The Journal of Emergency Medicine, Vol. 49, No. 6, pp. 928–936, 2015

0736-4679/$ - see front matter

ELSEVIER

http://dx.doi.org/10.1016/j.jemermed.2015.07.026

Pharmacology in Emergency Medicine

RANDOMIZED CONTROLLED NONINFERIORITY TRIAL COMPARING DAPTOMYCIN TO VANCOMYCIN FOR THE TREATMENT OF COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS IN AN OBSERVATION UNIT

George J. Shaw, MD, PHD,*† Jason M. Meunier, PHD,* Joseph Korfhagen, PHD,* Beth Wayne, RN, JD,* Kimberly Hart, PHD,* Christopher J. Lindsell, PHD,* and Gregory Fermann, MD*

*Department of Emergency Medicine and †Program in Biomedical Engineering, University of Cincinnati, Cincinnati, Ohio
Reprint Address: George J. Shaw, MD, PHD, Department of Emergency Medicine, University of Cincinnati, 231 Albert Sabin Way, ML 0769, Cincinnati, OH 45267-0769

☐ **Abstract—Background: Incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing in complicated skin and skin structure infection (cSSSI) presenting to emergency departments (EDs). Treatment is heterogeneous and can require inpatient admission to an observation unit (OU). Vancomycin is commonly used in the OU for treatment, but increasing MRSA resistance to vancomycin suggests the need for alternatives. Daptomycin is an alternative but it is not known how it compares with vancomycin. Objective: This study tested the hypothesis that daptomycin is noninferior to vancomycin for the treatment of cSSSI in an OU, using a relative risk (RR) of 1.3 as the noninferiority limit. Methods: Subjects admitted to an ED-based OU with a diagnosis of cSSSI were eligible. Consenting subjects were randomized 1:1 to intravenous (i.v.) vancomycin at 15 mg/kg dosing every 12 h or i.v. daptomycin at 4 mg/kg once. Subjects were followed until they met objective criteria for discharge home or hospital admission. Discharged patients were prescribed 10–14 days of oral cephalexin and trimethoprim-sulfamethoxazole, or clindamycin if allergic to either of these medications. The primary endpoint was meeting objective discharge criteria with no change in antibiotic therapy or return to the ED for the same cellulitis within 30 days of OU discharge. Results: There were 100 patients enrolled. RR for satisfying the endpoint was 1.07 (95% confidence interval 0.58–1.98) for daptomycin compared with vancomycin. Hospital admission rates were 36% and 32% for daptomycin and vancomycin treatment, respectively. Conclusion: Daptomycin was not inferior to vancomycin in the treatment of cSSSI in an OU.** © **2015 Elsevier Inc.**

☐ **Keywords—cellulitis; daptomycin; vancomycin; ED observation unit**

INTRODUCTION

The incidence of cellulitis has been increasing in the United States, from 1.2 million visits to emergency departments (EDs) in 1993 to over 3.4 million in 2005 (1). The majority of these infections are caused by Gram-positive organisms such as *Staphylococcus aureus*, with an increasing prevalence of methicillin-resistant *S. aureus* cellulitis (MRSA) (2). We have previously shown the proportion of infections attributable to MRSA to be as high as 58%, which is similar to that found in the inpatient population (3,4).

Currently, antibiotic therapy in the treatment of cellulitis is heterogeneous (5). Many centers use intravenous (i.v.) vancomycin when there is a high suspicion of MRSA. However, decreasing susceptibility of MRSA to vancomycin is an evolving concern, and there is a need to consider alternative agents (6). Daptomycin is an antibacterial agent with excellent bactericidal activity against Gram-positive bacteria, and is dosed once daily (7). Its mechanism of action is to bind to the cell membrane and disrupt the membrane electrical potential, which inhibits protein synthesis, thus

RECEIVED: 20 October 2014; FINAL SUBMISSION RECEIVED: 15 July 2015;
ACCEPTED: 25 July 2015

leading to bacterial death (8). Currently, this drug is approved for complicated skin and skin structure infections (cSSSI) caused by *S. aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *S. agalactiae*, *S. dysgalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

cSSSIs are defined as skin or soft tissue infections requiring admission to an inpatient or observation unit stay for treatment with i.v. antibiotics (9). ED physicians are more frequently treating cSSSI with i.v. antibiotics, usually vancomycin, in an observation unit (10–12). This allows the clinician to determine whether the patient is responding to the chosen course of treatment, and whether admission can be avoided (11). The reported admission rate for cSSSI after observation unit treatment with i.v. vancomycin ranges from 13–38%, suggesting the approach may be beneficial in over 60% of cases (10–12). Whether daptomycin is an acceptable agent for treating patients with cSSSI in the observation unit setting is unknown.

The goal of the study was to determine if daptomycin is noninferior to vancomycin for the treatment of cSSSI in an observation unit. Specifically, we tested the hypothesis that patients treated with daptomycin meet objective discharge criteria without the need for changing their antibiotic regimen and without readmission within 30 days no less frequently than patients treated with vancomycin.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, randomized, controlled, single-site, open-label, noninferiority trial comparing daptomycin to vancomycin patients admitted to an observation unit for treatment of cSSSI (NCT01549613). The study was reviewed and approved by the local Institutional Review Board.

Sample Size

Historically, the discharge rate for patients treated in our observation unit for cSSSI with vancomycin has been approximately 80%. If the relative risk margin of noninferiority is set to 1.3, the expected discharge rate in the treatment arm should be no greater than about 60%, and anything less than that should be detected (13). When the sample size in each group is 50, a comparison of proportions with a one-sided 5% significance level will have 80% power to reject the null hypothesis that daptomycin and vancomycin are not equivalent (the difference in proportions is > 20%) in favor of the alternative hypothesis that the proportions in the two groups are equivalent. Therefore, target enrollment was 100 total patients, with 50 randomized to each treatment arm.

Selection of Participants

Participants were recruited at the time of an admission to an observation unit from a busy (90,000 patients/year) urban ED of a Level I trauma center from May 2012 through July 2013. The observation unit admits patients requiring short-term (up to 23 h) treatment, and evaluation and care is provided using guideline-based protocols. The observation unit is supervised by an emergency medicine attending physician 24 h per day, 7 days per week.

Potential study participants were identified by Clinical Study assistants from among those with a chief complaint or differential diagnosis inclusive of cellulitis. When it was determined that the patient would be admitted to the observation unit protocol for treatment of cSSSI, they were approached for consent if they met the inclusion and exclusion criteria shown in Table 1.

Methods, Intervention, and Measurements

Consenting patients underwent a baseline evaluation. Vital signs, medical history, and social history were obtained from the patient or from the medical record. Testing and treatment, including wound drainage and culture, were guided by the protocol for managing patients with cSSSI in the observation unit. Laboratory tests and

Table 1. Inclusion and Exclusion Criteria for Study

Inclusion Criteria	Exclusion Criteria
• Admitted to OU for cellulitis • 18 years old or greater • Able and willing to give informed consent • Hemodynamically stable (systolic blood pressure > 90 mm Hg and heart rate < 120 beats/min)	• Antibiotics given prior to enrollment • Suspected necrotizing infection • Diabetic foot ulcer • Genitourinary involvement • Postoperative infection (not including simple wound closure infection) • Suspected gouty or septic arthritis • Chronic lymphangitis • Requiring routine hemodialysis • Patient reported allergy to vancomycin • Patient reported allergy to daptomycin • Participation in another investigational treatment study within 30 days prior to enrollment • Prisoner • Pregnant or breast-feeding • Facial cellulitis whereby images contain patient-identifying features

OU = Observation Unit.