Increasing Evidence of the Nephrotoxicity of Piperacillin/Tazobactam and Vancomycin Combination Therapy—What Is the Clinician to Do?

Richard R. Watkins1,2 and Stan Deresinski3
1Division of Infectious Diseases, Cleveland Clinic Akron General, and 2Department of Medicine, Northeast Ohio Medical University, Rootstown; and 3Department of Medicine, Division of Infectious Diseases and Geographic Medicine, Stanford University, California

Early administration of appropriate empiric antibiotics is essential for achieving the best possible outcomes in sepsis. Yet the choice of antibiotic therapy has become more challenging due to recent reports of nephrotoxicity with the combination of vancomycin and piperacillin/tazobactam, the “workhorse” regimen at many institutions. In this article we assess the evidence for nephrotoxicity and its possible mechanisms, provide recommendations for risk mitigation, address the advantages and disadvantages of alternative antibiotic choices, and suggest areas for future research.

Keywords. Sepsis; nephrotoxicity; vancomycin; piperacillin/tazobactam.

Sepsis represents a major threat to human health worldwide. The keys to patient survival in the management of sepsis are rapid recognition, appropriate fluid resuscitation, initiation of empiric antibiotic therapy, and adequate source control [1]. Factors that determine whether an empiric antibiotic regimen is optimal include the potential pathogens, microbiological history, suspected site of infection, local resistance patterns, cost, previous drug exposures, allergies, immune status, appropriate dosing, and comorbid illnesses. A commonly used regimen, vancomycin plus piperacillin/tazobactam, provides a broad spectrum of activity and has been perceived as relatively nontoxic. These characteristics likely account for the fact that the components of the combination ranked first and second among antibiotics administered to critical care patients in 2011 in 1 day prevalence surveys at 183 US hospitals, with vancomycin accounting for 34.9% and piperacillin/tazobactam for 25.6% of administered antibiotics [2]. Although it is likely that vancomycin and piperacillin/tazobactam were frequently administered in combination, this was not reported.

Acute kidney injury (AKI) is common in patients with sepsis and is associated with excess morbidity and mortality. One study documented an AKI incidence of 66% in patients admitted to the intensive care unit (ICU) [3]. Another found that sepsis-related AKI causes greater aberrations in hemodynamics and laboratory parameters, greater severity of illness, and higher need for mechanical ventilation and vasoactive therapy compared to nonseptic AKI [4]. AKI may be a consequence of sepsis itself or from therapeutic interventions including medications. Antimicrobials are high on the list of implicated drugs with the main offenders including acyclovir, amphotericin B, aminoglycosides, vancomycin, and the polymyxins [5].

The potential nephrotoxicity of vancomycin has long been recognized and was initially the result of impurities in early formulations of “Mississippi mud”—so-called because of the brown color of IV products at the time [6]. The introduction of the semisynthetic penicillins in the early 1960s led to a steep decline in vancomycin usage. However, the emergence of the methicillin-resistant Staphylococcus aureus (MRSA) epidemic in the 1990s saw a resurgence of vancomycin in hospitalized patients and, with it, increased recognition of the nephrotoxicity of modern IV formulations of vancomycin [7]. Risk factors for vancomycin-associated nephrotoxicity include high trough levels (especially >20 mg/L) or doses (>4 g/day), concurrent treatment with nephrotoxic agents, therapy > 7 days, severity of illness, history of kidney disease, and admittance to the ICU [8]. The mechanism of vancomycin-induced nephrotoxicity is uncertain and inadequately studied but may be related to injury to proximal tubule cells, with some evidence of interstitial nephritis [9]. The risk of nephrotoxicity is increased 3- to 4-fold when vancomycin is combined with aminoglycosides and other nephrotoxic agents [10]. Moreover, the risk of vancomycin-associated AKI is exposure-dependent. Although estimation of vancomycin area under the curve (AUC) using Bayesian inputs is more predictive of actual exposure (and efficacy) than is measurement of trough concentrations (Cmin), the latter are widely used for this purpose [11]. While the target trough concentration for some infections is 10–15 µg/mL, for serious infections...
(e.g., infections due to MRSA), current guidelines recommend trough concentrations of 15–20 µg/mL [12]. However, even when the trough is maintained within these ranges, multiple studies have reported an increase in the risk of AKI [13–15]. This may be related, at least in part, to reliance on trough vancomycin concentrations, which results in underestimation of AUC by a mean of 23%, thus leading to overdosing [11].

