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Haley J. Morrill
University of Rhode Island

Aisling R. Caffrey
University of Rhode Island, aisling_caffrey@uri.edu

See next page for additional authors

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Vancomycin Dosing Considerations in a Real-World Cohort of Obese and Extremely Obese Patients

Brief Report

Haley J. Morrill[a,b], Aisling R. Caffrey[a,b], Eunsun Noh[a,b], and Kerry L. LaPlante[a,b,c*]

[a]Veterans Affairs Medical Center, Infectious Diseases Research Program, Providence, Rhode Island

[b]University of Rhode Island, Department of Pharmacy Practice, College of Pharmacy, Kingston, Rhode Island

[c]Warren Alpert Medical School of Brown University, Division of Infectious Diseases, Providence, Rhode Island

*Author for correspondence:

Kerry L. LaPlante

University of Rhode Island, College of Pharmacy

7 Greenhouse Rd, Suite 295A

Kingston, RI 02881

Tel: 401.874.5560

e-mail: KerryLaPlante@uri.edu

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Running head: Vancomycin Dosing in Obese and Extremely Obese

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Abstract

Study Objective: To compare the effects of empiric vancomycin dosing regimens on attainment of optimal target trough concentrations in obese (body mass index [BMI] 30–40 kg/m^2) and extremely obese (BMI ≥ 40 kg/m^2) patients.

Design: Retrospective cohort study.

Data Source: National Veterans Affairs (VA) standardized databases.

Patients: A total of 263 obese and 71 extremely obese (actual body weight range 72–244 kg in both groups) inpatients from all VA facilities nationally who had suspected methicillin-resistant *Staphylococcus aureus* pneumonia and were treated with vancomycin between 2002 and 2012.

Measurements and Main Results: Patients with steady-state trough concentrations (measured ≤ 2 hours before the next vancomycin dose) and no evidence of acute kidney injury prior to vancomycin initiation were included. Logistic regression models were used to measure the effect of various vancomycin dosing regimens on attainment of optimal target trough concentrations (15–20 mg/L). The mean total daily vancomycin dose was lower in obese versus extremely obese patients (2005 ± 736 vs. 2306 ± 934 mg, $p<0.05$). The mean weight-based daily dose was higher in obese patients (20 ± 7 vs. 17 ± 7 mg/kg/day, $p<0.05$). In each group, about 20% of patients achieved optimal target trough concentrations. In obese patients, the standard dose of approximately 30 mg/kg/day was appropriate for target trough concentration attainment (odds ratio [OR] 5.15, 95% confidence interval [CI] 1.69–15.64). In extremely obese patients, a lower dose of 20–25 mg/kg/day was appropriate for target trough concentration attainment (OR 6.07, 95% CI 1.01–36.51).

Conclusion: In this real-world study, we offer additional consideration of vancomycin dosing in obese and extremely obese patients. Extremely obese patients may require a lower weight-based daily dose than obese patients to reach target vancomycin trough concentrations.

According to the Centers for Disease Control and Prevention, the prevalence of obesity has increased over the past 20 years.[1] More than one third of adults were obese in the United States in 2011-2012, which corresponds to over 78 million adults.[1] This is concerning since obesity is associated with an increased risk of infection as well as increased morbidity and mortality.[2-4]

For years, vancomycin, a glycopeptide antibiotic, has served as the standard of care for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[5-7] Vancomycin exhibits a time-dependent antibacterial effect, and the area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) ratio is the best predictor of clinical efficacy.[8] Several studies suggest a target AUC/MIC ratio of ≥ 400 to achieve clinical effectiveness.[9, 10] A vancomycin consensus review recommends maintaining serum trough concentrations between 15-20 mg/L for complicated infections, such as pneumonia, to achieve target AUC/MIC ratios when the vancomycin MIC is ≤ 1 mg/L.[8] Empiric vancomycin doses of 15-20 mg/kg of actual body weight (ABW) given every 8-12 hours are recommended for most patients with normal renal function to achieve these target serum concentrations.[8] Additionally, a loading dose of 25-30 mg/kg should be considered in seriously ill patients to achieve target concentrations quickly.[8] MRSA guidelines provide similar recommendations for vancomycin dosing and monitoring.[11]

Unfortunately, data are limited on the optimal dosing of vancomycin in obese patients. Moreover, it is presently unknown whether dosing recommendations should change based on different weight categories among obese patients. Despite this, the vancomycin consensus review recommends that initial doses for obese patients should be based on ABW and that dosage adjustments be made based on serum trough levels to achieve optimal concentrations.[8, 12] No special recommendations for extremely obese patients are provided.[8]

Optimizing vancomycin therapy in obese and extremely obese patients remains a challenge for clinicians. As knowledge of antimicrobial pharmacokinetics is limited, and assessment of distribution and elimination are skewed in extremely obese patients, underdosing

or overdosing can easily occur. A better understanding of the role of extreme patient weight on vancomycin dosing is needed. As such, we sought to compare the effects of empiric vancomycin dosing regimens on attainment of optimal target trough concentrations in a real-world cohort of obese and extremely obese patients.

