

Rationalization of Vancomycin Serum Concentration Monitoring

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ABSTRACT

The common practice of adjusting vancomycin dosage based on peak and trough serum levels is examined. To justify the routine monitoring of serum levels of any drug, it must have predictable pharmacokinetics; there must be a correlation between serum levels and effect; and the drug must have a narrow therapeutic index. Peak vancomycin levels are difficult to predict due to the drug's highly variable distribution phase half-life. Since troughs are drawn after distribution is complete, they are readily predictable. Vancomycin's ototoxic potential is doubtful and the incidence of nephrotoxicity is low in patients not receiving concomitant nephrotoxic drugs. There are several studies suggesting that vancomycin may potentiate the nephrotoxicity of other drugs. Trough vancomycin levels greater than 10 mg/L have been correlated to nephrotoxicity; there is no evidence correlating peak levels to ototoxicity or nephrotoxicity. Information relating the efficacy of vancomycin to serum levels is not available. However, based on the minimum inhibitory concentrations for susceptible bacteria and vancomycin's concentration-independent killing properties, trough levels between 5 and 10 mg/L would appear adequate. This information suggests that routine monitoring of trough, but not peak, vancomycin serum levels is justified. Initial vancomycin doses should be calculated using available nomograms. Trough vancomycin levels should be maintained between 5 and 10 mg/L by use of dosing nomograms or empiric adjustment.

Key Words: pharmacokinetics, serum levels, therapeutic drug monitoring, vancomycin

RÉSUMÉ

On a évalué la pratique courante selon laquelle on ajuste la dose de vancomycine selon les concentrations plasmatiques maximales et minimales. Le dosage plasmatique régulier de tout médicament n'est justifié que si sa pharmacocinétique est prévisible; s'il existe une corrélation entre les concentrations sériques et les effets observés; et si le médicament a une zone thérapeutique étroite. Il est difficile de prévoir les pics plasmatiques de la vancomycine parce que sa distribution et sa demi-vie sont grandement variables. Comme les creux plasmatiques sont prélevés après que la vancomycine soit complètement distribuée, ils sont donc facilement prévisibles. Le risque d'ototoxicité de la vancomycine est discutable et la fréquence de néphrotoxicité est faible chez les patients qui ne reçoivent pas concurremment d'autres médicaments néphrotoxiques. Les résultats de nombreuses études ont laissé croire que la vancomycine pouvait accroître le potentiel néphrotoxique d'autres médicaments. On a associé la néphrotoxicité à des concentrations plasmatiques minimales supérieures à 10 mg/L; on n'a cependant obtenu aucune preuve de corrélation entre l'ototoxicité ou la néphrotoxicité et des concentrations plasmatiques maximales. On ne dispose non plus d'aucune information sur le lien entre les concentrations plasmatiques de la vancomycine et l'efficacité de ce médicament. Cependant, en se basant sur les concentrations minimales inhibitrices de la vancomycine pour les bactéries qui y sont sensibles et sur son pouvoir bactéricide indépendant des concentrations, des concentrations minimales entre 5 et 10 mg/L semblent être suffisantes. Cette information porte à croire que la mesure systématique des concentrations plasmatiques minimales de la vancomycine, et non celle des concentrations maximales, est justifiée. Les doses initiales de vancomycine devraient être établies en utilisant les nomogrammes disponibles. Les concentrations minimales devraient être maintenues entre 5 et 10 mg/L en ayant recours aux nomogrammes ou à l'ajustement empirique de la dose.

Mots clés : concentrations plasmatiques, pharmacocinétique, surveillance pharmacothérapeutique, vancomycine

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INTRODUCTION

Vancomycin serum levels have been monitored for many years based on the recommendations of numerous pharmacokinetic researchers.¹⁻⁸ Recently, the validity of routinely monitoring blood concentrations of this drug has been questioned.⁹⁻¹² Despite this controversy, most institutions continue to adjust vancomycin doses based on peak and trough serum drug levels.