Piperacillin/tazobactam, like most beta-lactams, rarely causes AKI and according to the package insert, the incidence of nephrotoxicity is less than 1% [16]. In most instances the underlying pathophysiology is believed to be the development of acute interstitial nephritis [17, 18], although additional exogenous factors may contribute. Further investigation of how piperacillin/tazobactam leads to AKI is needed.

**VANCYMYCIN AND PIPERACILLIN/TAZOBACTAM ASSOCIATED NEPHROTOXICITY**

The risk of AKI from vancomycin and piperacillin/tazobactam (VPT) was first reported in 2 abstracts in 2011 [19, 20]. Although more robust evidence has subsequently emerged, no randomized clinical trial (RCT) results have been reported. A recent meta-analysis by Hammond et al. that included 14 studies reported that, in a comparison of VPT with vancomycin and “any beta-lactam,” the adjusted odds ratio (OR) for AKI in adults was 3.15 (95% confidence interval [CI], 1.72–5.76) and in children it was 4.55 (95% CI, 2.71–10.21) [21] (Table 1). The highest incidence of VPT-associated AKI was found among patients admitted to the ICU for whom the OR was 3.83 (95% CI, 1.67–8.78; P = .002). However, considerable statistical heterogeneity was found among the studies (I² = 78.1%), and only 8 of the 14 were of good quality. None of the studies reported concurrent use of other antibiotics such as aminoglycosides, which could have substantially magnified the risk for AKI. Indeed, the combination of VPT and an aminoglycoside is often used in ICUs and is one of the suggested empiric treatment options in the ventilator-associated pneumonia guidelines when empiric MRSA and double antipseudomonal/gram-negative coverage is deemed appropriate [22]. Another meta-analysis by Giuliano et al. included 15 observational cohort studies, 7 of which were included in the Hammond et al. study [23]. These investigators also found a significant risk for AKI with VPT compared to vancomycin with or without another beta-lactam (OR, 3.649, 95% CI, 2.157–6.174; I² = 83.5%; P < .001). Moreover, the association remained significant when VPT was compared to vancomycin alone (OR, 3.980, 95% CI, 2.749–5.763; I² = 31.4%; P < .001). Of importance is that, with limited exception, the available studies did not provide information regarding the severity or persistence of AKI nor the resultant need for renal replacement therapy.

One alternative regimen for broad-spectrum empiric coverage of sepsis is vancomycin and cefepime (VC). Several reports have compared the risk of developing AKI between VPT and VC [24–29] with most finding a greater risk among those who received VPT [24–28]. None of the studies, however, was an RCT, only one was prospective [28], and all the rest were retrospective cohort studies, the limitations of which (e.g., confounding by unmeasured variables) are well-known. Only one study failed to detect a significant difference between the 2 groups, perhaps because of the relatively small sample size [29]. Also strengthening the specific association of VPT with nephrotoxicity was the finding of Navalkele et al. that the onset of AKI was more rapid in patients who received VPT (median duration 3 days, interquartile range [IQR], 2–5 days) compared to VC (median duration 5 days, IQR, 3–7 days) [24]. Another study showed the highest daily incidence of AKI occurred on day 5 of VPT therapy [50]. It therefore seems logical that one way to reduce the risk of AKI with VPT is early and repeated reassessment of the regimen with a goal of de-escalation.

