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Use of vancomycin pharmacokinetic–pharmacodynamic properties in the treatment of MRSA infections

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Vancomycin is a commonly used antimicrobial in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Increasing vancomycin MIC values in MRSA clinical isolates makes the optimization of vancomycin dosing pivotal to its continued use. Unfortunately, limited data exist regarding the optimal pharmacokinetic–pharmacodynamic (PK–PD) goal to improve bacterial killing and clinical outcomes with vancomycin. The hallmark study in this area suggests that achieving an AUC to MIC ratio of over 400 improves the likelihood of achieving these outcomes. Challenges in the implementation of PK–PD-based dosing for vancomycin include current methodologies utilized in microbiology laboratories, as well as intra- and interpatient pharmacokinetic variability. Individualized dosing based on MIC and specific patient factors is important to achieve optimal outcomes from vancomycin therapy.

Keywords: critically ill • meningitis • MIC • MRSA • obesity • osteomyelitis • pharmacodynamic • pharmacokinetic • pneumonia • vancomycin

Clinical failures with vancomycin against methicillin-resistant *Staphylococcus aureus* (MRSA) infections have challenged vancomycin's standing as a first-line antimicrobial for these infections. In response to these failures, the Clinical Laboratory Standards Institute (CLSI) changed the vancomycin susceptibility breakpoint against MRSA in 2006 from 4 µg/ml or less to 2 µg/ml or less [1]. More recent studies have observed significantly worse clinical outcomes for patients infected by MRSA isolates with vancomycin MIC values of 1 µg/ml or more [2–6]. These studies have primarily consisted of patients with bacteremia or pneumonia due to MRSA.

Several recent clinical guidelines endorsed by the Infectious Diseases Society of America (IDSA) recommend higher trough concentrations, weight-based vancomycin dosing or both [7–9]. The IDSA, American Society of Health-Systems Pharmacists (ASHP) and Society of Infectious Diseases Pharmacists (SIDP) published a consensus review of vancomycin therapeutic monitoring in adult patients, which recommends vancomycin troughs of 15–20 µg/ml for patients with complicated MRSA infections if the vancomycin MIC is 1 µg/ml or less [10]. These recommendations are based on limited data, sparking debate in the scientific community.

What is the pharmacodynamic index & target value to optimize vancomycin therapy?

Efficacy

Animal studies have failed to provide a consistent conclusion regarding the pharmacokinetic–pharmacodynamic (PK–PD) parameter best associated with vancomycin's efficacy. Initial studies demonstrated that AUC was the optimal PK–PD parameter. Studies evaluating *Streptococcus pneumoniae* reported that the ratio of the peak concentration to the MIC value (peak/MIC) was the optimal PK–PD parameter [11,12]. Animal studies may not mimic human response rates due to pharmacokinetic and immunologic differences.

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Only one human study has evaluated the optimal PK–PD parameter associated with clinical and microbiologic success. The study evaluated 108 patients receiving vancomycin for *S. aureus* pneumonia to determine the pharmacodynamic index associated with vancomycin efficacy [13]. AUC to MIC ratios (AUC:MIC) of 350 or more were associated with clinical success (odds ratio: 7.19; range: 1.91–27.3). Patients whose vancomycin dosing regimens achieved an AUC:MIC more than 400 over 24 h was associated with faster bacterial eradication than those who did not achieve an AUC:MIC of 400 (10 vs 30 days). A total of 19 out of the 37 patients with MRSA experienced therapeutic failure, even though all vancomycin MIC values were 0.5 µg/ml (n = 28) or 1 µg/ml (n = 9). 57% of patients in the MRSA subgroup received empiric antimicrobials other than vancomycin. Empiric treatment with other antimicrobials may have delayed the provision of adequate therapy and increased the severity of illness for patients in the MRSA subgroup.

Extrapolation of an AUC:MIC target ratio of over 400 to infections other than pneumonia is common, but may not be valid. The clinical and microbiologic response for other infection sites may vary depending on vancomycin penetration to the infection site, and the immune system response. Traditionally, a dosing of 1 g every 12 h may be sufficient for uncomplicated skin and soft tissue infections. On the other hand, more aggressive dosing may be required for sites of infection that have decreased vancomycin penetration.

Vancomycin trough concentrations of 15 µg/ml or more correlate to an AUC:MIC of over 400, assuming a vancomycin MIC of 1 µg/ml or less. No randomized, interventional study has evaluated the efficacy or safety of the recommended target trough concentration.

A single-center, prospective cohort study evaluated low trough (<15 µg/ml) versus high trough (<5 µg/ml) vancomycin concentrations in 95 patients with MRSA infections [4]. The majority of patients in this study had pneumonia, bacteremia, or skin and soft tissue infections. Vancomycin was dosed to achieve a concentration four- to five-times the MIC as determined by E-test. Clinical response rates were similar for both the high trough and low trough groups (76 vs 75%). Patients infected with MRSA isolates with a vancomycin MIC of 2 µg/ml had an increased risk of mortality compared with patients infected with a MRSA with a lower vancomycin MIC (24 vs 10%; p = 0.16). No pharmacodynamic subgroup analysis was conducted for the MIC 2 µg/ml group.