Methods

Data Sources

We used national Veterans Affairs (VA) standardized databases to obtain *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic and procedure codes, microbiology results, pharmacy records for dispensings and barcode administration, and laboratory results.[13]

Study Design and Patient Population

We conducted a national retrospective cohort study of patients admitted to VA hospitals with positive MRSA cultures from a pulmonary site between 2002 and 2012, as described previously.[13] Patients exposed to at least one day of therapy with intravenous vancomycin were selected for inclusion. We included all obese patients with a body mass index (BMI) ≥ 30 kg/m^2.[14]

We included patients with trough concentrations measured at steady state (i.e., after at least three vancomycin doses) and measured ≤ 2 hours before the next vancomycin dose (Figure 1).[8] Patients were included if they had no evidence of acute kidney injury (defined as an increase in serum creatinine concentration of 0.5 mg/dL or 50% prior to starting vancomycin).[8] Only the first trough level after the third vancomycin dose, which met our steady-state definition, was assessed. Weight-based daily dosing categories were defined as follows: <10, 10-15, 15-20, 20-25, 25-30, and ≥ 30 mg/kg/day. Target vancomycin trough concentrations were defined

as 15-20 mg/L. Subtherapeutic concentrations were defined as < 15 mg/L, and supratherapeutic concentrations were defined as ≥ 20 mg/L.[8]

Study Groups

Patients were divided into two groups—obese (BMI 30-40 kg/m^2) and extremely obese (BMI ≥ 40 kg/m^2)—based on the World Health Organization's classification of obesity.[14]

Statistical Analysis

For categorical data, we used a Fisher exact or χ^2 test to evaluate differences between the obese and extremely obese groups. For continuous data, we used a *t* test for normally distributed data and the Wilcoxon rank sum test for nonparametric data. We used logistic regression models to measure the effect of initial maintenance weight-based daily vancomycin dosing regimens on target versus subtherapeutic and supratherapeutic trough attainment in obese and extremely obese patients, controlling for renal function. Renal function was estimated by using the Cockcroft-Gault equation using adjusted body weight. All analyses were performed using SAS statistical software (version 9.3; SAS Institute Inc., Cary, NC).

Results

We identified 334 vancomycin-treated patients from our original cohort with trough concentrations (Figure 1): 263 patients (78.7%) in the obese group and 71 patients (21.3%) in the extremely obese group (ABW range 72-244 kg in both groups) (Table 1). The initial maintenance doses ranged widely (4-46 mg/kg/day or 500-6000 mg/day). The most frequent daily maintenance dose was 2000 mg, which was dosed every 12 hours in most patients. The initial daily maintenance vancomycin dose was significantly lower for obese patients versus the extremely obese (2005 ± 736.3 vs. 2306 ± 934.4 mg/day), however the weight-based daily dose was higher for obese patients (20 ± 7.4 vs. 17 ± 6.8mg/kg/day).

No significant differences in mean serum vancomycin trough concentrations were noted between obesity groups (Table 1). In addition, the percentages of patients within the various trough level categories did not differ significantly between obesity groups (Figure 2). Only 19.4% (n=51) of the obese and 22.5% (n=16) of the extremely obese patients achieved target trough concentrations (15-20 mg/L). Mean weight-based daily doses were significantly higher for the obese versus extremely obese patients when trough levels were 10-15 mg/L or 15-20 mg/L (Table 2). At a target trough concentration of 15-20 mg/L, mean weight-based daily doses were about 21 and 14 mg/kg/day for obese and extremely obese patients, respectively.

The most frequent daily dose for patients who achieved target trough concentrations was 2000 mg in both groups (Figure 3). No significant difference was noted in attainment of target trough concentrations among those dosed at the standard dose of 1000 mg every 12 hours versus those who were not (21.1% [30/142 patients] vs. 19.3% [37/192 patients]).

