Antimicrobial Agents for Complicated Skin and Skin-Structure Infections: Noninferiority Margins, Placebo-Controlled Trials, and the Complexity of Clinical Trials

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(See the article by Spellberg et al on pages 383–91)

Hippocrates wrote of the natural history of soft-tissue infection as follows: “Criton, in Thasus, while still on foot, and going about, was seized with a violent pain in the great toe; he took to bed the same day, had rigors and nausea, recovered his heat slightly, at night was delirious. On the second, swelling of the whole foot, and about the ankle erythema, with distension and small bullae (phlyctaenae); acute fever; he became furiously deranged; alvine discharges bilious, unmixed, and rather frequent. He died on the second day from the commencement” [1, p. 377].

Although Hippocrates had no treatment available, we find ourselves in a similar dilemma as our antibiotics become less effective because of rapid evolution of antibiotic resistance among microbes that cause skin and skin-structure infections (SSSIs).

Physicians need new antibiotics to treat skin and soft-tissue infections. There is increasing evidence that the Infectious Diseases Society of America (IDSA), the pharmaceutical industry, and the US Food and Drug Administration (FDA) must work closely together to fulfill the mutual and medically necessary goal of providing new treatments for SSSIs. Over the past 5 years, the IDSA has clearly presented their case that accelerated production of new agents should be a high priority.

From drug discovery to FDA approval is currently a long and arduous journey. On the supply side, few pharmaceutical companies are developing antimicrobial agents, largely for financial reasons. In fact, few if any US pharmaceutical companies are currently offering, or are investigating, new antimicrobial agents. Pharmaceutical companies are for-profit organizations, yet there is a great difference between those that market generic compounds only and those that develop new forms of treatment and bring them to market. Clearly, novel agents will come only from the latter group. Perhaps prolonging the duration of patent rights or otherwise rewarding companies that reinvest a significant portion of their profits in research and development would stimulate innovation.

The second stage of antimicrobial development (ie, the design and execution of Phase III clinical trials) has become increasingly complex. For example, institutional review board approval, privacy issues, the requirement of larger numbers of subjects for improved statistical evaluations, enhanced research oversight, compliance issues, complex consent forms and changing FDA regulations are mindboggling to an investigator and have dramatically slowed the process of Phase III clinical trials. Today’s drug development environment is far different than that of the mid-1980s when a dozen or so oral second generation cephalosporins were approved in rapid succession by the FDA. All these agents were virtually identical, there was not a true clinical need, and the forces driving this process were an attempt of individual companies to achieve a 5%–10% market share of this lucrative business. The FDA is charged with evaluating hard evidence for efficacy and safety, and perhaps the circus of the 1980s has driven the FDA to apply ever increasing vigor to the modern approval process. However, given today’s urgent medical need for new agents to combat ever increasing antimicrobial resistance, it is clear that the entire process should be streamlined. It is critical that clear and reasonable agreement be reached between the sponsor and the FDA at the time of protocol inception.

Evaluation of clinical responses in patients with SSSI is complex. SSSIs constitute a broad spectrum of clinical mal-
adies and are caused by a wide variety of bacteria, viruses, fungi, rickettsia, and even helminthes [2]. The clinical manifestations of these infections are greatly influenced by the immune status of the host, underlying medical conditions, primary chronic diseases of the skin, and ancillary medications [2]. The progression of the infectious process can range from an indolent furuncle to a rapidly progressive process, such as necrotizing fascitis, gas gangrene, lymphangitis, or bacteremia [2].

The clinician must decide whether a given infection is attributable to indigenous skin flora, nosocomial acquisition (eg, postsurgical acquisition), or introduction by an animal or insect bite (eg, a louse or tick), because the appropriate antibiotic treatment varies as widely as the possible etiologic agents. In addition, continual microbial evolution further confounds the issue. Microbes undergo mutations or acquire mobile genetic elements that confer resistance to contemporary treatments or enhance their virulence such that the clinical presentation, rate of progression, or spectrum of disease is altered. In the face of this rapidly changing microbial landscape, evidence-based practice guidelines for SSSI are at risk of being obsolete by the time they are published.

Ambiguity of clinical definitions, etiological diagnosis, and consensus on evaluable markers of resolution of infection confound interpretation of clinical trial results. In an effort to narrow the spectrum of SSSIs and to provide objective criteria that can be evaluated statistically, modern clinical trials require identification of a specific pathogen and exclude patients with underlyng diseases, confounding medications, or more-severe infection, such as necrotizing fascitis, joint infection, gas gangrene, and osteomyelitis. The FDA has distinguished uncomplicated from complicated SSSIs. Uncomplicated SSSIs are typically impetigo, small abscesses, or furuncles. By definition, complicated SSSIs are those accompanied by some element of systemic illness such as fever, tachycardia, elevated white blood cell count, or greater than 10%–20% immature neutrophils. The next dilemma facing the clinical trial investigator is the identification of the causative agent. Clearly, this is easy for staphylococcal infections, such as an abscess or carbuncle. For cellulitis, this is problematic because of the difficulty in determining whether the diffuse nature of the infection, and the low yield of organisms upon aspiration or punch biopsy. As a result, most clinical trials are enriched for culture-amenable staphylococcal infections, giving the erroneous impression that these organisms are the most common cause of SSSI. Finally, because of the exclusion of patients with more-severe infections, there is virtually no data on the efficacy of antibiotic treatment of illnesses such as necrotizing fascitis and myonecrosis, and clinicians are left to base treatment recommendations on extrapolation of animal studies or in vitro testing. Thus, in reality, there are uncomplicated, complicated, and very complicated SSSIs.

