Successful Treatment of Staphylococcal Toxic Shock Syndrome with Linezolid: A Case Report and In Vitro Evaluation of the Production of Toxic Shock Syndrome Toxin Type 1 in the Presence of Antibiotics

Sir—We would like to report the following case. Three months prior to admission to a hospital in December 2004, a 56-year-old white male veteran with diabetes mellitus underwent abdominal surgery to remove shrapnel from a wound he sustained during the Vietnam War. Two weeks prior to this hospitalization, he received a 10-day course of amoxicillin-clavulananate because of a localized infection at the surgical site. On admission, he was confused, had a diffuse, erythematous rash over the face, trunk, and extremities, and a 10 × 2-inch open wound with granulation tissue and thin white discharge. His pulse was 145 beats/min, systolic/diastolic blood pressure was 87/46 mm Hg, and his temperature was 40°C. Laboratory test results were significant for a marked left shift in the WBC count, metabolic acidosis, renal impairment (creatinine level, 2.3 mg/dL), hypoalbuminemia, and hypocalcemia. Gram staining of a drainage specimen obtained from the abdominal wound revealed gram-positive cocci in clusters.

The patient was admitted to the intensive care unit, was aggressively fluid-resuscitated, and was given linezolid on the basis of a presumed diagnosis of staphylococcal toxic shock syndrome and the high likelihood of resistance to methicillin. Over the first 24 h, tachycardia (heart rate, 140 beats/min) and hypotension (mean arterial pressure, 60 mm Hg) persisted. Blood pressure and pulse were normal at 48 h, and urine output and azotemia resolved. Culture results at 48 h revealed *Staphylococcus aureus* susceptible to oxacillin, clindamycin, erythromycin, and linezolid. Results of the D-test were negative. At this time, the patient was switched to intravenous clindamycin and was discharged from the hospital 24 h later and given oral clindamycin.

**Microbiology and toxic shock syndrome toxin type 1 production.** The patient’s *S. aureus* isolate was cultured in magnesium-supplemented beef heart infusion medium to ensure optimal toxic shock syndrome toxin (TSST–1) production (see next section) [1–4]. MICs of antibiotics were determined in this media by the microdilution broth method, in accordance with National Committee for Clinical Laboratory Standards guidelines [5]. The MICs obtained for the *S. aureus* clinical isolate were as follows: vancomycin, 1.0 μg/mL; nafcillin, 0.8 μg/mL; linezolid, 4 μg/mL; and clindamycin, 0.1 μg/mL.

Experiments testing the effects of antibiotics on TSST-1 production required...
that a high starting inocula size (1 × 10^8 colony-forming units/mL) be used to obtain detectable toxin levels. To compensate for the increased inoculum size, the final antibiotic concentrations were 5 times the MIC. At various times, the number of viable bacteria was determined by plating duplicate 10-μL samples (or 10-fold dilutions thereof) onto blood-agar plates, and TSST-1 was measured by ELISA, as described elsewhere [6].

**Results and discussion.** The growth of the vancomycin-treated S. aureus culture was similar to the growth of the untreated control (figure 1A). In contrast, cultures treated with either nafcillin, clindamycin, or linezolid remained static up to 8 h after antibiotic treatment, after which time a slow killing was observed. Maximal TSST-1 production occurred between 8 and 24 h in the untreated, nafcillin-, and TSST-1–producing strains of methicillin-resistant S. aureus (MRSA), including staphylococcal toxic shock syndrome, have been documented worldwide [7]. Thus, empiric use of nafcillin is not a reasonable choice in patients with serious staphylococcal infections. In addition, inducible clindamycin resistance has been increasingly reported [8]. Presently, the best empiric choices for serious staphylococcal infections include vancomycin, linezolid, daptomycin, dalbavancin, and tigecycline.

Mounting evidence suggests that MRSA strains in general, as well as community-acquired MRSA strains in particular, have acquired additional toxin genes and that these strains are associated with worse outcomes [7]. Although no clinical trials will likely be conducted that compare cell wall active agents (vancomycin and nafcillin) with protein synthesis inhibitors (clindamycin and linezolid) in STSS, there is evidence that clindamycin is more efficacious that β-lactam antibiotics in cases of toxic shock due to group A streptococcus [9, 10]. The improved efficacy has been attributed, in large part, to the ability of these antibiotics to suppress toxin production. In vitro suppression of TSST-1 by clindamycin [6, 11, 12] has been demonstrated, and linezolid has been shown to suppress several staphylococcal exotoxins [13, 14]. However, to our knowledge, the present work is the first to demonstrate linezolid-induced suppression of TSST-1.

In summary, on the basis of findings of the initial gram stain and the presence of risk factors for MRSA, we treated this patient with linezolid. The patient improved rapidly, and when susceptibility testing and D-test results were available, his treatment was switched to clindamycin. We conclude that the ability of linezolid and clindamycin to suppress TSST-1 production in the patient’s S. aureus strain contributed to a good outcome in this case of STSS.

**Acknowledgments**

This material is the result of work supported with resources and the use of facilities at the Boise VA Medical Center.

**Financial support.** Medical Research Service, United States Department of Veterans Affairs, and Pfizer.

**Potential conflicts of interest.** D.L.S. has been a consultant to and/or has received research funding from Pfizer, Cubist, Vicuron, Roche, Amgen, and Arpida Pharmaceuticals. All other authors: no conflicts.

**References**