Jeffres *et al.* retrospectively evaluated the effect of pharmacokinetic indexes (AUC and trough concentration) on mortality in healthcare-associated pneumonia (n = 102) [14]. MIC values were not determined and time to the target trough concentration was not reported. A power calculation was not reported for the primary outcome. Nonsurvivors and survivors had similar vancomycin trough concentrations (13.6 vs 13.9 µg/ml) and mean calculated AUC values (354 vs 351). Nonsurvivors (n = 32) had significantly higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and were more likely to require mechanical ventilation and vasopressors. Selection bias may have occurred as more unwell patients may have received higher doses of vancomycin. A secondary analysis showed that mortality did not differ between steady state troughs in the 15 µg/ml or more group and under 15 µg/ml group (35.3 vs 29.4%; p = 0.546). Patients with increased trough concentrations tended to have higher APACHE II scores (19.9 vs 22.8; p = 0.088) and were more likely to receive mechanical ventilation (70.5 vs 85.3%; p = 0.143).

Mohr *et al.* used the pharmacokinetic data from the study by Jeffres *et al.* to conduct a PK–PD simulation study [15]. This PK–PD simulation study determined the probability of achieving an AUC:MIC ratio over 400 for a range of MIC values between 0.5 and 2 µg/ml using a high- (≥15 µg/ml) or low-trough (≤15 µg/ml) regimen. Both regimens were able to achieve a 100% target attainment rate for MRSA isolates with a MIC of 0.5 µg/ml or less. Neither dosing regimen could reach an AUC:MIC over 400 for isolates with a vancomycin MIC of 2 µg/ml or more. High-dose vancomycin therapy reached the PK–PD target approximately 20% more often for isolates with a vancomycin MIC of 1 µg/ml. Failure to obtain an appropriate AUC:MIC ratio may partially explain clinical failures with vancomycin-susceptible MRSA.

Rose and colleagues used two vancomycin-heteroresistant *S. aureus* (hVISA) isolates and one MRSA isolate to determine what AUC:MIC would suppress the upregulation of resistance [16]. The authors assumed a protein-bound concentration of 55%. Simulated vancomycin doses of 2500 mg (free drug AUC:MIC: 374) and 2000 mg every 12 h (free drug AUC:MIC: 271) suppressed the emergence of MIC increases in the hVISA strains. All simulated doses of vancomycin suppressed MRSA (MIC: 0.5 µg/ml) resistance, including 1000 mg every 12 h (free drug AUC:MIC: 552).

Data regarding the suppression of resistance are limited, but suggest that trough concentrations less than 10 µg/ml induce resistance in *S. aureus* strains with the accessory gene regulator (*agr*) gene [17,18]. Sakoulas *et al.* evaluated ten *S. aureus* isolates with the *agr* class II gene and found no increased resistance of the isolates when exposed to vancomycin concentrations of 16 µg/ml [18]. Tsuji *et al.* demonstrated that *agr* class I–IV gene isolates develop increased vancomycin resistance after exposure to vancomycin concentrations under 10 µg/ml [19]. These isolates had an initial MIC of 1 µg/ml, which increased to a MIC of 3–8 µg/ml over 72 h. The only clinical report supporting these findings to date is a patient on hemodialysis who was exposed to vancomycin concentrations over 10 µg/ml for 9 months with no development of resistance [17]. The isolate was subsequently exposed to suboptimal concentrations of vancomycin *in vitro* and vancomycin resistance developed.

Toxicity

The need for increased vancomycin doses raises new concerns regarding toxicity. Doses exceeding 1 g may be infused over a longer period of time (e.g., 2 h) to decrease infusion reactions. Slowing the rate of infusion is associated with a lesser degree of histamine release [20]. Histamine release is responsible, at least in part, for both vancomycin-induced 'red man syndrome' and

hypotension. Other possible adverse reactions include neutropenia, thrombocytopenia, ototoxicity and nephrotoxicity. Neutropenia usually develops with long-term vancomycin usage and is not related to total dosage received [21]. Thrombocytopenia with vancomycin is an immune-mediated antibody reaction, reaching a nadir at 7–8 days after start of vancomycin therapy [22]. It is unlikely to be dose-related owing to the reactions' immunogenic nature. A recent uncontrolled observational study regarding vancomycin ototoxicity observed that 12% of patients had a worsening of auditory function [23]. The severity of ototoxicity or its reversibility was not reported. Previous studies have observed that vancomycin-associated ototoxicity is typically mild, reversible and not associated with total dosage [24].

Several studies have recently suggested that increased vancomycin doses may be associated with increased rates of nephrotoxicity. A current consensus statement provides an in-depth review of the data surrounding the nephrotoxicity controversy [10]. Many of these studies have relied upon vancomycin trough concentrations as a surrogate for vancomycin exposure. A study by Lodise *et al.* published after the consensus statement also grouped patients according to vancomycin trough concentrations to determine vancomycin's nephrotoxicity risk [25]. This logic is flawed, as vancomycin concentrations can rise due to other causes of nephrotoxicity as well. Selection bias is another major limitation in many of these studies due to more ill patients receiving higher vancomycin dosing. These patients are also more likely to require concomitant nephrotoxic agents (i.e., aminoglycosides), which significantly increases the risk of nephrotoxicity [4,26,27]. One of these studies compared nephrotoxicity rates in patients receiving vancomycin doses of 4 g or more versus less than 4 g per day [28]. Nephrotoxicity occurred more often in the 4 g or more group (34.6 vs 10.9%; p = 0.001). A total of 81% of patients in the more then 4 g per day group received over 40 mg/kg/day, which is significantly higher than current IDSA guideline-recommended dosing regimens.

