

# High vancomycin serum trough is not associated with reduction of mortality in methicillin-resistant *Staphylococcus aureus* bloodstream infections

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## Abstract

The current Infectious Diseases Society of America (IDSA) and the American Society of Health-System Pharmacists (ASHP) guidelines recommend a vancomycin serum trough concentration of 15 to 20 mg/L in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI). The objective of this study was to evaluate the mortality difference in MRSA BSI pre and post hospital-wide implementation of higher serum trough concentration per IDSA/ASHP guidelines. This was a retrospective cohort study performed in an integrated hospital health system (2238 beds) in Southeast Michigan. We evaluated 1173 consecutive individual patients with MRSA BSI over a 9-year period. The vancomycin minimum inhibitory concentrations (MICs) were determined by Etest method for all isolates. Attainment of vancomycin serum trough concentration per IDSA/ASHP guidelines was implemented in January 2010 by clinical pharmacist as part of the antimicrobial stewardship program. During the study period, the mean vancomycin MIC was  $1.57 \pm 0.26$  mg/L, the percentage of MRSA isolates with vancomycin MIC  $\geq 2$  mg/L was 17.5%, and the 30-day all-cause mortality was 16.5%. There was no difference in mortality during the 9-year period ( $p=0.193$ ). There was no change in all-cause mortality for MRSA BSI after the hospital-wide implementation of higher vancomycin dose and serum trough concentration per IDSA/ASHP guidelines. Prospective multicenter, controlled studies evaluating optimal dosing strategies for vancomycin are warranted.

## Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection (BSI) is an important cause of morbidity and mortality with a 30-day all-cause mortality of up to 30% [1-5]. The current Infectious Diseases Society of America (IDSA) and the American Society of Health-System Pharmacists (ASHP) guidelines recommend a vancomycin loading dose of 25 to 30 mg/kg and target serum trough concentration of 15 to 20 mg/L in patients with MRSA BSI [6,7]. The rationale for these recommendations is based on a combination of evidence including outcomes using the ratio of the vancomycin area under the curve (AUC) to minimum inhibitory concentration (MIC) [AUC/MIC], clinical failure in patients with susceptible MRSA strains with higher vancomycin MICs, and inability to achieve target AUC/MIC in strains with higher MICs from earlier recommended therapy [6-14]. This was particularly important in Detroit, where increased resistance and reduced susceptibility to vancomycin in *S. aureus* have been a serious concern. The first MRSA cases in the United States were identified in Detroit in the 1980s, which resulted in frequent use of vancomycin [15]. Consequently, the first reported vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) emerged from Detroit [16].

There are limited published literatures on the impact of newer dosing strategies on patient outcomes. Therefore, we sought to evaluate mortality difference in MRSA BSI pre and post hospital-wide

implementation of higher vancomycin serum trough concentration per IDSA/ASHP guidelines in a large patient cohort over a 9-year period.

## Materials and methods

### Study design and patient identification

This was a retrospective cohort study conducted in a large integrated hospital health system (2238 beds) in Southeast Michigan. All patients who were  $\geq 18$  years of age with confirmed MRSA BSI from July 2005 to June 2014 identified via review of microbiology laboratory records were eligible. Patient demographics, comorbid conditions, clinical outcomes, and laboratory data were reviewed. Vancomycin serum trough concentration guidelines, following the publication of IDSA/ASHP recommendations, were implemented in the entire health system since January 2010 by clinical pharmacists as part of the antimicrobial stewardship program. Clinical pharmacists managed vancomycin dosing, monitored and audited levels, and

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used established pharmacodynamic dosing models both before and after implementation of the system wide change in dosing. Mortality was evaluated before and after the implementation of the published guideline in the entire health system.

### Susceptibility testing

The initial identification and susceptibility testing of isolates were performed by the clinical microbiology laboratory using VITEK 2 (bioMérieux, Inc., Durham, NC, USA) according to the manufacturer's instructions as set by the Clinical and Laboratory Standards Institute (CLSI) [17]. Vancomycin MICs for all isolates were also determined by Etest method (bioMérieux, Inc.) according to the manufacturer's instructions [18,19].

### Statistical analysis

All continuous data were described using means and standard deviations, while all categorical data were presented as counts and percentages. Univariate two-group tests were used to compare groups: two-group t-tests, analysis of variance, chi-square, and Fisher's exact as appropriate. A Spearman's rank correlation coefficient was used to examine the correlation between mean vancomycin Etest MIC over time. This nonparametric test was chosen due to the ordinal nature of the time variable. The trend in average vancomycin Etest MIC over time was fit using a general linear model. Statistical significance was set at  $p < 0.05$ . All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

