Editorial Response:  
Single Daily Dosing of Aminoglycosides—A Community Standard?

In this issue of the journal, Chuck et al. report the findings of a follow-up study that examines the prevalence of extended-interval dosing (EID) practices for aminoglycosides throughout the United States. In this survey, the investigators examine the rationale for institutions’ implementation of such practices and delineate critical physical elements incorporated into each institution’s program for EID. In this regard, the authors have provided a valuable service to the medical community.

See article by Chuck et al. on pages 433–9.

Comparing data collected by these investigators in 1993 with those in the present report shows that EID, despite considerable controversy, apparently has been widely accepted by both physicians and pharmacists. In theory, maximizing concentration-dependent killing by achieving high peak-to-MIC ratios and minimizing nephrotoxicity and ototoxicity by providing for an aminoglycoside-free period during the dosing interval would appear to be an appropriate strategy to optimize aminoglycoside therapy. However, before widespread acceptance of a new theory or practice by the medical community, the hypothesis or practice must be rigorously tested and substantiated with conclusive clinical data. The data supporting EID practices is inconclusive, despite numerous publications [1–5].

Without question, the study of Chuck et al. could be interpreted to mean that if your institution is not currently using an EID strategy, it is not practicing at the community standard. However, the reader cannot ascertain from the survey whether the EID concept described by the responding institutions is applied regularly to all patients or occasionally to only some. Furthermore, although part of their survey was designed to characterize the variability in what different institutions consider EID therapy, this same term is applied to all applications, which in our opinion confuses what is actually being reported.

So what exactly is the community standard or what should the community standard be for dosing of aminoglycosides? To our knowledge, prospective, randomized, double-blinded clinical trials among patients with documented infections that establish EID as either equivalent or superior to the multiple-dosing strategy are almost nonexistent. Virtually all of the currently available evaluations of EID were not blinded and, for the most part, were underpowered for determining whether a true difference exists in either safety or efficacy.

We are therefore surprised that so many institutions have in fact accepted this concept with so little conclusive evidence. The fact that 27% of respondents to the survey stated their belief that EID is innovative and progressive as a rationale for instituting this dosing method is quite alarming in an era of evidence-based medicine. As health care professionals, we pride ourselves on using an evidence-based approach to making clinical decisions. At the present time, it is very unlikely that the US Food and Drug Administration would consider changing the package labeling to incorporate an EID strategy, should they have to evaluate this approach with currently available data.

The survey also illustrates substantial variation from institution to institution in approaches to dosing and monitoring with EID. Among surveyed hospitals using EID, 61% monitor therapy by only a single determination of serum concentration, at 6–18 h after the aminoglycoside infusion. Can the clinician be confident that the use of 1 serum-concentration determination and a nomogram to predict the appropriate dosage interval will work, knowing that in a busy hospital ward or laboratory any variations in aminoglycoside serum concentration might likely be a discrepancy in nursing administration time, serum sample collection time, or laboratory variation?

The issue of whether this report established EID as a community standard raises 3 very practical concerns. First, if your institution is not using one of these ill-defined strategies for aminoglycoside dosing, are the patients receiving optimal care? Second, should your institution become a party to litigation regarding aminoglycoside therapy, were you practicing at what the courts would consider the community standard? Third, if your institution is using EID, the method considered by you as the community standard, and your facility becomes involved in litigation, are you at risk because of the paucity of clinical data supporting EID, which would call into question the decision to make EID the standard in your hospital?

A full critique of EID concepts is outside the scope of this report, but such critiques have been published elsewhere [6–9]. Suffice it to say that these methods have been criticized based on how the concepts were theoretically and pharmacokinetically derived. Any institution considering a decision to use EID practices should be thoroughly aware of these underlying arguments and should fully recognize that there are common clinical situations that would and would not justify the use of
larger doses and less-frequent dosage intervals for an aminoglycoside.

Although many clinicians seem to be under the impression that aminoglycoside nephrotoxicity and ototoxicity have gone away since the advent of EID concepts, the literature would suggest that EID also results in these toxicities [1–8]. We remain particularly concerned about the use of EID methods for the elderly, for patients with reduced renal function, in situations calling for prolonged therapy, against pathogens for which aminoglycoside MICs are relatively high, and/or in situations where the aminoglycoside does not readily achieve therapeutic concentrations at the site of infection.

At face value, the report by Chuck et al. would seem to offer an endorsement by the medical and pharmacy communities for the acceptance of EID of aminoglycosides as a new community standard. On closer examination, however, what is reported as EID in this survey, with respect to the daily dose, dosing interval, and monitoring practices, varies so much from institution to institution that the term itself lacks scientific meaning. Convincing clinical-efficacy and safety data to support the finding that over half of the surveyed institutions use EID are simply not available from the survey.

We are not critical of the report of Chuck et al. but rather question those responding as to their underlying rationale for moving to an EID-based concept. Accordingly, we would like to make certain that institutions considering the adoption of EID for aminoglycosides critically evaluate the literature themselves rather than be lulled by a false assumption that EID is now the community standard.

References