How does vancomycin susceptibility testing affect vancomycin pharmacodynamics?

Many microbiology laboratories report susceptibility testing results for vancomycin against MRSA isolates without specifying the MIC value. This may result in institutions not noticing a 'MIC creep', which occurs when MIC values increase but are not detected because the percentage of susceptible isolates remains relatively unchanged. MIC creep may be one reason for increasing vancomycin failure rates, since increased failure rates have been reported for MRSA strains with vancomycin MIC values of 1 µg/ml or more in patients with MRSA bacteremia and/or pneumonia [2–6]. One study tested MRSA isolates from 2001–2005 in one hospital to determine the rise in the geometric mean MIC using the E-test [29]. The vancomycin geometric mean MIC increased from 0.62 µg/ml in 2001 to 0.92 µg/ml in 2005.

Vancomycin MIC values can vary depending on the methodology utilized. Standard methods described in the CLSI manual for detecting vancomycin MIC values are broth or agar microdilution [30]. However, many microbiology laboratories utilize the E-test methodology. A comparison of CLSI broth and agar microdilution versus E-test using a standard inoculum was conducted for 101 MRSA isolates from 2002 to 2006 [31]. Modal MIC values were higher when measured by E-test compared with broth or agar microdilution (2 vs 1 µg/ml). The percentage of isolates with a vancomycin MIC over 1 µg/ml was also significantly greater when using the E-test (98 vs 12%). A recent study employing the E-test indentified 1050 out of 1800 strains of MRSA with a MIC of 1.5 µg/ml and 568 strains with a MIC of 2 µg/ml [32]. Only 2.7% of the strains were shown to have a MIC over 1µg/ml by broth microdilution. Similarly, Hsu and colleagues observed that E-test methodology was more likely to report higher vancomycin MIC values of 1 µg/ml or more (70 vs 7%) [33]. The E-test method detected 87% of hVISA strains compared with only 50% using broth microdilution.

What is the clinical significance of the MIC detection method utilized in the microbiology laboratory? The E-test method has been utilized by studies that observed worse clinical outcomes with increased vancomycin MIC values [3,31,33]. However, MIC values used to determine the PK–PD target for vancomycin were determined using broth microdilution. Determination of a separate PK–PD target to optimize vancomycin efficacy may be needed for laboratories who report MIC values using the E-test. This need is driven by an unclear correlation between MIC values observed using E-test methodology versus microdilution. At first glance, it might appear that there is a simple twofold difference between using broth microdilution and E-test methodologies. However, this conversion is not universally applicable as a MIC of 1 µg/ml by broth microdilution does not always equate to a MIC of 2 µg/ml by E-test.

What patient populations may require altered dosing to achieve vancomycin's pharmacodynamic target?

Several pharmacokinetic studies have evaluated vancomycin's ability to penetrate various sites of infection (Table 1) [34–41]. Other studies have focused on patient populations that may require altered vancomycin dosing due to changes in vancomycin's volume of distribution (Vd) or clearance (Cl) (Table 2) [42–48]. Some of these studies obtained pharmacokinetic data after only one dose of vancomycin [34,39,43]. While this information is valuable in knowing if vancomycin concentrations are adequate after the first dose is administered, it fails to provide any information regarding vancomycin pharmacokinetics at steady state. In addition, some studies utilize samples from participants without the disease of interest [34,39]. These results may fail to provide a full pharmacokinetic profile of vancomycin in these disease states as the disease itself may introduce pharmacokinetic variability. Last, one study collected convenience samples, for practical reasons, that yield little to no information regarding vancomycin's pharmacokinetics at the site of interest [39].

Pneumonia

Vancomycin's reported lung penetration has varied from 9 to 41% depending on the methodology utilized. The target tissue for antimicrobial action in pneumonia has been referred to in

Table 1. Vancomycin penetration.

Infection site	Study	Male/female	Age (years)	Weight (kg)	Dose or target concentration	Site penetration	Ref.
Lung	Cruciani *et al.*	23/7	62.1 ± 11.2	77 ± 14.3	1 g × one dose	Homogenized tissue: 24% (1 h), 41% (12 h)	[34]
	Georges *et al.*	6/4	65.5 ± 8.4	72 ± 11	30 mg/kg/day	Epithelial lining fluid: ≤9% (range: 6–12%)*	[35]
	Lamer *et al.*	11/3	60 ± 16	74.1 ± 17.1	Trough 15–20 µg/ml	Epithelial lining fluid: 18%	[36]
CSF	Viladrich *et al.*	5/6	39 (median)	NR	15 mg/kg/dose Q8H × 48 h, then 7.5 mg/kg/dose Q6H	CSF: 30.5% (range: 13–67%)	[37]
	Ricard *et al.*	8/6	52 ± 20	NR	15 mg/kg loading dose, then 60 mg/kg/day	CSF: 30%	[38]
Heart valves	Daschner *et al.*	20/13	Females: 59.7 Males: 50.4	Females: 64.7 Males: 74.8	15 mg/kg × one dose	Penetration rate NR	[39]
Bone	Graziani *et al.*: noninfected bone	8/6	67 ± 10	NR	15 mg/kg × one dose	Cancellous bone: 13 ± 24% Cortical bone: 7 ± 7%	[40]
	Graziani *et al.*: infected bone	5/0	55 ± 12	NR	Peak 20–40 µg/ml Trough < 12 µg/ml	Cancellous bone: 21% (n = 1) Cortical bone: 30 ± 12%	[40]
Skin	Skhirtladze *et al.*: patients with DM	4/2	69 ± 7	NR BMI = 26 ± 1 kg/m^2	80–120 mg/h	Tissue: 10%	[41]
	Skhirtladze *et al.*: control patients	6/0	56 ± 11	NR BMI = 26 ± 5 kg/m^2	80–120 mg/h	Tissue: 30%	[41]