Two additional studies further strengthen the specificity of the association of VPT with the occurrence of AKI. Sanz et al. found no difference in severe nephrotoxicity between patients who received the aminoglycoside amikacin with piperacillin/tazobactam compared to those who received amikacin with cefepime [30]. Rutter and Burgess found that VPT administration was associated with an increased likelihood of AKI compared with piperacillin/tazobactam alone (adjusted odds ratio [aOR], 1.77, 95% CI, 1.26–2.46) and, furthermore, that the administration of ampicillin/sulbactam with vancomycin was not associated with a significant increase in AKI compared with ampicillin/sulbactam monotherapy (aOR, 1.01, 95% CI, 0.48–1.97) [31].

**POSSIBLE MECHANISMS OF NEPHROTOXICITY**

Although the mechanism for the development of AKI with VPT therapy is not understood, some hypotheses have been proposed. One is that renal injury may occur as a result of subclinical interstitial nephritis caused by piperacillin/tazobactam that is augmented by the oxidative stress induced by vancomycin [27]. Another is that piperacillin/tazobactam might decrease the clearance of vancomycin, leading to its accumulation within the nephron [30, 32]. There is, however, no experimental evidence to support these hypotheses. Using a multiple effects model, Jensen et al. observed that piperacillin/tazobactam exposure in patients with sepsis-related renal dysfunction is associated with a lower rate of glomerular filtration rate (GFR) improvement compared with other antibiotics and that renal function improves rapidly after discontinuation of the drug [33]. The use and type of fluid resuscitation given with VPT might also negatively impact renal function. For example, a recent report by Erdman et al. showed concurrent administration of continuous intravenous 3% hypertonic saline with piperacillin/tazobactam to be an independent predictor of AKI (OR, 3.9, 95% CI, 1.7–9.3; P = .002) [34]. Further studies are needed to confirm this observation.
There was considerable variability among the previously mentioned studies in the results of their assessment of factors known to increase the risk of AKI, some of which were elevated vancomycin troughs, baseline renal failure, concurrent nephrotoxic agents, time in the ICU, comorbid illnesses, and duration of therapy. Furthermore, many had small sample sizes and were thus underpowered, and almost all were retrospective. It is possible that patients who received VPT were simply sicker and therefore more susceptible to AKI. Again, prospective RCTs are needed to help clarify this issue.

