ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2011, p. 5475–5479 Vol. 55, No. 12
0066-4804/11/$12.00 doi:10.1128/AAC.00168-11

Relationship between Vancomycin Trough Concentrations and Nephrotoxicity: a Prospective Multicenter Trial▽

John A. Bosso,[1,2]* Jean Nappi,[1] Celeste Rudisill,[1] Marlea Wellein,[3] P. Brandon Bookstaver,[1] Jenna Swindler,[4] and Patrick D. Mauldin[1]

Department of Clinical Pharmacy and Outcome Sciences, South Carolina College of Pharmacy, Charleston and Columbia, South Carolina[1]; Division of Infectious Diseases, Medical University of South Carolina College of Medicine, Charleston, South Carolina[2]; Department of Pharmacy, Trident Medical Center, Charleston, South Carolina[3]; and Department of Pharmacy Services, McLeod Regional Medical Center, Florence, South Carolina[4]

Received 8 February 2011/Returned for modification 23 July 2011/Accepted 14 September 2011

Several single-center studies have suggested that higher doses of vancomycin, aimed at producing trough concentrations of >15 mg/liter, are associated with increased risk of nephrotoxicity. We prospectively assessed the relative incidence of nephrotoxicity in relation to trough concentration in patients with documented methicillin-resistant *Staphylococcus aureus* (MRSA) infections at seven hospitals throughout South Carolina. Adult patients receiving vancomycin for at least 72 h with at least one vancomycin trough concentration determined under steady-state conditions were prospectively studied. The relationship between vancomycin trough concentrations of >15 mg/ml and the occurrence of nephrotoxicity was assessed using univariate and multivariate analyses, controlling for age, gender, race, dose, length of therapy, use of other nephrotoxins (including contrast media), intensive care unit (ICU) residence, episodes of hypotension, and comorbidities. Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg/dl or a ≥50% increase from the baseline for two consecutive measurements. MICs of vancomycin for the MRSA isolates were also determined. A total of 288 patients were studied between February 2008 and June 2010, with approximately one-half having initial trough concentrations of ≥15 mg/ml. Nephrotoxicity was observed for 42 patients (29.6%) with trough concentrations >15 mg/ml and for 13 (8.9%) with trough concentrations of ≤15 mg/ml. Multivariate analysis revealed vancomycin trough concentrations of >15 mg/ml and race (black) as risk factors for nephrotoxicity in this population. Vancomycin trough concentrations of >15 mg/ml appear to be associated with a 3-fold increased risk of nephrotoxicity.

Staphylococcus aureus has become a major cause of serious infections in both community and institutional settings, with methicillin-resistant strains causing numerous invasive infections, especially those involving the bloodstream (2, 13, 34). Due to concerns with efficacy as they relate to adequacy of dosing and related plasma concentrations, it is currently commonplace to administer vancomycin in doses intended to achieve trough concentrations of 15 mg/liter or higher in the treatment of methicillin-resistant *S. aureus* (MRSA) infections. A consensus paper published in 2009 recommended that patients be dosed with this end in mind (30). Some practitioners have extrapolated these dosing recommendations with associated trough concentration goals to all vancomycin use. However, evidence of superior efficacy is lacking, and results of several single-center, mostly retrospective trials have suggested that this more aggressive dosing may be related to an increased incidence of vancomycin-related nephrotoxicity (12, 14, 18, 20, 27) and ototoxicity (9). The results and conclusions of these studies have been questioned, to varying degrees, due to design limitations, including the failure to account for other risk factors for renal compromise, and/or their single-center nature. Another relevant study, using Monte Carlo simulations and considering various dosing regimens and staphylococcal MICs determined that the necessary doses to achieve a target therapeutic area under the curve (AUC)/MIC ratio of ≥400 for organisms with an MIC of 2 mg/liter would be associated with a 35% incidence of nephrotoxicity (26). This literature, including a number of studies available only in abstract form, has been nicely summarized and critically reviewed by the laboratory of Wong-Beringer et al. (36).

