Oxazolidinone Antibiotic Treatment Inhibits Virulence Factor Production in MRSA-Infected Burn Wounds

Jeffrey W. Shupp, MD[1], Rachel K. Truhan-Ortiz, MS[1], Lauren T. Moffatt, PhD[1], Daniel Y. Jo, BS[1], Pranay R. Randad, BS[1], Neil A. Mauskar, MD[1], Matthew J. Mino, MD[1], Bethany Amundsen, MD[1], Marion H. Jordan, MD, FACS[1]

[†]*The Burn Center, Department of Surgery, Washington Hospital Center, MedStar Health Research Institute, Washington DC*

Washington Hospital Center
The Burn Center
MedStar Health

Firefighters' Burn and Surgical Research Laboratory

Introduction

The mortality rate of burn patients is greatly increased if they experience complications of infection. Frequently, the organisms associated with such infections are Staphylococci, which include species such as MRSA that can be difficult to treat since they are antibiotic resistant. Virulence factor production can further complicate treatment as localized toxin presence may induce derailing of the healing process and allow for a more invasive infection, while toxin that becomes systemically circulating can induce shock and cause systemic host immune disruption.

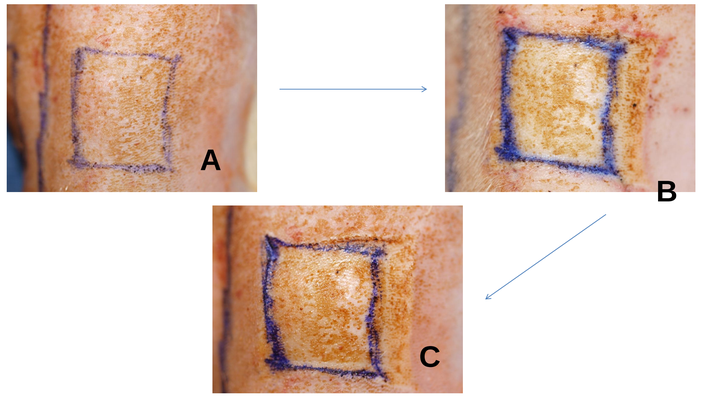


Figure 1: Digital Images of Pre-Burn (A), Post Burn (B) and 24 hr MRSA Inoculation

Methods

Male Sprague-Dawley rats were subjected to two (2 cm x 2 cm) deep partial thickness burn injuries on their dorsum (Figure 1). On the first post-injury day, wounds were inoculated with 1 x 10^8 CFU MRSA that produces Toxic Shock Syndrome Toxin-1 (TSST-1). Animals were then divided into three groups based on treatment: vancomycin, linezolid, or sham. For the remainder of the time course, animals received twice-daily antibiotic (or sham) treatment. Wound assessment, blood sampling and wound biopsies occurred daily for the 10-day time course. Quantitative cultures using MSA plates selective for Staph species, were performed on wound biopsies, with additional biopsies being used in an ELISA to detect TSST-1. Blood samples were analyzed according to similar protocols.

