Nephrotoxicity from Vancomycin Combined with Piperacillin-Tazobactam: A Comprehensive Review

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Keywords

Acute kidney injury · Drug toxicity · Antimicrobial toxicity · Drug interaction · Piperacillin-tazobactam · Vancomycin

Abstract

Background: Recent studies have identified the combination of vancomycin with piperacillin-tazobactam (VPT) to be associated with increased nephrotoxicity. Multiple, large cohort studies have found this widely used combination to have a higher risk of nephrotoxicity than other regimens in a variety of populations. **Summary:** This review summarizes the epidemiology and clinical features of VPT-associated acute kidney injury (AKI). Potential mechanisms involved in the pathogenesis of this phenomenon are also discussed. **Key Message:** VPT-associated nephrotoxicity is a recently recognized clinical entity. Clinical strategies to minimize the risk of toxicity in this setting include antimicrobial stewardship, monitoring of kidney function, and emerging data supporting the potential role for novel biomarkers in predicting and managing AKI.

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Introduction

Nephrotoxicity is a well-described complication of vancomycin therapy, and vancomycin-associated nephrotoxicity (VAN) occurs in up to 10% of patients treated with standard dosing [1]. Recent studies have found that treatment with the combination of vancomycin and piperacillin-tazobactam (VPT) is associated with a 2-fold increase in the incidence of acute kidney injury (AKI) [2], occurring in 22.2% for VPT as opposed to 12.9% for other antibiotic combinations with vancomycin in a recent meta-analysis [3]. The pathogenesis of this VPT-associated nephrotoxicity remains uncertain but may be a synergistic phenomenon since piperacillin-tazobactam alone has negligible nephrotoxicity. Despite mounting evidence of nephrotoxicity associated with VPT, this relatively inexpensive combination with broad-spectrum activity remains widely used in hospitalized patients. Furthermore, it is still uncertain whether the association between AKI and VPT is a reflection of the increased severity of illness and AKI risk of patients in whom it is prescribed or rather due to a true synergistic nephrotoxicity. The purpose of this review is to describe the most

recent evidence concerning the epidemiology and potential underlying causes of this phenomenon and to make recommendations for the selection, monitoring, and management of patients treated with the combination of vancomycin and PT.

Epidemiology of VPT-Associated AKI

PT alone is rarely associated with AKI. Most case reports suggest that acute interstitial nephritis (AIN) is the most common cause [4, 5]. Although PT has been approved since 1993 in the United States, concerns of an increased risk of AKI when combined with vancomycin were only reported from 2011 [6]. This delay, despite the widespread use, could be explained by the following: (1) there is a confirmed potential toxicity for these 2 agents when used separately (i.e., AIN and VAN), (2) patients who receive the combination of VPT often have risk factors (e.g., sepsis) known to be associated with AKI [7] and (3) large cohort studies were required to identify this potentially synergistic nephrotoxic effect [2, 6, 8]. In recent years, case reports of this phenomenon of nephrotoxicity with VPT have been followed by cohort studies, systematic reviews, and meta-analyses (Table 1).

Comparison of VPT with Alternative Vancomycin-Beta-Lactam Combinations

Multiple observational cohort studies have compared the risk of AKI with VPT against vancomycin combination with alternative broad-spectrum beta-lactams (cephalosporins or carbapenems), potentially reducing the confounding effects of comparing monotherapy with combination therapy [9–19]. In 2 recent studies comparing patients treated with VPT to a vancomycin-meropenem combination, the odds ratios for developing AKI were increased 6.8-fold (95% CI 1.5–30.9) [13] and 2.53-fold (95% CI 1.82–3.52) [20] in the VPT group, compared to those receiving a vancomycin-meropenem combination, respectively [13, 20]. Similarly, in a cohort of ICU patients, exposure to VPT was an independent predictor of AKI when compared to either vancomycin-meropenem or vancomycin-cefepime (VC; odds ratio: 2.16; 95% CI 1.62–2.88) [11]. Cohort studies comparing VPT to VC had similar findings [12, 15, 16, 19]. Although most of these observational studies have been retrospective in design, there are 2 recently published prospective observational studies on this topic which may have accounted for AKI risk factors more comprehensively by comparing dual-therapy regimens. In 242 patients exposed to antibiotics for at least 72 h, patients given VPT were more likely to develop AKI compared with those receiving a com-