In order to justify the time and expense of drawing and interpreting serum levels of any medication, several basic conditions must be met. First, the pharmacokinetics of the drug must be well understood so that serum levels can be predictably adjusted through dosage changes. In addition, there must be a correlation between serum levels and efficacy, toxicity, or both. Finally, the drug must have a narrow therapeutic index. That is, little difference should exist between levels which are therapeutic and levels which are toxic. If this last condition is not met, the drug may be effectively dosed without the precise adjustments achievable through serum level monitoring. For both peak and trough concentrations to be routinely monitored, each must comply with the above criteria.

In an effort to determine if routine monitoring of peak and trough vancomycin levels is justified, a computerized and manual MEDLINE literature search was carried out using the data base from January 1994 back to 1962 when vancomycin was first listed as a heading. The search was limited to human studies published in English.

Predictability of Vancomycin Pharmacokinetics

The literature on the predictability of vancomycin's pharmacokinetics is controversial. For example, despite rather extensive studies there is no agreement on the nature of

vancomycin's distribution. Vancomycin pharmacokinetics have been described by one¹, two², and three¹³⁻¹⁵ compartment models. This lack of agreement has led to inconsistencies with regard to the timing of drawing peak vancomycin levels. Assuming either a two or three compartment model, vancomycin undergoes an initial distribution phase during which serum levels are "falsely elevated" owing to incomplete distribution to the tissues. Since pharmacokinetic predictions are based on calculation of the post-distribution half-life, one must be certain that peak levels are drawn after distribution is complete. Levels drawn prior to this time will lead to significant underestimation of the elimination (beta) half-life. Literature recommendations regarding the timing of peak serum level determinations vary greatly. Some pharmacy departments have adopted a policy of waiting three hours after the end of the infusion before drawing peak levels.^{16,17} However, the initial decline of serum concentrations during this distribution phase has been shown to occur over up to five hours,^{18,19} and the predictability of the duration of this phase is questionable. The fact that studies have calculated this distribution half-life to be anywhere from 0.1 to 2.89 hr^{5,13,14,18,20,21} illustrates the variability which exists. In addition, it has been claimed that the distribution is not significantly affected by renal failure¹⁸ while others have demonstrated that declining renal function may influence the distribution half-life.¹⁹ Based on the above observations, waiting three hours or less after completion of the infusion may not be sufficient time to ensure complete distribution. On the other hand, waiting an extended period may leave less than the recommended two to three half-lives between levels for two point

determination of the elimination half-life,²² especially if one follows the manufacturer's recommendation of a one hour infusion followed by a six to 12 hour dosing interval.²³

Vancomycin Toxicity Ototoxicity

Vancomycin's potential for causing ototoxicity is highly suspect.^{24,25} Although it has been used for over 30 years, there are very few reports of auditory dysfunction associated with this drug: 36 cases according to a review published in 1988.²⁴ One of the first cases, reported by Geraci et al,²⁶ described a patient with a peak vancomycin concentration of 95 mg/L. Since that time, it has been claimed that peak vancomycin levels greater than 80 mg/L are associated with ototoxicity,^{27,28} although there is little evidence to support this claim. Most reports of auditory dysfunction in association with vancomycin use have involved patients who were either on concurrent ototoxic medications or had pre-existing auditory dysfunction.^{24,25}

Two recent studies have prospectively evaluated vancomycin ototoxicity. Meyerhoff studied 18 patients who received vancomycin for a minimum of eight weeks.²⁹ Serum levels were monitored, but the specific concentrations were not reported. The authors did state, however, that levels "never reached toxic range." Auditory threshold monitoring was carried out before, during, and after vancomycin treatment; no ototoxicity was reported. Van der Hulst included 13 continuous ambulatory peritoneal dialysis patients in his study.³⁰ They received a total of 15 vancomycin courses for up to two weeks. The only reference to serum levels indicated that they never were higher than 50 mg/L, although the timing relative to the dose was not stated. One patient experienced

limited ultra-high frequency hearing loss; however, there were no complaints of deafness, vertigo, or tinnitus.

