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Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with *Staphylococcus aureus* Lower Respiratory Tract Infections

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Abstract

Background: Vancomycin is commonly used to treat staphylococcal infections, but there has not been a definitive analysis of the pharmacokinetics of this antibacterial in relation to minimum inhibitory concentration (MIC) that could be used to determine a target pharmacodynamic index for treatment optimisation.

Objective: To clarify relationships between vancomycin dosage, serum concentration, MIC and antimicrobial activity by using data gathered from a therapeutic monitoring environment that observes failures in some cases.

Methods: We investigated all patients with a *Staphylococcus aureus* lower respiratory tract infection at a 300-bed teaching hospital in the US during a 1-year period. Clinical and pharmacokinetic information was used to determine the following: (i) whether steady-state 24-hour area under the concentration-time curve (AUC_{24}) divided by the MIC (AUC_{24}/MIC) values for vancomycin could be precisely calculated with a software program; (ii) whether the percentage of time vancomycin serum concentrations were above the MIC (%Time>MIC) was an important determinant of vancomycin response; (iii) whether the time to bacterial eradication differed as the AUC_{24}/MIC value increased; (iv) whether the time to bacterial eradication for vancomycin differed compared with other antibacterials at the same AUC_{24}/MIC value; and (v) whether a relationship existed between time to bacterial eradication and time to significant clinical improvement of pneumonia symptoms.

Results: The median age of the 108 patients studied was 74 (range 32–93) years. Measured vancomycin AUC_{24}/MIC values were precisely predicted with the A.U.I.C. calculator in a subset of our patients ($r^2 = 0.935$). Clinical and bacteriological response to vancomycin therapy was superior in patients with higher (≥400) AUC_{24}/MIC values ($p = 0.0046$), but no relationship was identified between vancomycin %Time>MIC and infection response. Bacterial eradication of *S. aureus* (both methicillin-susceptible and methicillin-resistant) occurred more rapidly ($p = 0.0402$) with vancomycin when a threshold AUC_{24}/MIC value was reached. *S. aureus* killing rates were slower with vancomycin than with other antistaphylococcal antibacterials ($p = 0.002$). There was a significant relationship

($p < 0.0001$) between time to bacterial eradication and the time to substantial improvement in pneumonia score.
Conclusions: Vancomycin AUC_{24}/MIC values predict time-related clinical and bacteriological outcomes for patients with lower respiratory tract infections caused by methicillin-resistant *S. aureus*.

Antibacterial selection is usually based on *in vitro* susceptibility testing. The use of this procedure assumes that there is a relationship between serum concentration of the antibacterial, minimum inhibitory concentration (MIC) for the organism and bacterial killing. However, many factors may alter pharmacokinetics between patients, and thus there is potential for a variable degree of interaction between concentration and MIC in each patient. The potential for variance exists in both MIC and blood concentration (exposure). This realisation has fostered the use of combined indices of exposure that are descriptive of the full range of possible interactions, such as the time above the MIC in a 24-hour period, or the 24-hour area under the concentration-time curve divided by the MIC (AUC_{24}/MIC; also called area under the inhibitory time curve or AUIC).

Our institution has investigated the pharmacodynamic indices of many antibacterials, alone and in combination, in patients. Our initial focus has been on antibacterials that have Gram-negative activity.[1-4] The best response has been observed as the AUC_{24}/MIC has approached 125.[1,4-7] This parameter may be considered the simplest means of expressing the reality of individual patient differences in pharmacokinetics and individual organism differences in susceptibility. Whenever patients display more complex interactions between bacterial killing rate and AUC_{24}/MIC, we have considered other indices, such as peak/MIC ratio for aminoglycosides and time above MIC for β-lactams. As most authors have pointed out, these indices tend to be highly correlated in human trials, whereas they may be less well correlated in animal or *in vitro* models.[8]

Vancomycin is the antibacterial of choice for difficult-to-treat *Staphylococcus aureus* infections that show resistance to β-lactams. However, oxacillin is the treatment of choice if the *S. aureus* is β-lactam susceptible. Vancomycin has approximately the same MIC for all *S. aureus* strains, regardless of whether they are susceptible to β-lactams, with a typical MIC range of 0.5–2.0 mg/L. Vancomycin is generally used only for β-lactam-resistant *S. aureus* (methicillin-resistant *S. aureus* [MRSA]). Early studies established the target peak concentration for vancomycin in the range of 30–35 mg/L, with troughs of 5–10 mg/L.[9,10] Although vancomycin is up to 65% protein bound, current clinical practice is to express target concentrations as total rather than free. Time above MIC is considered the target index, although it would appear with these blood concentration targets (and the usual staphylococcal MICs of ≤2 mg/L) that all patients would attain the target of 100% time above MIC.

There have always been reports of treatment failure in MRSA patients treated with vancomycin, although these seem to be increasing in frequency since the late 1990s. For example, Burnie and colleagues[11] studied 42 cases of septicaemia and found a mortality of 4% in cases treated with vancomycin and rifampicin (rifampin) where the organism was susceptible to both antibacterials. When the organism was treated with both but the organism acquired rifampicin resistance during treatment, mortality was 38%. Finally, mortality was 78% when the organism was only susceptible to vancomycin and not rifampicin, or when vancomycin monotherapy was given. All organisms in this analysis were vancomycin-susceptible according to the laboratory definition of an MIC <8 mg/L. Detailed analysis in the laboratory revealed most strains to be hetero-resistant to vancomycin, a strong correlate of vancomycin failure in other studies[12] as well as this one.

Thus far, although vancomycin failure is being noted around the world, there has not yet been a thorough study of time above MIC or AUC_{24}/MIC relationships versus microbiological and clinical outcomes in a patient population. Data collected in the US from January 1990 to May 1999 by the

National Nosocomial Infections Surveillance System (NNIS) of the Centers for Disease Control and Prevention (CDC) indicated that *S. aureus* was among the most common causes of nosocomial pneumonia.[13] Data from the NNIS hospitals showed an increase in nosocomial MRSA infections from 23% in 1987 to 56% in 1997.[14] Today, 70–90% of *S. aureus* strains are resistant to penicillin, and in larger hospitals approximately 45% are resistant to oxacillin.[15,16] Recently, *S. aureus* with reduced susceptibility to vancomycin have appeared.[17-24] As we have pointed out,[25] and as shown in comparative trials,[26,27] vancomycin treatment failures are not uncommon in patients with vancomycin-susceptible (by MIC) *S. aureus* infections.[25,27-30] Failure is especially frequent if vancomycin MIC is 4 mg/L, as shown recently by Fridkin et al.[29]

In spite of its failings, vancomycin remains the drug of first choice for the treatment of MRSA infections in most US hospitals. In randomised, comparative trials, all the newer agents have similar cure rates to vancomycin,[26,31-33] and at the same time the new agents are both more expensive and have toxicities that cause concern. As the use of vancomycin continues to increase, it may be anticipated that outcomes of treatment will worsen in an environment of intense selection pressure and steadily increasing use. This viewpoint has prompted a variety of strategies to improve the results of vancomycin therapy, such as higher doses, combination therapy and continuous infusion. A recent study showed no differences in outcome between intermittent and continuous vancomycin.[28] This study discussed the importance of time above MIC, yet the study analysis did not attend to MIC differences between bacteria or the possibility of different MICs influencing these conclusions.

