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Vancomycin and Nephrotoxicity; Just Another Myth?

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Abstract

BACKGROUND—Vancomycin is considered the drug of choice for Methicillin Resistant *Staphylococcus aureus* (MRSA) infection; however, it has also been linked with nephrotoxicity in the past, sometimes leading to its substitution with linezolid. We hypothesized that patients treated with vancomycin for gram-positive (GP) infections would have an increased incidence of rise in creatinine and need for hemodialysis (HD) compared to patients receiving linezolid.

METHODS—This was a retrospective cohort study of a prospectively maintained database of all surgical patients treated with either vancomycin or linezolid for GP infections in a single ICU from 2001–2008 and managed under a cycling antibiotic protocol. Patients were followed until hospital discharge. Categorical and continuous variables were evaluated. Multivariable logistic regression was performed.

RESULTS—545 patients were treated for 1046 GP infections (571 with vancomycin, 475 with linezolid) over 7 years. Patient demographics were similar between groups; however, the vancomycin group was associated with a longer treatment course (16.2±0.5 vs 14.3±0.5 days; p=0.022). Unadjusted outcomes were similar between groups. Multivariable analysis revealed that APACHE II score predicted an increase in creatinine levels greater than 1.0 following antibiotic therapy (RR=3.01; 95% CI=1.22–7.42) and subsequent need for HD (RR=3.07; 95% CI=1.23–

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CONFLICTS OF INTEREST

For the remaining authors no conflicts were declared.

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7.62). Additionally, initial creatinine level predicted an increase in creatinine levels greater than 1.0 following antibiotic therapy (RR=4.36; 95% CI=1.46–12.99) and subsequent need for HD (RR=10.83, 95% CI=3.19–36.77). Linezolid was found to be protective regarding rise in creatinine levels greater than 1.0 following antibiotic therapy; however this was only experienced when vancomycin trough levels greater than 20 were encountered (RR=5.4; 95% CI=1.19–24.51).

CONCLUSIONS—These data suggest that vancomycin is minimally nephrotoxic and has a similar nephrotoxic profile as compared to linezolid when appropriate dosing is utilized, even among critically ill patients with complex infections.

LEVEL OF EVIDENCE—Level II

STUDY TYPE—Therapeutic/Care Management

Keywords

Vancomycin; Linezolid; Nephrotoxicity; Critical Care; Gram-positive Infections

BACKGROUND

According to a recent study evaluating the National Health and Nutrition Examination Survey (NHANES) data, the prevalence of *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus* (MRSA) within the United States from 2003–2004 was approximately 28.6% (78.9 million persons) and 1.5% (4.1 million persons), respectively (1). Simple colonization with certain strains of MRSA has been shown to increase one's risk of developing both hospital- and community-acquired infections including: skin, surgical site, osteomyelitis, pneumonia, bacteremia, and endocarditis (1–4). Another study evaluating the National Hospital Discharge Survey (NHDS) data in 2005 determined that MRSA was responsible for approximately 278,203 hospitalizations within the United States (3).

Many antibiotics have been approved by the Food and Drug Administration (FDA) for the treatment of MRSA-related infections. Some of these include: vancomycin, linezolid, daptomycin, clindamycin, trimethoprim-sulfamethoxazole, quinupristin/dalfopristin, tigecycline, and tetracycline (5–7). Appropriate antibiotic selection is governed by the location of the infection. According to the most recent guidelines released by the Infectious Diseases Society of America, vancomycin and linezolid are recommended for the treatment of hospitalized patients with MRSA-related: skin and soft-tissue infections (A-I), pneumonia (A-II), bone and joint infections (B-II), and central nervous system (CNS) infections (B-II) (6).

Vancomycin is a slowly, bactericidal glycopeptide developed in the 1950's as a means to treat penicillin-resistant staphylococcal infections and was approved by the FDA in 1958 (8, 9). From its very inception, vancomycin has been commonly associated with nephrotoxicity; however, randomized control trials comparing vancomycin with placebo, and demonstrating causality are lacking within the literature. Additionally, results from other trials and observational studies demonstrating an association have been conflicting (9–22). We hypothesized that patients treated at a tertiary care center in an intensive care unit (ICU) with vancomycin for gram-positive (GP) infections would experience an increased incidence

of rise in creatinine than patients receiving linezolid therapy. Additionally, patients treated with vancomycin would experience a higher incidence of progressive renal failure necessitating hemodialysis (HD).