As acute renal injury or failure, regardless of cause, is associated with significant increases in hospital costs, length of stay, and mortality (8), it is important to resolve this issue. We completed a prospective, multicenter evaluation of the relationship between the incidence of nephrotoxicity and vancomycin trough concentrations to help clarify this issue.

(This work was presented in part at the Infectious Diseases Society of America Annual Meeting, Vancouver, British Columbia, Canada, October 2010 [abstract 290].)

MATERIALS AND METHODS

The primary objective of this study was to determine if there is a difference in the incidence of nephrotoxicity associated with high vancomycin trough concentrations (>15 mg/liter) and that associated with lower trough concentrations (≤15 mg/liter). Secondary objectives were to identify patient characteristics/risk factors, if any, that are associated with vancomycin nephrotoxicity, and to characterize the distribution of MICs of vancomycin for MRSA in South Carolina.

This was a multicenter, prospective, observational trial, and included both teaching and community hospitals from throughout the state of South Carolina (Table 1). The study protocol was approved by the Institutional Review Board at each participating institution. Patients included were at least 18 years of age, had documented MRSA infections, received vancomycin for at least 72 h, had baseline (pre-vancomycin) and intratherapy serum creatinine determined, and had at

* Corresponding author. Mailing address: South Carolina College of Pharmacy, 280 Calhoun St., Charleston, SC 29425. Phone: (843) 792-8501. Fax: (843) 792-1712. E-mail: bossoja@musc.edu.

▽ Published ahead of print on 26 September 2011.

TABLE 1. Participating institutions

Hospital no.	Hospital type	No. of beds	No. of patients enrolled
1	Community	453	33
2	Academic	709	90
3	Community	453	13
4	Community/academic	588	19
5	Community	296	16
6	Community/academic	650	100
7	Community	167	20

least one steady-state (2 to 4 days into therapy) vancomycin trough concentration determined. In cases in which more than one vancomycin trough was determined, an "average" weighted value, based on theoretical days at the various concentrations, was calculated in order to classify the patient as having a high or low trough. Exclusion criteria consisted of patients with concomitant amphotericin B or regularly scheduled nonsteroidal anti-inflammatory therapy, a history of receiving vancomycin for at least 72 h in the 30 days prior to inclusion in this study, a recent rise in serum creatinine (≥25% or 0.3 mg/dl from the baseline), a history of receiving any form of renal replacement therapy, neutropenia (absolute neutrophil count of <1,000 cells/mm^3), or cystic fibrosis. Nephrotoxicity was defined, for the purposes of this study, as an increase in serum creatinine of 0.5 mg/dl or a ≥50% increase from the baseline serum creatinine level for two consecutive laboratory determinations.

Patients enrolled in the study were dosed with vancomycin per the standard of care at each participating institution (per the prescribing physician, and/or protocol, and/or clinical pharmacist). The study methods did not include specific dosing guidelines or drug monitoring. An investigator observed the patients daily during their course of vancomycin therapy until vancomycin therapy was discontinued or the patient was discharged from the hospital, depending upon which occurred first. During the observation period, demographic information, including gender, race, age, and weight, were recorded along with the infection type (e.g., pneumonia) and whether it was community or hospital associated. The site of the positive MRSA culture (e.g., blood) was also noted. Total daily vancomycin doses and initial dosing frequency were recorded, as were all vancomycin trough concentration determinations. Additionally, exposure to other known risk factors for renal injury was noted on a daily basis. These risk factors included receipt of nephrotoxic agents, including radiographic contrast agents, aminoglycosides, cyclosporine A, tacrolimus, nonsteroidal inflammatory agents, and COX-2 inhibitors, as well as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blocking (ARB) agents, which are known to raise serum creatinine. Any episodes of hypotension (systolic blood pressure of less than 90 mm Hg) and residence in an intensive care unit (ICU) were noted daily. Finally, comorbidity information was collected for all patients to allow for determination of Charlson scores (4). Patients discharged with vancomycin to be administered outside the hospital did not have further information collected after discharge.