The above information suggests that ototoxicity cannot be conclusively associated with vancomycin use. In addition, two recent reviews on this topic conclude that vancomycin's ototoxic potential is doubtful when used alone.^{9,25} No conclusion can be made regarding the correlation between serum levels and this adverse effect.

Nephrotoxicity

Vancomycin nephrotoxicity may be evaluated from several different perspectives. First is the question of whether vancomycin alone causes nephrotoxicity. In addition, one must examine whether vancomycin can potentiate the nephrotoxicity of other drugs, namely aminoglycosides, and finally, the correlation between vancomycin serum levels and the incidence of nephrotoxicity must be examined. Review of the literature revealed several studies which specifically address the issue of vancomycin nephrotoxicity;^{8,31-39} however, results from these studies are conflicting and often inconclusive.

Vancomycin's Nephrotoxicity When Used Alone

Although vancomycin was widely used in the 1950s for the treatment of resistant *Staphylococcus* infections, early reports of nephrotoxicity lead to it being replaced with the semi-synthetic penicillins for this indication.³¹ Vancomycin preparations used when these early studies were conducted contained large quantities of impurities and it has been suggested that they were responsible for some of the adverse reactions reported during the 1950s and 1960s.⁴⁰⁻⁴³ The preparations used today are much more pure due to an updated manufacturing process.⁴⁰

It was not until the 1980s that vancomycin nephrotoxicity was studied in a controlled manner. Most of these studies concluded that vancomycin nephrotoxicity is uncommon when the drug is administered without concomitant nephrotoxic agents.^{8,31,33-36,39} The definition of nephrotoxicity is not consistent among the trials, although all studies based their definition on increases in serum creatinine measurements (typically an increase of 44 $\mu\text{mol/L}$ over baseline). While vancomycin levels were monitored in all the studies, many authors did not specify whether doses were adjusted to maintain levels within a specific range.^{31,33-36} If nephrotoxicity is related to serum levels, attempts to control serum levels may affect the incidence of nephrotoxicity.

One of the most quoted of these studies was a retrospective review of 98 patients treated with vancomycin conducted by Farber and Moellering for which a 5% incidence of nephrotoxicity was found when other nephrotoxic agents were not involved.³³ Other studies found incidences ranging from 0 to 17%.^{34-36,39,44} While most trials attribute at least some of the nephrotoxicity in their study patients to vancomycin,^{8,32,33,35} some authors dispute vancomycin's potential to induce nephrotoxicity. Downs et al³¹ found no significant difference between the incidence of nephrotoxicity seen in 66 vancomycin patients (7%) versus 57 controls (3%), and Salama et al³⁹ found no evidence of nephrotoxicity in 27 patients treated with vancomycin alone. Mellor et al concluded that their data "provide little support for the commonly held view that vancomycin is a nephrotoxic antibiotic."³⁴

Nephrotoxicity in Patients Receiving Vancomycin Plus an Aminoglycoside

Patients given vancomycin plus aminoglycosides are thought by

most clinicians to be at higher risk for developing nephrotoxicity than those given either agent alone. While some data support this concern, not all studies in this area reach the same conclusion. Again, Farber's study is one of the largest of those examining this issue and is often quoted by those supporting vancomycin's ability to potentiate the nephrotoxicity of other agents.³³ Farber found a 35% incidence of nephrotoxicity when vancomycin was used with aminoglycosides versus a 5% incidence when vancomycin was used alone. There were no results reported regarding the incidence of nephrotoxicity in patients receiving aminoglycosides alone. Although aminoglycoside and vancomycin serum levels were monitored, there was no indication whether doses were adjusted to maintain levels within a specific range. Also, the authors suggest possible bias based on the method of patient selection. Using a retrospective approach, patients were included only if they had antibiotic levels drawn. It is possible that patients given both vancomycin and an aminoglycoside were more likely to have levels drawn and were followed more closely, increasing the likelihood of detecting renal dysfunction. Also, patients on combination therapy may have been more seriously ill, and therefore, predisposed to renal dysfunction. In fact, six of these patients had endocarditis which can lead to renal insufficiency.⁴⁵