METHODS

Patients and Follow-up

Institutional review board approval was obtained before review of the data was initiated. This was a retrospective cohort analysis of a prospectively maintained database of all surgical patients seen at the University of Virginia Health System from 2001 to 2008 who were treated for infection as ICU patients on the general surgery, trauma, abdominal organ transplant, thoracic, vascular, and gynecologic units. We queried the database for patients treated with either vancomycin or linezolid (but not both) under a cycling antibiotic protocol during their hospitalization. Patients were excluded if they were receiving hemodialysis prior to antibiotic initiation or any additional antibiotic agents deemed to be nephrotoxic (e.g., aminoglycosides). Patient demographics, comorbidities, and outcomes were collected prospectively at the time of hospitalization and compared between patient groups. Patients were followed until hospital discharge.

Patient demographics and comorbidities evaluated included gender, age, race, diabetes (DM), hypertension (HTN), hyperlipidemia (HLD), cardiovascular disease (CVD), peripheral vascular disease (PVD), coronary artery disease (CAD), renal insufficiency (RI), HD, APACHE II score, acute physiological score (APS), initial creatinine (ICR) immediately preceding initiation of antibiotics, site of infection, presence of GP infection, type of GP infection, and duration of antibiotic therapy.

Patient outcomes evaluated included maximum creatinine (MCR) during antibiotic course, final creatinine (FCR) after completion of antibiotics, change in MCR and ICR, change in FCR and ICR, new onset HD, risk/injury/failure/loss/End Stage Renal Disease (RIFLE) criteria, length of hospital stay following antibiotic completion (LOS), and death.

Definition

Nephrotoxicity is defined as a 0.5 mg/dL increase in serum creatinine, a 50% increase in baseline serum creatinine, or a 50% decrease in baseline creatinine clearance (13, 14, 16, 23). End points of therapy were defined by unit guidelines, which suggested the following duration of therapy after adequate source control was obtained and antimicrobial appropriateness was documented, based on site of infection: bloodstream (10–14 days), lung (8–14 days), abdomen (5–7 days), vascular catheter (5 days), urine (5–7 days), and skin and skin structure (until resolution of surrounding cellulitis).

Statistical Analysis

Categorical data was analyzed using Chi-square analysis or Fisher's exact tests. Continuous variables were analyzed with independent t-test or Mann-Whitney U test depending on normalcy of distribution. Variables deemed clinically relevant were included in the

multivariate logistic regression model. Statistical significance was defined as a p-value of less than 0.05. SAS© Version 9.3 (Cary, NC) was used for all analyses.

RESULTS

A total of 545 patients with 1046 separately identified infections were identified as receiving either vancomycin or linezolid (but not both) at our institution between 2001 and 2008. Vancomycin or linezolid were given both empirically and as specific therapy for culture-proven GP infection. Of the 395 infections where only GP pathogens were isolated, 39.5% (n=156) were attributable to *Staphylococcus aureus*, which 49.4% (n=77) were attributable to MRSA. Other commonly encountered GP infections included: *Enterococcus faecalis* (110/395) and *Enterococcus faecium* (102/395), of which 31.6% (n=67) were Vancomycin-Resistant *enterococci* (VRE). Commonly identified sites of infection for all infections included: lung (326/1046), peritoneum (223/1046), blood (185/1046), urine (99/1046), wound (71/1046), intravenous/arterial line (57/1046), skin (35/1046), colon (25/1046), and pleura (21/1046).

Demographics and comorbidities for the 545 patients receiving GP therapy are provided in Tables 1 and 2. Fifty-five percent (n=298) of these patients received vancomycin and forty-five percent (n=247) received linezolid for antibiotic therapy. The two groups were comparable regarding patient demographics and comorbidities; however, the vancomycin group was associated with a longer antibiotic treatment course (16.2 ± 0.5 versus 14.3 ± 0.5 days; $p=0.022$) (not displayed in tables).