To characterize the distribution of MICs of vancomycin for MRSA, the MICs of all MRSA isolates from patients enrolled in the study were determined with by Etest according to manufacturer's instructions. The Etests were performed in the microbiology laboratory of the hospital where the specimens were collected. After standard test completion, a digital image was recorded and sent in a secure fashion to the principal investigator for interpretation.

To protect patient confidentiality, each patient was assigned a study number at each respective participating institution. Only the participating coinvestigator had access to the number code and the study data. Study data were transmitted to the principal investigator utilizing a secure server, where a new subject number was assigned.

Sample size determination and statistical analysis. A sample size of 223 per group (high and low trough concentrations) was originally estimated as that needed to detect an increase in nephrotoxicity from 5% to 12% with vancomycin trough concentrations of ≤15 and >15 mg/liter, respectively, with 80% power and an α of 0.05 using a one-tailed test based on the relevant literature published prior to the present study. Based on an interim analysis of the data, it was clear that far fewer patients would be needed. At 12 months, we had enrolled 135 patients with a fairly equal distribution of low and high vancomycin trough concentrations (representing well over 1/3 of the revised projected total enrollment). The interim analysis was based upon the first 103 patients enrolled. Of these, 23 had met our definition of nephrotoxicity and 18 (78%) had vancomycin trough concentrations above 15 mg/liter. Thus, the preliminary rates of vancomycin-related nephrotoxicity for those with trough concentrations above and equal to or less than 15 mg/liter were 31 and 12%, respectively. It should be noted, however, that this interim analysis did not take into account other risk factors for renal toxicity/compromise which were considered in our final analysis. Based on this analysis we projected a needed sample size of 83 per treatment group (before consideration of covariates) to detect the originally proposed difference in rates of nephrotoxicity (5 versus 12%) with vancomycin trough concentrations of ≤15 and >15 mg/ml, respectively, with 80% power and an α of 0.05 using a two-tailed test. We assumed that approximately 50% of patients enrolled in the study would continue to fall into each of the two groups (high and low trough concentrations). We continued to monitor our enrollment to evaluate this assumption and considered it prudent to continue enrollment for an addition 6 months to ensure similarly sized groups and adequate statistical power when controlling for other risk factors for renal compromise.

Both univariate and multivariate analyses were performed. For the univariate analysis, a chi-square test was used. Logistic regression was used for the multivariate analyses with nephrotoxicity (binary) serving as the dependent variable, and high vancomycin concentrations (>15 mg/liter) serving as the primary independent variable. Covariates included age, race, gender, hypotension, receipt of other nephrotoxic agents, length of vancomycin therapy, vancomycin dose per kg of body weight, ICU stay, and comorbidities. For the multivariate analysis, multicolinearity was assessed utilizing Pearson correlation coefficients. If independent variables were found to be highly correlated, they were dropped from the multivariate analysis. Levels and amounts (numbers of correlated variables) of correlations, as well as clinical input, determined this decision process. Similarly, comorbidities that rarely were present in the study population (i.e., <1%) were also dropped from the model. Statistical significance was determined at the 5% level. Microsoft Excel 2008 and SAS 9.1 were used for the statistical analysis.

RESULTS

Data were obtained for 291 patients, of which 166 were male, 183 white, and 97 African-American. The mean age (± standard deviation [SD]) was 55 (±17) years. Data were adequate, for purposes of our analysis, for 288 patients (the excluded patients had one or no serum creatinine determinations). Numbers enrolled from each participating hospital are included in Table 1, and more detailed patient demographics and study characteristics are presented in Table 2. Of the 288 evaluable patients, 206 were deemed to have hospital-acquired MRSA infections. The most common infections were wound infections, pneumonia, and bacteremia, with the vast majority confined to a single type. The average length of vancomycin therapy was 210 h or 9 days (median, 180 h or 7.5 days). One hundred sixteen received at least one other nephrotoxin, ACEI, or ARB agent during the course of vancomycin therapy. Of these, 24 patients received two such agents while two received three. The most commonly received were ACEIs and ARB agents. Twenty-five patients received contrast media. Fifty-four patients experienced one or more episodes of hypotension.