### Results

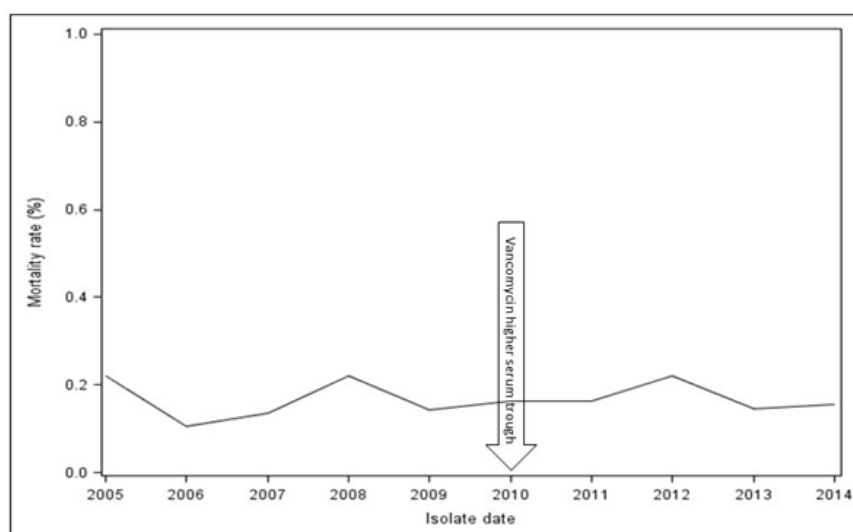
A total of 1,173 patients were evaluated from 2005 to 2014. Overall, the 30-day all-cause mortality was 16.5% and did not change after the implementation of the IDSA/ASHP guidelines (Figure 1). The mean MIC, percentage of MRSA isolates with vancomycin MIC  $\geq 2.0$  mg/L, and mortality per year are shown in Table 1. Mortality was 16.5% among patients with high vancomycin MIC ( $\geq 1.5$  mg/L) vs. 17.0% in patients with low vancomycin MIC ( $< 1.5$  mg/L). A summary of mortality over the 9 years in relation to vancomycin susceptibility is shown in Table 1. There was no statistically significant change in mortality over the 9 years period ( $p = 0.193$ ). The mean vancomycin MIC over the study period was  $1.57 \pm 0.26$  mg/L. When evaluating a

change in mean vancomycin MIC by Etest method over time, we found a weakly positive correlation coefficient of 0.156 ( $p < 0.001$ ), when using spearman's correlation. We did not find differences between the pre and post intervention periods ( $p = 0.188$ ) in MRSA isolates with MIC  $\geq 2$  mg/L.

### Discussion

This study demonstrated no impact on MRSA BSI mortality rates after the 2010 implementation of IDSA/ASHP guidelines for vancomycin use. Overall mortality (16.5%) found in our study was lower than rates published from other institutions [1-5]. We found no increase in vancomycin MICs pre and post intervention that would have an impact on the findings observed. Vancomycin was dosed and monitored by health system pharmacists before and after the guideline change, following established pharmacodynamic modes for dosing, with periodic auditing, and infectious disease physician review of desired targets. Importantly, this study illustrates that despite following dosing guidelines for vancomycin designed to improve outcomes, mortality rates of *S. aureus* bloodstream infections have remained stagnant in a large number of patients before and after implementation of the guidelines hospital wide and over a several year period.

Vancomycin has been routinely used to treat severe MRSA infections since the 1980s; however, despite its use for over 50 years, controlled trials of dosing strategies are not available and optimal dosing remains undefined. In August 2009, target dosing recommendations were altered based on earlier studies demonstrating outcomes of vancomycin therapy utilizing AUC/MIC. Additionally, concern over susceptible strains with higher MICs (MIC creep), failure of therapy due to these organisms, and their inability to achieve targeted AUC/MIC, contributed to the change in recommendations [6-14]. Nevertheless, studies of vancomycin MIC creep have shown variability. Some studies have shown that the MIC creep can be related to methods used for storage of strains, strain selection, single center analysis, year of study, and statistical methods used for analysis [20-26]. Conversely, other single-center and large-multicenter studies have not shown increases in MIC even when controlling for strain types [20-24]. When comparing susceptibility testing methods, the MICs reported by the Etest method are higher than those reported by the broth microdilution method [25,26].



**Figure 1.** Mortality of MRSA bloodstream infection by year since the implementation of IDSA/ASHP for vancomycin dosing guideline between 2005-2014.

**Table 1.** Vancomycin MICs and 30-day all-cause mortality of MRSA bloodstream infection from 2005-2014.

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
<b>Patients (n)</b>	36	123	119	144	118	137	145	141	147	61
<b>Mean MIC mg/L(±SD)</b>	1.58 (0.35)	1.59 (0.24)	1.45 (0.22)	1.53 (0.29)	1.66 (0.27)	1.51 (0.23)	1.51 (0.17)	1.59 (0.25)	1.68 (0.26)	1.66 (0.23)
<b>Percent (%) MRSA with vancomycin MIC ≥ 2 mg/L</b>	19.4	21.1	5	6.9	31.4	8.8	6.2	19.1	36	31.1
<b>Mortality (%)</b>	22.2	10.6	13.5	22.2	14.4	16.1	16.4	22.1	14.5	15