### Table 1. Studies on Nephrotoxicity from Vancomycin-Piperacillin/Tazobactam

<table>
<thead>
<tr>
<th>Authors, Year and Reference</th>
<th>Type of Study</th>
<th>Quality</th>
<th>Main Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hammond et al., 2017 [21]</td>
<td>Meta-analysis of 14 observational studies (n = 3549)</td>
<td>Good</td>
<td>VPT was more associated with AKI compared to vancomycin without PT (aOR, 3.11; 95% CI, 1.77–5.47)</td>
<td>Included studies on adults and children</td>
</tr>
<tr>
<td>Giuliano et al., 2016 [23]</td>
<td>Meta-analysis of 15 observational studies (n = 3256)</td>
<td>Good</td>
<td>Risk for AKI with VPT was higher compared to vancomycin alone (OR, 3.649; 95% CI, 2.157–6.174)</td>
<td>Many of the same studies were included in the above meta-analysis</td>
</tr>
<tr>
<td>Navsikele et al., 2017 [24]</td>
<td>Retrospective matched cohort (n = 558)</td>
<td>Good</td>
<td>AKI rate was higher with VPT (81/279, 29%) vs. VC (32/279, 11%)</td>
<td>Showed more rapid onset of AKI with VPT (3 days) vs. VC (5 days)</td>
</tr>
<tr>
<td>Rutter et al., 2017 [25]</td>
<td>Retrospective matched cohort (n = 4103)</td>
<td>Good</td>
<td>VPT was 2.18 times more likely to cause AKI vs. VC (95% CI, 1.64–2.94)</td>
<td>Vancomycin doses between 3 and 4 g daily also increased the risk for AKI</td>
</tr>
<tr>
<td>Moenster et al., 2014 [26]</td>
<td>Retrospective unmatched cohort (n = 139)</td>
<td>Moderate</td>
<td>No significant difference in AKI between VPT and VC in patients with osteomyelitis</td>
<td>Study was underpowered</td>
</tr>
<tr>
<td>Gomes et al., 2014 [27]</td>
<td>Retrospective matched cohort (n = 224)</td>
<td>Good</td>
<td>AKI rate was significantly higher for VPT group vs. VC (OR, 5.67; 95% CI, 1.66–19.33)</td>
<td>More pharmacist pharmacokinetic management with VPT group than with VC group</td>
</tr>
<tr>
<td>Peyko et al., 2017 [28]</td>
<td>Prospective observational cohort (n = 85)</td>
<td>Poor</td>
<td>Higher incidence of AKI with VPT (37.3%) vs. VC or vancomycin and meropenem (77.7%; P = .005)</td>
<td>Single center study; vancomycin duration not provided</td>
</tr>
<tr>
<td>Hammond et al., 2018 [29]</td>
<td>Retrospective unmatched cohort (n = 122)</td>
<td>Moderate</td>
<td>No difference in AKI or secondary outcomes between VPT and VC (P = .647)</td>
<td>Patients from ICUs at a single institution; group assignment was not random and may have led to confounding</td>
</tr>
<tr>
<td>Rutter and Burgess, 2017 [31]</td>
<td>Retrospective matched cohort (n = 2448)</td>
<td>Good</td>
<td>VPT increased the risk for AKI (aOR, 1.77; 95% CI, 1.26–2.48) but vancomycin and AS did not</td>
<td>Rates of AKI were similar for PT and AS without vancomycin</td>
</tr>
<tr>
<td>Burgess and Drew, 2014 [32]</td>
<td>Retrospective matched cohort (n = 191)</td>
<td>Moderate</td>
<td>Increased incidence of AKI with VPT compared to vancomycin alone (aOR, 2.48; 95% CI, &gt; 1.11)</td>
<td>Vancomycin trough ≥15 mg/L increased risk for AKI (OR, 3.67; 95% CI, 1.49–9.03)</td>
</tr>
<tr>
<td>Mousavi et al., 2017 [48]</td>
<td>Retrospective matched cohort (n = 280)</td>
<td>Good</td>
<td>No difference in rate of AKI with vancomycin plus standard infusion PT vs. extended infusion PT</td>
<td>Higher vancomycin troughs were observed in the extended infusion group</td>
</tr>
<tr>
<td>Davies et al., 2016 [52]</td>
<td>Retrospective unmatched cohort (n = 530)</td>
<td>Good</td>
<td>VPT did not increase the risk for AKI compared to vancomycin alone (RR, 1.1; 95% CI, 0.99–1.2)</td>
<td>When PT was discontinued, AKI resolved more rapidly compared to other antibiotic combinations</td>
</tr>
<tr>
<td>Fodero et al., 2016 [53]</td>
<td>Retrospective unmatched cohort (n = 453)</td>
<td>Good</td>
<td>VPT was an independent risk factor for AKI (OR, 3.21; 95% CI, 1.43–7.96)</td>
<td>Implementation of an ASP decreased overall risk for AKI</td>
</tr>
<tr>
<td>Kim et al., 2019 [54]</td>
<td>Retrospective matched cohort (n = 228)</td>
<td>Moderate</td>
<td>Odds of AKI with VPT were higher than with vancomycin alone (OR, 0.178; 95% CI, 0.058–0.544)</td>
<td>Vancomycin duration and trough data not reported</td>
</tr>
<tr>
<td>Sutton et al., 2015 [55]</td>
<td>Retrospective matched cohort (n = 292)</td>
<td>Good</td>
<td>VPT predicted an increased risk for AKI (OR, 5.17; 95% CI, 2.29–11.68)</td>
<td>Study investigated risk of AKI between 2 different vancomycin products and found no difference</td>
</tr>
<tr>
<td>Knoderer et al., 2015 [56]</td>
<td>Retrospective unmatched cohort (n = 167)</td>
<td>Moderate</td>
<td>VPT was an independent risk factor for AKI (OR, 2.61; 95% CI, 1.02–6.70)</td>
<td>Pediatric study; also showed increased risk of AKI with acyclovir and amphotericin</td>
</tr>
<tr>
<td>Meaney et al., 2014 [57]</td>
<td>Retrospective unmatched cohort (n = 129)</td>
<td>Moderate</td>
<td>VPT was associated with AKI (aOR, 5.36; 95% CI, 1.41–20.5)</td>
<td>Wide confidence interval</td>
</tr>
<tr>
<td>McQueen et al., 2016 [58]</td>
<td>Retrospective unmatched cohort (n = 185)</td>
<td>Moderate</td>
<td>Having a higher vancomycin trough ≥15 mg/L increased the risk of AKI with VPT (RR, 5.22; 95% CI, 2.407–11.306, P &lt; .0001)</td>
<td>Uneven group sizes may have influenced results (vancomycin n = 79 vs. VPT n = 109)</td>
</tr>
<tr>
<td>Jeon et al., 2017 [59]</td>
<td>Retrospective matched cohort (n = 5335)</td>
<td>Good</td>
<td>VPT was associated with a higher risk of AKI (aOR, 1.25; 95% CI, 1.11–1.42)</td>
<td>Large sample size</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; AS, ampicillin/sublactam; ASP, antibiotic stewardship program; CI, confidence interval; ICU, intensive care unit; PT, piperacillin/tazobactam; RR, relative risk; VC, vancomycin and cefepime; VPT, vancomycin and piperacillin/tazobactam