Fifty-five patients met the definition of nephrotoxicity, with 42 of these being in the high trough concentration group, reflecting incidences of 8.9 and 29.6% in the low and high trough concentration groups, respectively. Univariate analysis using a chi-square test with the occurrence of nephrotoxicity as the dependent variable and a trough concentration of >15 mg/liter as the independent variable revealed a highly significant and positive relationship ($P < 0.0001$). Pearson correlation coefficients determined a high correlation between length of vancomycin therapy and vancomycin dose per kg of body weight (correlation coefficient, 0.719; $P < 0.0001$), dictating inclusion of only one of these in the

TABLE 2. Demographics and characteristics for patients with and without nephrotoxicity

Characteristic	No. (%) of patients or no. of days	
	Nephrotoxicity group	Nonnephrotoxicity group
Total no. of patients	55	233
Male gender	28 (51)	137 (59)
Race		
White	29 (53)	154 (166)
Black	26 (47)	71 (30)
Other	0	8 (4)
Hospital-associated infection	44 (80)	161 (69)
Avg total vancomycin dose (g)[a]	19,749	18,769
Avg length of vancomycin therapy (days)	10.6	8.3
No. with initial dosing frequency of every 12 h ($n = 256$)	39 (76)	146 (72)
Trough concn, >15 mg/liter	41 (75)	101 (43)
Trough concn, ≤15 mg/liter	14 (25)	132 (57)
Receipt of ≥1 nephrotoxin	26 (47)	90 (39)
Receipt of ≥2 nephrotoxins	6 (10.9)	18 (7.7)
Avg no. of days other nephrotoxin received[b]	7	6.2
Hypotensive episode	11 (21)	43 (18)
Average no. of days with hypotensive episodes[c]	3.3	2.7
ICU stay	23 (42)	73 (31)
Avg no. of ICU days[d]	9.6	6.9
Any comorbidities[e]	36 (66)	132 (57)
Avg Charlson score[e]	1.8	1.2
Infection type		
Wound	16 (29)	91 (39)
Pneumonia	14 (25)	68 (29)
Bacteremia	12 (22)	48 (21)

[a] Total dose (in grams) for period of observation.
[b] For those receiving another nephrotoxin(s).
[c] For those having ≥1 day(s) with hypotension.
[d] For those who stayed in the ICU ≥1 day(s).
[e] Per Charlson et al. (4).

final model. As data relating to length of therapy were more complete, we chose to drop dose per kg of body weight from the final analysis. Multivariate analysis utilizing logistic regression and controlling for other risk factors and patient characteristics confirmed the strong relationship between nephrotoxicity and trough concentrations of >15 mg/liter (odds ratio, 3.643; 95% confidence interval [CI], 1.749 to 7.587) (Table 3). The higher the initial trough concentration for vancomycin, the more likely the occurrence of nephrotoxicity. The incidence of toxicity in those with initial trough concentrations of ≥20 mg/liter, ≥25 mg/liter, and ≥30 mg/liter were 32, 45, and 50%, respectively. Another factor statistically relating to the occurrence of toxicity was race (odds ratio, 2.589; 95% CI, 1.278 to 5.244) with a higher incidence in blacks (versus whites). Comorbidities associated with toxicity are shown in Table 3.

MICs were determined for 288 isolates from 277 patients. In generating descriptive statistics, only one isolate from each patient, the first isolated, was included, regardless of any apparent MIC differences. The mean, median, and modal MIC for these 277 isolates was 1.5 mg/liter.