In obese patients, the dose category of 25-30 mg/kg/day ABW was associated with a higher odds of target trough concentration attainment (odds ratio [OR] 5.15, 95% confidence interval [CI] 1.69-15.64) (Table 3). We found similar results for a subset of obese patients (n=146) with trough level measurements obtained within 30 minutes of the next vancomycin dose (OR 5.0, 95% CI 1.07–23.29). Additionally, in obese patients, the dose category of <10 mg/kg/day was associated with a lower odds of target trough concentration attainment (OR 0.19, 95% CI 0.05-0.70)

In extremely obese patients, the dose category of 20-25 mg/kg/day ABW was associated with a higher odds of target trough concentration attainment (OR 6.07, 95% CI 1.01-36.51). No other significant findings were observed.

Discussion

Clinicians face extreme difficulty when properly dosing vancomycin in obese and extremely obese patients. This is exemplified by the wide range of total daily doses observed in our study

patients (500-6000 mg/day). Almost half of our patients (48%) had subtherapeutic trough concentrations. Data are consistent with most published reports on vancomycin dosing in obese patients and ability to achieve "target concentrations."[15-17] In a small study that included 37 obese patients, 57% had trough levels <15 mg/L.[17] In a multicenter study, 99% (252/254 patients) of overweight and obese patients did not receive the recommended vancomycin dose (15 mg/kg/dose).[15] Underdosing vancomycin is a serious concern, as it can lead to inadequate serum vancomycin concentrations and poor penetration at the site of infection, development of resistance, and potentially poor clinical outcomes.[8, 10] In our study, in obese patients, doses <10 mg/kg/day were associated with a lower odds of target trough attainment.

We found that the standard vancomycin dose (~30 mg/kg/day) may be appropriate in obese patients. Previous studies have demonstrated that while obese patients required higher total daily doses than normal-weight patients, no significant differences in weight-based daily doses were required to reach target vancomycin concentrations.[12, 18] In both of these small studies, the standard dose of ~25-30 mg/kg/day was required to achieve target trough concentrations in both normal-weight and obese patients. However, both of these studies included young patients (aged 25-40 years) with good renal function. In our study, over 50% of our cohort were aged 65 years or older. Most patients (68%) had reduced renal function. This may explain why most patients in our study were dosed every 12-24 hours, despite recommendations that vancomycin be dosed more frequently in obese patients (every 8 hours) due to altered pharmacokinetic parameters, including a shorter half-life and increased clearance.[12, 18]

We also found that extremely obese patients may require lower weight-based daily doses (20-25 mg/kg/day) than obese patients. A single-center retrospective study found that a group of patients treated according to a revised protocol (n=74) using lower doses (10 mg/kg every 12 hours or 15 mg/kg every 24 hours) had improved attainment of target trough concentrations compared with a group of patients treated according to an original protocol

(n=64) using standard doses (15 mg/kg every 8-12 hours), with 56% attainment in the revised protocol group versus 36% in the original protocol group.[16] As expected, the mean dose administered was lower in the revised protocol group compared to the original protocol group (19 vs. 34 mg/kg/day). Patients in the revised protocol group had a higher mean BMI (~44 kg/m^2) than patients in the original protocol group (~39 kg/m^2). It is therefore likely that more patients in the revised protocol group met extremely obese BMI criteria (BMI ≥ 40 kg/m^2) than in the original protocol group, which may partly explain why patients treated according to the revised protocol had a higher percentage of target trough attainment despite using lower doses.

Almost half of our patients were dosed at the standard dose of 1000 mg every 12 hours. Despite the introduction of the updated vancomycin dosing recommendation in 2009,[8] a greater proportion of patients received the standard vancomycin dose in our study after 2009 compared with before 2009 (36.8% from 2002–2009 vs. 46.8% from 2009–2012), although the difference was not significant. Moreover, about 20% of patients achieved target trough concentrations before and after introduction of these guidelines. Among those who did achieve target trough concentration attainment (67 patients), the most frequent dose was the standard dose (2000 mg/day) in both obese and extremely obese patients. This is in contrast to a recent prospective pharmacokinetic study in extremely obese patients, in which dosing simulations indicated that much higher doses (4000-5000 mg/day) were necessary for a high probability of target attainment.[20] However, that study also found that patients with lower renal function may require lower doses. Our results suggest that the standard dose of vancomycin may be appropriate at least initially in obese and extremely obese elderly patients. If the standard dose is used initially, it is important to make dosage adjustments promptly based on therapeutic drug monitoring. Recent evidence suggests obtaining two serum vancomycin concentrations in obese patients to improve target trough attainment.[21]

There are several limitations to our findings. We only assessed trough levels associated with initial empiric vancomycin dosing. We did not assess changes in vancomycin dose or

trough concentrations later in therapy. Therefore, results may not extend to levels beyond this period. We cannot ensure that troughs remained at the levels we observed later in therapy. Moreover, as obese patients show an increased volume of distribution and clearance, vancomycin may not have been at steady state. Additionally, we did not assess the impact of loading doses, as the first dose was only higher than subsequent doses in < 5% of our patients, and this dose was often well below the recommended loading dose of 25-30 mg/kg.