*Six patients had undetectable epithelial lung fluid concentrations.
CSF: Cerebrospinal fluid; DM: Diabetes mellitus; NR: Not reported; Q6H: Administered every 6 h; Q8H: Administered every 8 h.

clinical studies as the alveoli and distal airways, although clinical effectiveness of this target has not been evaluated [49]. Alveoli and distal airway concentrations cannot be measured directly, so indirect measurements are used.

The highest lung penetration rate was reported by Cruciani *et al.* in patients without pneumonia after one dose of vancomycin [34]. Lung concentrations were measured using a homogenized lung sample from the biopsy. Homogenized tissue samples may not accurately describe vancomycin's Vd secondary to uneven distribution, or interference of cellular components or enzymes [50].

Subsequent studies used a method for determining medication concentrations by bronchoalveolar lavage (BAL) that has been validated prospectively [35,36]. This method correlates concentrations in the epithelial lung fluid (ELF) to concentrations in the alveoli. Georges *et al.* evaluated vancomycin concentration in critically ill patients with a positive BAL sample for *S. aureus* [35]. BAL was performed 24 h after the start of vancomycin administration. Mean trough concentrations were 22.2 µg/ml in the serum and 2 µg/ml in the ELF. Six out of the ten patients had undetectable concentrations in the ELF.

An increased lung penetration rate of 19% was detected by Lamer *et al.* who evaluated vancomycin concentrations in the ELF in critically ill patients [36]. BAL was performed after at least 5 days of vancomycin therapy at the same time the vancomycin trough was obtained. The mean serum trough concentration was 24.5 µg/ml with a mean trough ELF concentration of 4.5 µg/ml. A subgroup analysis was conducted to determine the effect that inflammation had on vancomycin ELF concentrations. Patients with greater inflammation, based on a BAL albumin concentration of 3.4 mg/ml or more, had increased penetration when compared with those with BAL albumin concentrations under 3.4 mg/ml (24.6 vs 14%). This result suggests that the disease process and immunologic response may also play an important role in pharmacokinetic variability.

Meningitis

Methicillin-resistant *S. aureus* meningitis occurs primarily in trauma patients and patients with intraperitoneal shunts [51]. One common dilemma in the empiric treatment of meningitis is whether steroids affect antimicrobial concentrations in the cerebrospinal fluid (CSF). This is particularly concerning given vancomycin's molecular size and CSF penetration in the absence of steroids.

Table 2. Patient groups with an altered vancomycin volume of distribution or clearance.

Patient group	Study	Male/female	Age (years)	Weight (kg)	CrCl (ml/min)	Dose	Vd	Vancomycin Cl	Ref.
Overweight and obesity	Blouin *et al.*: normal weight	4/0	27 ± 2.4	74.5 ± 10.1	138 ± 28.1	1 g × one dose	0.39 l/kg	1.112 ml/min/kg	[43]
	Blouin *et al.*: morbidly obese	2/4	30.8 ± 3.7	165.6 ± 44	180.2 ± 43.9	1 g × one dose	0.26 l/kg	1.085 ml/min/kg	[43]
	Bauer *et al.*: normal weight	14/10	40 ± 7	68 ± 6	110 ± 17	NR	46 l	77 ml/min	[44]
	Bauer *et al.*: morbidly obese	14/10	41 ± 7	165 ± 46	209 ± 35	NR	52 l	197 ml/min	[44]
	Ducharme *et al.*: ABW/IBW < 0.8	37*	45.4	53.9	65.4	NR	43.8 l	60.5 ml/min	[45]
	Ducharme *et al.*: ABW/IBW 0.8–1.3	559*	43.3	70.4	85.2	NR	44.4 l	81 ml/min	[45]
	Ducharme *et al.*: ABW/IBW > 1.3	108*	50	94.3	59.7	NR	51.6 l	74.4 ml/min	[45]
Critically ill patients	Llopis-Salviva *et al.*	11/19	67 ± 21	75 ± 12.5	68.45	17.3 ± 8.4 mg/kg/day	1.73 l/kg	57.6 ± 32.7 ml/min	[46]
	del Mar Fernandez *et al.*	30/16	59.3 ± 16.9	71.5 ± 12.8	65.5 ± 48.1	21.5 ± 8.3 mg/kg/day	1.68 ± 2.19 l/kg	60.0 ± 2.19 ml/min	[47]
Patients with burns	Dailly *et al.*	70*	42.8 ± 17.9	77.8 ± 19.5	173.3 ± 93.4	NR	NR	7.03 ± 3.79 l/h	[48]
	Rybak *et al.*: patients with burns	5/5	36.4 ± 14.9	NR	110 ± 28.3	42.7 ± 18.5 mg/kg/day	0.59 l/kg	142.8 ml/min	[42]
	Rybak *et al.*: control patients	8/2	38 ± 11.9	NR	68.3 ± 30.4	29.4 ± 6 mg/kg/day	0.52 l/kg	67.7 ml/min	[42]

*Numbers of male/female patients were not reported.
ABW: Actual body weight; CrCl: Creatinine clearance; Cl: Clearance; IBW: Ideal body weight; NR: Not reported; Vd: Volume of distribution.

