Recent changes in vancomycin use in renal failure

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Vancomycin is a key tool in the treatment of serious Gram-positive infections. A progressive increase in vancomycin resistance with consequent treatment failure has been observed in staphylococci. Therefore, new dosing guidelines advocating much higher vancomycin doses have been issued. Target trough levels of 15–20 μg/ml are proposed. Whether and how these targets can be achieved in patients with chronic kidney disease or those on dialysis are still under evaluation. The higher vancomycin doses to achieve these treatment targets carry a substantial risk for nephrotoxicity. This risk is incremental with higher trough levels and longer duration of vancomycin use. Critically ill patients, patients receiving concomitant nephrotoxic agents, and patients with already compromised renal function are particularly at risk for vancomycin-induced nephrotoxicity.

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Infections are only preceded by cardiovascular disease as cause of mortality in hemodialysis patients.[1] The annual risk for bacteremia in hemodialysis patients ranges from 7.6 to 14.4%, and 60–100% of these episodes are caused by staphylococcal species, especially *Staphylococcus aureus*.[1] Given the rapid disperse of staphylococcal species with a decreased susceptibility to β-lactam antibiotics and the attractive pharmacokinetics (PK) of the drug, vancomycin has been a cornerstone anti-staphylococcal agent in hemodialysis for decades.[1] In recent years, two evolutions in vancomycin use with a major impact on the management of patients with renal insufficiency have been observed. First, a progressive creep in minimal inhibitory concentration (MIC) for vancomycin in *S. aureus* has dictated the need for much higher therapeutic targets.[2] The achievability of these targets in patients with renal failure is a moot point.[2] Second, these higher dose recommendations impart an important nephrotoxicity, especially in already vulnerable patients.[3]

VANCOMYCIN

Vancomycin, introduced in 1958, is a large glycopeptide antibiotic with a molecular weight of 1446 Da.[2] Vancomycin inhibits the bacterial cell wall synthesis of Gram-positive bacteria by the formation of a stable complex with murein pentapeptides, thus causing an inhibition of further peptidoglycan formation.[1] The killing effect of vancomycin is characterized by a slow mode of action, and is further hampered by large bacterial inoculates, stationary growth phase, and anaerobic conditions.[2]

The key PK and PD (pharmacodynamic) characteristics of vancomycin in patients with normal or decreased kidney function are summarized in Table 1. Vancomycin has no significant oral absorption. After injection, vancomycin has a complex concentration-time profile.[2] Tissue penetration of vancomycin is often poor, with a penetration of 0–18% in uninflamed meninges, 36–48% in inflamed meninges, 41–51% in the lung, 17% in ventilated lung tissue, and 10 to 30% in diabetic and normal skin and soft tissues, respectively.[2]

The PK/PD parameter best predicting activity of vancomycin against staphylococcal species is the 24-h area under the concentration curve over the MIC (AUC/MIC or AUIC).[4] In one trial of *S. aureus* respiratory tract infections, AUC/MIC > 400 and AUC/MIC > 850 correlated with clinical and microbiological success, respectively.[4] On the basis of these observations, an AUC/MIC ⩾ 400 has been adopted as the

Table 1 | Key vancomycin pharmacokinetic and pharmacodynamic characteristics in patients with a normal and decreased kidney function

	Normal renal function		Renal failure
Oral absorption		Very low	
α-Distribution phase		30–60 min	
Half-life (hours)	6–12		9.1 (CrCl > 60) 32.3 (60 > CrCl > 10) 146.7 (10 > CrCl)
Renal clearance		3.66+(0.689 × CrCl) ml/min	
Extrarenal clearance (%)	5–8.5		Unknown
Dialysance (%)		89.6–93.4	
Protein binding (%)	50–55		20
Tissue penetration		Variable, but generally low	
Volume of distribution	0.4–1 l/kg		0.72–0.9 l/kg
PK/PD parameter		AUC/MIC	
Drug monitoring		Trough levels (target 15–20 μg/ml)	
Post-antibiotic effect		0.2–2 h (in *S. aureus*)	

Abbreviations: AUC, area under the concentration curve; CrCl, creatinine clearance; MIC, minimal inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics; *S. aureus*, *Staphylococcus aureus*.