Unadjusted outcomes between the two groups were comparable, including new onset of HD and RIFLE classification for acute kidney injury (Table 3). A multivariate logistic regression model was then assembled using clinically relevant variables (i.e., Age, DM, CAD, HTN, PVD, APACHE II (20–30), APACHE II (>30), ICR (1.2–1.5), ICR (1.5–2.0), ICR (>2.0), and vancomycin/linezolid choice) to predict rise in ICR and need for HD. Adjusted results between the two groups revealed that an APACHE II score greater than 30 and an increasing creatinine predicted creatinine rise > 1.0 compared to baseline as well as the new onset need for HD. Linezolid was found to be protective regarding rise in creatinine levels greater than 1.0 following antibiotic therapy (RR=0.49, 95% CI=0.25–0.94), but not the need for HD (Tables 4 and 5).

The relationship between vancomycin levels and toxicity was further analyzed. Of the 298 patients who received vancomycin, only 183 had recorded trough levels found within their electronic medical record (EMR). The mean trough level was 14.64 ± 8.78 mg/L with an interquartile range of 13.00 (9.20, 17.45). Patients were then stratified by vancomycin trough level. Of the 183 patients, 29.5% (n=54) had trough levels less than 10 mg/L, 32.8% (n=60) had trough levels between 10 and 15 mg/L, 18.6% (n=34) had trough levels between 15 and 20 mg/L, and 19.1% (n=35) had trough levels greater than 20 mg/L. Table 6 shows the unadjusted, relative risk for rise in creatinine by 1.0 stratified by vancomycin trough level. A trough level greater than 20 mg/L corresponded with a significantly elevated risk for rise in creatinine.

DISCUSSION

A causal association linking vancomycin with nephrotoxicity is inconsistently documented within the literature. Early use of vancomycin was thought to be associated with “toxicities” (i.e., venous irritation, chills, rash, ototoxicity, and nephrotoxicity), although this was largely attributable to impurities resulting from the manufacturing and purification process and has since been improved (8, 14, 16). More recent associations with nephrotoxicity have been suggested due to usage of higher than recommended concentrations.

According to the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists, the current recommended guidelines for vancomycin dosing are 15–20 mg/kg (actual body weight) given every 8 to 12 hours for most patients with normal renal function to achieve optimal trough concentrations no less than 10 mg/L so as to avoid development of resistance (24). A study performed by the National Center for Infectious Diseases, Centers for Disease Control and Prevention looking at ICU-related, nosocomial infections in the United States, found that pneumonia was the most common hospital-acquired infection (*Staphylococcal aureus* being the most common isolate) (25). Due to passive transport of vancomycin across two membrane barriers and lymphatic clearance, the pharmacokinetics for pulmonary penetrance is quite poor (<12% of plasma levels) (9, 26). Low penetrance may contribute to the recently observed rise in MRSA minimum inhibitory concentrations (MIC), necessitating higher minimum trough concentrations of 15mg/L (higher doses) to generate a target area under the curve (AUC):MIC of 400 (5, 9, 17, 24). However, higher dosing concentrations result in increased episodes of nephrotoxicity (5, 7, 9, 17, 21–23, 27, 28). Additional groups thought to be at increased risk for nephrotoxicity include patients with baseline renal insufficiency, patients who are critically ill, and patients simultaneously exposed to other nephrotoxic agents (i.e., aminoglycosides, intravenous contrast dyes, and vasopressors) (9, 13, 14, 16, 19, 21). Our study supports the finding that critical illness, as determined by APACHE II score, along with baseline renal insufficiency, as low as a creatinine of 1.2, may increase ones risk for nephrotoxicity and subsequent need for hemodialysis.

Linezolid is a bacteriostatic, oxazolidinone approved by the FDA in 2000, whose mechanism of action against GP infections is unique and therefore has not encountered bacterial resistance (29, 30). As such, the recommended therapeutic dose to achieve an AUC/MIC ratio of 50:100 is 600 mg twice daily, which has been shown to be successful against organisms with MIC up to two to four µg/mL (29). Additionally, linezolid exhibits good pulmonary penetrance (41.5% of plasma levels) (9, 29). Many recent studies are now recommending linezolid as a plausible substitution when encountering patients with complex GP infections (osteomyelitis, meningitis, and hospital acquired pneumonia secondary to MRSA) and concomitant risk factors for heightened nephrotoxicity (pre-existing renal insufficiency, aminoglycosides, intravenous contrast dyes, vasopressors, and critical illness) (5, 9, 22, 27, 28, 31–36). However, use of linezolid is not without its own risks, including: myelosuppression, peripheral/optic neuropathy, lactic acidosis, convulsions, and serotonin-like syndrome purported to be caused by inhibition of mitochondrial protein synthesis (9, 29, 30).