Our primary purpose in the present study was to clarify relationships between vancomycin dosage, serum concentration, MIC and antimicrobial activity by using data gathered from a therapeutic monitoring environment that observes failures in some cases. We have previously reported on a subset of patients with both MRSA and methicillin-susceptible *S. aureus* (MSSA) lower respiratory tract infections that were treated with vancomycin.[25,34,35] In this subset, a calculated vancomycin AUC_{24}/MIC value of 345 was found to correlate with clinical success at test-of cure. However, the validation for the use of the calculated AUC_{24}/MIC values was not reported in the investigation, and this is pertinent if calculated AUC_{24}/MIC values are to be considered in the design of a patient's antibacterial regimen.

This analysis extends our previous work in that our focus here is on lower respiratory tract infections (LRTIs) caused by *S. aureus*. In the selected LRTI population, the analysis considers all antimicrobial treatments for all staphylococci, both MRSA and MSSA. Perhaps for the first time, we are considering all antibacterials used for *S. aureus* LRTI, including combinations of antibacterials that include vancomycin. This analysis also emphasises a very important endpoint that has not yet been studied in a patient population with *S. aureus* LRTIs, which is the time to bacterial eradication. Time to bacterial eradication analysed in relation to AUC_{24}/MIC is necessary to determine whether there is any suggestion of concentration-dependent killing behaviour in association with vancomycin. In particular for *S. aureus*, if a threshold AUC_{24}/MIC value is associated with a quicker time to bacterial eradication then the drug may exhibit some concentration-dependent response and optimising AUC_{24}/MIC values could offer the potential for a shorter duration of treatment.

This analysis considered a population of patients with *S. aureus* LRTI and had the following goals: (i) to validate the use of computer-calculated AUC_{24}/MIC values for vancomycin versus measured blood concentrations; (ii) to determine whether the percentage of time vancomycin serum concentrations are above the MIC (%Time>MIC) is as good a (or a better) determinant of response than its AUC_{24}/MIC value; (iii) to examine the time to bacterial eradication for vancomycin in relation to achieved AUC_{24}/MIC values; (iv) to examine the time to bacterial eradication for vancomycin compared with all other antibacterials used to treat the LRTI; and (v) to determine whether a relationship exists between time to bacterial eradication and significant improvement of pneumonia symptoms.

Patients and Methods

Study Design and Selection of Patients

All hospitalised patients with *S. aureus* isolated from a respiratory specimen between 1 January 1998 and 31 December 1998 were considered, provided that they had antibacterials ordered within 72 hours of the culture. Patients were identified using the Clinical Pharmacokinetics Lab (CPL) computer database, and the hospital medical records of all of these patients were then reviewed in order to identify the final population. Patients included were adults, 18 years of age and older, treated with antibacterial therapy for 3 or more days for a documented LRTI. Patients were required to have an *S. aureus* LRTI based on the clinical, radiographic and microbiological criteria defined by the Division of Anti-Infective Drug Products, Center for Drug Evaluation and Research.[36]

Patients were excluded if they had endocarditis, osteomyelitis and/or a central nervous system infection in addition to their LRTI. Patients were also excluded if an investigational antibacterial was administered as the primary treatment agent.

Data Collection

Data were collected beginning with the initiation of antibacterial treatment, and patients were followed throughout hospitalisation or for 14 days after the last dose of antibacterials, whichever endpoint was reached first. The following patient data was abstracted from the patient's medical record: age, sex, height, baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) score[37] (on the day antibacterial therapy for the *S. aureus* LRTI was initiated), length of hospital stay (days) prior to occurrence of the LRTI, type of hospital bed occupied (intensive care unit [ICU] or non-ICU) at baseline, baseline ventilator status (intubated or not intubated), susceptibility of the *S. aureus* isolate, results of all follow-up cultures, all vancomycin serum concentration measurements, daily bodyweight, daily serum creatinine, presence of underlying respiratory illness and clinical parameters used to calculate a daily pneumonia score, as presented in table I.

Clinical and bacteriological responses were assessed at the end of antibacterial treatment (while the patient was still hospitalised) and 14 days after treatment was discontinued (test-of-cure). Criteria for clinical and microbiological responses were similar to those used in phase III clinical trials and have

Table I. Modified clinical pneumonia scoring (reproduced from Luzier et al.,[38] with permission)

Parameter	Criteria for score of:			
	1	2	3	4
Rales/crackles[a]	None	Mild	Moderate	Severe
Decreased breath sounds[a]	None	Mild	Moderate	Severe
Oxygen use	Room air	Mask aerosol T vent (≤40%)	Ventilator (41–60%)	Ventilator (≥61%)
Peripheral WBC count ($\times 10^9$/L)	<10	10–15	15.1–30	>30
Differential (% band neutrophils)	<5	5.1–15	15.1–39.9	≥40
CNS status	Alert and fully oriented	Alert but not fully oriented	Not alert, responsive only to pain	Nonresponsive
Tube sign[b] (no. of tubes)	0–2	3–5	6–9	>9
Sputum or tracheal secretions	None	Suction every shift or cough occasionally	Suction every 2–3 hours or cough continuously	Suction every 0.5–1 hour
Maximum temperature [°F] (°C)	97.0–99.0 (36.1–37.2)	99.1–100.9 (37.3–38.2)	101.0–102.9 (38.3–39.3)	≥103.0 (≥39.4)
Serum albumin (g/dL)	≥3.9	3.0–3.8	1.9–2.9	≤1.8

a New parameter, replacing daily Gram stain results.

b Tubes considered include the sum of: endotracheal tube, Foley catheter, ureteral stent, indwelling venous catheter, nasogastric tube, central line, Swan-Ganz catheter and surgical drainage tubes.

WBC = white blood cell.

been detailed previously.[25] For patients who were discharged before the test-of-cure evaluation at 14 days after the last antibacterial dose, the test-of-cure evaluation was defined on the last day of hospitalisation, provided that the patient was not readmitted to the institution with a relapse of their infection in the interim period.

Calculation of Pharmacodynamic Indices

Predicted AUC_{24}/MIC values of all antimicrobial agent(s) active against *S. aureus* were computed daily for each patient with A.U.I.C. software (©1998, Martin H. Adelman and Jerome J. Schentag; available at www.schentag-ce.com). This software calculates AUC_{24}/MIC values using the estimated creatinine clearance (CL_{CR}) of the patient,[39] the 24-hour administration regimen and the measured MIC for the bacterial isolate.[40] The equation used for vancomycin AUC_{24} in the software is as follows (equation 1):[41]

$$AUC_{24} = \frac{D}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06} \quad \text{(Eq. 1)}$$

where AUC_{24} is expressed as mg • h/L, CL_{CR} is expressed as mL/min and D is vancomycin dosage in mg/24 hours. Exact MIC values (measured by microbroth dilution) were available for patients with an MIC of at least 1 mg/L; however, if the MIC of the isolate was ≤0.5 mg/L, a value of ≤0.5 mg/L was reported. For the latter cases, a value of 0.5 mg/L was used for the calculation of AUC_{24}/MIC by the software.[2,40] Although a recent commentary suggested that AUC/MIC ratios should have the units of hours,[42] this neglected the 18–24 hour incubation time consideration that is integral to the MIC test.[43] Therefore, since MIC should be reported with units of mg • h/L over 24 hours, we will continue to express AUC/MIC as a ratio, without units.