Another study which suggests that vancomycin and gentamicin may cause additive nephrotoxicity was conducted by Rybak et al in 1987.³⁶ They measured 24-hour creatinine production, β_2 -microglobulin elimination, as well as a newer marker of renal damage, alanine aminopeptidase elimination. Although alanine aminopeptidase results indicated additive

nephrotoxicity between vancomycin and gentamicin, β_2 -microglobulin results were less clear. The latter agent, chosen for comparison "since it has traditionally been used to detect renal damage", yielded a higher average five-day excretion rate for gentamicin alone than for concomitant vancomycin and gentamicin. This suggests a protective rather than an additive effect of vancomycin, although no statistics were reported to indicate whether or not this difference was significant. There were no changes noted in creatinine clearance, as determined by the method of Wagner,⁴⁶ for any of the treatment groups. The authors did not state whether serum levels were controlled through dose adjustment.

Rybak et al⁸ demonstrated a 22% incidence of nephrotoxicity in 63 patients receiving vancomycin plus an aminoglycoside compared to a 5% incidence in 168 patients receiving vancomycin alone. Eleven percent of 103 patients receiving gentamicin alone became nephrotoxic. The combination group received a longer mean duration of vancomycin therapy (22.7 ± 15.8 days versus 20.3 ± 14.1 days, no statistical analysis reported) and vancomycin therapy for longer than 21 days was associated with nephrotoxicity. Vancomycin doses were adjusted to maintain one-hour peaks of 30 to 40 mg/L and troughs of less than 15 mg/L.

Salama demonstrated an increased incidence of nephrotoxicity in patients receiving a combination of vancomycin and an aminoglycoside (25%) compared those receiving vancomycin alone (0%) or an aminoglycoside alone (4.5%).³⁹ Doses were adjusted to maintain one-hour peaks of 20 to 40 mg/L and troughs of less than 10 mg/L. There was a significantly greater proportion of patients with malignancy in those receiving combination therapy and univariate analysis showed that malignancy was associated with nephrotoxicity. Pauly

detected a 27% incidence of nephrotoxicity in a retrospective review of 105 patients receiving vancomycin plus an aminoglycoside.³⁷ There was no comparison to patients receiving either drug alone. Vancomycin doses were adjusted based on the Lake and Peterson⁴ nomogram to achieve 15 minute peaks of 20 to 30 mg/L and troughs of 5 to 10 mg/L.

Several studies cast doubt on the ability of vancomycin to potentiate nephrotoxicity. Sorrell³⁵ detected nephrotoxicity in four of 54 patients (8%) on vancomycin, all of whom received concomitant aminoglycosides. However, the authors cite their own unpublished data suggesting a 14% rate of gentamicin-induced nephrotoxicity. Based on these results, the addition of vancomycin to an aminoglycoside regimen does not add to the likelihood of developing renal dysfunction. Downs³¹ conducted a controlled study examining vancomycin nephrotoxicity and found no significant difference in the incidence of renal dysfunction between 54 patients treated with vancomycin alone and 12 patients receiving vancomycin and an aminoglycoside. The incidence of renal dysfunction in patients receiving aminoglycosides alone was not reported. Nahata demonstrated no nephrotoxicity in 90 pediatric patients studied prospectively who received concomitant vancomycin and gentamicin.³⁸ Similarly, Swinney et al showed no nephrotoxicity in eight pediatric patients receiving this combination.⁴⁷ Finally, Cimino et al in an uncontrolled study involving 229 patients showed no cumulative toxicity with concurrent administration of vancomycin and an aminoglycoside compared to an aminoglycoside alone.³² None of these authors clearly state whether doses were adjusted in an effort to maintain serum levels within a specific range.