The two studies conducted to answer this question have observed CSF penetration rates of approximately 30% [37,38]. Both studies administered steroids before or with the first dose of vancomycin. Vancomycin was administered intermittently by Viladrich *et al.* [37], as opposed to continuous infusion by Ricard *et al.* [38]. Blood and CSF samples were obtained after at least 48 h of vancomycin therapy for drug concentration analysis.

Viladrich *et al.* reported that six out of the ten patients were deemed clinically cured after 48 h of therapy [37]. Clinically cured patients had slightly higher median trough concentrations in the CSF (2.9 vs 2.1 µg/ml) and in the serum (9.5 vs 7.6 µg/ml). Ricard *et al.* observed mean concentrations of vancomycin in the serum and CSF of 25.2 and 7.2 µg/ml, respectively [38]. Concentrations in the CSF were positively correlated with serum concentrations ($r = 0.68$; $p = 0.01$). A positive correlation between vancomycin concentrations and protein concentration ($r = 0.66$; $p = 0.01$) was also observed, suggesting increased vancomycin penetration with increased permeability of the blood–brain barrier.

A study evaluating the use of continuous infusion vancomycin also observed increased vancomycin penetration of the CSF in patients with meningitis (n = 7) compared with those who did not have meningitis (n = 6) [52]. These patients were between 25 and 58 years of age with no details regarding gender or body weight. Patients with renal dysfunction were excluded, but patient-specific creatinine clearance (CrCl) values were not reported. All patients received a loading dose of vancomycin (15 mg/kg) followed by a continuous infusion (50–60 mg/kg/day). The vancomycin CSF penetration rate for meningitis patients was 48% compared with only 18% for those without meningitis.

Endocarditis

Vegetations may not be entirely exposed to vascular access as MRSA can adhere to platelets and fibrin [53]. These factors may make treatment success more difficult since they decrease vancomycin penetration of heart valves. Most endocarditis penetration studies have been conducted in animals because obtaining tissue from heart valves or the endocardium in patients is difficult [53].

A 15 mg/kg dose of vancomycin was given to 33 patients undergoing open-heart surgery [39]. The vancomycin dose was administered between 9 h and immediately prior to surgery. Mean vancomycin plasma concentrations declined from 28.9 to 3 µg/ml in the 9 h after vancomycin was administered.

Vancomycin concentrations after administration were highest in heart valve tissue (2.3–4.2 µg/ml), with similar concentration ranges for both heart subcutaneous (1.3–3.4 µg/ml) and muscle tissue (1.2–3.2 µg/ml).

Vancomycin is routinely given for 4 weeks or more to patients with osteomyelitis and endocarditis. Nakayama *et al.* determined that patients who received therapy for over 4 weeks had decreased vancomycin Cl (2 vs >3.2 l/h) [54]. This was likely owing in part to the lower CrCl for patients who received more than 4 weeks of vancomycin (65.8 vs 71.8–83 ml/min). On the other hand, the vancomycin Cl/CrCl ratio also decreased as length of treatment increased (4–7 days: 0.82; 8–14 days: 0.79; 15–21 days: 0.77; 22–28 days: 0.69; >4 weeks: 0.49). Therefore, vancomycin Cl in patients receiving over 4 weeks of therapy decreased due to both renal and nonrenal routes of elimination.

Osteomyelitis

Osteomyelitis requires prolonged duration of antibiotic usage due to decreased penetration into the area of infection secondary to necrotic tissue and bone [55]. Graziani *et al.* evaluated vancomycin bone penetration in 14 patients undergoing hip arthoplasty and five patients with osteomyelitis [40]. In the healthy bone group, a dose of 15 mg/kg was given prior to hip arthoplasty and a sample was taken a mean of 77 min after the end of vancomycin infusion. Patients in the infected bone group were on vancomycin for 48 h dosed to a peak of 30–40 µg/ml and a trough of 12 µg/ml or less. Peaks were drawn at a mean of 154 min after the end of infusion in both the bones and serum. Cortical bone penetration was increased in infected patients (30 vs 7%). Cancellous bone penetration in patients with healthy bones was 13%. Only one specimen was obtained for the cancellous bone owing to the schlerotic nature of the infected bones. In addition to disease effects, vancomycin concentrations in the infected group may also have been higher because these patients received more vancomycin doses prior to sampling for drug concentrations was conducted.

Diabetic skin & soft tissue infections

Skhirtladze *et al.* evaluated vancomycin's skin penetration in six patients with diabetes diagnosed for a minimum of 5 years versus six patients without diabetes [41]. All patients were status-post cardiac surgery and did not have an active infection. Vancomycin was given as a 1-g loading dose, followed by a continuous infusion at 80–120 mg/h. Patients with diabetes had a lower mean baseline CrCl. Vancomycin concentrations were obtained after a median of 8 days of therapy. Interstitium soft tissue concentrations in the thigh were obtained by microdialysis. Median steady state serum concentrations were similar for diabetics and controls (36.5 vs 37.6 µg/ml). However, tissue concentrations were significantly decreased in patients with diabetes (3.7 vs 11.9 µg/ml; p = 0.002). The mean tissue 24 h AUC was 86.4 mg•h/l for patients with diabetes versus 275 mg•h/l for control patients. The authors concluded that vancomycin should be dosed aggressively in patients who have diabetes and skin infections.