Software Validation

Validation of the A.U.I.C. software for prediction of AUC_{24}/MIC values within this patient population was performed by comparing vancomycin AUC_{24}/MIC values derived from the patient's steady-state serum vancomycin concentrations with AUC_{24}/MIC values that were calculated by using the A.U.I.C. software. The validation was performed in the subset of patients who had two or more steady-state vancomycin serum concentration measurements and whose renal function remained stable during vancomycin therapy (serum creatinine did not increase or decrease by more than 0.2 mg/dL). Individual pharmacokinetic parameters were estimated for each patient by use of ADAPT II software. Vancomycin serum concentrations were fitted to a two-compartment volume-clearance model[41,44-46] using the maximum *a posteriori* probability (MAP) Bayesian approach to parameterise individual patient pharmacokinetic profiles. The average of the daily predicted AUC_{24}/MIC values were used for the analysis in situations where renal function was changing. Once a patient's pharmacokinetic parameters were estimated based on his/her vancomycin serum concentrations, the steady state AUC_{24}/MIC was computed based on the patient's 24-hour daily dose, fitted vancomycin clearance (calculated from the patient's creatinine clearance and bodyweight) and the MIC of the infecting pathogen.

Combination Therapy

There is a large body of clinical information on combination treatment for *S. aureus*, as it is unusual for hospitalised patients given vancomycin to receive only this antibacterial as monotherapy.[28] Typical agents used with vancomycin include rifampicin,[11] cephalosporins, aminoglycosides and newer agents such as quinupristin/dalfopristin.[47] However, there has been no definitive pharmacodynamic study of regimens that involve vancomycin. Studies of rifampicin in combination with vancomycin have demonstrated both synergism and antagonism.[48,49] There have been occasional case reports indicating a benefit of adding rifampicin;[11,50,51] however, there are also data indicating no benefit.[52] Investigations of vancomycin in combination with aminoglycosides appear to demonstrate mild synergism against some isolates of *S. aureus*.[53,54] However, one study found the addition of an aminoglycoside to vancomycin to be additive and not synergistic for some *S. aureus* isolates.[55] Mouton and colleagues[56] found that efficacy of combination therapy (ticarcillin plus tobramycin, ceftazidime plus netilmicin, ceftazidime plus ciprofloxacin, and ciprofloxacin plus netilmicin) in animal models could best be explained

by the combination of the two pharmacodynamic indices that each best explained the response for the agent given singly. They did not examine vancomycin, nor did they test their animal model against *S. aureus* infections. But if the 'addition of like mechanisms' approach[56] were applied to vancomycin, it would be additive with β-lactams and the procedure would be to combine their values for time above MIC or AUC_{24}/MIC to test for additivity.

The average daily total AUC_{24}/MIC was calculated by taking the average of the daily sum of the calculated AUC_{24}/MIC value for each separate antibacterial administered on days when cultures remained positive for *S. aureus*. The latter sometimes included days when vancomycin was not administered, but other antibacterials were used. For example, the antibacterials administered during empirical therapy while culture results were pending did not always include vancomycin. In addition, vancomycin was not always continued when all culture results were available, as, on occasion, the regimen was streamlined. When combination therapy was administered, vancomycin was considered both as a sole active agent and as a part of the sum of the predicted AUC_{24}/MIC value of each of the separate antibacterials. Because there is no definitive answer (synergistic, additive or antagonistic) on combination treatment, our goal was to determine if a summation of the individual AUC_{24}/MIC values could explain differences in outcomes of patients with *S. aureus*-associated LRTIs.

Efficacy Assessments

The clinical efficacy of the antibacterial(s) used for the *S. aureus* LRTI was categorised by the treating clinician, who was blinded to the pharmacokinetic-pharmacodynamic data and the pneumonia scoring results. Clinical response was determined at the test-of-cure as one of the following: (i) clinical success, defined as the resolution of signs and symptoms of the LRTI noted at baseline; (ii) clinical failure, defined as the persistence of presenting signs or symptoms and/or new unfavourable findings relating to efficacy measures subsequent to baseline; or (iii) indeterminate, defined as inability to classify as one of the above due to confounding circumstances.

The bacteriological response was determined for each baseline *S. aureus* pathogen at test-of-cure as one of the following: (i) eradication (documented or presumed), defined as the culture-proven elimination of *S. aureus* from the sputum or the absence of adequate culture material for evaluation due to clinical improvement; (ii) persistence (documented or presumed), defined as failure to eradicate *S. aureus* at all post-baseline points whether signs of infection were present or not, or continued clinical symptoms of infection from baseline in the absence of microbiological data; or (iii) indeterminate, in which confounding circumstances precluded classification to one of the above categories.

Available disease scoring methods like APACHE are not designed for serial usage or for pharmacodynamic evaluations. We therefore adapted a previously validated tool[38,57] for scoring nosocomial pneumonia response to antibacterials. The daily pneumonia scoring protocol considered ten clinical parameters (table I). In this instrument, each clinical parameter was assigned values ranging from 1 to 4, with the higher values in each instance representing poorer clinical status. The lowest possible score a patient could achieve was 10, indicating a satisfactory clinical state. The highest possible score a patient could achieve was 40, and patients with a score of this magnitude were typically moribund. Each patient was scored daily for the duration of antistaphylococcal antibacterial treatment, beginning on the day antimicrobial therapy was initiated. The daily pneumonia scores of all patients were then standardised to baseline, so the score on day 1 was zero. From baseline, the changes in score (points) from day 1 were used to express changes.

Statistical Analysis

Comparison of patient demographic variables and other characteristics was performed with Pearson chi-square and Fisher exact tests for categorical variables. Continuous variables were compared with Kruskal-Wallis analysis of variance. Goodness of fit of measured AUC_{24}/MIC versus predicted AUC_{24}/MIC was assessed with McFadden's rho-squared.

Multivariable logistic regression analysis was performed on clinical success using backward stepping, with $p \leq 0.1$ required for inclusion in the model. Variables identified as being borderline sig-

nificant in our univariate analysis ($p < 0.15$) were used for the analysis.

Factors predictive of time to eradication were explored by using interval analysis. The time to event for each patient was the day to eradication for subjects who achieved eradication and was the duration of treatment with antibacterial(s) for censored patients. The variables tested were rate of bacterial eradication and AUC_{24}/MIC values for patients receiving vancomycin as part of a regimen, and rate of bacterial eradication and primary treatment agent (vancomycin vs non-vancomycin). Kaplan-Meier plots were used to illustrate the probability of bacterial eradication over time in relation to the AUC_{24}/MIC ratio.

The changes in clinical pneumonia score from baseline in the two groups (clinical success and clinical failure) were compared on specific days by Kruskal-Wallis analysis of variance with the Bonferroni adjustment for pair-wise contrasts, with significance defined as $p < 0.05$. The relationship between changes from baseline in clinical scores on days 3, 4 and 5 and probability of clinical success was explored using recursive partitioning and was also tested using the chi-square statistic.

The relationship between time to substantial improvement in pneumonia score and time to bacterial eradication was tested with Spearman's correlation (R_S). Substantial improvement in clinical score was defined as the time (in days) until the clinical score decreased (i.e. improvement in symptoms) by at least 4 points. For patients whose clinical score did not improve with treatment, the time was documented as the number of days the patient received antibacterial therapy.

Results

Study Population

The CPL computer database identified 160 patients with *S. aureus* isolated from a respiratory specimen between 1 January 1998 and 31 December 1998 and with antibacterials ordered within 72 hours of culture report. Of these 160 patients, 13 patients were excluded because they received <72 hours of antibacterial therapy in the hospital, 11 patients were excluded because there was no proof of pneumonia on chest radiograph before or within 48 hours of antibacterial initiation, and 21 patients did not have the required signs and/or symptoms of a LRTI. In addition, four patients had a concomitant central nervous system infection and two patients had osteomyelitis in addition to the LRTI. One patient was also excluded for receiving an investigational antibacterial as a primary treatment agent. The remaining 108 patient cases were analysed. The median age of the 108 patients was 74 (range 32–93) years, 53.7% were male, 67.6% occupied an ICU bed at baseline and 67.6% were on the ventilator at baseline. Table II summarises the primary antibacterials used to treat the *S. aureus* LRTIs. Table III summarises the clinical characteristics of the 55 treatment successes and the 35 treatment failures. The remaining 18 patients could not be assessed for final clinical outcome.