recommended target in a consensus review of the American Society of Health-System Pharmacists, The Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists.[2] However, these values are hardly obtainable in *S. aureus* strains with an MIC of 2 μg/dl.[2] For example, administration of 1 g vancomycin in a patient weighing 80 kg and with a normal kidney function results in an AUC/MIC of ~250.[2] The calculation of AUC/MIC is not practical for routine use. However, there is a good correlation between total drug exposure given by the AUC/MIC and vancomycin trough levels.[2,3] Trough levels are therefore recommended as the most accurate and practical monitoring tool in clinical practice.[2,3]

Elimination of vancomycin is almost exclusively renal. About 80–90% of the drug is excreted unchanged in the urine within 24 h in patients with normal renal function.[2,5] Approximately 5–8.5% of vancomycin clearance is extrarenal, possibly by hepatic conjugation, leading to vancomycin crystalline degeneration products.[6,7] Owing to the accumulation of these vancomycin crystalline degeneration products, some—mainly older—tests may overestimate the active vancomycin concentration in hemodialysis patients.[6]

Vancomycin clearance decreases with creatinine clearance in a linear mode,[5,8] resulting in a half-life of up to 100–200 h in anuric patients.[5] Several nomograms for vancomycin dosing have been proposed for patients with various degrees of renal failure.[5,8]

Owing to its high molecular weight, vancomycin is hardly eliminated with conventional low-flux membrane hemodialysis, permitting a once-weekly dosing schedule in this setting. Contemporary high-flux membranes, however, eliminate vancomycin more efficiently, with an estimated vancomycin clearance of 43.3–120 ml/min.[7] This high dialytic vancomycin clearance combined with a low extrarenal clearance is also reflected by a high vancomycin dialysance (F_{HD}) of 89.6–93.4%.[7] Vancomycin removal during high-flux dialysis is independently determined by the multiplication of body weight and duration of hemodialysis.[9] Filter reuse slightly decreases vancomycin clearance. When using high-flux dialysis, thrice weekly dosing after or at the end of each dialysis session is required.[7] The high vancomycin clearance by high-flux dialyzers also fuelled the debate whether vancomycin should be administered during the last hour of dialysis or after dialysis. Although administration of vancomycin after dialysis is theoretically the best option,[7] intradialytic administration of the drug during the last half to two hours of dialysis is more practical in outpatients. When vancomycin was administered during the last hour of dialysis rather than after dialysis, a supplementary drug elimination of 12.8% with high-flux dialysis and 26.3% with high-flux hemodiafiltration was reported.[10] Consequently, higher doses of vancomycin are required in this setting to obtain the same trough levels.

Only fragmental data are available on vancomycin clearance during continuous renal replacement therapy. All modes of continuous renal replacement therapy cause a constant elimination of vancomycin, with a higher clearance for continuous venovenous hemodiafiltration than for continuous venovenous hemofiltration.[11]

THE NEED FOR HIGHER VANCOMYCIN TROUGH LEVELS

In *S. aureus*, a steady increase in the MIC of vancomycin has been observed, with the emergence of vancomycin-intermediary *S. aureus* (VISA) and vancomycin-resistant *S. aureus*.[1] *S. aureus* strains with a vancomycin MIC of >2 and <16 μg/ml, caused by a progressive thickening of the peptidoglycan staphylococcal cell wall, are defined as VISA.[1] *S. aureus* strains with a median MIC as high as 512 μg/ml, caused by the acquisition of the enterococcal vancomycin resistance gene *vanA* and resulting in an altered murein pentapeptide target with strongly decreased binding affinity for vancomycin, are referred to as vancomycin-resistant *S. aureus*.[1] Both VISA and vancomycin-resistant *S. aureus* are associated with slower bacteriological clearance and higher treatment failure rates. In hemodialysis patients, bacteremia with methicillin-resistant *S. aureus* (MRSA) with a vancomycin MIC of >2 μg/ml is associated with increased mortality and cost.[1] Moreover, up to 11% of apparently vancomycin-susceptible MRSA strains contain vancomycin-intermediary sub-populations that are easily missed in the routine laboratory.[1] These strains are known as heterogeneous VISA or hVISA and predispose to reduced treatment response.[1] Even within the group of susceptible staphylococci, strains with an MIC between 1 and 2 μg/dl are more resistant to treatment than more susceptible strains.[1,12,13] The fraction of *S. aureus* strains with an MIC between 1 and 2 μg/dl is steadily increasing, accounting for 16.2% of strains in the United States in 2005. Most, but not all, *S. aureus* strains with a reduced susceptibility to vancomycin are also MRSA.[1]

