in Aboriginal communities in central and northern Australia, where trachoma is endemic, was changed to include azithromycin [2]. Unfortunately, the pediatric formulation available overseas was not then available for use in children in Australia; approval and marketing of azithromycin in Australia had been limited to use of the capsule formulation in adults for treatment of respiratory and skin infections. More recently, in recognition of the high rates of trachoma and other health care needs of our indigenous minority, special approval from the Australian Therapeutic Goods Administration has enabled Pfizer, Inc. (New York) to supply azithromycin suspension specifically for treatment of trachoma.

In our previously reported evaluation of azithromycin for treatment of trachoma in Aboriginal children, completed before azithromycin suspension became available in Australia, we used azithromycin capsules and xanthan gum to make a suspension for use in children [3]. As expected from the results of studies conducted overseas, the program was very successful, confirming the efficacy of azithromycin for trachoma; the rate of trachoma among Aboriginal children was reduced from 44% to 15%, 6 months after children with trachoma and their childhood household contacts were treated [3]. We also studied upper respiratory tract carriage of Streptococcus pneumoniae in children treated for trachoma, and this study was the basis of our publication [4]: following single-dose azithromycin therapy, there was a substantial reduction in pneumococcal carriage, but the proportion of azithromycin-resistant strains increased from 1.9% to 54.5% of isolates at 2–3 weeks after treatment. This proportion subsequently decreased to 5.9% at 6 months [4].

The criticisms of Peterson and Treadway cannot alter these empirical findings. We stand by our conclusion that “it appears that the selective effect of azithromycin allowed the growth and transmission of preexisting azithromycin-resistant strains” [4]. Our results are unique in the published literature but are not surprising and are consistent with the emergence of macrolide-resistant S. pneumoniae, attributed to increasing macrolide usage [5]. Similar emergence of macrolide-resistant Streptococcus pyogenes has been well documented and has been correlated with macrolide usage [6, 7]. The internal data from Pfizer showing low levels of azithromycin resistance in S. pneumoniae are useful baseline data for future comparisons of resistance after more extensive exposure of S. pneumoniae to azithromycin.

Azithromycin has clear advantages over other drugs for treatment of chlamydial urethritis and trachoma, and for donovanosis, for which supervised weekly therapy has been very successful [8]. We support the conclusions of Khan et al. [9] that “Delaying the onset of resistance requires that the drug not be used for conditions for which antimicrobial therapy is not required or for conditions in which the older, less expensive, and narrower spectrum agent might be used. Limiting the use of azithromycin requires the combined efforts of pharmaceutical companies that market the drug, practitioners who prescribe drugs, and government organizations that play a role in health care.”

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Nutritional Status and Aminoglycoside Dosing

Sir—We read with interest the articles [1–3] and editorial responses [4, 5] concerning the relative merits of single vs. multiple daily dosing of aminoglycosides. Many studies and meta-analyses have been published, without a clear consensus of opinion about treatment success or toxicity. These meta-analyses suggest that the absolute differences in clinical outcomes between the dosing regimens are small. The critical question remains: How can nephrotoxicity and ototoxicity be minimized? This question is important with respect to drugs other than aminoglycosides, as demonstrated by recent reports of severe renal injury after administration of a single dose of cidofovir [6]. The dosing interval may be a less important determinant of adverse outcome than the magnitude of the dose itself. An overdose is an overdose, whether given all at once or at timed intervals.

Two major considerations in determining the appropriate dose of an aminoglycoside are its volume of distribution and rate of clearance. The former is related to the volume of plasma and certain tissue compartments, whereas the latter is related to creatinine clearance, which reflects renal function. To avoid the need for making these measurements, body weight (or ideal body weight) is used in estimating equations such as the Cockcroft-Gault equation [1, 7]. However, limitations in the relationships between weight and these variables may introduce sig-
significant errors in calculation and lead to overdosing or underdosing, irrespective of the administration schedule.

The potential error in use of weight to estimate the percentage of body water is easily illustrated by comparing two subjects of equal age, height, and weight, one of whom is a competitive bodybuilder, whereas the other is an obese, sedentary individual. The bodybuilder may have >30% more total body water than the sedentary subject, which would lead to a significantly lower peak serum concentration of drug after the same dose had been administered. There are also limitations to the use of body weight or ideal body weight for estimating creatinine clearance. As we stated at the 34th Annual Meeting of the Infectious Diseases Society of America, use of the Cockcroft-Gault equation, with either actual or ideal body weight, results in a systematic error in estimation [8]. We showed that creatinine clearance is closely correlated with body cell mass. Variation in the relationship between body cell mass and weight, as a result of malnutrition or obesity, led to errors in estimation. By using the Cockcroft-Gault equation and ideal body weight, creatinine clearance was overestimated in severely malnourished subjects by ≤150% in comparison with actual measurements.

Evaluation of dosing intervals is an important consideration for controlling the cost of drug administration but does not address the medical or personal costs associated with the sequelae of drug toxicity. Development and application of more accurate predictors of volume of distribution and creatinine clearance are essential for limiting the costs associated with over- or underdosing of aminoglycosides and other therapeutic agents that are eliminated through the kidneys.

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Reply

Sir—Kotler and Sordillo have raised concerns regarding the use of ideal body weight (IBW) in determining the magnitude of single daily dosing (SDD) of aminoglycosides and cautioned that this approach may cause an overdose, leading to toxicities in malfourished and elderly patients.

In bringing to our attention the shortcomings of applying creatinine clearance estimates to aminoglycoside dosing, they have reaffirmed earlier observations, particularly among critically ill patients [1, 2]. However, both multiple daily dosing (MDD) and SDD are initially based on population guidelines with use of a suggested mg/kg (IBW), and creatinine clearance is used to determine the magnitude of the dosing interval rather than the magnitude of the dose [3]. Moreover, certain special populations require more aggressive dosing because of the above-average volumes of distribution associated with these patients’ conditions [4]. Susceptibility to aminoglycoside-related nephrotoxicity may not be exclusively related to the dosing magnitude in patients without preexisting renal dysfunction, since age, comorbidity (e.g., the presence of shock, septicemia, or diabetes), concurrent use of nephrotoxic medications, duration of therapy, and electrolyte status are believed to enhance the risk of nephrotoxicity [5, 6]. We are unaware of dosing recommendations based on alternative measures of body mass such as fat-free mass or body-cell mass and look forward to learning from the application of these measures by using bioelectrical impedance in studies of clinical therapeutics [7].

Quantitative systematic reviews (i.e., meta-analyses) are used to summarize, critically appraise, and reconcile the published evidence regarding a clinical problem [8, 9]. The lack of consensus regarding SDD may not be due to the quantitative synthesis of results obtained from a meta-analysis but rather to the interpretation of these results. For example, the pooled average estimates of nephrotoxicity from our meta-analyses suggest that SDD is associated with a 13% and 22% lower absolute risk than is MDD in immunocompetent (n = 1,625) and immunocompromised (n = 811) patients, respectively. However, the upper end of the 95% confidence interval for this estimate includes the possibility of a 26% increase in the absolute risk of nephrotoxicity for the former group and a 94% increase in absolute risk for the latter group. Additional randomized trials involving SDD vs. MDD, combined in a cumulative meta-analysis, will assist in obtaining a more precise location of toxicity risk estimates by narrowing the 95% confidence interval. Clearly, not all patients who receive SDD experience toxicities. It remains to be clinically determined, in a prospective subgroup analysis, whether Kotler and Sordillo’s