bination of vancomycin plus either cefepime or meropenem (OR 6.65, 95% CI 2.79–15.84, $p < 0.001$). The second prospective study reported similar findings in a small cohort with an AKI incidence of 37.3% in the VPT group versus 7.7% in the vancomycin plus cefepime-or-meropenem group ($p = 0.005$). However, the authors failed to report duration of vancomycin treatment and timing of AKI, so a temporal relationship of AKI to VPT therapy is difficult to ascertain [21]. Taken together, this observational literature demonstrates a consistently higher incidence of AKI in patients receiving vancomycin with PT, compared to combinations of vancomycin with other broad-spectrum agents (carbapenems and cephalosporins). Although the comparator cohorts are less likely to be confounded by greater severity of illness and AKI risk, because of the use of combination therapy in all groups, superior data from randomized controlled trials are lacking.

Insights from Pediatric Studies

Although pediatric patients have different underlying etiologies and chronic comorbidities from adult populations, acutely ill children are also at increased risk of AKI, and data on VPT nephrotoxicity in pediatric patients are similar [22–25]. In a retrospective matched-cohort study (1:1) of 228 children receiving VPT or VC, the AKI incidence (KDIGO criteria) was 28.9% in patients exposed to VPT, compared to 7.9% in the group receiving the cefepime combination ($p < 0.001$). After adjusting for age, sex, concomitant nephrotoxins, vancomycin dose, and antibiotic indication, the hazard ratio to develop AKI when treated with VPT was 2.9 (95% CI 1.3–6.1) [23]. Studies in cystic fibrosis [26] and hematology/oncology patients [27] yielded similar results. However, 2 large studies in critically ill children had conflicting results. In a study involving 1,915 children receiving vancomycin and a beta-lactam during their ICU hospitalization, 8.2% had antibiotic-associated AKI. After adjustment for age, level of care, receipt of nephrotoxins, and hospital center, VPT was associated with higher odds of AKI compared with vancomycin plus either meropenem, imipenem/cilastatin, cefepime, or ceftazidime (OR: 3.40; 95% CI 2.26–5.14) [24]. In contrast, in a study of 5,686 children hospitalized in pediatric ICUs, 785 children treated with VPT were compared to 265 children treated with VC within the first 48 h of ICU admission [28]. Although the incidence of stage 2 or 3 AKI (KDIGO) in the VPT group was significantly higher (16.7%) compared to the cefepime group (10.6%, $p = 0.02$), the adjusted odds ratio for AKI risk did not reach the level of significance (OR: 1.38, 95%

Table 1. Published meta-analyses on the association between the combination of VPT and the risk of AKI