TABLE 3. Results of multivariate analysis[a]

Variable	Odds ratio for nephrotoxicity	95% CI
Trough concn, >15 mg/liter	3.643	1.749–7.587
Hypotension	1.055	0.444–2.503
LOT with vancomycin	1.002	1.000–1.004
Other nephrotoxins given	1.201	0.606–2.381
Gender (male)	0.986	0.488–1.995
Race (black)	2.589	1.278–5.244
ICU stay	1.408	0.700–2.834
Age	0.999	0.978–1.020
Cerebrovascular disease	0.253	0.051–1.243
Myocardial infarction	0.284	0.027–2.965
Peripheral vascular disease	2.326	0.402–13.456
Ulcer disease	1.283	0.217–7.574
Heart failure	3.666	1.017–13.208
Diabetes without end organ damage	1.038	0.512–2.104
Hemiplegia	1.079	0.106–10.946
Any tumor	1.153	0.313–4.249
Mild hepatic disease	3.856	0.179–83.135
Moderate hepatic disease	0.280	0.021–3.716
Metastatic solid tumor	5.877	1.370–25.204
AIDS	0.697	0.032–15.063

[a] Shown are results of multivariate analysis ($n = 280$). Eight observations were deleted from the multivariate model due to missing values. LOT, length of therapy.

DISCUSSION

Despite a report of a recent decline in invasive MRSA infections (15), this pathogen remains a major cause of serious infection. The pathogen is encountered mainly in health care-associated infections, although onset is common in both institutional and community settings (16). *S. aureus* infections, particularly those with MRSA, are associated with significantly increased morbidity, mortality, lengths of hospital stays, and health care costs (1, 5, 7, 11, 25), which are sometimes explained by inadequate initial therapy (16).

Inadequacy of therapy could be due to failure to consider *S. aureus* as a causative pathogen, failure to consider methicillin resistance, or subtherapeutic dosing of vancomycin. Some studies have suggested that higher vancomycin MICs for MRSA relate to higher treatment failure rates (3, 10, 12, 19, 32), and we know that certain risk factors, such as previous vancomycin therapy and ICU stay, are associated with infection with these species (21, 23). Further, there have been reports, from single institutions, indicating a rise in average vancomycin MICs over time (28, 33, 35).

It has been determined that the parameter best relating to the antibacterial effect of vancomycin is the pharmacodynamic parameter AUC/MIC (6, 29). The apparent target associated with superior response rates is an AUC at 24 h (AUC_{24})/MIC of ≥400 (24). However, traditional doses of vancomycin (1 g every 12 h) are unlikely to achieve this target in adults with normal renal function and vancomycin MICs above 1 mg/liter. The observations of rising vancomycin MICs in MRSA, decreasing clinical response associated with those higher MICs, together with those regarding the drug's pharmacodynamics, has led many to theorize the need for higher doses. In fact, the aforementioned consensus statement recommends doses to achieve vancomycin trough concentrations of 10 to 20 mg/liter for treatment of MRSA infections. This necessitates higher

doses, and the specter of vancomycin-related nephrotoxicity has once again emerged. A number of single-center studies have explored this issue (12, 14, 18, 20, 27). They have focused on either trough concentrations or the magnitude of total daily dose, and most determined that it is the trough concentration that best describes the drug exposure-toxicity relationship (22), although a study by Lodise et al. reported an association with total daily doses of ≥4 g (20). While higher rates of nephrotoxicity (11 to 35%) were observed in these studies, higher rates of clinical cure were not observed for those with trough concentrations of ≥15 mg/liter. As these studies reported single-center experiences, in some cases were retrospective in design, and in others failed to consider other risk factors for renal injury, the present study was undertaken.