aIn the absence of randomized trials, our assessment of the quality of the observational studies was based on the size and completeness of description of the cohorts, the presence or absence of matching and the completeness of the treatment information.
**POTENTIAL STRATEGIES TO REDUCE NEPHROTOXICITY RISK**

**Alternative Antibiotic Combinations**

An obvious approach to avoid the apparent nephrotoxicity associated with VPT is the substitution of an alternative antibiotic for either or both components. Potential substitutes for vancomycin include the oxazolidinones, lipoglycopeptides, and daptomycin. The oxazolidinones, linezolid and tedizolid, are not nephrotoxic and extend the Gram-positive spectrum to include vancomycin-resistant enterococci (VRE), but their use may be precluded in some cases by the potential of drug interactions. Furthermore, in some limited circumstances, their bacteriostatic nature may be a drawback. Among the lipoglycopeptides, telavancin is likely to be an effective substitute for vancomycin (although empiric data remain limited), but its potential for nephrotoxicity does not solve the problem at hand [35]. The extraordinary long half-lives of dalbavancin and oritavancin (together with the lack of data in this setting) make them inappropriate choices for empiric therapy, which, almost by definition, is likely to require alteration. Daptomycin is not nephrotoxic and, like the oxazolidinones (and oritavancin), extends the spectrum to include VRE [36]. It is, however, ineffective in the treatment of pneumonia because of its inactivation by pulmonary surfactant and its use is further restricted because of its current extraordinary cost, especially at the high doses now in widespread use. As with other antimicrobials, the pharmacokinetics of daptomycin are altered and variable in critically ill patients with sepsis, a finding that has led to a recommendation for therapeutic drug monitoring [37], which, unfortunately, is not available to most clinicians.