These changing patterns in epidemiology and susceptibility to vancomycin in *S. aureus* underscore the need for new dosing guidelines for vancomycin.[2] In seriously ill patients, a loading dose of 25–30 mg/kg body weight is recommended with a maximal infusion rate of 10–15 mg/min.[2] Optimal trough concentrations are 15–20 mg/l.[2] In patients with normal renal function, these levels are obtained with a daily maintenance dose of vancomycin of 15–20 mg/kg administered 2–3 times a day.[2] In patients with normal renal function receiving vancomycin for more than 3–5 days, trough levels should be obtained in a steady-state condition, which is just before the fifth dose, and thereafter on a weekly basis.[2] In unstable patients or patients at risk for nephrotoxicity, 'more frequent' trough level monitoring is recommended.[2] The significance of 'more frequent' should be tailored according to individual patient characteristics.

Most available nomograms for vancomycin dosing in patients with various degrees of renal failure have much lower trough targets.[5] At present, only limited evidence is available on how to obtain the new targets in chronic kidney disease (CKD) stage II–V with intermittent vancomycin dosing schedules. On the basis of vancomycin PK in CKD,[5] on the linear relationship between vancomycin clearance and creatinine clearance[8] and on the new dosing guidelines,[2] a non-validated extrapolation to obtain these targets is proposed in Table 2.

One well-designed trial in critically ill patients examined the achievability of vancomycin trough levels of 15–20 μg/ml while using vancomycin continuous infusion.[8] A loading dose of 15 mg/kg body weight, followed by a maintenance dose administered as continuous infusion and calculated by the equitation (infusion rate (g per 24 h) = (0.029 × CrCl (ml/min) + 0.94) × target trough level × 24/1000) is proposed.[8] The use of vancomycin continuous infusion is based on the assumption that the time above the MIC is the PK/PD parameter best predicting vancomycin activity in men. This assumption turned out to be false, however, with the AUC/MIC being the key PK/PD parameter for vancomycin.[4] On the basis of these insights and the lack of benefit of continuous versus intermittent administration in available trials, vancomycin continuous infusion is discouraged in the consensus vancomycin dosing guidelines of the American Society of Health-System Pharmacists, The Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists.[2]

Table 2 | Proposed vancomycin dosing in patients with normal renal function and in CKD

Vancomycin intermittent dosing schedule
Loading dose: 25–30 mg/kg in all patients, with maximum infusion rate of 15 mg/min

Maintaining dose CKD stage	CrCl (ml/min per 1.73 m^2)	Vancomycin dose
0	>90	15–20 mg/kg per 12 h
2	60–89	20–30 mg/kg per 24 h
3A	45–59	15–20 mg/kg per 24 h
3B	30–44	10–15 mg/kg per 24 h
4	15–29	7–10 mg/kg per 24 h
5	<15	10 mg/kg per 48 h

Vancomycin continuous infusion
Loading dose: 15 mg/kg in all patients, with maximum infusion rate of 15 mg/min

Maintaining dose
Infusion rate (g per 24 h)=(0.029 × CrCl (ml/min)+0.94) × target trough level × 24/1000

Abbreviations: CKD, chronic kidney disease; CrCl, creatinine clearance.

In patients undergoing high-flux hemodialysis, 42.7% did not achieve the minimum target of 15 μg/ml when a 1000 mg loading dose followed by 500 mg doses after each hemodialysis session was administered.[14] When a similar schedule was given during the last hour of dialysis, only 12% of patients achieved the minimum target of 15 μg/ml.[15] In an algorithm using a 1000 mg loading dose, followed by a maintenance dose of 1000 mg at trough levels of 0–7.9 μg/ml, 500 mg at trough levels of 8–15.9 μg/ml, or no dose at trough levels of ⩾16 μg/ml, the target trough level of >15 μg/ml was obtained in only 25.2% of patients.[9] The use of fixed doses may be especially problematic in patients with high body mass index and should be discouraged. Target trough levels were more rapidly obtained when a total body weight-based loading dose of 20–25 mg/kg was used instead of a fixed dose of 1000 mg.[14] One additional shortcoming of these algorithms is that they do not account for residual renal function.[9,14,15]

No clear dosing guidelines exist to obtain these higher trough levels during continuous renal replacement therapy.[11] The recommended maintenance doses vary from 500 mg per 24 h to 1500 mg per 48 h.[11]

In conclusion, the new vancomycin trough level target of 15–20 μg/ml is not obtained in the majority of hemodialysis patients with current dosing practices.