The studies cited above indicate

that there is controversy surrounding vancomycin's ability to potentiate the nephrotoxicity of aminoglycosides. Since there are several trials which suggest this potentiation may exist, it may be prudent to monitor patients receiving vancomycin and aminoglycosides more cautiously. Whether this monitoring should be accomplished through the measurement of serum levels relies on the evidence correlating serum concentrations to nephrotoxicity.

Correlation Between Serum Levels and Nephrotoxicity

Although several trials have been designed to monitor serum levels while assessing patients for the development of renal failure, few studies have attempted to statistically correlate the two parameters. One study, which did attempt such a correlation, was conducted by Cimino et al in 229 patients given either vancomycin, an aminoglycoside or a combination of the two.³² They found a statistically significant correlation between elevated vancomycin trough concentrations (greater than 10 mg/L) and the development of renal toxicity, irrespective of whether vancomycin was administered alone or with an aminoglycoside. They used a definition of an increase in serum creatinine of 44 $\mu\text{mol/L}$ or more over a baseline measurement. No correlation was found between peak vancomycin concentrations and nephrotoxicity. The investigators aimed for peaks of 20 to 40 mg/L, although the timing of these peaks in relation to the dose was not given.

Rybak demonstrated in 231 patients receiving vancomycin that those with trough levels greater than 10 mg/L were 7.9 times as likely to develop nephrotoxicity than those patients with a trough level less than 10 mg/L.⁸ The duration of therapy was also found to be associated with nephrotoxicity. No correlation was found between

vancomycin peak serum concentrations and nephrotoxicity.

Pauly demonstrated a correlation between both elevated peak and trough serum vancomycin levels and the development of nephrotoxicity.³⁷ One hundred and five patients receiving concurrent aminoglycoside and vancomycin therapy were retrospectively studied; vancomycin was dosed and monitored using the method described by Lake and Peterson.⁴ That is, peak levels were drawn 15 minutes after the end of the infusion which is clearly before distribution is complete. Peak levels in patients developing nephrotoxicity were higher than those whose renal function was unaffected (28.1 mg/L versus 23.74 mg/L, $p = 0.008$), but were still within the target therapeutic range of 20 - 30 mg/L. Trough levels were 10.22 mg/L in the nephrotoxic group versus 7.83 mg/L in the nephrotoxic group ($p = 0.0022$). Twenty-two of 28 nephrotoxic patients had other risk factors known to contribute to nephrotoxicity.

Downs et al measured vancomycin levels in 66 patients and found mean peak and trough levels to be higher for nephrotoxic patients than for those who did not develop renal dysfunction (peaks 47 mg/L vs. 34 mg/L, troughs 29 mg/L vs. 16 mg/L, respectively).³¹ However, these differences were not statistically significant. Peaks were measured one hour after the infusion, while troughs were taken 30 minutes before the next dose.

In the study by Salama et al, there was no correlation found between peak (one hour after the infusion) or trough vancomycin levels and nephrotoxicity in 91 vancomycin patients studied.³⁹ Results from other studies have suggested that elevated serum levels are associated with nephrotoxicity, although no attempt to define a correlation was undertaken. Peak levels were either not mentioned or were drawn at inconsistent times including during the distribution phase.^{33,48} No conclusions

about the relationship between vancomycin serum levels and the development of renal dysfunction can be drawn from these data.

Schumacher evaluated the results from the Cimino and Downs trials to determine the performance of using 10 mg/L vancomycin trough concentrations in predicting nephrotoxicity.⁷ Thirty percent of patients with trough concentrations greater than 10 mg/L and 100% of patients with troughs less than or equal to 10 mg/L were correctly classified as having nephrotoxicity or non-nephrotoxicity, respectively. That is, the negative predictive value of trough vancomycin concentrations appears high according to these results.