We found a statistically significant and positive relationship between the occurrence of nephrotoxicity and vancomycin trough concentrations of greater than 15 mg/liter, even when accounting for other risk factors. Our findings support the observations of previous, single-center studies in terms of trough concentrations greater than 15 mg/liter being related to higher rates of toxicity. Also, we are not the first to observe a rising rate of nephrotoxicity with rising trough concentrations (18). However, we did not corroborate the finding of others that concomitant administration of other nephrotoxins accentuated this risk. Lodise et al. also did not detect a contribution of concomitant aminoglycoside therapy to vancomycin-induced nephrotoxicity (20). However, it is important to note that in examining absolute differences in rates or percentages with various risk factors in the groups with and without toxicity, a consistent trend for higher incidence was observed in the toxicity group although not to a statistically significant degree (Table 2). We are unable to explain the apparent association between race and vancomycin-induced nephrotoxicity.

The finding that higher vancomycin dosing resulting in higher vancomycin concentrations leads to an increased risk of nephrotoxicity does not necessarily pose an argument against that practice. The consensus statement published in 2009 recommended the practice based upon potential failure to achieve putative pharmacodynamic targets with traditional dosing, especially for MRSA isolates with higher MICs (30). Further, it could be argued that higher vancomycin dosing has already become a standard of care, at least in the setting of MRSA infections. Further, a recently published study provides evidence supporting the higher dosing practice from an efficacy standpoint (18). Nonetheless, our findings draw attention to the increased risk of this side effect and the apparent need to carefully monitor renal function in patients in which this dosing strategy is employed.

Finding a mean (also median and mode) MRSA MIC of 1.5 mg/liter in a state-wide study is noteworthy. However, with no previous data available for comparison, this indicates only what the situation was at the time of specimen collection. Whether this represents an increase from previous years is open to speculation only, regardless of likelihood. Further, our findings should also be interpreted with the knowledge that the methodology employed, while practical for this study, is known to provide results systematically higher than with the reference broth microdilution method (31). Even if our modal MIC were truly 1 mg/liter, that value is perhaps higher than it was in earlier years and thus may have implications for empirical antibiotic therapy because, as already mentioned, a decreased therapeutic response to vancomycin (regardless of dose) has been observed for patients infected with strains exhibiting higher (1.5 to 2 mg/liter) MICs, including heterogeneous vancomycin-intermediate *S. aureus* (hVISA) strains which are not detected with routine testing (6, 20–22).

A number of limitations of this study should be appreciated. Almost two-thirds of the patients included were hospitalized at two institutions. While these were the two largest hospitals, they represented 41% of the summed bed capacity of all participating centers. It is possible that differences in patient types and acuity in these two hospitals influenced our results to some degree. However, we were not able to demonstrate any interinstitutional influences within our results (data not shown). Due to the observational nature of the study, we were not always able to monitor patients through the conclusion of their course of vancomycin therapy (when completed at home or at another health-care facility). Therefore, our ability to completely and accurately assess the influence of length of therapy and total cumulative dose of vancomycin on nephrotoxicity was somewhat compromised and we could not assess time to recovery of normal renal function. It has been noted by other investigators that nephrotoxicity is related to total daily and therefore, possibly, cumulative dose (20). To attempt to corroborate this observation, it would be necessary to monitor renal function daily until the time that the definition of toxicity was first noted so that total cumulative dose leading up to toxicity could be accurately determined. One could speculate that toxicity may be better related to exposure, which would be better quantified as area under the plasma concentration versus time curve (rather than cumulative dose or trough concentrations). Our observational study did not allow this, as a day-to-day determination of each patient's pharmacokinetics would have been necessary. Also, it could be argued that our method of assigning patients with multiple trough determinations to the high or low trough concentration group was less than ideal. Without daily determinations, it would be difficult to determine an average or median trough concentration. However, our weighting method did allow classification based on whether the trough concentration was high or low for the majority of days of observation. We did not fully quantitate some of the risk factors for renal injury. For example, an episode of hypotension was simply predicated on a systolic blood pressure of ≤90 mm Hg being recorded in the patient's chart. Information regarding length of the episode was not available. This may partially explain the lack of a statistically significant association between this risk factor and the occurrence of nephrotoxicity. Similarly, while the use of other nephrotoxins, ACEIs and ARB agents, including their number, was recorded, we did not quantify length of exposure for individual agents. Again, this may help explain our failure to corroborate an influence on occurrence of nephrotoxicity. Recommendations for more ideal studies of this issue have recently been published elsewhere (36).