Software Validation

All patients given vancomycin had a calculated AUC_{24}/MIC value each day for each antibacterial. These calculated values are displayed in the analyses. The correlations between measured AUC_{24}/MIC values and calculated AUC_{24}/MIC values for vancomycin in a software validation subset of 30 patients are shown in figure 1. A subset of 30 patients qualified for this analysis by virtue of sufficient blood concentration measurements (at least four) and stable renal function. Their demographics are representative of the overall population, in that their median age was 73 years (range 40–90 years) and 63% were male. Their median calculated creatinine clearance was 64 mL/min (range 26–201 mL/min). This analysis appears to support the use of the A.U.I.C. calculator software for estimating steady-state vancomycin AUC_{24}/MIC values with precision

Table II. Primary treatment agent (n = 108)

Primary treatment agent	Number (%)
Vancomycin	63 (58)
Cephalosporin	15 (14)
Oxacillin	6 (6)
Ciprofloxacin	6 (6)
β-Lactam/β-lactamase inhibitor combination	6 (6)
Clindamycin	5 (5)
Cotrimoxazole (trimethoprim-sulfamethoxazole)	3 (3)
Other	4 (4)

Table III. Characteristics of treatment successes and treatment failures

Characteristic	Treatment successes (n = 55)	Treatment failures (n = 35)	p-Value
Age (years) [mean ± SD (median)]	69.5 ± 15.3 (74.0)	71.3 ± 13.7 (73.0)	0.7687
Male [number (%)]	33 (60)	16 (46)	0.1846
MRSA isolated as organism [number (%)]	14 (25)	19 (54)	0.0057
ICU at baseline [number (%)]	36 (65)	19 (54)	0.2893
On ventilator at baseline [number (%)]	35 (64)	20 (57)	0.5379
FiO_2 >60% [number (%)]	9 (16)	8 (23)	0.4429
Two or more lobes involved [number (%)]	13 (23)	22 (64)	0.0002
Baseline APACHE II score [mean ± SD (median)]	16.4 ± 6.5 (16)	20.0 ± 7.2 (18)	0.0258
Baseline weight (kg) [mean ± SD (median)]	73.8 ± 29.5 (69)	71.0 ± 21.8 (71)	0.6728
Baseline CL_{CR} (mL/min) [mean ± SD (median)]	52.6 ± 26.5 (52)	44.5 ± 28.8 (44)	0.1216
Length of stay (days) prior to occurrence [mean ± SD (median)]	21.9 ± 38.7 (4)	30.0 ± 48.6 (6)	0.5607
Calculated average AUC_{24}/MIC [mean ± SD (median)]	463.1 ± 374.2 (400)	323.0 ± 229.2 (288.5)	0.1934
Serum albumin at baseline (g/dL) [mean ± SD (median)]	3.1 ± 0.6 (3.2)	2.6 ± 0.6 (2.6)	0.0019
Baseline pneumonia score [mean ± SD (median)]	24.8 ± 3.2 (25)	24.4 ± 4.9 (23)	0.2248
Antibacterial treatment (days) [mean ± SD (median)]	13.2 ± 6.2 (12)	10.5 ± 6.1 (9)	0.0235
Respiratory illness as a primary underlying comorbidity [number (%)]	18 (33)	12 (35)	0.8045
Vancomycin as primary antibacterial [number (%)]	27 (49)	21 (64)	0.1871

APACHE = Acute Physiology and Chronic Health Evaluation; **AUC_{24}/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; **CL_{CR}** = creatinine clearance; **FiO_2** = inspired oxygen fraction; **ICU** = intensive care unit; **MRSA** = methicillin-resistant *Staphylococcus aureus*.

(r^2 = 0.935), as shown in figure 1. The median percentage error was −5.2% (range −41.3% to +19.8%). Twenty-one of the 30 validation patients had predicted AUC_{24}/MIC values within 15% of the measured AUC_{24}/MIC value. Twenty-seven patients had predicted values within 25% of the measured value.

Range and Spread of Pharmacodynamic Index in Vancomycin-Treated Patients

Stem and leaf plots of the AUC_{24}/MIC values for patients treated with vancomycin show first-quartile AUC_{24}/MIC values between 72 and 277. The second-quartile AUC_{24}/MIC values were between 278 and 413. The third-quartile AUC_{24}/MIC values were between 414 and 673. The fourth-quartile AUC_{24}/MIC values were between 674 and 7544. This variability is not unexpected given the 4-fold range of MIC values typically encountered in *S. aureus* isolates.

Probability of Clinical Success and Bacteriological Eradication

Overall cure rate (61.1%) was consistent with cure rates in recent clinical trials comparing vancomycin with newer agents. Independent variables that were tested for association with probability of clinical success (at test-of-cure) were evaluated in both univariate and multivariate analyses.

The univariate analysis (table III) found that a significantly greater proportion of patients who failed to respond clinically to antibacterial therapy had MRSA isolated (54% of patients experiencing treatment failure had MRSA vs 25% of patients experiencing clinical treatment success; p = 0.0057). Significantly more patients with initial multilobe LRTI failed to respond clinically (64% vs 23%; p = 0.0002). Patients classified as clinical treatment failures had significantly lower albumin levels at baseline (p = 0.0019), received antibacterial for a shorter duration (p = 0.0235) and had higher baseline APACHE II scores (p = 0.0258). Nineteen patients had a bacteraemic pneumonia. Of the 19 bacteraemic patients, 15 were clinically evaluable, of

which 10 (66.7%) had successful clinical responses, a percentage similar to the population overall.

Clinical Risk Factors

Since it is possible that confounding clinical factors might explain associations between outcomes and AUC_{24}/MIC values, stepwise logistic regression was used to examine the multivariate relationship. Logistic regression identified five statistically significant factors that were associated with improved clinical outcome: higher vancomycin AUC_{24}/MIC value, organism isolated (MSSA vs MRSA), involvement of single versus multiple lobes, baseline serum albumin and baseline creatinine clearance, as shown in table IV. The odds of a successful clinical response for vancomycin-treated patients with an AUC_{24}/MIC value of at least 350 are approximately seven times better than for patients with AUC_{24}/MIC values <350. The odds of a successful clinical response for patients with an LRTI caused by MSSA are approximately four times better than for patients with an LRTI caused by MRSA. The odds of a successful clinical response for patients with single lobe involvement are approximately six times better than for patients with multilobe involvement. For each 1 g/dL increment in baseline serum albumin, the odds of a clinical success increase approximately 4-fold. In addition, the odds of a successful clinical response increase by 1.04-fold for each 1 mL/min increase in baseline creatinine clearance; or, for every 10 mL/min increase in baseline creatinine clearance, the odds of a successful clinical response increase by approximately 10-fold.

Table IV. Odds ratios for clinical success

Characteristic	Odds ratio	95% CI	p-Value
Vancomycin AUC_{24}/MIC value ≥350	7.19	1.91, 27.3	0.0036
MSSA as pathogen	3.88	1.10, 14.8	0.0359
Single lobe involvement	6.32	1.56, 25.6	0.0099
Baseline serum albumin (per 1 g/dL)	3.73	1.09, 12.8	0.0364
Baseline CL_{CR} (per 1 mL/min)	1.04	1.01, 1.07	0.0154

AUC_{24}/MIC = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; **CL_{CR}** = creatinine clearance; **MSSA** = methicillin-susceptible *Staphylococcus aureus*.