Interestingly, our patient population was critically ill, pneumonia was the primary infectious source, and some patients had been exposed to nephrotoxic agents (e.g., intravenous contrast dyes); however, a significant difference between the two groups (vancomycin versus linezolid) regarding need for hemodialysis and mortality was not appreciated. One explanation for this might involve using therapeutic doses maintaining trough levels between 10 and 15 mg/L. A meta-analysis of both retrospective and prospective studies evaluating nephrotoxicity in patients treated with vancomycin found a reduction in nephrotoxicity when trough levels were less than 15 mg/L (13). Our study supports these findings and suggests that a vancomycin-induced rise in creatinine greater than 1.0 is not generally encountered until trough levels in excess of 20 mg/L are reached.

Finally, many studies have compared cost-effectiveness between vancomycin and linezolid for the treatment of MRSA and have found that treatment strategies incorporating linezolid result in decreased duration of intravenous antibiotic treatment and hospital length of stay (37–40). This in turn results in decreased resource utilization and ultimate cost burden. While cost-effectiveness analysis was beyond the scope of this study, it is important to note that on average, our vancomycin patients were treated for a significantly longer duration than our linezolid patients.

We report one of the largest groups of patients studying the relative toxicities of vancomycin and linezolid. While although antibiotic therapy in our study was based upon a cycling antibiotic protocol, this was a retrospective cohort analysis and thus is limited by selection bias, potentially confounding the interpretation of outcomes between study groups. For example, we cannot exclude the fact that critical illness among our patient population may have affected the change in creatinine observed between both treatment groups. Fifty-four percent (n=297) of our critically ill patient population received blood product transfusions during their antibiotic treatment period. While information on vasopressor use was not captured by our database, blood product transfusion might serve as a marker for hemodynamic instability; thus, potentially confounding the association observed between antibiotic use and nephrotoxicity. Additional use of intravenous contrast dyes was also not accounted for by our analysis; however it can be reasonably assumed that critical illness, blood product transfusion, and use of intravenous contrast dyes were evenly distributed between both treatment groups. This was a single center study, and thus external validity may be limited in generalizing results to other areas as the demographics and comorbidities of our patient population may differ. Our study is further limited by our lack of information regarding cost-effectiveness calculations.

Vancomycin is still considered to be the gold standard regarding treatment of MRSA. However, as vancomycin resistance continues to develop and result in MIC creep, alternative treatment strategies incorporating linezolid may be considered as equally efficacious although not without unique consequence. Until then, careful dosing and frequent monitoring remain important in patients with complicated, MRSA infections (osteomyelitis, meningitis, and hospital acquired pneumonia) and concomitant risk factors for heightened nephrotoxicity (aminoglycosides, intravenous contrast dyes, vasopressors, critical illness, but especially pre-existing renal insufficiency).