As vancomycin has a half-life of 5-8 hours, collection of a level within 2 hours before the next dose may not reflect a true trough level, therefore leading to misclassification of the trough as target, subtherapeutic, or supratherapeutic. Ideally, a trough level should be measured just before the next dose; however, this is not always feasible in clinical practice.[8] This is exemplified by the fact that by using our "relaxed" criteria of collection of a level within 2 hours (and also relaxed acute kidney injury criteria), only ~10% of our original vancomycin-treated cohort of over 2500 patients met inclusion criteria. However, we did find similar results in a subset of obese patients with a trough level obtained within 30 minutes of the next vancomycin dose.

Due to the retrospective nature of this study, multiple serum vancomycin concentrations and MICs were not available for all patients, thus precluding our ability to calculate AUC/MIC ratios. As the purpose of trough measurement is to serve as a surrogate of AUC, this is a major limitation of our study. Our study, however, reflects real-world clinical practice, where it is often infeasible to calculate AUC/MIC ratios. Many busy clinicians lack the time for collection of multiple levels and/or the training needed for subsequent AUC/MIC calculation.

As the focus of our study was to evaluate empiric vancomycin dosing in obese and extremely obese patients, we did not assess outcomes or toxicity. We assumed that a trough level of 15-20 mg/L was the most optimal target for our obese and extremely obese patients based on vancomycin consensus recommendations.[8] It is largely unknown which trough level is most optimal and associated with the best outcomes in obese and extremely obese patients

with MRSA pneumonia. Furthermore, vancomycin does not display simple pharmacokinetics. Therefore, the ability to reach this narrow window may be limited, and it may not be the best target for clinical success.

Our study is further limited by the relatively small sample size. Finally, the generalizability of our findings to general U.S. population may be limited, as our study was conducted in a VA population, consisting of mostly older men.

Conclusion

We contribute to the literature by offering additional consideration on the dosing of vancomycin in our real-world cohort of obese and extremely obese patients. The standard dosing of approximately 30 mg/kg/day may be appropriate for obese patients (BMI 30-40 kg/m^2) to reach target trough levels of 15-20 mg/L. Extremely obese patients (BMI ≥ 40 kg/m^2) may require lower weight-based daily doses than obese patients to achieve target vancomycin trough concentrations. Further research is warranted to determine if our results extend to other study populations and to determine which vancomycin trough levels are associated with the best outcomes in obese and extremely obese patients with MRSA infections.

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among adults: United States, 2011-2012. NCHS data brief 2013;131:1-8.

2. Kornum JB, Norgaard M, Dethlefsen C, et al. Obesity and risk of subsequent hospitalisation with pneumonia. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 2010;6:1330-6.

3. Hingston CD, Holmes TW, Saayman AG, Wise MP. Obesity and risk of pneumonia in patients with influenza. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology 2011;5:1299; author reply 99-300.

4. Falagas ME, Kompoti M. Obesity and infection. The Lancet infectious diseases 2006;7:438-46.

5. Lodise TP, Jr, McKinnon PS. Burden of methicillin-resistant Staphylococcus aureus: focus on clinical and economic outcomes. Pharmacotherapy 2007;7:1001-12.

6. Sakoulas G, Moellering RC, Jr. Increasing antibiotic resistance among methicillin-resistant Staphylococcus aureus strains. Clin Infect Dis 2008;S360-7.

7. Grace E. Altered vancomycin pharmacokinetics in obese and morbidly obese patients: what we have learned over the past 30 years. J Antimicrob Chemother 2012;6:1305-10.

8. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2009;1:82-98.

9. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clinical pharmacokinetics 2004;13:925-42.

10. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2011;8:975-81.

11. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2011;3:e18-55.

12. Blouin RA, Bauer LA, Miller DD, Record KE, Griffen WO, Jr. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrobial agents and chemotherapy 1982;4:575-80.

13. Caffrey AR, Noh E, Morrill HJ, LaPlante KL. The Effects of Obesity on the Comparative Effectiveness of Linezolid and Vancomycin in Suspected Methicillin-resistant Staphylococcus aureus Pneumonia. Advances in Pharmacoepidemiology & Drug Safety 2015 (accepted).

14. World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation of Obesity. Geneva, 3-5 June 1997.

15. Hall RG, 2nd, Payne KD, Bain AM, et al. Multicenter evaluation of vancomycin dosing: emphasis on obesity. The American journal of medicine 2008;6:515-8.