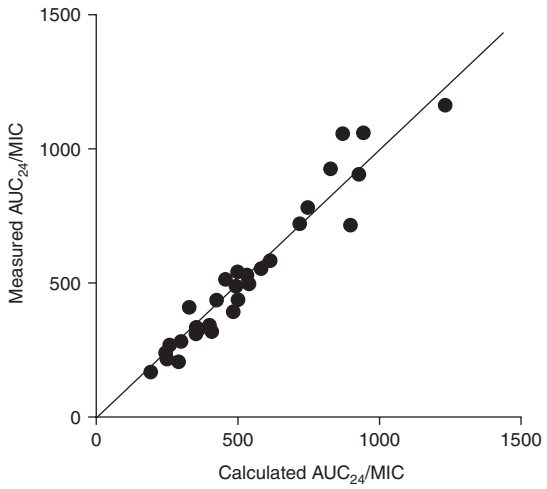

Fig. 1. Relationship between measured AUC_{24}/MIC (fitted with ADAPT II software) and predicted AUC_{24}/MIC for vancomycin. The data represent the values obtained from 30 patients. The diagonal is the line of best fit, which did not differ from the line of identity (r^2 = 0.935). **AUC_{24}/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.

A striking finding about the subset of vancomycin-treated patients was that they had a 54% (27 of 50 clinically evaluable patients) clinical success rate and a 50% (28/56) bacteriological eradication rate. Microbiological failure was nearly always predictive of clinical failure in this population. Among the 45 patients who received any antibacterial other than vancomycin as primary treatment, there was a 71% clinical success rate and a 70% bacteriological eradication rate in the clinically (n = 34) and microbiologically (n = 37) evaluable patients. The primary treatment agent of the 34 clinically evaluable patients who did not receive vancomycin included: cephalosporin (n = 9), fluoroquinolone (n = 7), clindamycin (n = 4), azithromycin (n = 4), oxacillin (n = 4), cotrimoxazole (trimethoprim-sulfamethoxazole) [n = 3], β-lactam/β-lactamase inhibitor combination agent (n = 2) and erythromycin (n = 1). In patients receiving oxacillin (n = 4) treatment for an MSSA LRTI, we found a 100% clinical success rate and a 100% bacteriological eradication rate.

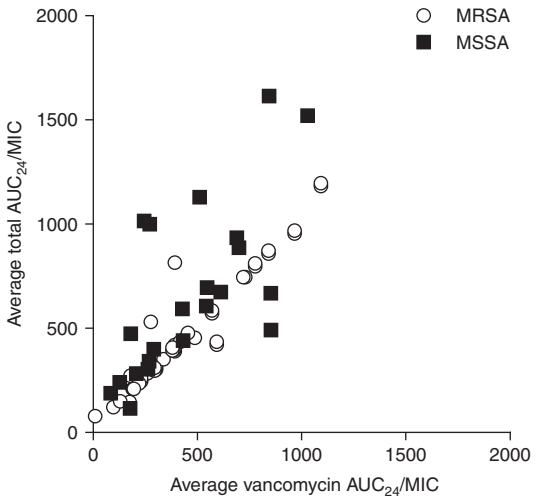

Fig. 2. Relationship between average daily vancomycin AUC_{24}/MIC and average daily total AUC_{24}/MIC for patients who received vancomycin as part of their antibacterial regimen. The data represent the values obtained from 59 patients who received vancomycin for at least 3 days as part of their antibacterial regimen. Four of the initial 63 patients who received vancomycin for at least 3 days were not included in the analysis because the total AUC_{24}/MIC values could not be calculated from available information. The different symbols represent patients infected with methicillin-resistant *S. aureus* (MRSA) or methicillin-susceptible *S. aureus* (MSSA). **AUC_{24}/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.

Corrections for the Effects of Combination Therapy

We examined the relationship between average daily vancomycin AUC_{24}/MIC and average daily total (assuming additivity) AUC_{24}/MIC (figure 2).

Fifty-nine of the 63 patients who received vancomycin for at least 3 days as part of their antibacterial regimen were evaluable for this analysis. Four patients were not included because the total AUC_{24}/MIC values could not be calculated for these patients based on available information. As shown in figure 2, the majority of average daily total AUC_{24}/MIC values were along the line of identity, meaning that vancomycin alone was the active antibacterial. Thus, most of the total antimicrobial activity, especially against MRSA, resulted from treatment with vancomycin.

Effect of methicillin Sensitivity on Vancomycin Pharmacodynamics

Of the 63 patients who received vancomycin, 37 had MRSA and 26 had MSSA. Of the MRSA-infected patients, MIC values were 0.5 and 1.0 mg/L in 28 and 9 patients, respectively. Of the MSSA-infected patients, MIC values were 0.5 and 1.0 mg/L in 23 and 3 patients, respectively. Vancomycin MIC values in patients with MSSA did not differ significantly from those in patients with MSSA ($p = 0.2$). In spite of similar MICs, AUC_{24}/MIC values differed for patients receiving vancomycin as part of regimens for MSSA and MRSA LRTIs. AUC_{24}/MIC values for vancomycin-treated patients with MSSA and MRSA were 962.9 ± 1489.0 (mean $\pm$ SD) and 421.8 ± 262.2, respectively ($p = 0.01$). As a consequence of the additional active antibacterial, MSSA treated with vancomycin in combination with a second active antibacterial is subjected to more antibacterial activity overall than is MRSA treated with vancomycin alone. This may account for the observed faster eradication of MSSA than MRSA.

Pharmacodynamic Indices and Outcomes of Vancomycin-Treated Patients

Figure 3 shows the relationship between two pharmacodynamic indices (AUC_{24}/MIC and %T>MIC), and clinical and bacteriological responses to vancomycin. All patients in this study (both successes and failures) had %T>MIC = 100%, establishing that vancomycin %T>MIC at the 100% target is not predictive of outcome. Although vancomycin does not exhibit concentration-dependent killing, the AUC_{24}/MIC ratio appears to be the major pharmacodynamic index correlating with infection response.

Time to Bacterial Eradication

Time (duration of treatment) to bacterial eradication, defined as the treatment day that the culture first became negative and remained negative upon repeat culture, was modelled versus the AUC_{24}/MIC using proportional hazards regression in 34 patients. This analysis was restricted to the subset of the patient population that had cultures obtained at least every 4 days and received vancomycin for the

duration of treatment of the *S. aureus* LRTI. The results are shown in figure 4. At an AUC_{24}/MIC < 400 (n = 16), the median time to eradication is in excess of 30 days; the exact value is non-identifiable, as only 20% of this group had organism eradication. At an AUC_{24}/MIC ≥400 (n = 18), the median time to eradication was 10 days (p = 0.0402).

Also, the time to bacterial eradication was modelled versus primary antibacterial treatment (figure 5). The primary treatment agent of the patients receiving 'any other agent' was most commonly a β-lactam; two patients received trimethoprim-sulfamethoxazole for the majority of their treatment. The median time to bacterial eradication was slower in vancomycin-treated patients (n = 35) compared with those receiving any other agent (n = 16) for an *S. aureus* LRTI (p = 0.002).