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References

1. Gorwitz RJ, Kruszon-Moran D, McAllister SK, McQuillan G, McDougal LK, Fosheim GE, Jensen BJ, Killgore G, Tenover FC, Kuehnert MJ. Changes in the prevalence of nasal colonization with *Staphylococcus aureus* in the United States, 2001–2004. *The Journal of infectious diseases*. 2008; 197(9):1226–34. [PubMed: 18422434]
2. Kuehnert MJ, Kruszon-Moran D, Hill HA, McQuillan G, McAllister SK, Fosheim G, McDougal LK, Chaitram J, Jensen B, Fridkin SK, et al. Prevalence of *Staphylococcus aureus* nasal colonization in the United States, 2001–2002. *The Journal of infectious diseases*. 2006; 193(2):172–9. [PubMed: 16362880]
3. Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999–2005. *Emerging infectious diseases*. 2007; 13(12): 1840–6. [PubMed: 18258033]
4. Ellis MW, Hoshenthal DR, Dooley DP, Gray PJ, Murray CK. Natural history of community-acquired methicillin-resistant *Staphylococcus aureus* colonization and infection in soldiers. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2004; 39(7):971–9. [PubMed: 15472848]
5. Maclayton DO, Hall RG 2nd. Pharmacologic treatment options for nosocomial pneumonia involving methicillin-resistant *Staphylococcus aureus*. *The Annals of pharmacotherapy*. 2007; 41(2):235–44. [PubMed: 17299012]
6. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, 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; 52(3):e18–55. [PubMed: 21208910]
7. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Archives of internal medicine*. 2006; 166(19):2138–44. [PubMed: 17060545]
8. Levine DP. Vancomycin: a history. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2006; 42 (Suppl 1):S5–12. [PubMed: 16323120]
9. Pletz MW, Burkhardt O, Welte T. Nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia: linezolid or vancomycin? - Comparison of pharmacology and clinical efficacy. *European journal of medical research*. 2010; 15(12):507–13. [PubMed: 21163725]
10. Williams ME, Harman C, Scheld M, Hess CE, Donowitz GR. A controlled study of ticarcillin plus clavulanic acid versus piperacillin as empiric therapy for fever in the immunocompromised host. *The American journal of medicine*. 1985; 79(5B):67–72. [PubMed: 3907343]
11. Wang LS, Liu CY, Wang FD, Fung CP, Chiu ZH, Cheng DL. Chromatographically purified vancomycin: therapy of serious infections caused by *Staphylococcus aureus* and other gram-positive bacteria. *Clinical therapeutics*. 1988; 10(5):574–84. [PubMed: 2856600]
12. Goren MP, Baker DK Jr, Shenep JL. Vancomycin does not enhance amikacin-induced tubular nephrotoxicity in children. *The Pediatric infectious disease journal*. 1989; 8(5):278–82. [PubMed: 2657616]
13. Wong-Beringer A, Joo J, Tse E, Beringer P. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. *International journal of antimicrobial agents*. 2011; 37(2): 95–101. [PubMed: 21130609]
14. Hazlewood KA, Brouse SD, Pitcher WD, Hall RG. Vancomycin-associated nephrotoxicity: grave concern or death by character assassination? *The American journal of medicine*. 2010; 123(2):182, e1–7. [PubMed: 20103028]

15. Menichetti F, Martino P, Bucaneve G, Gentile G, D'Antonio D, Liso V, Ricci P, Nosari AM, Buelli M, Carotenuto M, et al. Effects of teicoplanin and those of vancomycin in initial empirical antibiotic regimen for febrile, neutropenic patients with hematologic malignancies. Gimema Infection Program. Antimicrobial agents and chemotherapy. 1994; 38(9):2041–6. [PubMed: 7811016]
16. Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. European journal of clinical pharmacology. 2012; 68(9):1243–55. [PubMed: 22411630]
17. Bosso JA, Nappi J, Rudisill C, Wellein M, Bookstaver PB, Swindler J, Mauldin PD. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. Antimicrobial agents and chemotherapy. 2011; 55(12):5475–9. [PubMed: 21947388]
18. Kureishi A, Jewesson PJ, Rubinger M, Cole CD, Reece DE, Phillips GL, Smith JA, Chow AW. Double-blind comparison of teicoplanin versus vancomycin in febrile neutropenic patients receiving concomitant tobramycin and piperacillin: effect on cyclosporin A-associated nephrotoxicity. Antimicrobial agents and chemotherapy. 1991; 35(11):2246–52. [PubMed: 1839490]
19. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrobial agents and chemotherapy. 2008; 52(4):1330–6. [PubMed: 18227177]
20. Cohen E, Dadashev A, Drucker M, Samra Z, Rubinstein E, Garty M. Once-daily versus twice-daily intravenous administration of vancomycin for infections in hospitalized patients. The Journal of antimicrobial chemotherapy. 2002; 49(1):155–60. [PubMed: 11751780]
21. Cano EL, Haque NZ, Welch VL, Cely CM, Peyrani P, Scerpella EG, Ford KD, Zervos MJ, Ramirez JA, Kett DH. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. Clinical therapeutics. 2012; 34(1):149–57. [PubMed: 22284995]
22. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, McGee WT, Reisman A, Chastre J. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2012; 54(5):621–9. [PubMed: 22247123]
23. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. Clinical therapeutics. 2007; 29(6):1107–15. [PubMed: 17692725]
24. Martin JH, Norris R, Barras M, Roberts J, Morris R, Doogue M, Jones GR. 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. The Clinical biochemist Reviews/Australian Association of Clinical Biochemists. 2010; 31(1):21–4. [PubMed: 20179794]
25. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in combined medical-surgical intensive care units in the United States. Infection control and hospital epidemiology: the official journal of the Society of Hospital Epidemiologists of America. 2000; 21(8):510–5. [PubMed: 10968716]
26. Scheetz MH, Wunderink RG, Postelnick MJ, Noskin GA. Potential impact of vancomycin pulmonary distribution on treatment outcomes in patients with methicillin-resistant *Staphylococcus aureus* pneumonia. Pharmacotherapy. 2006; 26(4):539–50. [PubMed: 16553514]
27. Ferrara AM. Treatment of hospital-acquired pneumonia caused by methicillin-resistant *Staphylococcus aureus*. International journal of antimicrobial agents. 2007; 30(1):19–24. [PubMed: 17475449]
28. Stein GE, Wells EM. The importance of tissue penetration in achieving successful antimicrobial treatment of nosocomial pneumonia and complicated skin and soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*: vancomycin and linezolid. Current medical research and opinion. 2010; 26(3):571–88. [PubMed: 20055750]

