Editorial Response: β-Lactam Drugs and Tuberculosis

On the surface, the idea of using β-lactam drugs to treat tuberculosis seems counterintuitive. Clinical experience is replete with examples of patients receiving β-lactam agents for presumed bacterial pneumonia whose conditions fail to improve and who subsequently are found to have tuberculosis. Furthermore, considering the widespread use of β-lactam drugs, it seems that if they had clinically relevant activity against tubercle bacilli, this would have been apparent long ago.

However, experiences with the atypical mycobacteria suggest that β-lactam drugs may have activity and make the treatment of tuberculosis with such drugs appear reasonable. For example, selected β-lactam agents, including cefoxitin and imipenem, are useful in the treatment of Mycobacterium fortuitum infections [1, 2]. Furthermore, cycloserine, a second-line drug in the treatment of tuberculosis, is a D-alanine analogue that interferes with peptidoglycan synthesis. As β-lactam drugs also inhibit peptidoglycan synthesis, it seems plausible that they should also be effective.

See the article by Chambers et al. on pages 874–7.

Data showing the in vitro activity of β-lactam drugs against Mycobacterium tuberculosis have accumulated slowly over the past 5 decades. Studies in the 1940s demonstrated that under certain culture conditions penicillin inhibits M. tuberculosis [3, 4]; however, it was soon recognized that tubercle bacilli produce a β-lactamase that inactivates penicillin [5, 6]. In the 1960s, this β-lactamase was found to be inhibited by the anti-staphylococcal penicillins [7, 8], and in the 1980s, by clavulanic acid, sulbactam, and tazobactam [9, 10].

β-lactamase inhibition markedly enhances the in vitro activity of β-lactamase-labile antibiotics, including penicillin G, amoxicillin, and ampicillin [7–10]. In addition, other β-lactam drugs, including ceforanide, cefitoxime, cephalasin, and imipenem, have been found to exhibit in vitro activity against M. tuberculosis without the addition of β-lactamase inhibitors [11–13]. Screening of 600 cephalosporins in vitro against M. tuberculosis suggested that compounds containing a pyridyl or aminomethylphenyl side-chain have the greatest activity, with some exhibiting MICs of <2 μg/mL [11].

In vivo studies also have suggested an effect of β-lactam drugs on M. tuberculosis. Kasik et al. demonstrated that the once-daily administration of large doses of penicillin G and dicloxacillin from days 3 to 19 after infection of mice with M. tuberculosis prolonged median survival to 35 days, vs. 17 days for mice receiving penicillin alone [8]. Inhibition of M. tuberculosis β-lactamase by dicloxacillin, consequently preventing the degradation of penicillin, was believed to be responsible for the superior efficacy of the combination. In another study, two cephalosporin derivatives were reported to have efficacy in a murine model of tuberculosis [11]. Randhawa et al. found that 3 months of therapy with ampicillin/sublactam eradicated Mycobacterium leprae from the footpads of mice [14], further validating the concept that β-lactam-β-lactamase inhibitor combinations are active against the slow-growing mycobacteria in vivo.

In this issue of Clinical Infectious Diseases, Chambers et al. [15] provide the strongest evidence to date that selected β-lactam drugs might be of value in treating tuberculosis. Using quantitative methods for culturing M. tuberculosis from sputum and a randomized, prospective, unblinded study design, they found that amoxicillin/clavulanate administered as a single agent thrice daily for 7 days to 10 persons reduced the mean number of viable tubercle bacilli in sputum by 0.7 log10 cfu/mL (i.e., about fivefold) in comparison with pretreatment values.

Virtually all of this reduction occurred in the first 3 days of treatment. The reduction in log10 cfu/mL at 2 days with amoxicillin/clavulanate was comparable to that observed with ofloxacin but less than that seen with isoniazid. As the few previous reports of treating tuberculosis with β-lactam drugs have been uninterpretable because the β-lactam agent was part of a multidrug regimen [16, 17], this study represents the first time that β-lactam drugs have been shown to be active against tuberculosis in the clinical setting.

Although this study suggests a benefit from β-lactam therapy for tuberculosis, more in vitro and in vivo data are needed to define which agents are the most active as well as how to administer them most effectively. In particular, a better understanding of β-lactam resistance mechanisms in M. tuberculosis is needed. As β-lactamase appears to be more important than low-binding-affinity penicillin-binding proteins and/or cell wall permeability barriers [18] in the expression of β-lactam resistance in M. tuberculosis, identification and characterization of its β-lactamase(s) will be fundamental in identifying the best β-lactam drugs for clinical use.

Some progress has been made in this area. The major β-lactamase is a class A β-lactamase with predominant penicillinase activity identifiable by dual bands on isoelectric focusing with pl values of 5.1 and 4.9 [19–21]. It is encoded on cosmide Y49 of the M. tuberculosis cosmide library sequenced by the Sanger Centre, in Cambridge, United Kingdom [22], and has been overexpressed and purified as a biologically active recombinant enzyme in Escherichia coli [21]. A second β-lactamase with relatively greater cephalosporinase activity and a pl value
of 4.5 also has been identified recently, and there are some data to suggest the presence of a third β-lactamase [21].

Evidently, *M. tuberculosis* has a complex defense against β-lactam drugs that will need to be inactivated (by adding β-lactamase inhibitors) or sidestepped (by using agents with intrinsic stability) in order for the full potential of β-lactam drug therapy against tuberculosis to be realized. Although the reasons given by Chambers et al. for selecting amoxicillin/clavulinate for evaluation in their study were logical and the wisdom of their choice is evident in their results, a more methodical and formal analysis of β-lactamase-β-lactam interactions should help to identify β-lactam drugs and β-lactam-β-lactamase inhibitor combinations with even greater potential as antituberculous agents.

At the current time, it is unclear what, if any, role β-lactam drugs ultimately will have in the management of tuberculosis. On the basis of experiments showing strong bactericidal activity of ampicillin/sulbactam against exponential-phase cultures of *Mycobacterium tuberculosis* and only minimal activity against stationary-phase cultures, Herbert et al. have suggested that they may be useful in the early stages of treatment and in preventing the emergence of resistance to other drugs but doubt they will be effective as sterilizing agents [23]. The findings of Chambers et al. in this study support this opinion.

Finally, the possibility of using β-lactam drugs for tuberculosi is especially intriguing in that antibiotics already well-known and available to us may be shown to be active, as was done in this study. The falling rates of tuberculosis in the United States and other developed countries and the limited financial resources of developing countries where tuberculosis is most problematic are a strong disincentive to pharmaceutical companies involved in antibiotic development. How nice it would be to be able to take an old drug off the shelf and use it in a new way against an old enemy.

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**References**