In summary, this multicenter, prospective study supports previous reports of an increased risk of vancomycin-associated nephrotoxicity in patients with trough concentrations above 15 mg/liter independently of other known risk factors for renal injury. Renal function should be carefully and regularly mon-

itored in patients receiving doses intended to produce these higher trough concentrations.

ACKNOWLEDGMENTS

This work was supported, in part, by an investigator-initiated research grant from Pfizer, Inc., New York, NY.

We thank the following individuals for their contributions to this study in the form of data collection: Alex McDonald, Darrell Willm, and Holly Balcer.

REFERENCES

1. **Abramson, M. A., and D. J. Sexton.** 1999. Nosocomial methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*: at what costs? Infect. Control Hosp. Epidemiol. **20:**408–411.
2. **Centers for Disease Control and Prevention.** Accessed 9 December 2010. Active bacterial core surveillance (ABCs) report, emerging infections program network, methicillin-resistant *Staphylococcus aureus*, 2008. http://www.cdc.gov/abcs/reports-findings/survreports/mrsa08.html.
3. **Charles, P. G. P., P. B. Ward, P. D. R. Johnson, B. P. Howden, and M. L. Grayson.** 2004. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus.* Clin. Infect. Dis. **38:**448–451.
4. **Charlson, M. E., P. Pompei, K. L. Ales, and C. R. MacKenzie.** 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J. Chron. Dis. **40:**373–383.
5. **Cosgrove, S. E., et al.** 2003. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin. Infect. Dis. **36:**53–59.
6. **Craig, W. A.** 2003. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect. Dis. Clin. North Am. **17:**479–501.
7. **Engemann, J. J., et al.** 2003. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with *Staphylococcus aureus* surgical site infection. Clin. Infect. Dis. **36:**592–598.
8. **Fischer, M. J., B. B. Brimhall, D. C. Lezotte, J. E. Glazner, and C. R. Parikh.** 2005. Uncomplicated acute renal failure and hospital resource utilization: a retrospective multicenter analysis. Am. J. Kidney Dis. **46:**1049–1057.
9. **Forouzesh, A., P. A. Moise, and G. Sakoulas.** 2009. Vancomycin ototoxicity: a reevaluation in an era of increasing doses. Antimicrob. Agents Chemother. **53:**483–486.
10. **Haque, N. Z., et al.** 2010. Relationship of vancomycin minimum inhibitory concentration to mortality in patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired, ventilator-associated, or health-care-associated pneumonia. Chest **138:**1356–1362.
11. **Harbarth, S., O. Rutschmann, P. Sudre, and D. Pittet.** 1998. Impact of methicillin resistance on the outcome of patients with bacteremia caused by *Staphylococcus aureus.* Arch. Int. Med. **158:**182–189.
12. **Hidayat, L. K., D. I. Hsu, R. Quist, K. A. Shriner, and A. Wong-Beringer.** 2006. High dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections. Arch. Intern. Med. **166:**2138–2144.
13. **Hidron, A. I., et al.** 2008. Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the national healthcare safety network at the Centers for Disease Control and Prevention, 2006-2007. Infect. Control Hosp. Epidemiol. **29:**996–1011.
14. **Jeffres, M. N., W. Isakow, J. A. Doherty, S. T. Micek, and M. H. Kollef.** 2007. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. Clin. Ther. **29:**1107–1115.
15. **Kallen, A. J., et al.** 2010. Health-care associated invasive MRSA infections, 2005-2008. JAMA **304:**641–648.