Authors [Ref.]	Studies included (total), <i>n</i>	Patients (total), <i>n</i>	Main results on the risk of AKI, adjusted odd ratio (95% CI)	Authors' conclusion
Giuliano et al. [31]	15	3,258	VPT versus V + BL: 3.65 (2.16–6.17) VPT versus V: 3.98 (2.75–5.77) VPT versus V + BL ¹ : 3.03 (0.94–9.74)	VPT was associated with an increased risk of AKI compared with V ± β-lactam
Hammond et al. [35]	14	3,549	VPT versus V + BL: 3.11 (1.77–5.47) VPT versus V: 2.50 (0.41–15.44)	Increased AKI with concomitant VPT should be considered when determining β-lactam therapy
Mellen et al. [32]	6	963	VPT versus V + BL or V: 2.26 (1.41–3.63)	Adding PT to V increases the risk of nephrotoxicity when compared to V alone or V with either cefepime or meropenem
Chen et al. [30]	8	10,727	VPT versus V + BL: 1.57 (1.13–2.01) VPT versus V + BL: ¹ 1.49 (1.06–1.92)	Regarding β-lactam therapy in clinical practice, an elevated risk of AKI due to the combined use of V and PT should be considered
Luther et al. [3]	32	24,799	VPT versus V + BL: 2.68 (1.83–3.91) VPT versus V: 3.40 (2.57–4.50) VPT versus PT: 2.70 (1.97–3.69) VPT versus V + BL: ² 1.43 (0.83–2.47)	The combination of V plus PT increased the odds of AKI over V monotherapy, PT monotherapy and V plus cefepime or carbapenem
Ciarambino et al. [33]	6	9,672	VPT versus V: 2.77 (1.94–3.96)	Association of V and PT appears to be associated with greater risk of AKI compared to V in monotherapy
Bellos et al. [34]	47	56,984	VPT versus V: 2.05 (1.17–3.46) VPT versus VC: 1.80 (1.13–2.77) VPT versus VM: 1.84 (1.02–3.10) VPT versus V: ³ 4.18 (1.01–17.29) VPT versus VC: ³ 3.71 (1.08–11.24)	The combination of V and PT is associated with higher AKI rates than its parallel use with meropenem or cefepime

VPT, vancomycin-piperacillin-tazobactam; AKI, acute kidney injury; V, vancomycin; PT, piperacillin-tazobactam; BL, beta-lactams; VC, vancomycin-cefepime; VM, vancomycin-carbapenem. ¹ When abstracts and low-quality studies were removed. ² Subanalysis of 968 critically ill ICU patients. ³ Subanalysis of pediatric patients.

CI 0.85–2.24) [28]. Duration of exposure to agents was not reported, and as short course therapy has been associated with lower rates of AKI [29], it is plausible this may have affected the results. In summary, there is consistent observation of VPT carrying a 2–3 fold higher risk of AKI in various pediatric populations, as in adults, compared to other dual regimens.

Combining the Evidence: Meta-Analyses

Although the recognition of VPT nephrotoxicity is a relatively new development, the clinical importance of the phenomenon and the widespread use of the antibiotic combination have led to the conduct of numerous observational studies, and more recently, multiple meta-analyses. To date, at least 7 meta-analyses have been published on the relationship between VPT and AKI, as de-

tailed in Table 1 [3, 30–35]. Although meta-analyses based entirely on the same pool of observational studies may amplify bias [36], there is a strong and consistent signal of apparently synergistic nephrotoxicity of the VPT combination in these meta-analyses.

Risk Factors for VPT-Associated AKI

Severity of Illness: VPT-Associated AKI in Critically Ill Patients

Kidney injury is common in the critically ill and often multifactorial. There are 6 studies published on VPT nephrotoxicity in the intensive care setting. In the majority of studies, AKI was frequent, occurring in 18–34% of all patients. Two studies showed increased risk with VPT

when compared against other antipseudomonal agents (cefepime or meropenem) in combination with vancomycin [11] and against vancomycin monotherapy [9]. In both studies, illness severity, nephrotoxins and comorbidities were also independent predictors of renal injury overall. Four of the 6 studies found no difference when comparing VPT with comparators and vancomycin alone [10, 18, 19, 29]. In one subanalysis of critically ill patients, the authors found an increased risk of VPT compared to vancomycin monotherapy but not when compared with other beta-lactam/vancomycin combinations [3]. Thus, there is conflicting evidence that VPT exposure contributes to excess renal injury in this population compared to other antibiotics alone or in combination.