29. Falagas ME, Vardakas KZ. Benefit-risk assessment of linezolid for serious gram-positive bacterial infections. *Drug safety: an international journal of medical toxicology and drug experience*. 2008; 31(9):753–68. [PubMed: 18707190]
30. Beekmann SE, Gilbert DN, Polgreen PM. Toxicity of extended courses of linezolid: results of an Infectious Diseases Society of America Emerging Infections Network survey. *Diagnostic microbiology and infectious disease*. 2008; 62(4):407–10. [PubMed: 18929458]
31. Alaniz C, Pogue JM. Vancomycin versus linezolid in the treatment of methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: implications of the ZEPHYR trial. *The Annals of pharmacotherapy*. 2012; 46(10):1432–5. [PubMed: 22947593]
32. Dodds TJ, Hawke CI. Linezolid versus vancomycin for MRSA skin and soft tissue infections (systematic review and meta-analysis). *ANZ journal of surgery*. 2009; 79(9):629–35. [PubMed: 19895519]
33. Kohno S, Yamaguchi K, Aikawa N, Sumiyama Y, Odagiri S, Aoki N, Niki Y, Watanabe S, Furue M, Ito T, et al. Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* in Japan. *The Journal of antimicrobial chemotherapy*. 2007; 60(6):1361–9. [PubMed: 17913720]
34. Weigelt J, Itani K, Stevens D, Lau W, Dryden M, Knirsch C. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. *Antimicrobial agents and chemotherapy*. 2005; 49(6):2260–6. [PubMed: 15917519]
35. Beibei L, Yun C, Mengli C, Nan B, Xuhong Y, Rui W. Linezolid versus vancomycin for the treatment of gram-positive bacterial infections: meta-analysis of randomised controlled trials. *International journal of antimicrobial agents*. 2010; 35(1):3–12. [PubMed: 19900794]
36. Itani KM, Dryden MS, Bhattacharyya H, Kunkel MJ, Baruch AM, Weigelt JA. Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be caused by methicillin-resistant *Staphylococcus aureus*. *American journal of surgery*. 2010; 199(6):804–16. [PubMed: 20227056]
37. Bounthavong M, Hsu DI, Okamoto MP. Cost-effectiveness analysis of linezolid vs. vancomycin in treating methicillin-resistant *Staphylococcus aureus* complicated skin and soft tissue infections using a decision analytic model. *International journal of clinical practice*. 2009; 63(3):376–86. [PubMed: 19222624]
38. Mullins CD, Kuznik A, Shaya FT, Obeidat NA, Levine AR, Liu LZ, Wong W. Cost-effectiveness analysis of linezolid compared with vancomycin for the treatment of nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Clinical therapeutics*. 2006; 28(8):1184–98. [PubMed: 16982296]
39. De Cock E, Krueger WA, Sorensen S, Baker T, Hardewig J, Duttagupta S, Muller E, Piecyk A, Reisinger E, Resch A. Cost-effectiveness of linezolid vs vancomycin in suspected methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia in Germany. *Infection*. 2009; 37(2):123–32. [PubMed: 19277465]
40. McCollum M, Sorensen SV, Liu LZ. A comparison of costs and hospital length of stay associated with intravenous/oral linezolid or intravenous vancomycin treatment of complicated skin and soft-tissue infections caused by suspected or confirmed methicillin-resistant *Staphylococcus aureus* in elderly US patients. *Clinical therapeutics*. 2007; 29(3):469–77. [PubMed: 17577468]

Table 1
Stratification of Patients by Initial Primary Diagnosis and/or Initial Primary Surgery Type (N=545).