The rationale for the newer AUC/MIC targets was based on studies that demonstrated susceptible strains with higher MICs were associated with treatment failure [27]. The most recent meta-analysis of 38 studies consisting of 8291 episodes of *S. aureus* bacteremia showed an overall mortality of 26.1% [27]. Mortality was 26.8% in patients with high vancomycin MIC ( $\geq 1.5$  mg/L) vs. 25.8% in patients with low vancomycin MIC ( $< 1.5$  mg/L). Additionally, there were no significant differences in risk of death in subgroups with high vs. low vancomycin MIC across different study designs, microbiological susceptibility assays, MIC cutoffs, clinical outcomes, duration of bacteremia, previous vancomycin exposure, and treatment with vancomycin [28]. Furthermore, an optimal vancomycin AUC/MIC has not been established. Although an AUC:MIC  $\geq 400$  is the prevailing target, this recommendation is based on data derived from mouse models and uncontrolled trials, which also suggest that the current trough targets are not associated with better outcomes [29-31]. In a study of 200 consecutive patients with MRSA BSI, there was no difference in outcomes comparing patients with vancomycin serum trough levels of  $< 15$  mg/L or  $\geq 15$  mg/L [29]. Finally, the commonly cited AUC/MIC of 400 as the target is based on broth microdilution MICs, which are lower than Etest MICs, and are achievable using lower dosing strategies [30,31]. The MIC by Etest method of 1.5-2.0 mg/L observed in our study is equivalent to 0.5-1.0 mg/L by broth microdilution, which is within achievable targets.

The goal of achieving a serum vancomycin trough of 15-20 mg/L for bacteremia must be balanced with toxicity. With earlier serum vancomycin targeted trough of 5-15 mg/L, the rate of nephrotoxicity was relatively low. However, with higher serum vancomycin targeted trough (15-20 mg/L), risk of nephrotoxicity is increased, and it can be difficult to maintain levels within the targeted range in patients with fluctuating renal function [31]. Additionally, there is evidence to suggest that there is a significant increase in the rate of nephrotoxicity associated with higher serum vancomycin trough [32]. In a review of 176 patients at 2 teaching hospitals (2008-2011) who received  $> 7$  days of vancomycin and attained high troughs (15-20 mg/L), 14% experienced nephrotoxicity (creatinine rise of 0.5 mg/dL or 50% over baseline on 2 consecutive days) [32]. Risk factors included admission to a general medicine unit, extended duration of treatment ( $> 7$  days), gastrointestinal comorbidity, malignancy, and febrile neutropenia [32]. In a study consisting of 188 intensive care unit patients from 4 centers who received vancomycin for the treatment of pneumonia, nephrotoxicity occurred in 15.4% of vancomycin-treated patients. Multivariate analysis showed the following variables to be independently associated with nephrotoxicity: initial vancomycin trough levels  $\geq 15$  mg/L (odds ratio [OR], 5.2 [95% CI, 1.9-13.9];  $p=0.001$ ), concomitant aminoglycoside use (OR, 2.67 [95% CI, 1.09-6.54];  $p=0.03$ ), and duration of vancomycin therapy (OR for each additional treatment day, 1.12 [95% CI, 1.02-1.23];  $p=0.02$ ). The incidence of nephrotoxicity increased as a function of the initial vancomycin trough level, rising from 7% at a trough  $< 10$  mg/L to 34% at  $> 20$  mg/L ( $p=0.001$ ). The mean time to nephrotoxicity decreased from 8.8 days at vancomycin trough levels  $< 15$  mg/L to 7.4 days at  $> 20$  mg/L (Kaplan-Meier analysis,

$p=0.0003$ ) [33]. Conversely, other studies have shown that vancomycin is minimally nephrotoxic when appropriate dosing is utilized, even among elderly and critically-ill patients with complicated infections [34,35]. However, the collective literature indicates that an exposure-nephrotoxicity relationship for vancomycin exists. The probability of a nephrotoxic event increases as a function of trough concentration and duration of therapy. A systematic review of 15 studies, selected from a total of 240 publications from 1996-2012, showed higher vancomycin trough ( $\geq 15$  mg/L) was associated with increased nephrotoxicity after adjustment for independent risk factors (Odds Ratio 2.67; 95% CI: 1.95-3.65). An incremental increase in nephrotoxicity was observed with a longer duration of vancomycin. The toxicity was reversible in most cases, with required temporary dialysis in 3% of toxicity cases, and no mention of end stage renal disease [36].

This study has several limitations, including single center trial, retrospective study design, lack of information on individual dosing of patients and serum trough levels, and uncontrolled confounding variables associated with mortality. Strengths include large numbers of patients with *S. aureus* bacteremia over a several year period, and dosing carefully done and monitored by experienced hospital pharmacists. Importantly, this study illustrates that despite various advances in medical therapy mortality rates of *S. aureus* bloodstream infections have remained stagnant in a large number of patients. We support the recommendations of individualized vancomycin dosing while taking into consideration the patient's source of infection, underlying medical conditions, particularly renal function, *in vitro* susceptibility, and previous vancomycin exposure. Therefore, it is incumbent on us to seek better methods of preventing infections and improving dosing strategies and outcomes. Most importantly, our study demonstrates the need for randomized controlled studies of optimal vancomycin dosing strategies that include patient safety as well as outcomes.

## Authorship

All authors mentioned above gave substantial intellectual contribution to this manuscript.

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## Competing interests

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