VPT Dosing and Administration

There is significant heterogeneity in how studies have reported vancomycin treatment and monitoring strategies. Variable reporting of average troughs [37], initial troughs, and incidence of supratherapeutic levels limits comparison between studies. Karino et al. [38] found that receipt of vancomycin loading doses increased the odds of AKI in those receiving VPT. Interestingly, one relatively small study (558 patients) found that high troughs predicted AKI in a group receiving VC but was not predictive in the VPT group [17]. Anderson and colleagues [39] found that despite the high frequency of doses >4 g in the vancomycin (23%) and VPT (19%) groups, this was not found to be predictive of AKI. Compared to patients receiving vancomycin-meropenem, Robertson et al. [13] found that both high doses (>4 g/day) and supratherapeutic troughs were predictive of AKI in the VPT group only. Studies in the critically ill have also identified a higher risk of AKI with initial troughs >15 µg/mL [11] or >20 µg/mL [10]. Results to date have yielded mixed results, which likely reflect the limitations of monitoring vancomycin trough levels to prevent nephrotoxicity. Trough levels are a putative surrogate marker for area under the curve (AUC), but in a modelling study, trough-guided regimens were shown to exceed the target AUC in 60% of adults [40]. Furthermore, a recent meta-analysis that included 2 studies of AUC- versus trough-guided dosing showed reduced rates of nephrotoxicity with the latter [41]. There is substantial evidence that high troughs often precede renal injury, but it is unclear whether this implies causation or is an effect of decreased clearance [42]. Emerging literature suggests that AUC-guided dosing may prove to be an effective alternative approach to monitoring trough vancomycin levels to guide therapy and

prevent nephrotoxicity, but this approach has not been adequately validated yet.

In contrast with vancomycin, the dosage of beta-lactam administered does not seem to be an aggravating risk factor, as shown by Moenster et al. [37], who found that patients treated with high-dose PT (≥18 g/day) had similar incidence of AKI than those treated with standard dosing. The effect of infusion strategy has also been assessed, as the use of extended infusions has been adopted in some critical care settings due to its association with improved outcomes and safety in severe infections [43]. Beta-lactam infusion strategy does not seem to alter the risk of nephrotoxic AKI with beta-lactams [44] and specifically with PT therapy in combination with vancomycin. In a matched-cohort of 2,390 patients receiving intravenous beta-lactam antibiotics, Cotner et al. [45] showed that extended infusion was not a risk factor for AKI with any antipseudomonal agent. Similarly, 2 retrospective studies confirmed the absence of effect between the infusion strategy and the incidence of AKI in patients receiving PT in combination with vancomycin [38, 46].

Obesity

High BMI is a known risk factor for VAN [47]. In a cohort study of patients exposed to vancomycin, the risk of AKI increases by 1.02 (95% CI 1.0–1.03) for every 1 kg increase in body weight [48]. Similarly, in a retrospective study of patients receiving VPT, total body weight over 91 kg increased the risk of AKI, despite weight-adjusted dosing [49].

Chronic Kidney Disease

CKD is a recognized risk factor for VAN [50]. Most observational studies of VPT combination therapy have therefore excluded patients with CKD stage 3 and above. Patients have also been excluded from analysis if they are deemed “at risk” – meaning they have had prior AKI or requirement for renal replacement therapy (RRT) [11, 19, 51]. In studies including pre-existing renal impairment or prior AKI, those patients have comprised between 13.6 and 38% of the cohort. These studies suggest that baseline renal function or pre-existing renal disease is not associated with higher risk of AKI when treated with VPT as opposed to vancomycin alone. Renal impairment has not been shown to be predictive of VPT nephrotoxicity [14, 15, 51–54] nor in other dual antimicrobial combinations with vancomycin [54]. In small studies, the limited numbers of patients with renal impairment precluded analysis for association with AKI [13]. Studies in the critically ill

have yielded similar results [9, 18] with the exception of a single study by Blevins et al. [11]. Here, the authors found an increased risk (OR = 2.22) of AKI in patients with CrCl <60 mL/min and an incidence rate of 55% in patients with CrCl <30 mL/min. Renal impairment remains an AKI risk factor in patients receiving vancomycin with or without PT.