16. Reynolds DC, Waite LH, Alexander DP, DeRyke CA. Performance of a vancomycin dosage regimen developed for obese patients. Am J Health Syst Pharm 2012;11:944-50.

17. Richardson J, Scheetz M, O'Donnell EP. The association of elevated trough serum vancomycin concentrations with obesity. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 2015.

18. Bauer MP, Kuijper EJ, van Dissel JT, European Society of Clinical M, Infectious D. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2009;12:1067-79.

19. Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. European journal of clinical pharmacology 1998;8:621-5.

20. Adane ED, Herald M, Koura F. Pharmacokinetics of Vancomycin in Extremely Obese Patients with Suspected or Confirmed Staphylococcus aureus Infections. Pharmacotherapy 2015.

21. Hong J, Krop LC, Johns T, Pai MP. Individualized vancomycin dosing in obese patients: a two-sample measurement approach improves target attainment. Pharmacotherapy 2015;5:455-63.

Table 1: **Demographics and Clinical Characteristics of the Study Patients by Obese Category**

Characteristics	Obese Group (BMI 30-40 kg/m^2) (n=263)	Extremely Obese Group (BMI ≥ 40 kg/m^2) (n=71)	P-value
Age (yrs)	66.7 ± 11.1	64.4 ± 7.6	NS
Male sex	259 (98.5)	70 (98.6)	NS
Weight (kg)			
Actual body weight	102.7 ± 13.1 (range 72-149)	139.2 ± 31.1 (range 89-244)	<0.05
Adjusted body weight	83.9 ± 9.1	97.4 ± 16.4	<0.05
Ideal body weight	71.3 ± 7.3	69.5 ± 8.6	NS
Percentage above ideal body weight (%)	44.1 ± 11.5	99.7 ± 31.0	<0.05
Body mass index (kg/m^2)	33.1 ± 2.4	45.9 ± 7.0	<0.05
WHO BMI Class			<0.05
Obese class 1 (BMI 30.0–34.9 kg/m^2)	211 (80.2)	—	
Obese class 2 (BMI 35.0– 39.9 kg/m^2)	52 (19.8)	—	
Obese class 3: extremely obese (BMI ≥ 40.0 kg/m^2)	—	71 (100)	
Height (cm)	176.0 ± 8.9	173.8 ± 10.0	NS
[a]CrCl at vancomycin initiation (ml/min)	79.4 ± 37.8 (range 21- 251	84.8 ± 25.2 (range 30–140)	<0.05
CrCl category			<0.05
> 90 ml/min	74 (28.1)	32 (45.1)	
60-90 ml/min	109 (41.4)	29 (40.9)	
30-60 ml/min	70 (26.6)	10 (14.1)	
< 30 ml/min	10 (3.8)	0	
Serum creatinine concentration at vancomycin initiation (mg/dL)	1.2 ± 0.6	1.2 ± 0.5	NS
BUN at vancomycin initiation (mg/dL)	29.2 ± 19.8	29.0 ± 17.2	NS
First dose higher than subsquent two doses; weight-based dose range if higher first dose (mg/kg)	10 (3.8); 9–22	< 5; 12–15	NS
Maintenace vancomycin dose			
Total daily dose (mg)	2004.6 ± 736.3 (range 500–4500)	2306.1 ± 934.4 (range 750–6000)	<0.05
Weight-based daily dose (mg/kg/day)	19.7 ± 7.4 (range 4–44)	17.0 ± 6.8 (range 6–46)	<0.05
Standard dose of 1000 mg every 12 hours	118 (44.9)	24 (33.8)	NS
Vancomycin dosing interval			NS
Every 8 hours	5 (1.9)	< 5	
Every 12 hours	191 (72.6)	53 (74.7)	
Every 18 hours	5 (1.9)	< 5	
Every 24 hours	56 (21.3)	12 (16.9)	

Every 36 hours	< 5	< 5	
Every 48 hours	< 5	< 5	
Vancomycin serum trough concentration (mg/L)	17.0 ± 8.3 (range 1–46)	19.7 ± 10.9 (range 6–55)	NS

Data are mean ± SD values or no. (%) of patients unless otherwise specified.

[a]Caluculated by using the Cockcroft-Gault equation with adjusted body weight.

BMI= body mass index; NS= not signficant; WHO= World Health Organization; CrCl = creatinine clearance; BUN = blood urea nitrogen

Table 2: **Mean Vancomycin Weight-Based Daily Dose in the Obese and Extremely Obese Groups by Trough Level**

	Weight-Based Daily Dose (mg/kg/day)		
Trough Level Category	Obese Group (BMI 30-40 kg/m^2) (n=263)	Extremely Obese Group (BMI ≥ 40 kg/m^2) (n=71)	P-value
<10 mg/L	17.0 ± 6.2	16.8 ± 5.8	NS
10-15 mg/L	19.0 ± 7.5	13.0 ± 3.7	<0.05
15-20 mg/L	20.5 ± 7.2	14.4 ± 5.9	<0.05
≥ 20 mg/L	21.7 ± 7.5	21.0 ± 7.3	NS

Data are mean ± SD values.

