned by Srivastava et al. is in line with their prior simulations using the hollow-fiber model and provides a rationale for the activation and effectiveness of pyrazinamide in severe lung lesions (4).

When interpreting our results, it is important to keep in mind a few points, including the characteristics of our patient cohort and the methods used in measuring pH. The cohort consisted of 10 patients with chronic multidrug-resistant pulmonary tuberculosis, with most having been treated for 1 year prior to undergoing surgical resection due to a suboptimal response to antituberculosis therapy. It is hard to draw definitive conclusions from such a relatively small sample size, and there may have been possible selection bias from enrolling patients not responding well to treatment. Such patients may have had progression of lung lesions characterized by persistent inflammation and acidic by-products. Given the types of patients in our study cohort, the tissue pH results may or may not be generalizable to all patients with tuberculosis. Additionally, there were 2 of 10 patients with a neutral pH, demonstrating that there exists a variation in the pHs of extracellular environments. The two samples with neutral pHs were also the only two to harbor high numbers of acid-fast organisms, a correlation which demands further investigation. To measure pH, we utilized pH test strips applied to the centers of lung lesions approximately 3 h after surgical resections. As mentioned in our paper, it is unclear how this delay may have affected results, and we plan to take measurements immediately after resection in the future.

These limitations aside, our results do demonstrate that an extracellular acidic environment does exist and persists in certain patients with pulmonary TB. This finding has important implications for the use of pyrazinamide and indicates that prolonged use may be beneficial, as shown in a recent meta-analysis of patients with isoniazid-resistant tuberculosis (5). As mentioned by Srivastava et al., our work also demonstrates the importance of corroborating animal studies in humans. While we are flattered to be credited with solving an academic riddle, we feel that additional investigations are warranted and hope that our results stimulate additional work in the area. Further study of a larger and more diverse set of human tissue samples is needed to provide more definitive answers regarding the lung tissue pH among patients with tuberculosis.
REFERENCES