Clinical Course and Outcomes of VPT-Associated AKI

Onset

Recent studies suggest VAN typically occurs 5–7 days after vancomycin commencement [1]. However, reports suggest that the apparently synergistic toxicity due to VPT may occur earlier than in vancomycin monotherapy or in vancomycin combinations with other antipseudomonal agents. A matched-cohort study identified that AKI occurred earlier in the VPT group compared to those treated with a VC combination; the median time for serum creatinine (SCr) to reach AKI criteria was 5 versus 8 days, respectively ($p = 0.0001$) [12]. Two other studies found a similarly shorter time to onset of AKI when VPT was compared to cefepime (3 vs. 5 days, $p < 0.0001$) or meropenem (3 vs. 7 days, $p = 0.009$) combinations with vancomycin [13, 17]. However, this pattern was not confirmed in critically ill patients. Blevins et al. [11] showed that AKI in ICU patients receiving VPT occurred slightly later (median: 3.2 days) compared to VC (2.6 days, $p = 0.03$) or vancomycin-meropenem (2.2 days, $p = 0.003$). Similarly, a meta-analysis by Luther and colleagues [3] found that time to AKI was not significantly shorter in the subgroup of critically ill patients treated with VPT. Finally, a network analysis of 11 studies by Bellos et al. [34] did not show a significant difference in time to AKI in patients treated with VPT (4.35 days) versus comparators (4.29–4.41 days) or vancomycin monotherapy (4.65 days). Accordingly, the observed pattern of earlier rise in SCr in VPT-treated patients may be limited to non-critically ill patients.

Severity

AKI definitions vary between studies (RIFLE, AKIN, and KDIGO, etc.), with the latter two definitions including more cases with smaller SCr increments (>0.3 mg/dL) than the RIFLE system, which requires a $\geq 50\%$ increase to define an AKI case (RIFLE stage “R”/“Risk”); the chosen definition thus impacts the incidence of stage 1 AKI but effects comparator groups equally [3, 38]. Furthermore, the definitions of moderate (RIFLE “I”; stage 2

AKIN or KDIGO-doubling SCr) or severe cases (RIFLE “F”; stage 3 AKIN or KDIGO-tripling SCr or RRT) are equivalent in all three classification systems [3, 38]. It is notable that the increased risk of AKI due to VPT mainly results in non-severe AKI. In a large retrospective cohort study of 10,236 patients receiving a vancomycin dual-antibiotic combination, when using RIFLE-defined criteria, incidence rates of only *risk* and *injury stages of AKI* were significantly increased in the VPT group ($p = 0.006$ and $p = 0.005$, respectively), while *failure* was not significantly increased, compared to vancomycin-meropenem therapy (4.2 vs. 2.1%, $p = 0.068$) [20]. However, fewer patients in the vancomycin-meropenem *failure* group compared to the VPT *failure* groups may have impacted statistical significance. Most case series have not included details of the incidence of severe AKI requiring acute RRT in VPT versus comparator groups. Mullins et al. [55] reported higher rates of requiring RRT with VPT, but this did not reach significance (3 vs. 0, $p = 0.057$). In 122 ICU patients, Hammond and colleagues [19] found that although AKI incidence was similar in VPT versus VC patients (32.7 vs. 28.8%, respectively, $p = 0.65$), RRT requirement was not significantly higher in the VPT group (18.8 vs. 38.1% in the VC group, $p = 0.277$). Similarly, in a 224 patient cohort, Gomes and colleagues [16] found that AKI developed in 34.8% of VPT-treated patients, versus 12.5% of VC-treated patients, with a significantly greater proportion of stage 1 AKI in the VPT group (64.1%) versus the VC group (42.9%, $p < 0.05$); acute RRT requirement was very rare in this cohort: VC ($n = 1$) versus VPT ($n = 0$), $p = 1.00$. Taken together, these data demonstrate that VPT most frequently causes stage 1 AKI; however, it is unclear what the incidence is of RRT in VPT-treated patients versus comparator groups due to limited and conflicting data.

Long-Term Impacts

Data are few regarding the long-term renal and non-renal outcomes of VPT nephrotoxicity since most studies focus on the incidence rather than the outcomes of AKI. One ICU study of 723 patients exposed to antibiotic combination found an increased risk in the composite outcome of death or dialysis at 9 months in those treated with VPT (48%) compared to monotherapy with either vancomycin (29%) or PT alone (35%) ($p = 0.048$) [56]. Studies in critically ill populations have not found an increased risk of persistent renal dysfunction or need for chronic dialysis with VPT compared with cefepime- [19, 29] or meropenem-vancomycin [29]. Meta-analyses have largely confirmed this finding [34].