Overweight & obesity

Many clinicians utilize a fixed dosing regimen of vancomycin (i.e., 1 g every 12 h) that is recommended by the prescribing information [56,57]. This recommendation is in opposition to the IDSA/ASHP/SIDP consensus review, which recommends dosing vancomycin based on total body weight (TBW) [10]. Four studies have evaluated the extent to which obesity alters vancomycin pharmacokinetics [39–42]. The results of these studies have varied due to different participant populations being studied.

Blouin *et al.* described vancomycin pharmacokinetics in four normal weight patients and six morbidly obese patients (111.4–226.4 kg) that were 37 years of age or younger [43]. The morbidly obese patients were status-post-gastric bypass surgery. Obese participants had a larger mean Vd (0.39 vs 0.26 l/kg) and increased Cl (0.65 vs 0.066 l/h/kg) compared with normal weight participants. TBW correlated well with Vd (r = 0.943) and Cl (r = 0.981). The morbidly obese group had a shorter mean half-life compared with normal weight patients (3.2 vs 4.8 h).

Vance-Bryan *et al.* examined 213 patients (age: 18–92 years) divided into nine groups categorized by 10% increases over lean body weight (LBW) to identify factors that affect vancomycin Cl and Vd with vancomycin [58]. A total of 47% of these patients were in the obese groups. Baseline CrCl did not differ between the groups. Actual body weight had negative correlation with Cl (r = -0.009), but was not clinically significant. Other factors that were negatively correlated with Cl were age (r = -0.0012) and baseline serum creatinine (r = -0.68). Vd did correlate with TBW (r = 0.814). The authors concluded that initial vancomycin dose should be based on TBW.

Bauer *et al.* observed that morbidly obese patients had a significantly higher CrCl than normal weight patients [44]. CrCl was determined for morbidly obese patients by the Salazar–Corcoran equation and the Cockcroft–Gault equation in the normal weight group. Morbidly obese patients had an increased mean Cl (11.82 vs 4.62 l/h) and Vd (52 vs 46 l). Vancomycin's half-life was markedly shorter in obese patients due to the increased Cl (3.3 vs 7.2 h). Vancomycin Cl was correlated with TBW (r = 0.948) and with Vd to a lesser extent (r = 0.49).

Ducharme *et al.* performed a large pharmacokinetic study in 704 patients [45]. Patients were divided into groups based on weight, age and gender. Normal weight patients were categorized as having a TBW to ideal body weight ratio (TBW:IBW) of 0.8–1.3 and obese patients had a TBW:IBW ratio over 1.3. Age was categorized as under 40, 40–60 or over 60 years. Vd increased as age increased in all groups and also with obesity classification (p < 0.0001). Cl decreased with increasing age and increased with increasing obesity classification (p < 0.0001). Women had a larger Vd compared with men at 0.79 versus 0.64 l/kg. Vancomycin Cl was higher for men (5.1 vs 3.8 l/h), but may have been due to a higher baseline CrCl (88 vs 59.4 ml/min).

Critically ill patients

del Mar Fernández retrospectively evaluated vancomycin pharmacokinetics in 46 critically ill patients with a mean APACHE II score of 18.9 [47]. Patients had an increased mean Vd of 1.68 l/kg. A Monte-Carlo simulation using a prescpecified

MIC distribution determined that an AUC:MIC over 400 was achieved in 43.75% (1 g/day), 78% (2 g/day) and 89% (3 g/day). An equation was developed using regression analysis to determine vancomycin Cl using patient-specific factors ($r^2 = 0.68$; $p < 0.01$):

$$Cl\,(ml/min/kg) = \left(0.872 - 0.015 \times age\,[years]\right) - \left(0.007 \times APACHEII\ Score\right) + \left(0.234 \times serum\ albumin\right) + 0.346\,ClCr\,(ml/min/kg)$$

CrCl was determined by using the Levey equation [59]. This equation has not been validated prospectively.

Both studies in critically ill patients emphasized a large change in Vd [46,47]. Loading doses of vancomycin may be important in this population, especially due to the high mortality seen with these patients. Vancomycin Cl will be variable and will correlate largely with kidney function. It is important to monitor frequent concentrations in these patients during the initial period of infection to ensure adequate serum drug concentrations.

Burns

Burn patients have increased Cl of many drugs including vancomycin. Dailly *et al.* retrospectively evaluated 70 burn patients (mean age: 42 years) to determine an equation for vancomycin dosing [48]. Patients had a mean CrCl of 173.3 ml/min and a mean vancomycin Cl of 7.03 l/h. A significant correlation was seen with vancomycin Cl and CrCl ($r = 0.5$; $p < 0.001$). The authors postulated that mechanisms other than renal filtration may affect vancomycin Cl. The authors derived an equation for dosing vancomycin in this population:

$$Dose\,(g/day) = \left(0.0205 \times CrCl\,[ml/min] + 3.47\right) \times \left(Target\ concentration\ steady\ state\left[\mu g/ml\right]\right) \times \left(\frac{24}{1000}\right)$$

This equation has not yet been validated.