NEPHROTOXICITY OF VANCOMYCIN

Vancomycin is generally well tolerated when administered slowly. Vancomycin-related toxicities such as the red man syndrome, agranulocytosis, hypersensitivity reactions, and ototoxicity are rare and have been discussed in other papers.[2] Nephrotoxicity was mainly a concern with early, impure vancomycin preparations (called 'Mississippi mud'). Until recently, many experts considered nephrotoxicity with purified vancomycin as an infrequent (risk of <5%) and reversible event.[3,16] Coadministration of other nephrotoxic medications such as aminoglycosides substantially increases this risk and *vice versa*.[16]

Emerging data, however, suggest higher rates of nephrotoxicity with doses aiming to achieve the currently recommended trough level of 15–20 μg/ml.[2,3,12,17–19] These data are summarized in Table 3. In a prospective analysis of 95 patients treated for invasive MRSA infections, clinical response and mortality were compared for high MIC (⩾2)

Table 3 | Studies evaluating the nephrotoxicity of higher vancomycin doses

	No. of patients	Design	Definition nephrotoxicity	% With nephrotoxicity			Independent risk factor for nephrotoxicity
				Total	Trough <15	Trough ⩾15	
Hidayat *et al.*[12]	95	Prospective cohort study Adult patients with MRSA infusions Vanco for >72 h	↑ creat of 0.5 mg/dl or ⩾50% of baseline	11.6	0	17.4	Concurrent nephrotoxic agents High trough levels Incremental with duration of therapy
Jeffres *et al.*[17]	94	Retrospective hospital-based observational study Adult patients with MRSA health care-associated pneumonia	↑ creat of 0.5 mg/dl or 50% of baseline	42.6	28.9	55.1	High trough levels ⩾14 days of therapy
Ingram *et al.*[18]	102	Retrospective cohort, adult patients with MRSA osteoarticular infections Vanco continuous infusion	↑ creat ⩾50% of baseline	15.7	NA	NA	Steady-state conc>28 Concurrent aminoglycosides, loop diuretics Hypertension
Lodise *et al.*[13,19]	291	Cohort study, 220 patients vanco<4 g per day; 26 patients ⩾4 g per day; 45 patients linezolid	↑ creat of 0.5 mg/dl or ⩾50% of baseline	34.6% in vanco⩾4 g per day 10.9% in vanco<4 g per day 6.7% in linezolid group			Vanco dose ⩾4 g per day CrCl⩽86.6 ml/min Body weight ⩾101.4 kg ICU stay
Lodise *et al.*[3]	166	Retrospective study, vanco>48 h	↑ creat of 0.5 mg/dl or ⩾50% of baseline	12.7	10.1	25.9	Empiric trough value ICU stay
Hutschala *et al.*[21]	149	Retrospective cohort of ICU patients after open-heart surgery; continuous infusion (CI) versus intermittent administration (IA)	↑ creat of ⩾0.3 mg/dl or ⩾50% of baseline, or ↓ in urinary output to <0.5 ml/kg per h for >6 h	29.5 overall 27.7% in CI 36.7% in IA			NA

Abbreviations: CrCl, creatinine clearance; creat, creatinine; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; vanco, vancomycin.

versus low MIC (<2) infections and nephrotoxicity for high (⩾15 μg/ml) versus low (<15 μg/ml) maximum vancomycin trough levels.[12] Nephrotoxicity, defined as a 0.5 mg/dl increase in creatinine or ⩾50% decrease in creatinine clearance (CrCl), occurred in 12% of high vancomycin trough patients and in none of the low vancomycin trough patients.[12] Nephrotoxicity was independently predicted by the vancomycin trough level, the use of concurrent nephrotoxic medication such as aminoglycosides or amphotericin B, and the duration of vancomycin high trough treatment (6.3% if <7 days, 21.1% if 8–14 days, and 30% if >14 days).[12]

In a retrospective observational hospital-based cohort of 94 patients receiving vancomycin treatment, 42.7% of the patients developed nephrotoxicity, defined as a 0.5 mg/dl increase in creatinine or ⩾50% decrease in CrCl.[17] Independent predictors of nephrotoxicity were maximum trough levels of >15 μg/ml and the duration of vancomycin exposure.[17] Mean decline in CrCl in the entire cohort was 13.5 ml/min, with a mean decline of 18.9 ml/min in the group with maximum serum trough levels of ⩾15 μg/ml versus 7.6 ml/min in the group with maximum serum trough levels <15 μg/ml.[17] The subgroup with renal toxicity had a higher hospital mortality (45 versus 15%) and a longer hospital stay (44.8 versus 28.7 days).[17] A recovery to baseline creatinine was observed in 72.5% of the patients who had developed nephrotoxicity.[17]