Pneumonia Scores Versus Bacterial Eradication

The median change in clinical symptom score from baseline was tested between groups (clinical success and clinical failure) for days 2–16; sample size was too small at later times. The two groups differed significantly (p < 0.05) on all days over this interval except days 2, 13 and 14. The earliest day that the clinical symptom score was predictive of eventual clinical success was treatment day 3. For

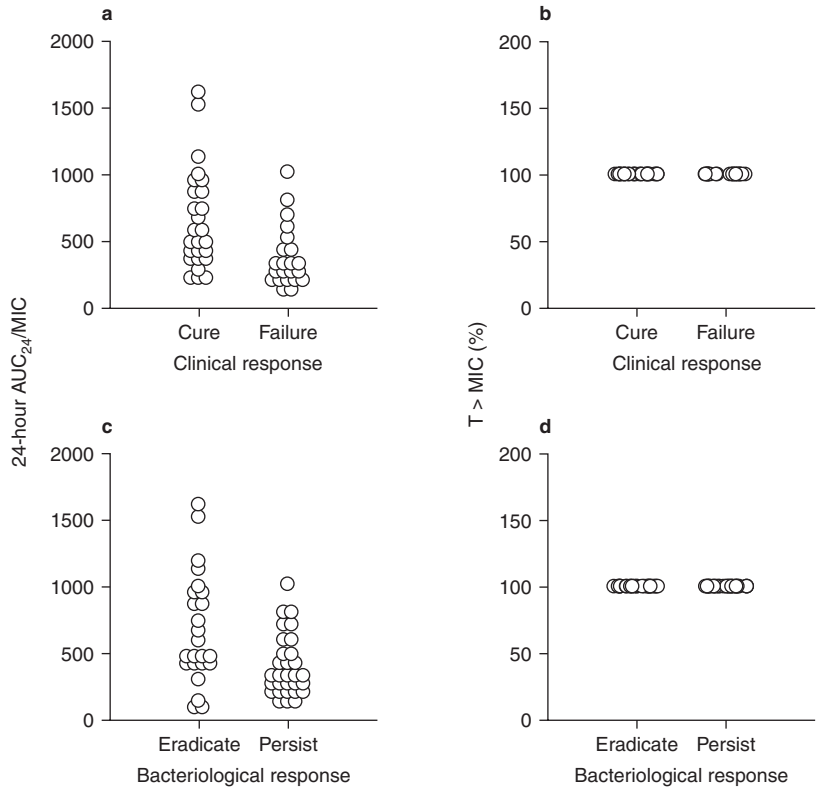

Fig. 3. Relationship between clinical and bacteriological responses and two pharmacodynamic indices: AUC_{24}/MIC and %T>MIC. Each point represents data for one patient. (**a**) Mean ± SD (median) vancomycin AUC_{24}/MIC values were 655 ± 374 (535) in patients whose infection outcomes were classified as vancomycin treatment successes (cure) and 378 ± 225 (306) in those whose infection outcomes were classified as treatment failures (p = 0.0029). (**b**) Vancomycin serum concentrations were above the MIC 100% of the time in all clinical treatment successes and failures. (**c**) AUC_{24}/MIC values for vancomycin-treated patients were 951 ± 1432 (593) when *S. aureus* was eradicated compared with 405 ± 224 (312) when the organism persisted (p = 0.0046). (**d**) %T>MIC was also 100% in all patients whose *S. aureus* was eradicated and in all patients who remained culture-positive. **AUC_{24}/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration; **%T>MIC** = percentage of time that serum concentrations exceed the MIC.

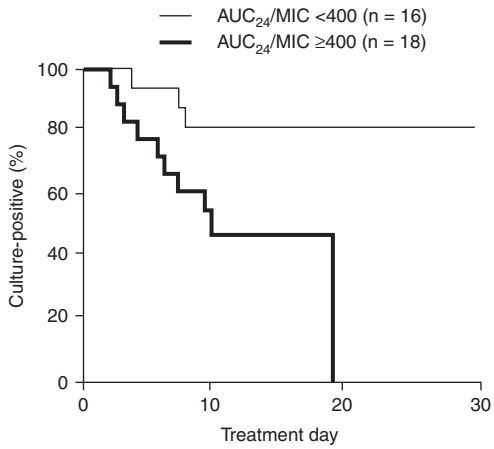

Fig. 4. Time (days of therapy) to bacterial eradication vs vancomycin AUC_{24}/MIC <400 and AUC_{24}/MIC ≥400 illustrated by a Kaplan-Meier survival plot of day of therapy vs the percentage of patients remaining culture-positive on that day. The two AUC_{24}/MIC groups differed significantly (p = 0.0402). **AUC_{24}/MIC** = steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration.

patients with no change or worsening in score from baseline to day 3, 32% experienced a clinical success and 68% experienced a clinical failure. For patients having a 1–3 point decrease in score by day 3 of therapy, 59% experienced a clinical success and 41% experienced a clinical failure. Having at least a 4-point decrease in clinical score by day 3 correlated with an 83% success rate, with 25 of the 30 patients in this group having a successful clinical outcome.

We also found a highly significant relationship between the days to substantial decrease in clinical score and days to bacterial eradication (R_S = 0.570, $p < 0.0001$; figure 6). The data suggest that cultures tend to stay positive approximately 50% longer than the time for clinical symptoms to improve substantially. Clearly there are unidentified sources of additional variability beyond the two variables investigated, but there is a clear link between time to eradication of the pathogen and time to resolution of infection signs and symptoms.

Discussion

There are many studies examining the relationship between vancomycin dosage and blood concentration (peak and/or or trough concentrations).[9,44,45,58] However, the studies do not consider the potential impact of variations in organism MIC on the differences in outcome, and thus far there has not been a link made between clinical and microbiological outcomes in relationship to vancomycin pharmacokinetic-pharmacodynamic parameters. Wysocki et al.[28] examined vancomycin AUC_{24} over intermittent and continuous administration regimens and did not find a relationship when evaluating mean vancomycin AUC_{24} values and clinical cure as an outcome. They did not investigate AUC_{24}/MIC values, meaning that no adjustment was made for organisms having different MIC values. The MIC values in their patients ranged 4-fold (from 0.5 to 2.0 mg/L), which would produce greater AUC_{24}/MIC variability in a setting where blood concentrations are adjusted to a similar target across the treated patient population. Given the variance in AUC_{24}/MIC that would result from a 4-fold range in MIC values, it is not surprising that reliance on the pharmacokinetic parameter AUC_{24} did not correlate with outcome, since dosage adjustments to target serum concentrations should make AUC_{24} values similar in all patients (successes and failures). Most patients (82.4% of the population), like our own, received many antibacterials in addition to vancomycin. In addition, their study population consisted of patients with a broader array of methicillin-resistant staphylococcal infections (including endocarditis, pneumonia, meningitis and catheter-related infections), with 79.8% (95/119) of patients having *S. aureus* infections and the remainder with coagulase-negative staphylococcal infections. We analysed only patients with *S. aureus*-associated LRTIs.

Hyatt and colleagues[43] demonstrated that patients treated with vancomycin monotherapy for enterococcal infections who achieved AUC_{24}/MIC values <125 had a higher probability of failure and selection of vancomycin-resistant *Enterococcus faecium*. This AUC_{24}/MIC value is associated with *E. faecium* MICs of ≥4.0 mg/L. Although the breakpoint of 125 was considered in the current investigation, only a few patients with a vancomycin AUC_{24}/MIC value <125 were evaluable. One patient was clinically evaluable and three patients were bacteriologically evaluable in the AUC_{24}/MIC range of 0–125. Therefore, we did not have sufficient numbers of patients with *S. aureus* MICs of ≥4.0 mg/L to determine if another, much lower,

AUC_{24}/MIC breakpoint may have existed around a threshold of 125. However, the data of Fridkin et al.[29] may be consistent with this hypothesis, although AUC_{24}/MIC was not reported in those patients with MICs of ≥4.0 mg/L.