	Trauma (209)	Gen Surg (155)	Txp* (88)	CR (57)	HB (24)	Thoracic (8)	Vascular (2)	Gyn (2)
Initial Surg	65% (n=135)	92% (n=143)	78% (n=69)	96% (n=55)	100% (n=24)	88% (n=7)	100% (n=2)	100% (n=2)
Open(n)	120	93	62	53	22	5	2	2
Lap(n)	--	26	--	2	--	1	--	--
Debr(n)	5	16	--	--	--	--	--	--
Perc(n)	10	6	6	--	2	--	--	--
Endo(n)	--	2	1	--	--	1	--	--
Reoperation	34% (n=72)	54% (n=84)	44% (n=39)	40% (n=23)	50% (n=12)	75% (n=6)	50% (n=1)	50% (n=1)
Open(n)	61	65	33	17	5	5	1	1
Lap(n)	--	--	--	--	--	--	--	--
Debr(n)	4	8	--	3	--	1	--	--
Perc(n)	7	9	3	3	7	--	--	--
Endo(n)	--	2	3	--	--	--	--	--
Transfusion	70% (n=146)	40% (n=62)	51% (n=45)	46% (n=26)	50% (n=12)	50% (n=4)	50% (n=1)	50% (n=1)

*Txp [liver (n=69), kidney (n=16), kidney/pancreas (n=2), liver/kidney (n=1)]; colorectal (CR), debridement (Debr), endoscopy (Endo), general (Gen), gynecology (Gyn), hepatobiliary (HB), laparoscopic (Lap), percutaneous (Perc), surgery (Surg), transplant (Txp).

Table 2

Univariable Analysis of Demographics and Comorbidities Between Patient Groups Treated with Either Vancomycin or Linezolid.

Demographics/Comorbidities	Vancomycin (298)	Linezolid (247)	P-Value
Gender (Male)	63.8% (n=190)	64% (n=158)	0.960
Age (Years)	52.8±1.0	53.8±1.0	0.510
Race (White)	84.2% (n=251)	85.8% (n=212)	0.630
Race (Black)	12.4% (n=37)	10.5% (n=26)	0.500
Race (Hispanic)	2.3% (n=7)	2.4% (n=6)	1.000
Diabetes Mellitus	18.5% (n=55)	23.9% (n=59)	0.120
Hypertension	30.5% (n=91)	38.1% (n=94)	0.065
Hyperlipidemia	4.0% (n=12)	7.7% (n=19)	0.066
Cardiovascular Disease	4.0% (n=12)	3.6% (n=9)	0.820
Peripheral Vascular Disease	4.4% (n=13)	5.7% (n=14)	0.480
Coronary Arterial Disease	17.1% (n=51)	21.5% (n=53)	0.200
Renal Insufficiency	5.7% (n=17)	3.6% (n=9)	0.260
Hemodialysis	10.4% (n=31)	8.9% (n=22)	0.560
APACHE II Score	18.8±0.5	18.5±0.5	0.680
Acute Physiological Score	13.4±0.4	12.9±0.5	0.450
Initial Creatinine (<1.2)	66.8% (n=199)	63.6% (n=157)	0.470
Initial Creatinine (1.2 to 1.5)	8.4% (n=25)	10.9% (n=27)	0.380
Initial Creatinine (1.5 to 2.0)	7.7% (n=23)	8.5% (n=21)	0.750
Initial Creatinine (>2.0)	17.1% (n=51)	17.0% (n=42)	1.000

Categorical data is reported as %(n); the Fisher's Exact Test or Chi-Square was used to assess the statistical significance of the difference in proportions.

Continuous data is reported as mean ± standard deviation; the Mann-Whitney U or Independent t-test was used to assess the statistical significance of the difference in means.

Table 3

Univariable Analysis of Outcomes Between Patient Groups Treated with Either Vancomycin or Linezolid.