16. **Kaye, K. S., et al.** 2008. The deadly toll of invasive methicillin-resistant *Staphylococcus aureus* infection in community hospitals. Clin. Infect. Dis. **46:**1568–1577.
17. **Klevens, R. M., et al.** 2007. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA **298:**1763–1771.
18. **Kullar, R., S. L. Davis, D. P. Levine, and M. J. Rybak.** 2011. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. Clin. Infect. Dis. **52:**975–981.
19. **Lodise, T. P., et al.** 2008. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. Antimicrob. Agents Chemother. **52:**3315–3320.
20. **Lodise, T. P., B. M. Lomaestro, J. Graves, K. A. Rodvold, and G. L. Drusano.** 2008. Larger vancomycin doses (≥4 grams/day) are associated with an increased incidence of nephrotoxicity. Antimicrob. Agents Chemother. **52:**1330–1336.
21. **Lodise, T. P., et al.** 2008. Predictors of high vancomycin MIC values among patients with methicillin-resistant *Staphylococcus aureus* bacteremia. J. Antimicrob. Chemother. **62:**1138–1141.
22. **Lodise, T. P., N. Patel, B. M. Lomaestro, K. A. Rodvold, and G. L. Drusano.** 2009. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin. Infect. Dis. **49:**507–514.
23. **Maclayton, D. O., K. J. Suda, K. A. Coval, C. B. York, and K. W. Garey.** 2006. Case-control study of the relationship between MRSA bacteremia with a vancomycin MIC of 2 μg/mL and risk factors, costs, and outcomes in inpatients undergoing hemodialysis. Clin. Ther. **28:**1208–1216.
24. **Moise-Broder, P. A., A. Forrest, M. C. Birmingham, and J. J. Schentag.** 2004. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin. Pharmacokinet. **43:**925–942.
25. **Noskin, G. A., et al.** 2005. The burden of *Staphylococcus aureus* infections on hospitals in the United States: an analysis of the 2000 and 2001 nationwide inpatient sample database. Arch. Intern. Med. **165:**1756–1761.
26. **Patel, P., et al.** 2011. Vancomycin: we can't get there from here. Clin. Infect. Dis. **52:**969–974.
27. **Pritchard, L., et al.** 2010. Increasing vancomycin serum trough concentration and incidence of nephrotoxicity. Am. J. Med. **123:**1143–1149.
28. **Rhee, K. Y., D. F. Gardiner, M. Charles.** 2005. Decreasing in vitro susceptibility of clinical *Staphylococcus aureus* isolates to vancomycin at the New York Hospital: quantitative testing redux. Clin. Infect. Dis. **40:**1705–1706.
29. **Rybak, M. J.** 2006. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin. Infect. Dis. **42:**S35–S39.
30. **Rybak, M., et al.** 2009. 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. Am. J. Health-Syst. Pharm. **66:**82–98.
31. **Sader, H. S., P. R. Rhomberg, and R. N. Jones.** 2009. Nine-hospital study comparing broth microdilution and Etest method results for vancomycin and daptomycin against methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. **53:**3162–3165.
32. **Sakoulas, G., et al.** 2004. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J. Clin. Microbiol. **42:**2398–2402.
33. **Steinkraus, G., R. White, and L. Friedrich.** 2007. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001-2005. J. Antimicrob. Chemother. **60:**788–794.
34. **Styers, D., D. J. Sheehand, P. Hogan, and D. F. Sahm.** 2006. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among *Staphylococcus aureus*: 2005 status in the United States. Ann. Clin. Microbiol. Antimicrob. **5:**2.
35. **Wang, G., et al.** 2006. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J. Clin. Microbiol. **44:**3883–3886.
36. **Wong-Beringer, A., J. Joo, E. Tse, and P. Beringer.** 2011. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. Int. J. Antimicrob. Agents. **37:**95–101.