Acute Bacterial Skin and Skin Structure Infection Trials: The Bad is the Enemy of the Good

To the Editor—Drs Corey and Stryjewski are to be congratulated for their thoughtful and extremely polite advice to “not let the perfect be the enemy of the good” in setting regulatory standards for clinical trials of acute bacterial skin and skin structure infections (ABSSSIs) [1]. Although numerous facets of current thinking about ABSSI trial designs are fundamentally flawed, the most egregiously flawed is the primary efficacy end point, for which success is defined as cessation of lesion spread after 48–72 hours of treatment. To put this in perspective, consider the patient who presents to his or her provider with cellulitis and receives antibiotic therapy. The patient returns in 3 days with a lesion of exactly the same size only to be told by the provider, “Congratulations, you are a treatment success.” When I describe this end point to both medical and lay audiences during lectures, the unvarying reaction I receive is disbelief that this is a real end point.

The authors write, “cessation of spread only indicates that the patient is on the path to recovery” [1]. However, having a lesion of the same size after 48–72 hours is not an indicator of being on the road to recovery; rather, it is an indicator of failing therapy. Indeed, the fundamental flaw of this end point is that it cannot distinguish patients in whom therapy is failing from those whose infections are improving. No amount of statistical manipulation can alter this fundamental fact.

A second fundamental flaw of this end point is that it has no assay sensitivity (ie, it cannot distinguish more effective from less effective therapy). In the historical data used to justify the end point, according to the Food and Drug Administration’s own analysis and as cited by Drs Corey and Stryjewski [1], oral prontosil rubrum and sulfanilamide had ≥98% treatment success rates when this end point was used [2]. We know that penicillin reduced the mortality rate associated with cellulitis by 10-fold, compared with results achieved with oral sulfa drugs in the 1930s [3, 4]. Therefore, there is no question that oral sulfonamide therapy was much less effective than β-lactam antibiotics. If drugs that we know were less effective than modern therapy had ≥98% success rates with use of this end point, there is no way that this end point...
can distinguish more effective from less effective therapy. It is ironic that unsubstantiated fear that noninferiority clinical trials using prior end points could allow less effective drugs on the market has resulted in selection of a revised end point that could certainly allow less effective drugs on the market [5].

The rules governing conduct of antibacterial clinical trials are being rewritten in a manner that is contrary to common sense. Physicians will be in the position of prescribing drugs because they result in skin lesions not changing in size after 3 days of therapy. Patients will be in the position of potentially being treated with such drugs. It is time for clinicians who understand the practice of medicine to make our voices heard in this debate. Our patients deserve as much.

Notes

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