In a retrospective cohort study of 102 patients receiving vancomycin continuous infusion for mainly osteoarticular infections, 15.7% of the patients developed nephrotoxicity, defined as ⩾50% increase of serum creatinine.[18] Independent risk factors for nephrotoxicity were arterial hypertension (relative risk 5.3), the concurrent use of aminoglycosides (relative risk 6.6) or loop diuretics (relative risk 8.1), and a vancomycin steady-state concentration of >28 μg/ml (relative risk 21.1).[18] In a similar (and overlapping?) study from the same authors comparing outpatient vancomycin continuous infusion with outpatient intermittent administration, an overall nephrotoxicity of 15.6% was found.[20] Although the onset of nephrotoxicity was slower in the continuous infusion group, the ultimate prevalence of nephrotoxicity was identical and associated with cumulative vancomycin exposure.[20]

Another retrospective cohort study compared vancomycin continuous infusion (119 patients) with intermittent administration (30 patients) in intensive care unit patients after elective open-heart surgery.[21] Nephrotoxicity, defined according to the Acute Kidney Injury Network classification as an acute (within 48 h) decrease in kidney function, specified as an increase in serum creatinine of ⩾0.3 mg/dl, an increase in ⩾50% of baseline serum creatinine, or a decrease in urinary output to <0.5 ml/kg per h for >6 h, was observed in 27.7 and 36.7%, respectively, of the patients.[21] This difference was

not significant, and the intermittent administration group tended to have a higher baseline serum creatinine.[21]

In a large cohort study of 291 patients prospectively randomized to linezolid or vancomycin for the treatment of invasive *S. aureus* infections, the risk for nephrotoxicity was retrospectively analyzed.[13] Nephrotoxicity, defined as a 0.5 mg/dl increase in creatinine or $\geqslant$50% decrease in CrCl, was observed in 6.7% of patients receiving linezolid, in 10.7% of those treated with usual doses of vancomycin ($<$4 g per 24 h), and in 34.6% of patients administered high doses of vancomycin ($\geqslant$4 g per 24 h). The differences were highly significant.[19] The median increase in serum creatinine was 0.95 mg/dl. The risk of nephrotoxicity was greater with increasing body weight, intensive care unit stay, and a baseline CrCl $<$ 86.6 ml/min.[19]

Taken together, these studies show an incremental risk of nephrotoxicity associated with higher vancomycin doses, ranging from 12 to 42.7% of patients. The risk increases with higher vancomycin maximum trough levels, longer duration of vancomycin use, concomitant use of other nephrotoxic agents, and in patients who are critically ill or have a previously compromised renal function. Data on the degree of renal recovery are scarce. The vancomycin exposure–nephrotoxicity response relationship is best predicted by vancomycin trough levels, and not by the AUC/MIC.[3] The mechanism of vancomycin toxicity has been unraveled only partially.[2] Animal data suggest that vancomycin stimulates oxidative phosphorylation in renal proximal tubule epithelial cells, thus acting as an oxidative stressor.[3] Severe vancomycin nephrotoxicity may present histologically as a tubulo-interstitial nephritis, sometimes with granulomas.[22]

CONCLUSIONS

Although vancomycin is historically known to have an inferior activity against susceptible staphylococci species compared with β-lactam antibiotics and to have a slow mode of action and a poor tissue penetration, it has been used for decades as one of the main anti-staphylococcal agents.[1] Emerging resistance, mainly in staphylococcal species, urges the implementation of much higher dosing guidelines to obtain an AUC/MIC of $>$400.[2] Data on how to obtain these targets in patients with CKD or on renal replacement therapy are limited. Studies on the optimal dosing strategy for vancomycin in CKD patients and those on dialysis are urgently required. The proposed vancomycin trough target of 15–20 μg/ml engenders an important and incremental risk for nephrotoxicity. Several new drugs for the treatment of serious Gram-positive infections are fortunately available, such as the lipopeptide daptomycin, the oxazolidin linezolid, and the minocycline derivate tigecycline.[1] Other agents are in the pipeline, such as the lipoglycopeptides dalbavancin, telavancin, and oritavancin and the broad-spectrum cephalosporins with good activity against MRSA ceftobiprole and ceftaroline.[1] The exact positioning of these drugs, especially in CKD patients and hemodialysis, however, is not yet clear.

DISCLOSURE

The authors declared no competing interests.

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