The usual alternatives to piperacillin/tazobactam in critical care patients at most US hospitals include an anti-pseudomonal β-lactam (e.g., cefepime or ceftazidime) or a carbapenem, antibiotics with broad and overlapping coverage of Gram-negative pathogens. The choice among these should be informed by local pathogen susceptibility. Thus, although the rates of antibiotic resistance to cefepime and piperacillin/tazobactam in *Pseudomonas aeruginosa* are generally similar, patterns may vary in different regions or even locally [38]. If the institutional (or, preferably, unit) antibiogram shows high levels of susceptibility of Gram-negative pathogens to cefepime, then it would be a reasonable choice for pairing with vancomycin or one of its alternatives. However, if piperacillin/tazobactam administration appears to be indicated, then using it along with an alternative Gram-positive drug (e.g., linezolid) may avert the nephrotoxicity associated with VPT. Carbapenems have the advantage of activity against extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, widely recognized as an emerging threat in both the hospital and community [39]. However, a retrospective cohort study by Ng et al. found that, although 30-day mortality was similar in a comparison of patients who received empiric piperacillin/tazobactam or a carbapenem (29 [30.9%] vs. 17 [29.8%]), P = 0.89, those who received empiric piperacillin/tazobactam had a lower 30-day acquisition of multidrug resistant (MDR) and fungal infections (7 [7.4%] vs. 14 [24.6%]), P < 0.01) [40]. A carbapenem is a reasonable empiric choice for patients with sepsis who have risk factors for infection with ESBL-producing organisms, which are reported to include having had an outpatient procedure within 1 month, prior infections or colonization with ESBL-producing *Enterobacteriaceae* within 12 months, and the number of prior courses of β-lactams and/or fluoroquinolones used within 3 months [41]. One concern with carbapenem use is that it may facilitate the emergence and spread of carbapenem-resistant *Acinetobacter baumannii* [42] and of carbapenem-resistant *Enterobacteriaceae*. A combination of ceftaroline plus an antipseudomonal fluoroquinolone or an aminoglycoside also provides broad coverage, but there are no published clinical data supporting this approach. Finally, ceftazidime/avibactam and ceftolozane/tazobactam, which are likely to be effective for sepsis, are best reserved at this time to limited circumstances requiring their use in order to maintain their effectiveness against MDR infections [43, 44].

In consideration of the appropriate response to the problem of VPT related toxicity, it is necessary to recognize that heterogeneity of antibiotic use (antibiotic “mixing”) may be important in limiting the emergence of antibiotic resistance. Heterogeneity involves using all reasonable antibiotic classes, determined by infection source and antimicrobial surveillance data, in a diverse way among patients in particular wards and throughout the institution [45]. Although empiric evidence is insufficient to demonstrate its unequivocal benefit, the theoretical basis of this approach is strong and must be considered.

**Early Reassessment of Empiric Therapy: Antibiotic Time-Outs**

The availability of microbiological information, as well as observation of the patient's clinical course, allows for critical reassessment of the initial empiric regimen. Although a formal antibiotic time-out to make this assessment is recommended to be performed at 48–72 hours, this process should be carried out on at least a daily basis [1]. Such reevaluations may provide the opportunity to discontinue piperacillin/tazobactam with the intention of avoiding the nephrotoxicity associated with VPT use. However, the finding in one study that the median duration of VPT before onset of AKI is 3 days [24] means that, although an early antibiotic timeout with regimen alteration is likely to reduce VPT nephrotoxicity, half of the episodes of AKI will have already occurred by 72 hours, the time when sufficient information is usually available to make such changes. Nonetheless, nephrotoxicity continues to occur throughout therapy, with a reported peak incidence among those remaining at risk at day 5, thus indicating that benefit may result from alteration of therapy at any time prior to the onset of AKI.
Increasing Evidence of Nephrotoxicity of Piperacillin/Tazobactam and Vancomycin Combination Therapy

CONCLUSIONS

Although no prospective randomized trials have been reported, the accumulating evidence is increasingly consistent with the conclusion that treatment with VPT is associated with an excess incidence of AKI relative to the use of other β-lactams in combination with vancomycin. It is critical that a definitive prospective randomized trial is performed that unequivocally resolves this issue.

