# Impact of Weight on Treatment Efficacy and Safety in Complicated Skin and Skin Structure Infections and Nosocomial Pneumonia Caused by Methicillin-Resistant *Staphylococcus aureus*

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## ABSTRACT

**Background:** There are few data on dose optimization and clinical outcomes of antimicrobial agents based on patients' weight, despite the rising prevalence of obesity. Because there are physiologic, pharmacologic, and dosing differences related to weight, it is important to evaluate the impact of weight on antimicrobial agents to optimize clinical outcomes.

**Objectives:** This study compared effects of weight on efficacy and safety in patients treated with linezolid or vancomycin for complicated skin and skin structure infections (cSSSIs) and nosocomial pneumonia (NP) caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

**Methods:** We analyzed data from 2 clinical trials of patients randomized to receive a fixed dose of linezolid or weight-based dosing of vancomycin for the treatment of cSSSIs or NP caused by MRSA. For each study, patients were stratified into quartiles (Q1–4 [lowest to highest weight, respectively]). Clinical success, microbiologic success, and adverse events (AEs) were evaluated.

**Results:** The analysis included 632 patients with cSSSIs (linezolid, n = 316; vancomycin, n = 316) and 447 patients with NP (linezolid, n = 224; vancomycin, n = 223). Among patients with cSSSIs, clinical success rates at the study end with fixed-dose linezolid were similar across all weight quartiles and similar to weight-based dosing of vancomycin for Q1–3. Among Q4 (the highest weight quartile [97–295 kg]), clinical success with vancomycin was significantly lower compared with linezolid (69.5% vs 86.2%; $P = 0.03$). Among patients with NP, no significant differences in success rates between fixed-dose linezolid and weight-based dosing of vancomycin were observed across all quartiles. Frequencies of AEs were consistent across the quartiles for both indications and by treatment.

**Conclusions:** Except for Q4 within the vancomycin-treated patients for MRSA cSSSI, the efficacy of fixed-dosed linezolid and weight-based dosing of vancomycin was maintained across all weight quartiles and MRSA infection types. The AEs were consistent with the known safety profiles of each drug regardless of weight quartile. ClinicalTrials.gov identifiers: NCT00087490 and NCT00084266. (*Clin Ther*. 2013;35:1557–1570) 

**Key words:** cSSSI, MRSA, linezolid, nosocomial pneumonia, vancomycin, weight.

## INTRODUCTION

The prevalence of obesity among adults exceeds 30% in the United States and 20% in several European countries.[1,2] The World Health Organization estimates that ~60% of the world's population will be classified as overweight or obese by 2030.[3] Despite the high prevalence of obesity, heavier patients are often excluded from clinical studies. This exclusion limits the amount of pharmacokinetic and pharmacodyna-

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mic data in this patient population and diminishes the opportunity for evidence-based dosing optimization among patients infected with serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections such as complicated skin and skin structure infections (cSSSIs) and nosocomial pneumonia (NP).

Physiologic differences in heavier patients may affect the pharmacokinetic and pharmacodynamic properties of various therapeutic agents,[4,5] including antimicrobial agents.[6,7] Guidelines for the use of vancomycin, an antibiotic that is indicated for serious MRSA infections,[8] recommend that the initial dose be based on weight and subsequently adjusted according to trough levels.[9,10] However, increased weight, body composition, and higher dose could alter the pharmacokinetics and toxicity of vancomycin. Individuals with increased weight have differences in the volume of distribution of vancomycin and increases in serum protein binding compared with those of normal weight.[11] These findings result in altered free serum vancomycin concentrations and increased renal clearance of vancomycin. Calculation of ideal dosing in weight-based regimens can be problematic because of the differences in these related pharmacokinetic parameters, particularly with hydrophilic drugs such as vancomycin, because adipose tissue is composed of ~30% water. In addition, there is debate on using total weight, versus ideal weight or adjusted weight, as the optimum dosing parameter.

Linezolid is a synthetic antibacterial agent indicated for the treatment of cSSSIs and NP caused by *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant strains).[12–14] Linezolid penetrates into the lung and other soft tissues at the current recommended fixed dose of 600 mg every 12 hours (ie, no weight-based adjustments are necessary).[15,16] The pharmacokinetic properties of linezolid have been studied as part of the clinical development program, but there are limited outcome data available specifically related to weight and treatment of MRSA cSSSI and NP.[14,17] Studies have described treatment of cellulitis and pneumonia with linezolid in obese patients, noting equivalent rates of clinical success despite lower linezolid serum concentrations compared with nonobese patients.[18,19] Other studies have shown prolonged inhibitory activity against typical pathogens causing skin and skin structure infections, including MRSA.[17,20]A recent case report found the association of subtherapeutic linezolid concentrations with decreased clinical efficacy in a morbidly obese man with MRSA and quinolone-resistant *Escherichia coli* pneumonia.[21] In addition, a study by Pea et al[22] describes the variation in linezolid plasma exposure during routine, fixed-dose administration. Although the authors suggested that patient characteristics, comorbid conditions, or coadministration of other drugs may account for the variability in drug exposure, they could not find a significant association with either weight or creatinine clearance.

In addition to the differences in physiochemical properties between different weight groups, heavier patients may be at greater risk of serious infections with MRSA.[23–27] Increased weight can affect skin as a functional barrier, compromise wound healing, and impair the lymphatic system and circulation.[25] All these factors can affect the susceptibility to, and treatment of, cSSSIs. In addition, heavier patients are more likely to have reduced lung volume (affecting pulmonary function), demonstrate difficulty maintaining artificial airways, and incur delays in detection of infection and onset of complications resulting from diminished radiologic findings.[28–30] Although the obesity-associated risk of MRSA NP has not been specifically elucidated, increased weight has been shown to be an independent risk factor for various nosocomial infections.[26–28]

There is an inherent complexity in the treatment of resistant pathogens, including MRSA, that lead to variability in clinical outcomes, and increased weight augments the current difficulties in management. The limited data regarding treatment outcomes in relation to weight in serious and life-threatening MRSA infections necessitate further investigation. The objective of the present study was to compare the effect of patient weight on clinical and microbiologic outcomes and adverse events (AEs) of linezolid and vancomycin in the treatment of cSSSIs and NP caused by MRSA using data from prospective Phase IV clinical trials.[13,31] Because there are no dose-adjustment recommendations for linezolid, it was hypothesized that there would be no effect of weight on the clinical and AE profiles of linezolid in the treatment of patients with cSSSIs and NP caused by MRSA.

## PATIENTS AND METHODS

### Patients

Data from patients enrolled in 2 prospective, randomized, multicenter Phase IV clinical trials were