Rybak *et al.* performed a trial with ten patients with burns, ten intravenous drug users, and 14 control patients [42]. The mean CrCl was statistically significantly different in patients with burns than in control patients (111 vs 85 ml/min; $p < 0.05$). Vancomycin Cl was also increased in patients with burns (8.66 vs 4.06 l/h; $p < 0.05$), resulting in lower mean AUC values (189 vs 250 mg•h/l). The authors concluded that changes in vancomycin Cl were not solely due to renal filtration but possibly renal tubular secretion.

What can be done to optimize vancomycin pharmacodynamics?

In clinical practice, the AUC is not typically measured. Rather, it can be estimated using the formula [13]:

$$AUC_{24} = \frac{D}{\left[\left\{\left(CrCl \times 0.79\right) + 15.4\right\} \times 0.06\right]}$$

In this equation, D = vancomycin dosage in 24 h and CrCl is estimated using the modified Cockcroft–Gault method [60]. This equation has not been validated in patients who are underweight, obese, or those with fluctuating CrCl. The correlate to this equation can be used to identify the minimum daily dose required to achieve target AUC.

For example, a patient receiving vancomycin 1 g every 12 h with a CrCl of 100 ml/min using the aforementioned equation would have an AUC of 353, which would be sufficient only for MRSA isolates with a vancomycin MIC of 0.5 µg/ml or less. Current dosing recommendations start empiric vancomycin dosing at 15–20 mg/kg every 8–12 h [10]. Even when using these new recommendations, the dosing strategies advocated may not achieve an AUC:MIC ratio over 400 for isolates within the susceptible range. Using the example above, an AUC of 800 would be needed to achieve an appropriate ratio for a MIC of 2 µg/ml. This would require 4500 mg of vancomycin per day or 32 mg/kg every 12 h through weight-based dosing. This dosing regimen would likely be associated with trough concentrations over 20 µg/ml, which may increase the probability of toxicity.

Loading doses of vancomycin are used to obtain therapeutic concentrations at a rapid rate. This may be useful in critically ill patients who have a large Vd upon presentation. Loading doses of 25 mg/kg have been employed in nomograms such as the Matzke nomogram [61]. A recent study evaluating seven different vancomycin dosing nomograms found that the Matzke nomogram had the best combination of the least bias and highest precision in determining appropriate trough concentrations [62]. Current consensus recommendations suggest using a 30-mg/kg loading dose in critically ill patients [10]. Only one study (n = 28) has evaluated the safety of a loading dose of vancomycin [63]. A 25-mg/kg loading dose showed no increase in infusion reactions when administered at 500 mg/h. Nephrotoxicity and ototoxicity rates were not reported. The mean serum concentration 1 h after the completion of the vancomycin infusion was 26.4 µg/ml.

Studies comparing continuous infusions of vancomycin to intermittent infusions have produced similar safety and efficacy results [64,65]. These results are expected since vancomycin's killing activity is best associated with the AUC:MIC. Wysocki *et al.* suggested a savings in cost with continuous infusion versus intermittent infusion (US$454 vs 321) over 10 days of vancomycin therapy [66]. Total cost was determined by amount of drug and cost of laboratory tests. Clinical and microbiologic outcomes were similar for both groups. This study used frequent vancomycin concentration monitoring to determine each patient's dosing regimen. The benefit of cost-saving from reduced vancomycin monitoring may not be seen with current practices. This study did correlate the equivalence of safety and efficacy of intermittent trough concentrations of 10–15 µg/ml to plateau concentrations of 20–25 µg/ml from continuous infusion. While continuous infusions of vancomycin may be used, there is no compelling indication for its use in most patients.

Expert commentary

Vancomycin remains a first-line antimicrobial recommended for the empiric treatment of MRSA infections in several clinical practice guidelines. Unfortunately, no alternative MRSA agent

has data supporting its use for all of the serious MRSA infections vancomycin has been used for as an empiric agent for decades. Therefore, vancomycin is still one of the most commonly used antimicrobials within hospitals.

The implementation of PK–PD principles with limited safety data has resulted in a clinical quandary. Investigators have suggested that these new dosing regimens have increased nephrotoxicity rates, making vancomycin an unattractive antimicrobial compared with alternative anti-MRSA medications. More data are needed to address this question since most investigators have focused on the association of vancomycin trough concentrations and nephrotoxicity, creating a 'chicken and egg' conundrum. Specifically, it is unknown whether increased vancomycin trough concentrations are a cause of nephrotoxicity or simply a result of decreased vancomycin Cl in patients experiencing nephrotoxicity.

Similarly, the lack of randomized, controlled trials evaluating aggressive vancomycin dosing regimens has created confusion in the healthcare community. PK–PD simulation studies suggest that only patients infected by MRSA isolates with a vancomycin MIC of 1 µg/ml have an improved likelihood of clinical success with aggressive vancomycin dosing. A retrospective study also suggests there is no difference in outcome based on vancomycin troughs. As expected, more unwell patients were more likely to have increased vancomycin troughs. A similar mortality rate in a sicker patient population may support the use of aggressive doses. On the other hand, a prospective, cohort study observed no differences in the final outcome of patients regardless of traditional or aggressive dosing strategies. The aforementioned argument regarding nephrotoxicity is mute if success rates are not improved with aggressive dosing regimens.

These issues combined with a lack of correlation between E-test and broth microdilution make dosing decisions with vancomycin very confusing. With the current data, we recommend that clinicians maintain trough concentrations of 10 µg/ml or more, as limited data suggest lower concentrations are associated with the development of hVISA. We recommend aggressive vancomycin dosing (or use of an alternative MRSA agent) for infections where the site is difficult to penetrate (i.e., pneumonia, endocarditis, meningitis, osteomyelitis or diabetic skin/soft tissue) and for patients who have characteristics that negatively affect vancomycin pharmacokinetics (i.e., burns, overweight or obese).