In the meantime, besides dealing with other modifiable risk factors for AKI, it is necessary to consider alternative or mitigating therapeutic approaches to what has become, for many clinicians, a reflexive use of VPT for empiric therapy. Two examples of its frequent inappropriate use are most cases of community-acquired pneumonia and cellulitis. We believe that in order to maintain heterogeneity of antibiotic use, VPT should be continued among the choices of empiric therapy but at a significantly decreased frequency. For most patients in whom antibiotic resistance is a concern, other effective empiric regimens include vancomycin plus either an antipseudomonal cephalosporin (preferably cefepime) or an antipseudomonal carbapenem. If infection with VRE is a concern, linezolid or daptomycin may be used. This should be followed by daily reassessment of whichever antibiotic regimen is chosen. If vancomycin or linezolid is administered for fear of MRSA pneumonia, it can rapidly (within hours) be discontinued if nasal colonization is absent or, in the absence of nasal testing, if the respiratory specimen does not yield MRSA. If a Gram-negative pathogen is isolated and the organism is susceptible to an alternative nontoxic agent, it may be substituted for piperacillin/tazobactam. Finally, the multiple decision points in choosing empiric antibiotic therapy in sepsis indicate a need for intense surveillance by antimicrobial stewardship programs to optimize patient outcomes.

Note

Potential conflicts of interest. R. R. W. has received research grant support and serves on an advisory committee for Allergan. S. D. has no reported disclosures. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Table 2. Suggested Approaches to Decrease Risk of Nephrotoxicity with Vancomycin-Piperacillin/Tazobactam

- Avoid coadministration of other nephrotoxic agents
- Avoid dehydration
- Avoid vancomycin loading dose when not indicated
- If available, adjust doses based on estimates of vancomycin exposure using Bayesian inputs
- Avoid unnecessarily prolonged administration of VPT
- Close monitoring of renal function
- Early and repeated reassessments of empiric antibiotic therapy with appropriate alterations
- Consider use of daptomycin (in absence of pneumonia) or linezolid in place of vancomycin
- Use alternatives to piperacillin/tazobactam such as cefepime or an anti-pseudomonal carbapenem

Abbreviation: VPT, vancomycin/piperacillin-tazobactam.

Avoiding Concurrent Nephrotoxic Agents

When VPT is administered for sepsis, great care should be taken to avoid concurrent exposure to known nephrotoxic agents. Karino et al. reported that receiving any nephrotoxin while on VPT was an independent risk factor for AKI (OR, 2.44; 95% CI, 1.41 to 4.22) [50]. In another analysis of VPT and concurrent nephrotoxic use, multivariate logistic regression found the following drugs increased the risk for AKI: ACE inhibitors, amphotericin B, tacrolimus, loop diuretics, and tenofovir [51]. Other strategies to lessen the risk of AKI while on VPT, especially for patients in the ICU, include avoiding intravenous contrast agents, maintenance of adequate hydration, and daily monitoring of renal function (Table 2).

Extending Infusion Time?

The use of extended infusion (EI) protocols for piperacillin/tazobactam in order to optimize pharmacodynamic parameters has been adopted in many hospitals. The safety of EI compared to standard infusion (SI) of piperacillin/tazobactam when combined vancomycin was evaluated by Mousavi et al. in a retrospective cohort study [48]. Using 2 different scoring criteria for nephrotoxicity (RIFLE and AKIN), they found that the rate of AKI was similar with both dosing methods. Another cohort study presented in abstract form at 2015 IDWeek using the RIFLE criteria found AKI occurred in 52 (32.5%) of patients when VPT is administered for sepsis, great care should be taken to avoid concurrent exposure to known nephrotoxic agents. Karino et al. reported that receiving any nephrotoxin while on VPT was an independent risk factor for AKI (OR, 2.44; 95% CI, 1.41 to 4.22) [50]. In another analysis of VPT and concurrent nephrotoxic use, multivariate logistic regression found the following drugs increased the risk for AKI: ACE inhibitors, amphotericin B, tacrolimus, loop diuretics, and tenofovir [51]. Other strategies to lessen the risk of AKI while on VPT, especially for patients in the ICU, include avoiding intravenous contrast agents, maintenance of adequate hydration, and daily monitoring of renal function (Table 2).