Surgical drainage, antibiotic treatment, or both? Focal infections caused by staphylococci range in severity from minor pimples to deep abscesses. Clearly, pimples and furuncles are readily cured by superficial drainage alone, whereas carbuncles and deeper abscesses require surgical drainage. In the latter instance, there is great controversy regarding the need for antibiotics. There is general agreement that none are required for small foci (<2.5 cm in diameter) in immunocompetent patients without fever or leukocytosis. Such patients certainly would not meet the criteria for inclusion in a complicated SSI clinical trial. Whereas many patients resolve minor staphylococcal abscesses or furuncles without surgical intervention or antibiotics, some develop late complications. For example, a history of prior minor cutaneous infection is typical among patients with epidural abscess, discitis, hematogenous osteomyelitis, cavernous vein thrombosis, and vertebral osteomyelitis. Although unproven, it seems likely that organisms from the skin lesion spread hematogenously to seed distant sites, resulting weeks to months later in life-threatening or debilitating staphylococcal infection. Thus, even minor SSSIs pose risks for subsequent complications in normal individuals. In the current era of prosthetic heart valves, vascular grafts, and a plethora of joint replacements, not to mention the widespread occurrence of methicillin-resistant Staphylococcus aureus, minor staphylococcal soft-tissue infections will likely pose even greater risks for the patient and more significant treatment dilemmas for clinicians.

For focal infections with >5.0 cm of erythema, the issue is more complex. General recommendations are for incision and drainage alone if the patient has no fever, tachycardia, or leukocytosis. Although this rigid recommendation might work for the FDA definitions for clinical trials, the individual clinician must consider whether the patient’s immune status (eg, human immunodeficiency virus infection, diabetes, cancer, or immunotherapy) and the lesion’s location (eg, face or genitals) warrants antibiotic treatment. Thus, in a given patient, clinical judgment should always supersede guidelines set forth by the FDA or IDSA.

Another factor that greatly influences outcomes following incision and drainage is the procedure itself. We all assume that incision and drainage is standard fare, yet for complex abscesses or carbuncles, incision and drainage must be performed correctly. Whereas less-skilled caregivers may use an 18-gauge needle to aspirate or drain an abscess, an experienced surgeon will usually use a scalpel and then pack the cavity open. The time to healing or resolution, or the need for further drainage are used to quantify antibiotic efficacy in clinical trials. However, inadequate drainage may skew the results and ultimately cause the statistician to conclude that the test agent is less efficacious than the comparator, when in fact the variable is the extent of incision and drainage. In a clinical trial involving multiple study
sites, the means of incision and drainage should be clearly defined.

**Reports from the preantibiotic era reveal the natural history of untreated SSSIs.** In the current issue of *Clinical Infectious Diseases*, Spellberg et al. [3] provide an in-depth analysis of the natural course of SSSIs in the preantibiotic era, including reports describing the efficacy of penicillin and sulfonamides in these infections. In a sense, these early studies constitute the placebo control trial that the FDA has suggested is necessary to calculate a reasonable noninferiority index. Interpretation of these early efficacy studies is complex, especially given the limited robustness of the clinical trial design and the primitive statistical tools used to evaluate efficacy at that time in history. Nonetheless, the study clearly demonstrates that, in the early 1930s in the absence of antibiotics, the mortality of erysipelas and major abscesses was approximately 11%–17% and >6%, respectively [3]. In terms of clinical outcomes, a marked increase in cure rates in both of these categories was observed after the advent of penicillin. Thus, Spellberg and colleagues’ study accomplishes 3 major objectives. First, it clearly obviates the need for a placebo-controlled clinical trial of SSSIs. This is important, because in today’s reality, institutional review board approval for such a study would clearly be denied on ethical grounds. Second, the authors present a strong case for changing the current noninferiority margins for SSSIs. Third, they provide reasonable noninferiority margins for each of the various types of SSSIs. They state: “In practice, the noninferiority margin for a specific complicated SSSI trial should be weighted for the proportion of enrolled patients with cellulitis/erysipelas, wound or ulcer infections, and major abscesses” [3, p. 388].

**Future directions.** Clearly, antibiotic resistance among staphylococci and streptococci, the 2 most common causes of SSSI, has increased dramatically during the past decade, and this phenomenon has altered our clinical practice. Gone are the days when an oral cephalosporin, dicloxacillin, or clindamycin were all that was necessary for successful treatment of most infections of the skin caused by indigenous flora. Thankfully, in the past 6–7 years several new agents have been approved by the FDA for treatment of these infections. Vancomycin has been a workhorse for treatment of a variety of methicillin-resistant *S. aureus* infections, but problems with minimum inhibitory concentration creep for both methicillin-susceptible *S. aureus* infections and methicillin-resistant *S. aureus* infections have been described; vancomycin-resistant, methicillin-resistant *S. aureus* infections have emerged; and vancomycin heteroresistance and intermediate resistance are causes of treatment failures. Resistance to newer agents, such as linezolid and especially daptomycin, has also been well described. Thus, there is a great need for development of new antimicrobials, new clinical trials, and FDA approval to provide the clinician with an arsenal of additional agents effective against these formidable and ever-changing microbial adversaries.

**Acknowledgments**

This material is the result of work that was supported with resources and use of facilities at the Veterans Administration, Boise, Idaho.

**Potential conflicts of interest.** D.L.S. has received research grant support from Pfizer, Arpida, Cubist, and Wyeth.

**References**