In summary, three studies^{8,32,37} have shown a statistically significant correlation between trough levels and nephrotoxicity while two studies^{31,39} have not. Vancomycin trough concentrations may be better at predicting who will not develop nephrotoxicity (i.e., those patients with troughs less than or equal to 10 mg/L) than those who will develop this adverse effect. One study has associated high peak serum levels with the development of renal dysfunction, although peak levels were drawn in the distribution phase and many patients had contributing risk factors.³⁷

Correlation Between Serum Levels and Efficacy

Correlating the efficacy of vancomycin to blood concentrations is also important in justifying the monitoring of vancomycin serum levels. Although there are limited data on this subject, some conclusions can be drawn from the available literature. Minimum inhibitory concentrations (MIC) for gram positive organisms including most enterococci,^{49,50} are generally much less than 4.0 mg/L.^{18,49,50} Some organisms may be resistant to vancomycin;⁵⁰ however, the resistance of these organisms should be detected by routine

susceptibility testing. The National Committee for Clinical Laboratory Standards inhibition zone cut-off for susceptibility to vancomycin corresponds to an MIC of ≤ 4 mg/L.⁵¹

Since vancomycin exhibits time-dependent (concentration-independent) killing, the time above the MIC and not the peak concentration is most important.^{52,53} In fact, it has been demonstrated that increasing the vancomycin concentration above 2 mg/L does not affect the killing rate for *Staphylococcus* species isolated from patients with various infections.^{53,54} The post antibiotic effect of vancomycin may also contribute to bacterial eradication if serum levels fall below the MIC for part of the dosing interval.⁵⁵ Therefore, maintaining trough serum levels of 5 to 10 mg/L should ensure adequate killing of organisms which are considered susceptible to vancomycin.

Unfortunately, there are no studies in humans which correlate serum levels to clinical outcome. Schaad et al⁵⁶ found that in 16 patients with *staphylococcal* disease, peak vancomycin levels greater than 25 mg/L (drawn immediately after the end of the infusion) and troughs less than 12 mg/L produced satisfactory inhibitory and bactericidal titers. They did not, however, attempt to correlate serum levels to rate of cure. Louria et al⁵⁷ showed that in two of eight patients who did not attain a bactericidal concentration in the blood (i.e., bactericidal titre of 1:8 or greater), there was no significant reduction in *staphylococcal* counts. They also did not directly correlate serum concentration to outcome.

Recommended Approach

The goal when dosing vancomycin is to devise a regimen which will yield serum levels high enough to kill the offending bacteria without causing nephrotoxicity. Routine susceptibility testing will detect when MICs are higher than 4 mg/mL

and vancomycin should not be used in these situations (unless serum bactericidal titres are followed). Several vancomycin nomograms have been developed for susceptible bacteria.^{1,3-6} The three most studied nomograms are those developed by Matzke,¹ Moellering,³ or Lake and Peterson.⁴ Doses based on these nomograms have been shown to yield serum levels which, based on the above information, should be effective with minimum potential for nephrotoxicity.⁵⁸ The Moellering nomogram is the least aggressive of these⁵⁸ and may yield troughs substantially less than 5 mg/L when a twenty-four hour dosing interval is used. Therefore, if the Moellering method is utilized, a six, eight or twelve hour interval may be preferable. One author has recommended against the use of the Moellering nomogram,⁵⁹ while others have concluded it leads to "clinically acceptable performance."⁶⁰

Nomograms have been shown to accurately predict trough vancomycin levels. Rybak demonstrated no significant difference between the Matzke nomogram and individualized adjustment using a one-compartment pharmacokinetic model for predicting trough vancomycin concentrations.⁵⁹ The Matzke method has also been shown to have no significant difference in bias for predicting trough concentrations than the Bayesian method.⁶¹ Such accuracy in predicting troughs is not surprising. As stated by Garrelts et al⁶¹ "Nomograms in general may do an adequate job in predicting trough concentrations for renally eliminated drugs, since these methods are designed to adjust drug clearance for the level of renal function... Since the volume of distribution is a major determinant of peak serum drug concentrations, nomograms using fixed volume of distribution are likely to have difficulty in accurately predicting this value."