Color version available online

Fig. 1. Representation of potential mechanisms associated with VPT nephrotoxicity. PT exposure inhibits OAT1 and OAT3 tubular transporters, while vancomycin may reduce the cellular expression of these transporters, decreasing the tubular secretion of Cr, referred as *pseudotoxic* drug interaction. Potential toxicity may be related to (1) AIN associated with beta-lactam agents and (2) direct tubular toxicity associated with vancomycin. Vancomycin-associated cast nephropathy may also be involved in some patients. The addition of the potential toxicity from vancomycin and PT exposure to the tubular secretion pharmacodynamic interaction may lead to a synergistic toxicity (identified with an asterisk). VPT, vancomycin-piperacillin-tazobactam; OAT1, organic anion transporter 1; OAT3, organic anion transporters 3; AIN, acute interstitial nephritis.

Pathogenesis of VPT-Associated AKI: Proposed Mechanisms of Nephrotoxicity and AKI

Despite the strong and consistent epidemiologic associations between VPT combination and AKI, our understanding of the pathogenesis of this phenomenon is still mainly based on hypotheses. It is intriguing that despite the numerous cohort studies and meta-analyses consistently reporting the VPT-AKI association, an animal experimental model did not show synergistic tubular toxicity of this drug combination [57], and histological correlations from human kidney biopsies are few. Only a few case reports described this phenomenon and its associated findings on kidney biopsy. One case reported severe AKI and a petechial rash in a 16-year-old male with acute leukemia who received VPT for febrile neutropenia. He had a kidney biopsy 23 days after initiation

of hemodialysis that showed interstitial edema, tubular damage, and tubulointerstitial nephritis with marked inflammatory infiltrate [58]. There are 2 other case reports of biopsy-proven VAN in which patients were exposed to concomitant PTZ. The first case was a 41-year-old man who was treated for Fournier's gangrene. He developed AKI and a renal biopsy showed ATN and focal AIN in the medullary rays [59]. Another case described a 71-year-old female treated with VPT for pneumonia and MRSA bacteremia. Renal biopsy showed ATN with no interstitial pathology [60]. Thus, the limited number of published case reports that include kidney biopsies report either ATN, AIN, or both, in VPT-associated AKI cases, but these data are very limited. Although there are some data supporting the theory that piperacillin synergistically increases vancomycin nephrotoxicity, or increases the risk of allergic AIN, other data suggest that a significant component of the observed increases and apparent AKI caused by VPT therapy may be mediated by impairment of renal tubular Cr secretion, without actual tubular damage or loss of GFR: a phenomenon termed *pseudo-nephrotoxicity* [61, 62], which is shown schematically in Figures 1 and 2. We will next review the data supporting these hypotheses.

Synergistically Augmented Vancomycin Toxicity?

The correlation between vancomycin and AKI was initially associated with formulation impurities [63]. Since technological improvement in drug manufacturing has eliminated this issue, the risk factors associated with VAN now include high trough levels, concurrent nephrotoxic agents, therapy >7 days, obesity, severity of illness, and CKD. Although the pathogenesis underlying VAN is not fully understood, experimental studies support the involvement of mitochondrial dysfunction, proinflammatory oxidative stress, and renal tubular cell apoptosis [47]. Vancomycin induces free oxygen radicals, affecting cell metabolism and enzymatic activity. In animal models, co-administration of vancomycin and an antioxidant agent attenuated proximal tubular injury [64, 65]. Mitochondrial stress is also induced by these superoxides, leading to the release of cytochrome-C. The latter can lead to apoptosis by caspase activation [47, 66]. Alterations in DNA repair has also been described in rats exposed to vancomycin [67]. Direct tubular toxicity was similarly confirmed by increases in NGAL and other tubular injury biomarkers elevation in various animal and human models of vancomycin-induced AKI [1, 68].