Klepser et al.[59] suggested that a trough vancomycin concentration of >10 mg/L was associated with more rapid bacterial eradication than were lower trough concentrations, but did not measure time to bacterial eradication. Most of their patients with

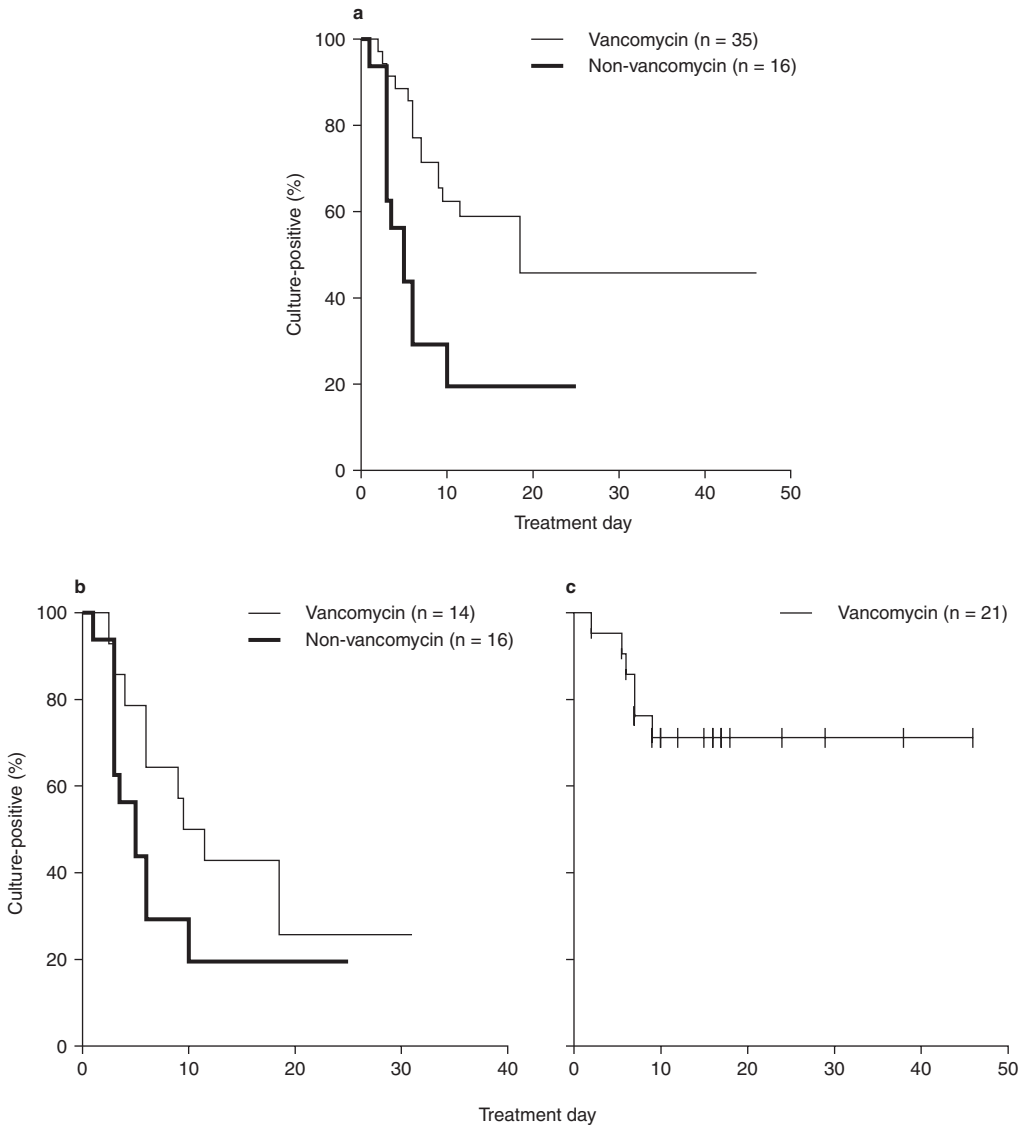

Fig. 5. Time (days of therapy) to bacterial eradication vs vancomycin as primary therapy and other (non-vancomycin) antibacterials as primary therapy illustrated by Kaplan-Meier survival plots of day of therapy vs the percentage of patients remaining culture-positive on that day. (**a**) The two antibacterial groups differed significantly for all *S. aureus* lower respiratory tract infections (p = 0.002). (**b**) Although bacterial eradication appeared to occur more quickly in patients with methicillin-susceptible *S. aureus* infections treated with antibacterials other than vancomycin, the difference was not statistically significant (p = 0.132). (**c**) Time to bacterial eradication in 21 patients with methicillin-resistant *S. aureus* infections.

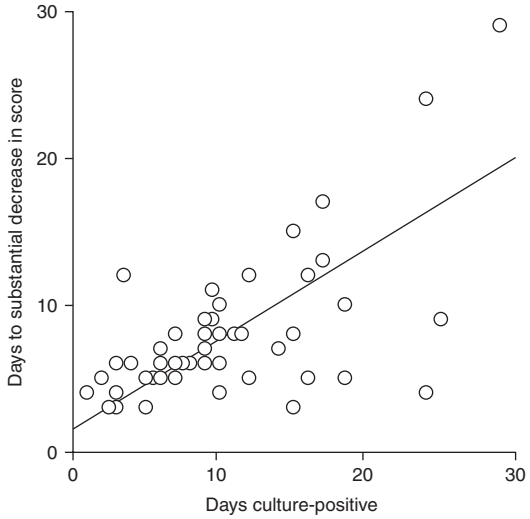

Fig. 6. Relationship between days culture-positive for *S. aureus* and days to substantial decrease in pneumonia clinical symptom score ($r^2 = 0.57$; $p < 0.0001$).

unsatisfactory outcomes had infections due to organisms with vancomycin MIC values >1 mg/L. This may have resulted in subtherapeutic AUC_{24}/MIC values, because the target trough of 10 mg/L is typically associated with a vancomycin AUC_{24} in the range of 250 mg • h/L, and this AUC divided by an MIC of 2 mg/L is an AUC_{24}/MIC of approximately 125.

Other investigators have suggested that optimal peak serum concentrations of vancomycin may be 25 mg/L[60] or 30–40 mg/L,[61] and that optimal vancomycin trough concentrations are 5–10 mg/L.[61] The allowed ranges in recommended vancomycin peak concentrations for optimal outcome may be the anticipated consequence of the fact that vancomycin MIC values vary over a 4-fold range, and this results in varying AUC_{24}/MIC values even when the target vancomycin serum trough concentration of 10 mg/L is achieved.[6] Studies targeting vancomycin peak and trough concentrations of 30 and 10 mg/L, respectively, yet also reporting MICs of 2 mg/L and higher associated with failure to eradicate, do support the premise that higher AUC_{24}/MIC values may correlate with improved outcomes, as we have also demonstrated in this analysis.

