sult of causes frequently reported in this patient population, primarily progression of malignancy and organ failure.

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References

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Tuberculosis Drug Serum Levels

Str—The fine paper by Narita and colleagues [1] does not show a direct correlation between the serum concentrations of the tuberculosis drugs and the recurrence of tuberculosis disease. It is possible that the use of different breakpoint values (e.g., one-half of the target ranges) might have yielded different results. Ongoing research sponsored by the Centers for Disease Control and Prevention (Atlanta) suggests that, in certain situations, low serum concentrations of the tuberculosis drugs are associated with worse treatment outcomes. Some of these data were presented at the annual meeting of the American Thoracic Society in May 2001 [2, 3]. The available data suggest that failure of tuberculosis treatment or recurrence of disease results from a complex and poorly understood combination of factors that likely varies from patient to patient. The use of antibiotic serum concentrations rarely has perfect predictive value to guide the choice of drug dosage [4–10]. I would like to suggest an approach to the use of antibiotic serum concentrations that may be useful.

First, it is clear that some drug concentration is required to achieve a therapeutic effect, and target ranges should be designed with a margin of safety with respect to their efficacy. Thus many “below-range” patients should be within this margin of safety. Second, the concentrations required for patients who are receiving multiple antibiotics may be lower than the target ranges for the individual drugs [11]. Third, for certain patients, achieving critical concentrations is the difference between success and failure [12, 13]. However, it is very difficult to identify these patients a priori, and it is highly unlikely that the same target concentrations will be successful in all situations. Typically, the pharmacodynamic relationship between serum drug concentrations (X) and therapeutic efficacy (Y) creates an S-shaped curve that is described mathematically by Hill equations [14].

Fourth, once the decision is made to use a given antibiotic, a goal should be set for the desired serum concentrations, and the goal should be achieved with the greatest precision possible [15]. That is where carefully timed serum concentrations are particularly helpful. Fifth, there are separate probability curves for serum drug concentrations (X) and selected drug toxicities (Y). These relationships also must be considered when setting serum concentration goals. Furthermore, if the disease state is potentially fatal, some toxicity may need to be accepted to effect a cure.

Sixth, the decision to determine serum concentrations during the course of treatment is the decision to change the dose if necessary. Some patients will require doses greater than the “usual” or “recommended” doses. I would suggest that treatment guidelines avoid the term “maximum” [16]. The “maximum” dose for any patient is the dose that produces the desired therapeutic effect with an acceptable degree of toxicity. In addition, our concept of what constitutes “usual” doses needs to be adjusted in light of the possibility of drug-drug interactions, the degree of which can be unpredictable in an individual patient [17].

One is unlikely to find a perfect relationship between serum concentrations (1 variable) and treatment outcomes, which depend on multiple variables. However, we do know that treatment fails in selected patients because of inadequate serum concentrations. Therefore, if patients with tuberculosis fail to respond appropriately to directly observed treatment, monitoring of serum concentrations and repeated susceptibility testing should be performed. Critically ill patients with tuberculosis should receive as many tuberculosis drugs as possible intravenously (i.e., isoniazid, rifampin, streptomycin or amikacin, and levofloxacin). For the tuberculosis drugs that cannot be given intravenously, serum concentrations should be checked as soon as possible, and the dosage adjusted as needed.

Finally, for the treatment of multiple drug-resistant tuberculosis, the achievable serum concentrations of the “second-line” tuberculosis drugs barely exceed the amounts needed to inhibit mycobacteria [10]. Therefore, I would advocate checking the serum concentrations and adjusting the drug dosages before embarking on 30 months of potentially toxic treatment. In conjunction with sound clinical judgment, therapeutic drug monitoring allows the clinician considerable flexibility in managing even the most difficult cases of infectious disease, including tuberculosis and multiple drug-resistant tuberculosis.
**Good’s Syndrome: The Association of Thymoma with Immunodeficiency**

Sir—We read with interest the case report of a patient with Good’s syndrome by Arend et al. [1]. We would like to add some comments based on our recently reported review of the literature on 51 documented cases of infectious diseases in patients with Good’s syndrome, including 5 patients we treated at our institutions [3].

Arend et al. [1] indicate that patients with Good’s syndrome have a worse prognosis than do patients with common variable immunodeficiency (CVID), another primary immunodeficiency syndrome with recurrent infections. It is important to point out that Good’s syndrome is a combined immunodeficiency (humoral and cellular) that is now classified as an entity separate from CVID (“immunodeficiency with thymoma”) [2]. Unlike CVID, Good’s syndrome is characterized by (sometimes profound) B cell lymphopenia and, variably, defects in cellular immunity with CD4⁺/CD8⁺ T cell lymphopenia and an inverted CD4⁺/CD8⁺ T cell ratio. Compared with patients who have CVID, patients who have Good’s syndrome are more often present with opportunistic infections, including severe cytomegalovirus disease, Pneumocystis carinii pneumonia, and persistent mucocutaneous candidiasis. There are a number of reports in the literature regarding cases of Good’s syndrome and a potentially treatable disseminated infection that were only diagnosed at autopsy.

We recommend that all patients with thymoma should have serum immunoglobulin levels measured. For patients with presumed CVID or thymoma who develop unusual or unusually severe infections, a comprehensive attempt to establish a microbiological diagnosis should be made. Immunological investigations should be performed at an early stage: at a minimum, levels of T cell subsets (measured by use of flow cytometry), levels of B cells, and quantitative immunoglobulin levels should be determined. If results are in the normal range and clinical suspicion of Good’s syndrome persists, these tests should be repeated periodically, given the well-described interval (often several years) that can occur between the infectious complications of the immunodeficiency and the diagnosis of thymoma (or vice versa). The clinical course of the disease may be more severe in the substantial minority of patients who require immunosuppressive treatment for associated autoimmune conditions (such as myasthenia gravis or pure red cell aplasia). Chest CT scanning may be more sensitive not only for the evaluation of pulmonary complications, as Arend et al. [1] point out, but also for the detection of thymoma, which is missed by standard radiography in 20%–40% of cases [4].

We are interested in receiving infor-