Avoiding Concurrent Nephrotoxic Agents

When VPT is administered for sepsis, great care should be taken to avoid concurrent exposure to known nephrotoxic agents. Karino et al. reported that receiving any nephrotoxin while on VPT was an independent risk factor for AKI (OR, 2.44; 95% CI, 1.41 to 4.22) [50]. In another analysis of VPT and concurrent nephrotoxic use, multivariate logistic regression found the following drugs increased the risk for AKI: ACE inhibitors, amphotericin B, tacrolimus, loop diuretics, and tenofovir [51]. Other strategies to lessen the risk of AKI while on VPT, especially for patients in the ICU, include avoiding intravenous contrast agents, maintenance of adequate hydration, and daily monitoring of renal function (Table 2).

Table 2. Suggested Approaches to Decrease Risk of Nephrotoxicity with Vancomycin-Piperacillin/Tazobactam

- Avoid coadministration of other nephrotoxic agents
- Avoid dehydration
- Avoid vancomycin loading dose when not indicated
- If available, adjust doses based on estimates of vancomycin exposure using Bayesian inputs
- Avoid unnecessarily prolonged administration of VPT
- Close monitoring of renal function
- Early and repeated reassessments of empiric antibiotic therapy with appropriate alterations
- Consider use of daptomycin (in absence of pneumonia) or linezolid in place of vancomycin
- Use alternatives to piperacillin/tazobactam such as cefepime or an anti-pseudomonal carbapenem

Abbreviation: VPT, vancomycin/piperacillin-tazobactam.

CONCLUSIONS

Although no prospective randomized trials have been reported, the accumulating evidence is increasingly consistent with the conclusion that treatment with VPT is associated with an excess incidence of AKI relative to the use of other β-lactams in combination with vancomycin. It is critical that a definitive prospective randomized trial is performed that unequivocally resolves this issue.

In the meantime, besides dealing with other modifiable risk factors for AKI, it is necessary to consider alternative or mitigating therapeutic approaches to what has become, for many clinicians, a reflexive use of VPT for empiric therapy. Two examples of its frequent inappropriate use are most cases of community-acquired pneumonia and cellulitis. We believe that in order to maintain heterogeneity of antibiotic use, VPT should be continued among the choices of empiric therapy but at a significantly decreased frequency. For most patients in whom antibiotic resistance is a concern, other effective empiric regimens include vancomycin plus either an antipseudomonal cephalosporin (preferably cefepime) or an antipseudomonal carbapenem. If infection with VRE is a concern, linezolid or daptomycin may be used. This should be followed by daily reassessment of whichever antibiotic regimen is chosen. If vancomycin or linezolid is administered for fear of MRSA pneumonia, it can rapidly (within hours) be discontinued if nasal colonization is absent or, in the absence of nasal testing, if the respiratory specimen does not yield MRSA. If a Gram-negative pathogen is isolated and the organism is susceptible to an alternative nontoxic agent, it may be substituted for piperacillin/tazobactam. Finally, the multiple decision points in choosing empiric antibiotic therapy in sepsis indicate a need for intense surveillance by antimicrobial stewardship programs to optimize patient outcomes.

Note

Potential conflicts of interest. R. R. W. has received research grant support and serves on an advisory committee for Allergan. S. D. has no reported disclosures. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.
References