Outcomes	Vancomycin (298)	Linezolid (247)	P-Value
Max Creatinine During Treatment ^a	1.8±0.1	1.7±0.09	0.29
Max Creatinine During Treatment ^β	1.1 (0.8,1.9)	1.2 (0.8,2.0)	0.9
Final Creatinine After Treatment ^a	1.4±0.07	1.2±0.07	0.24
Final Creatinine After Treatment ^β	0.9 (0.7,1.4)	0.9 (0.7,1.4)	0.92
Change in Creatinine (Max-Initial) ^a	0.4±0.04	0.3±0.04	0.16
Change in Creatinine (Max-Initial) ^β	0.1 (0.0,0.3)	0.1 (0.0,0.3)	0.55
Change in Creatinine (Final-Initial) ^a	-0.1±0.05	-0.2±0.05	0.44
Change in Creatinine (Final-Initial) ^β	-0.1 (-0.3,0.1)	-0.1 (-0.3,0.1)	0.62
New Onset Hemodialysis	9.4% (n=28)	9.7% (n=24)	0.9
Risk (RIFLE Criteria)	7.0% (n=21)	6.1% (n=15)	0.73
Injury (RIFLE Criteria)	3.0% (n=9)	0.8% (n=2)	0.122
Failure (RIFLE Criteria)	10.4% (n=31)	7.7% (n=19)	0.3
Loss (RIFLE Criteria)	1.0% (n=3)	1.6% (n=4)	0.707
ESRD (RIFLE Criteria)	0.7% (n=2)	0.4% (n=1)	1
Length of Stay After Treatment (Days) ^a	28.3±1.4	26.2±1.7	0.35
Length of Stay After Treatment (Days) ^β	20 (11,38)	19 (11,32)	0.15
Death	17.8% (n=53)	16.6% (n=41)	0.72

^aMean ± Standard Deviation^βMedian and Interquartile Range end stage renal disease (ESRD), risk injury failure loss ESRD (RIFLE)
end stage renal disease (ESRD), risk injury failure loss ESRD (RIFLE)

Table 4

Multivariable Logistic Regression Evaluating Risk Factors for Rise in Initial Creatinine by More Than 1.0 During Antibiotic Treatment.

Risk Factor	Relative Risk	95%CI	Used/Read	C-Statistic
Age	1.00	0.97–1.02	545/545	0.801
Diabetes Mellitus	1.20	0.56–2.60		
Coronary Artery Disease	0.86	0.35–2.12		
Hypertension	0.67	0.32–1.36		
Peripheral Vascular Disease	0.55	0.11–2.82		
APACHE II (20–30)	1.30	0.62–2.73		
APACHE II (30)	3.01	1.22–7.42		
Initial Creatinine (1.2–1.5)	4.36	1.46–12.99		
Initial Creatinine (1.5–2.0)	9.99	3.78–26.38		
Initial Creatinine (>2.0)	9.10	3.88–21.35		
Choice of Antibiotic	0.49	0.25–0.94		

confidence interval (CI)

Table 5

Multivariable Logistic Regression Evaluating Risk Factors for New Onset Hemodialysis During Antibiotic Treatment.

Risk Factor	Relative Risk	95%CI	Used/Read	C-Statistic
Age	1.00	0.98–1.03	545/545	0.864
Diabetes Mellitus	1.48	0.70–3.12		
Coronary Artery Disease	0.44	0.17–1.15		
Hypertension	0.86	0.43–1.75		
Peripheral Vascular Disease	1.79	0.47–6.80		
APACHE II (20–30)	1.14	0.52–2.46		
APACHE II (30)	3.07	1.23–7.62		
Initial Creatinine (1.2–1.5)	10.83	3.19–36.77		
Initial Creatinine (1.5–2.0)	14.88	4.56–48.53		
Initial Creatinine (>2.0)	27.28	9.54–77.95		
Choice of Antibiotic	0.98	0.51–1.89		

confidence interval (CI)

Table 6

Univariable Analysis Evaluating Vancomycin Trough Levels and the Corresponding Relative Risk of Rise in Creatinine by More Than 1.0.

Vancomycin Trough Levels	Relative Risk	95%CI
<10	ref	---
10–15	1.35	0.23–7.78
15–20	2.38	0.42–13.53
>20	5.4	1.19–24.51

confidence interval (CI)