Trough levels should be monitored

with a target range of 5 to 10 mg/L. This will assure that the nephrotoxic potential of vancomycin is kept to a minimum while maintaining efficacious serum concentrations. Some authors have advocated higher target trough concentrations (12 - 15 mg/L) in patients with renal failure due to assay interference by a vancomycin breakdown product, crystalline degradation product (CDP-1), which accumulates in renal dysfunction.^{54,62} Serum creatinine should be monitored and caution should be exercised in patients receiving concomitant nephrotoxic drugs. Peak levels may be warranted in patients being treated for meningitis in order to estimate cerebrospinal fluid (CSF) concentrations. CSF levels, however, would be more valuable.¹² If trough levels fall outside the target range, the regimen can be adjusted according to changing renal function by means of one of the nomograms mentioned above. If renal function has not changed, the dosing interval may be adjusted empirically and the trough levels verified at predicted steady-state. The dosing nomogram developed by Rice utilizes trough levels for vancomycin dosing adjustment.⁶³ This may be a reasonable approach, although it has not been tested prospectively and was developed specifically for burn patients. Research examining the efficacy and toxicity of vancomycin regimens determined using trough versus both peak and trough serum levels is warranted.

There is a cost savings associated with the elimination of routine peak vancomycin levels. More importantly, however, the accuracy of pharmacokinetic interpretation may be improved by avoiding incorrect calculations based on peak levels drawn in the distribution phase. Also, the turn around time for assessment of levels would improve since using three-hour, post-infusion peaks adds at least four hours to the time required

for drawing and interpreting levels. This four-hour period is often long enough to delay delivery to the lab past the cut-off time for running vancomycin levels, thus delaying interpretation and recommendation until the next day. Furthermore, using only trough levels is more convenient for all hospital staff involved. Other authors have supported the routine monitoring of trough, but not peak, vancomycin levels.^{9,64}

Some authors have advocated abandoning the routine monitoring of both peak and trough vancomycin levels.⁹⁻¹¹ The primary difference in their argument stems from the interpretation of the information correlating trough levels of nephrotoxicity. While the relationship between elevated trough levels and nephrotoxicity has not been conclusively established, there are several studies that have shown such a correlation. One of the papers suggesting neither peak nor trough levels should be monitored was published before much of the work on this topic was reported.¹⁰ Furthermore, it has been shown that pharmacokinetic monitoring of vancomycin can be cost-effective in terms of drug expenditures,¹⁶ although such cost savings may be limited if initial doses are based on the nomograms mentioned earlier. Monitoring troughs will also ensure that therapeutic levels are attained. Until such time that the current information on vancomycin troughs can be refuted, monitoring trough levels should be a routine practice.

In conclusion, from the information presented above, it seems appropriate to recommend that trough vancomycin levels be routinely monitored since they are predictable and troughs greater than 10 mg/L are associated with nephrotoxicity. Peak levels should not be routinely followed as they are not predictable and have not been reliably associated with toxicity. Pharmacokinetic calcula-

tions based on peak levels drawn during the distribution phase will be incorrect and could lead to potentially toxic vancomycin dose recommendations through underestimation of the serum half-life. Clinical outcome has not been correlated to specific peak or trough levels. However, since MICs are generally less than 4 mg/L and vancomycin exhibits concentration-independent killing, trough levels of 5 - 10 mg/L are adequate for bacterial eradication. Initial vancomycin doses should be calculated based on available nomograms. Trough levels should be maintained between 5 and 10 mg/L by use of dosing nomograms or empiric adjustment.

Although there is a tendency to rely on peak levels so that specific pharmacokinetic parameters can be calculated, the usefulness and accuracy of this practice is questionable and should be reassessed by those involved in clinical pharmacokinetic services. ☒

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