An argument could be made based on the PK–PD modeling data that the CLSI did not decrease the vancomycin breakpoint sufficiently [1,15]. The MIC breakpoint that would be chosen by this model would be 1 µg/ml at the highest and could even be decreased further to 0.5 µg/ml. It is unlikely that CLSI will decrease the vancomycin breakpoint to 1 µg/ml as the MIC value that predicts an inferior clinical outcome has varied between 1, 1.5 and 2 µg/ml depending on the study referenced. Another factor that will likely discourage further movement of the vancomycin CLSI breakpoint is the sparse amount of data available describing the clinical outcomes of patients treated with alternative anti-MRSA antimicrobials for MRSA isolates with a vancomycin MIC of 1 µg/ml or more.

Five-year view

Vancomycin use will likely decrease over the next 5 years as additional data for newer anti-MRSA agents continues to be published. This is due, in part, to the lack of funding available to conduct large-scale randomized, controlled trials for a generic medication such as vancomycin. For example, we have known for years that vancomycin should be based on TBW according to pharmacokinetic studies in patients with normal renal function. However, randomized, prospective studies to evaluate the safety and efficacy of weight-based regimens versus the standard 1 g every 12 h regimen have yet to be conducted. Therefore, the prescribing information for this agent has not changed in spite of the scientific community adopting what seems to be a sound dosing regimen based on pharmacokinetic principles. A solution for stimulating clinical research to effectively and safely implement new findings with generic drugs is needed. One potential mechanism for helping fund the research needed to implement these findings would be to mandate a surcharge on all generic medications, which is required to specifically fund clinical research for generic medications. However, the economic strain resulting from this approach would need to be taken into account given the high costs already associated with healthcare.

The extent to which vancomycin use decreases will depend on several factors including:

- The incidence of vancomycin MIC values 2 µg/ml or more within institutions
- Data for newer anti-MRSA agents against MRSA infections with a vancomycin MIC value 2 µg/ml or more
- Data for newer anti-MRSA agents in serious infections (i.e., meningitis or endocarditis)
- Development of resistance to newer anti-MRSA agents
- The discovery of novel adverse events or drug interactions with newer anti-MRSA agents
- Cost

The decreased efficacy of vancomycin against MRSA infections with a MIC value 2 µg/ml or more has been established. Unfortunately, no data are currently available describing the clinical outcomes of patients treated with newer anti-MRSA agents for MRSA infections with a vancomycin MIC value of 2 µg/ml or more. The addition of this data will advise clinicians as to whether PK–PD principles are the primary reason for vancomycin failures in these patients or if these strains have increased virulence, resulting in worse outcomes regardless of the agent used.

There may also be unintended consequences of increasing the use of newer anti-MRSA agents. Vancomycin resistance has developed to clinically meaningful levels over 50 years. This time period has included 25 years where vancomycin has been heavily utilized as the mainstay of treatment for MRSA infections. The development of resistance with linezolid and tigecycline occurred within the first 10 years of their approval by the US FDA. Increased daptomycin MIC values have also been observed in patients receiving daptomycin for endocarditis. Vancomycin use

would be expected to rise again if these agents are found to promote their own resistance rapidly when used as a primary empiric agent for MRSA infections.

Another factor that could result in vancomycin use returning to previous levels is the discovery of adverse events or drug interactions as newer anti-MRSA agents are used more commonly. Such an occurrence would not be the first time a commonly used drug suddenly disappeared owing to an unexpected event. For example, gatifloxacin was a widely utilized fluoroquinolone before data concerning glucose excursions caused its removal from the USA market.

The cost of newer anti-MRSA agents is expected to decrease as more competitors (i.e., ceftaroline, ceftobiprole, dalbavancin, iclaprim, oritavancin and telavancin) make their way from the drug development pipeline to clinical practice. This will also make the use of vancomycin less appealing given the laboratory and personnel costs associated with therapeutic drug monitoring.

Vancomycin has been and continues to be a valuable member of the antimicrobial armamentarium. Optimizing vancomycin dosing according to PK–PD principles has the potential to maximize vancomycin's efficacy against MRSA isolates with a vancomycin MIC of 1 µg/ml and slow the incidence of hVISA. Additional studies using a consistent definition of nephrotoxicity that do not focus on vancomycin trough concentrations are needed to define the true incidence of this adverse event with more aggressive dosing of vancomycin.

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Key issues

- The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates with increased vancomycin MIC values has increased this decade.
- Vancomycin MIC values of 1 µg/ml or more have been associated with worse clinical outcomes for MRSA infections.
- Total daily vancomycin exposure has been associated with improved clinical outcomes for patients with *S. aureus* pneumonia.
- Vancomycin trough concentrations more than 10 µg/ml may prevent the emergence of heterogeneous vancomycin resistance in MRSA isolates.
- MIC values determined via E-test and broth microdilution are not always the same and can significantly affect dosing decisions.
- Aggressive vancomycin dosing is more important with sites of decreased penetration.
- More frequent vancomycin dosing is likely needed for patients with increased vancomycin clearance.
- Increased dosing may increase the incidence of nephrotoxicity, although damage is more likely if receiving concomitant nephrotoxic agents.

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