BMI= body mass index; NS= not signficant

Table 3: Odds of Target Trough Attainment (15–20 mg/L) in the Obese and Extremely Obese Groups at Various Vancomycin Weight-Based Daily Doses

Outcome	Odds Ratio (95% CI)	P value
Obese Patients (n=263) (BMI 30-40 kg/m^2)		
Target vs. subtherapeutic trough at a vancomycin dose of < 10 mg/kg/day using actual body weight	0.19 (0.05-0.70)	<0.05
Target vs. subtherapeutic trough at a vancomycin dose of 25-30 mg/kg/day using actual body weight	5.15 (1.69-15.64)	<0.05
Extremely Obese (n=71) BMI ≥ 40 kg/m^2)		
Target vs subtherapeutic trough at a vancomycin dose of 20-25 mg/kg/day using actual body weight	6.07 (1.01 - 36.51)	<0.05

BMI= body mass index; CI= Confidence Interval; NS= not significant

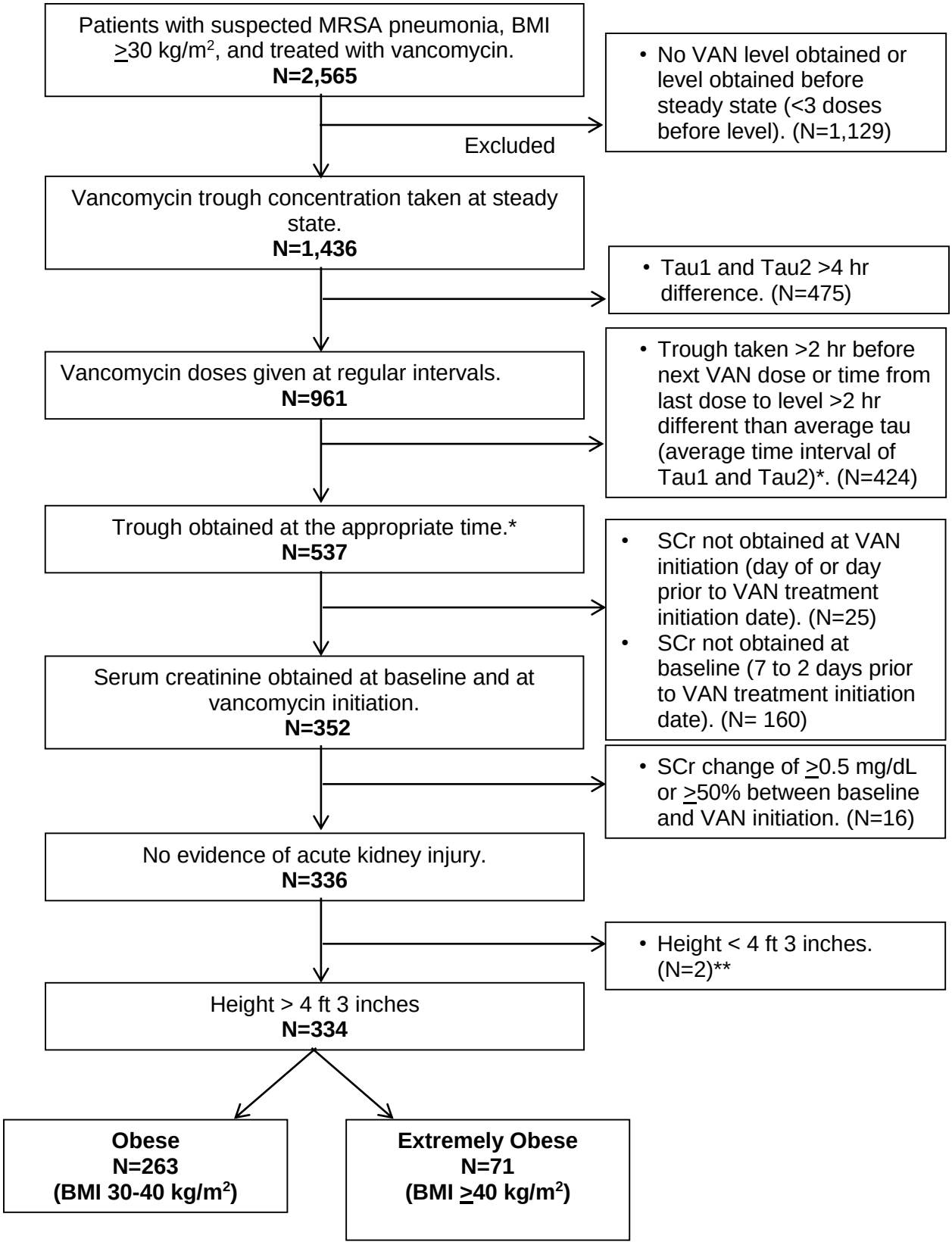
Patients with suspected MRSA pneumonia, BMI ≥30 kg/m2, and treated with vancomycin.
N=2,565
• No VAN level obtained or level obtained before steady state (<3 doses before level). (N=1,129)
Excluded
Vancomycin trough concentration taken at steady state.
N=1,436
• Tau1 and Tau2 >4 hr difference. (N=475)
Vancomycin doses given at regular intervals.
N=961
• Trough taken >2 hr before next VAN dose or time from last dose to level >2 hr different than average tau (average time interval of Tau1 and Tau2)*. (N=424)
Trough obtained at the appropriate time.*
N=537
• SCr not obtained at VAN initiation (day of or day prior to VAN treatment initiation date). (N=25)
• SCr not obtained at baseline (7 to 2 days prior to VAN treatment initiation date). (N= 160)
Serum creatinine obtained at baseline and at vancomycin initiation.
N=352
• SCr change of ≥0.5 mg/dL or ≥50% between baseline and VAN initiation. (N=16)
No evidence of acute kidney injury.
N=336
• Height < 4 ft 3 inches. (N=2)**
Height > 4 ft 3 inches
N=334
Obese
N=263
(BMI 30-40 kg/m2)
Extremely Obese
N=71
(BMI ≥40 kg/m2)