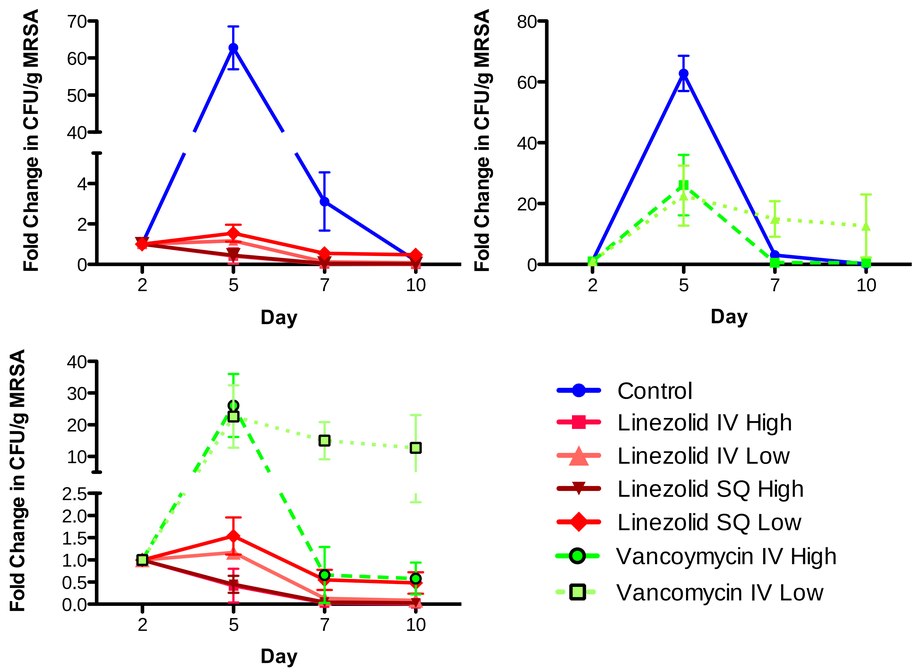


Figure 2: Quantitative cultures

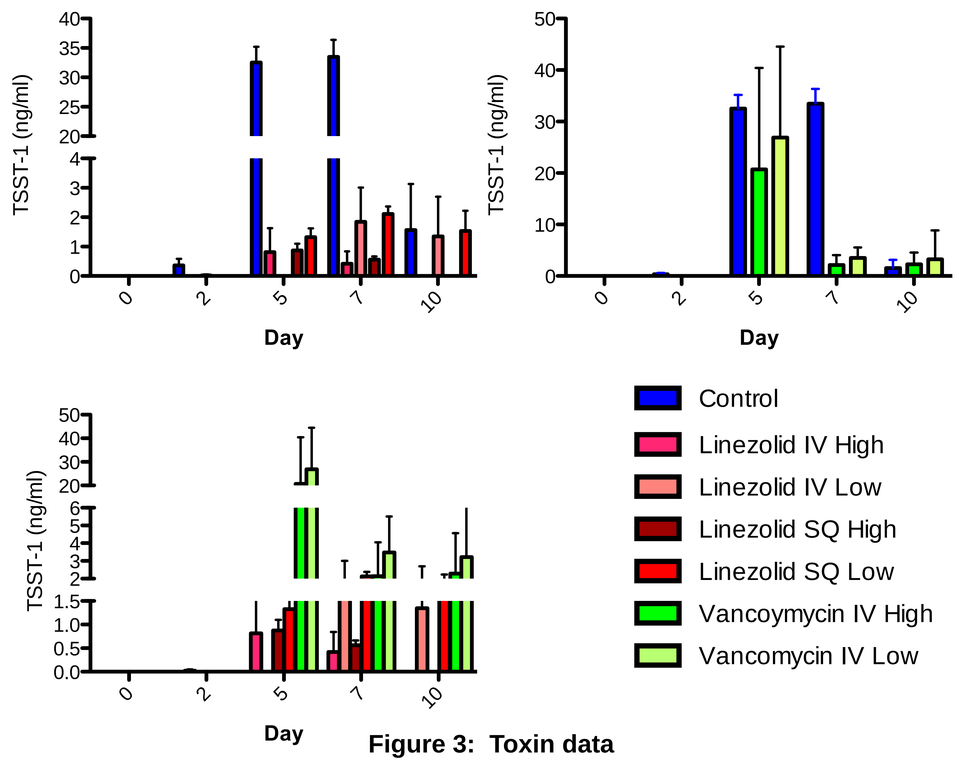


Figure 3: Toxin data

Results

All animals had wound quantitative cultures that exceeded 1 x 10^8 CFU/g one day following inoculation. Linezolid treatment significantly reduced the bacterial counts in the wounds. Positive controls and vancomycin-treated animals had toxin in their wounds by day 5 and this remained throughout the study (ranging from 20-80 ng/ml). Linezolid-treated animals had significant reduction in toxin production (< 5 ng/ml), and in most cases toxins were undetectable. No animals became systemically infected with bacteria at any point during the study.

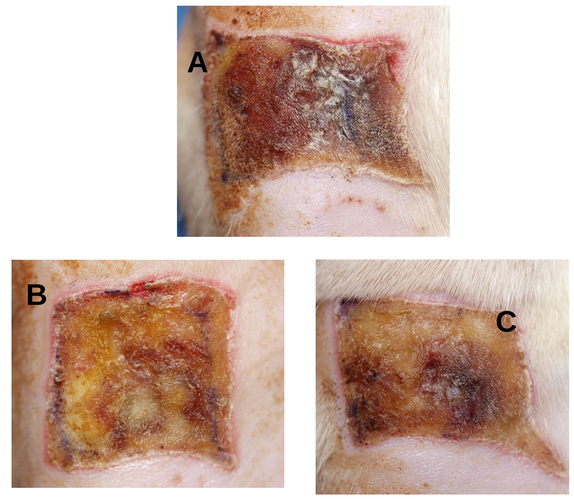
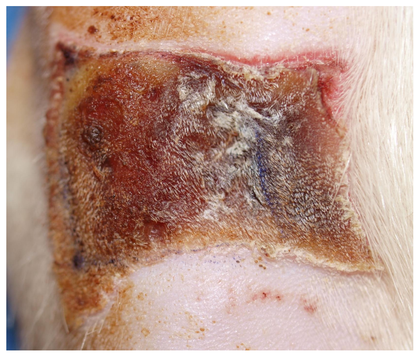


Figure 4: Day 10 Digital Images of Infected (A) High Dose Linezolid (B) and High Dose Vancomycin (C)

Conclusion

Superantigen production in burn wounds has morbid consequences in terms of long-term wound healing. A *S. aureus* burn wound infection model was created that allowed study of the effect of two standard-use antibiotics on local burn wound pathophysiology. Most noteworthy is that low-dose linezolid arrested toxin production in the wound.

Diseased



Linezolid