In a population of elderly hospitalised patients with *S. aureus* LRTIs, our data show that AUC_{24}/MIC values predict clinical and bacteriological outcomes for patients with MRSA LRTIs that are treated with vancomycin. Because %Time>MIC was not predictive, we are unable to propose any useful dosage guidance for %Time>MIC in patients given vancomycin. With current blood concentration targets, all patients (both successes and failures) have %Time>MIC = 100%. The clinical factors that further improved the prediction of favourable response were also not surprising. A favourable outcome was associated with single lobe pulmonary involvement (compared with multiple lobes involved), a higher baseline serum albumin and a higher baseline creatinine clearance. In addition, patients with an MSSA LRTI had a higher probability of success compared with patients with an MRSA LRTI. This may be associated with the relatively poor efficacy of vancomycin compared with β-lactams, as others have found,[62,63] and does not necessarily indicate that MRSA strains are more virulent. Gonzalez and colleagues[63] found a higher mortality rate among patients treated with vancomycin (compared with those treated with other 'appropriate' antibacterials) for MRSA (50%) or MSSA (47%) LRTIs. In addition, these investigators found the mortality rate among MSSA-infected patients treated with cloxacillin to be zero. Rello and colleagues[62] found a 2.6% mortality rate in patients receiving cloxacillin for MSSA LRTIs and a 54.5% mortality rate in patients receiving vancomycin for MRSA LRTIs.

Our data are entirely consistent with, and extend, the observations of Gonzalez et al.[63] and Rello et al.[62] We found significantly lower success rates among patients treated with vancomycin compared with those treated with any other antibacterial. In addition, among MSSA-infected patients receiving oxacillin, we also found a 100% success rate. We also found a higher clinical success rate in the subset of vancomycin-treated patients with AUC_{24}/MIC values >350 (or approximately 400 for bacterial eradication) compared with those with AUC_{24}/MIC values <350 (or 400 for bacterial eradication). This AUC_{24}/MIC value is virtually impossible to achieve with conventional vancomycin peak and trough concentrations at MICs of 2, 4 or 8 mg/L. Of course, time above MIC remains 100% with troughs of 10

mg/L and MICs of 8 mg/L, therefore this particular target is uninformative as long as troughs are targeted at 10 mg/L. Finally, these calculations with vancomycin are based on serum concentrations as they apply to a rapidly equilibrating site of infection, as is typical of pneumonia. It does not appear logical to conclude that vancomycin fails because of low tissue concentrations, since the organisms are exposed to extravascular fluid concentrations and, thus, AUC_{24}/MIC values at the site of infection are similar to those in serum.[64-66] Furthermore, agents with good tissue penetration, such as linezolid, have equivalent cure rates in randomised trials against vancomycin.[26] There must be other factors beyond tissue penetration that account for the outcomes with these drugs.

In the conventional administration of vancomycin or other agents for *S. aureus* LRTIs, only renal function is employed to make dosage adjustments.[67] Currently, neither MIC nor AUC_{24} are usually considered when determining vancomycin dosage regimens, but perhaps this practice should change, with the potential benefit of extending the lifetime of this important antimicrobial. These data show a strong correlation between the pharmacodynamic index AUC_{24}/MIC and outcome with vancomycin, which may offer a potential advantage when a threshold value is reached.

We did not measure vancomycin free fraction in these patients and, although the protein binding of this drug has been reported to vary between a low value of 29%[68] and a high value of 71%,[69] vancomycin has been considered for purposes of calculation to be approximately 60% protein bound[6] If the target AUC_{24}/MIC is corrected on the basis of a free fraction of 40%, then a total drug AUC_{24}/MIC of 400 (the current study) becomes a free value of 160, and 345 (our previous studies) becomes 138. Although these values place vancomycin into the target AUC_{24}/MIC range of 125 and are consistent with the AUC_{24}/MIC breakpoints of most other antibacterials, it is important to validate the use of free fraction in each patient, and this has yet to be done in a vancomycin-treated population.

To our knowledge, no studies of vancomycin have examined the time to eradication in relationship to its pharmacodynamics, and there has not yet been a clear link between the time to bacterial eradication on vancomycin therapy and the time to resolution of infection signs and symptoms. As figure 6 demonstrates, our results clearly show an association between changes in clinical symptoms (pneumonia score) from baseline and time to bacterial eradication. This observation agrees with what has been reported for bacteriological eradication in patients with Gram-negative pneumonia,[38] where a similar clinical scoring system was used to demonstrate a significant difference in the percentage change in clinical score on day 3 of therapy with ciprofloxacin, cefmenoxime or ceftazidime in patients with bacteria that were eradicated compared with those with persistent organisms.[57] This scoring system appears quite sensitive to early indications of infection response and shows that both concentration-dependent and time-dependent antibacterials have a good outcome if the symptom score has improved by day 3. In our investigation we used a pneumonia scoring system that was slightly modified from the one used in both of these primarily Gram-negative scoring studies. Since this analysis was retrospective, we did not always have daily sputum cultures available. Since we observed vancomycin to kill *S. aureus* slowly, this lack of daily cultures may be considered only a minor flaw in the database. We did not have daily Gram stains in these patients, therefore we replaced the two Gram stain components (amounts of polymorphonuclear leucocytes and bacteria seen on low-magnification field) with the two clinical characteristics rales and decreased breath sounds, which were reported frequently throughout the day on all of our patients.

Hospitalised patients typically receive many antibacterials for an infection. For example, initially a patient may receive broad coverage with more than one antibacterial while culture results are pending; then, the regimen may be streamlined to target the known organism or organisms; finally, the antibacterial(s) may be switched from intravenous to oral. Even though more than one antibacterial is typically used in hospitalised patients, most clinical trials and other investigations with vancomycin have only analysed the vancomycin regimen. Our data examined the potential for additive AUC_{24}/MIC values, and we found that taking all active agents into account clearly improved the overall prediction capability of these models for MSSA but made little

difference for MRSA, since here most of the activity comes from vancomycin (figure 2). It may be considered controversial to add antibacterial activity indices in these patients. However, the concept of additivity between antibacterials in combination clearly has less overall impact when the question is applied to vancomycin in MRSA infections, since figure 2 shows that there is little added activity beyond that of vancomycin alone in these cases. Vancomycin versus MRSA may represent one of the few remaining opportunities to study single-agent AUC_{24}/MIC values in a real world setting.

One question to be asked is how to improve the treatment of the 40% of patients in whom vancomycin treatment results in slow bacterial eradication and slowly resolving pneumonia. One approach may be to raise the vancomycin dosage for those patients with higher MIC organisms in order to reach an AUC_{24}/MIC value of at least 400. Another may be combination therapy with a number of agents. Rifampicin and quinupristin/dalfopristin appear the best combination agents with vancomycin, as both are synergistic with vancomycin against *S. aureus*. The other combination therapy choices (aminoglycosides, β-lactams, linezolid and tetracyclines) are either non-additive or, in some cases, antagonistic. The third possibility is replacement of vancomycin with one of the newer agents such as quinupristin/dalfopristin or linezolid. To some extent, we and others have tested these strategies in severely ill patient populations who have failed to respond to vancomycin.[70-72] Daptomycin has recently been released in the US, but it should not be used for LRTIs because it has failed in the clinical trials and is, therefore, not recommended. Clearly, more work with treatment failure populations will be necessary to define the best strategy for each patient, but it is clear from this analysis that vancomycin failure cannot be properly characterised without calculation of an AUC_{24}/MIC value in the patient being evaluated.

Conclusions

The results of this study indicate the following: (i) vancomycin AUC_{24}/MIC values could be precisely predicted with the A.U.I.C. calculator in a validation subset of our patients; (ii) clinical and bacteriological response to vancomycin therapy was superior in patients with higher AUC_{24}/MIC values; (iii) no relationship was found between the percentage of time vancomycin serum concentrations are above the MIC and infection response; (iv) bacterial eradication of *S. aureus* (both MSSA and MRSA) occurred more rapidly with vancomycin when a threshold AUC_{24}/MIC value was reached; (v) *S. aureus* killing rates were slower with vancomycin compared with other antistaphylococcal antibacterials; (vi) a significant relationship was found between the time to substantial improvement in pneumonia score and the time to bacterial eradication.

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