Figure 1. Diagram of the study cohort identification process. *Patients were included if they had an appropriately collected through level. This was defined as a trough that was measured < 2 hours before the next vancomycin dose or within 2 hours of the average interval between the 2 prior vancomycin doses. To avoid not including patients in whom a next dose was never given or was given late, we also defined an appropriate trough as one in which the time from the last dose before the level to the level was < 2 hours different that the average tau (the average interval between the 2 prior vancomycin doses). **Patients who were shorter than 4 ft 3 inches were likely amputees since this is a Veteran population. To increase the generalizability to the general United States population, patients under this minimum height were exlcuded. BMI= body mass index; MRSA= methicillin-resistant *Staphylococcus aureus*; VAN= vancomycin; SCr= serum creatinine concentration

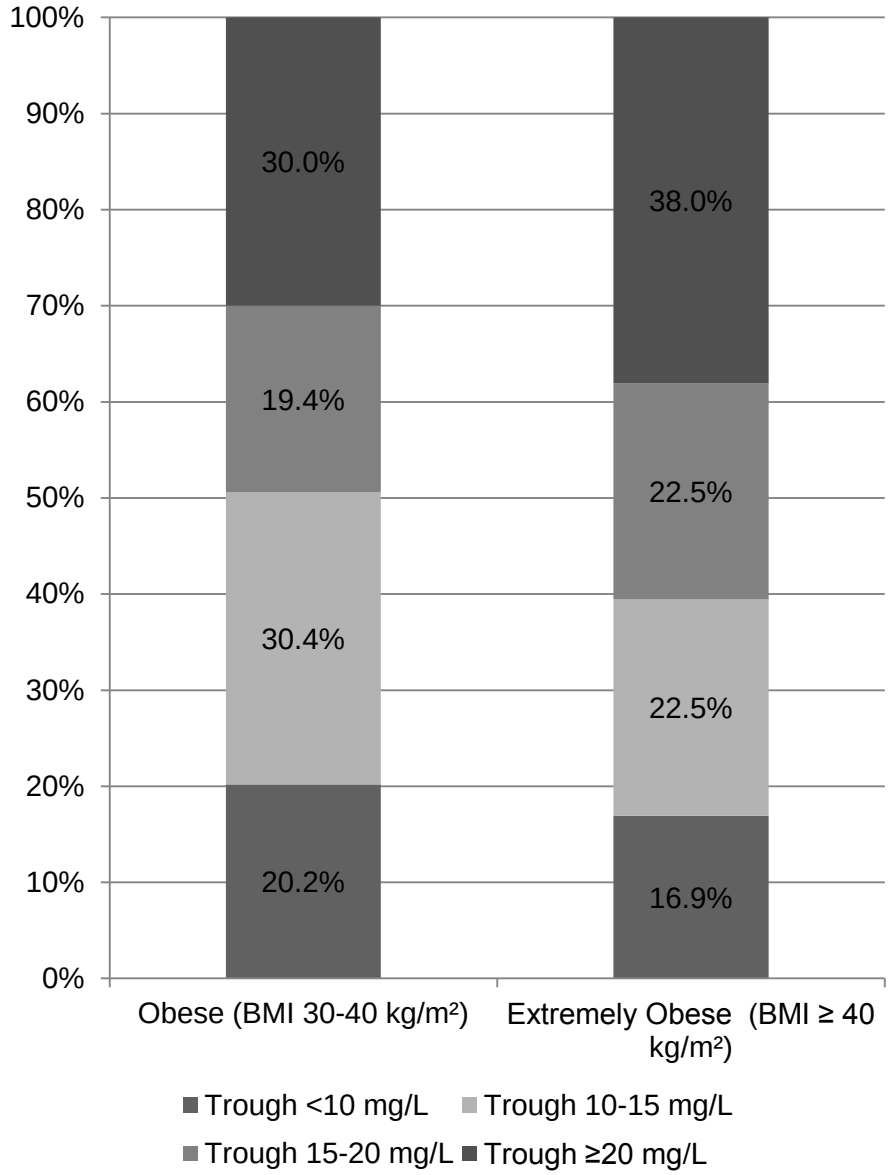

Figure 2. Trough level attainment by obese category. No significant difference by obesity category. BMI= body mass index.

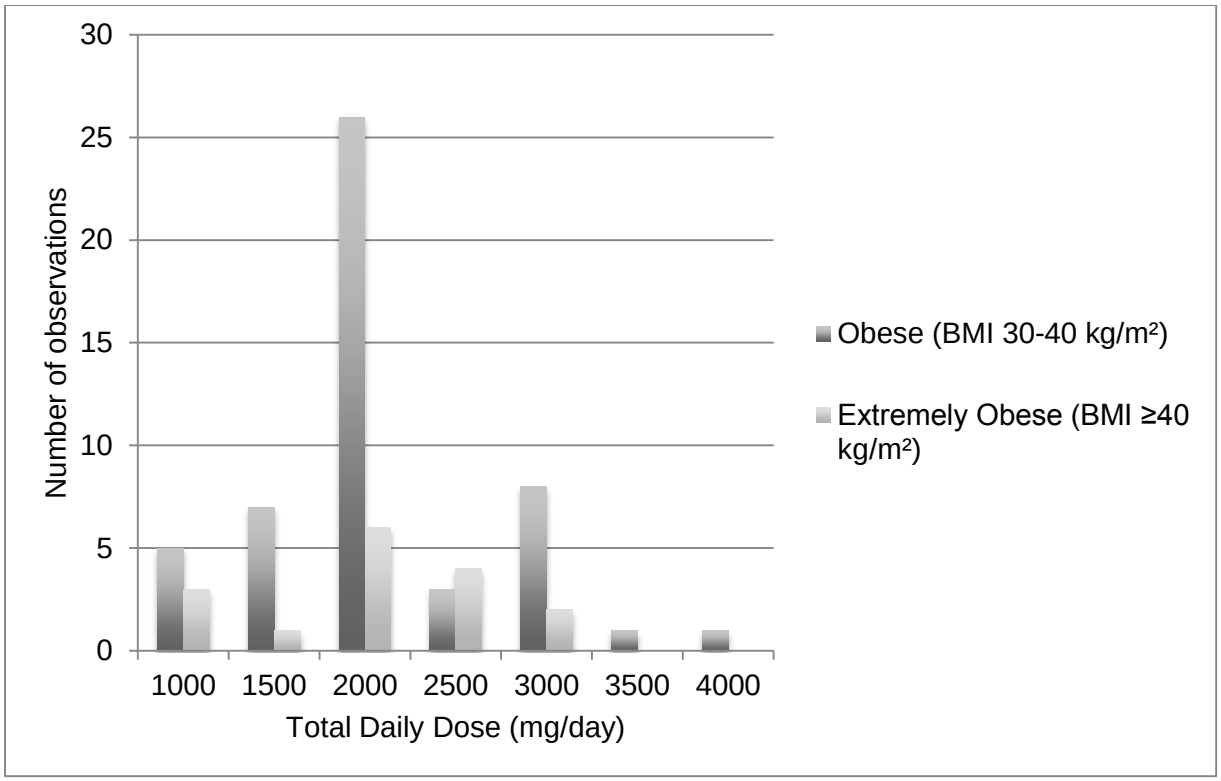

Figure 3. Histogram of total daily dose distribution for patients who achieved target trough concentrations (15–20 mg/L) by obese category. BMI= body mass index.