Fig. 2. Hypothetical mechanisms of nephrotoxicity associated with VPT combination. **a** Drug interaction. Cr is secreted into the tubular lumen partly through the use of OAT1-OAT3 and OCT2-OCT3 transporters (basal membrane) and MATE1-MATE2K (apical membrane). PT is a more potent substrate of OAT1 and OAT3, limiting the passage of Cr into the tubular cell. In vivo, vancomycin has been shown to reduce the expression of mRNA associated with OAT1-OAT3 externalization. **b** PT, as other beta-lactams agents, may be associated with AIN. Vancomycin exposure is associated with variable signs of acute tubular necrosis including proximal toxic vacuolization (**c**) and dilatation of tubules with some loss of their brush border (**d**). **e** Vancomycin induces reactive oxygen species which may affect cell metabolism and various enzymatic activities. Vancomycin may also increase mitochondrial stress, releasing cytochrome-c and activating the caspase pathway, resulting in cellular stress and apoptosis. **b-d** Periodic acid-Schiff stain. VPT, vancomycin-piperacillin-tazobactam; OAT1, organic anion transporter 1; OAT3, organic anion transporters 3; MATE1, multidrug and toxin extrusion transporters 1; MATE2K, multidrug and toxin extrusion transporters; AIN, acute interstitial nephritis; mRNA, messenger RNA.

Although kidney biopsy is rarely performed in context of suspected VAN, a few case reports have been published. The histological findings in the majority are compatible with acute tubular necrosis or AIN [47]. Recently, Luque et al. [69] reported vancomycin-associated cast nephropathy in patients exposed to supratherapeutic doses of vancomycin; however, the clinical importance of this finding in the pathogenesis of VAN remains unclear. No report mentions an increased risk of cast formation – by intratubular vancomycin crystallization – in patients receiving an appropriate therapeutic dosage, or simultaneously treated with PT. Finally, there are no data from experimental models or human kidney biopsies or biomarker studies that demonstrate synergistically increased acute tubular injury by the combination of PT with vancomycin, compared to vancomycin alone.

Increased Risk of Allergic AIN?

Beta-lactams, including piperacillin, are well-known to cause drug-induced AIN [70, 71]. The classic triad of rash, fever, and eosinophilia occur in less than 10% of patients, so the diagnosis of drug-induced AIN generally relies on maintaining a high index of suspicion [71]. Several case reports with kidney biopsies confirmed AIN in patients receiving PT monotherapy [4, 5, 58]. Given the broad spectrum of AIN presentation, it has been hypothesized that in patients previously sensitized to PT, re-exposure could lead to an AIN and AKI without systemic manifestations [16, 72]. To explain the observed lower incidence of AKI when using the combination of ceftipime and vancomycin compared to VPT as reported above, Gomes et al. [16] speculated that the lower immunogenicity of 4th generation cephalosporins compared to piperacillin, with decreased risk of inducing AIN could

potentially explain the observed decrease in AKI incidence compared to the VPT combination, but this remains an unproven hypothesis.

Pseudonephrotoxicity: Reduction in Tubular Cr Secretion

Active secretion by proximal tubular cells is responsible for 10–15% of the total Cr clearance, and that proportion may increase up to 50% in patients with CKD caused by progressive glomerular disease [73]. Over the last decade, our knowledge of the mechanisms involved in the renal tubular secretion of Cr has considerably evolved [74]. Although many transporters implicated are now well described, the predominant pathway is still unconfirmed [75]. In vitro and in vivo data demonstrate contributions of organic anion transporters 1 and 3 (OAT1 and OAT3) and organic cation transports 2 and 3 at the basolateral membrane, allowing passage of SCr from peritubular capillaries into the intracellular compartment of proximal tubular cells (Fig. 2). At the apical membrane, the multidrug and toxin extrusion transporters 1 and 2-K secrete Cr into the tubular lumen [76, 77]. In humans, the absolute contribution of these transporters is still unclear due to their relatively low affinity for creatinine and difficulties translating animal models to human cell models [36, 76, 78]. Theoretically, this low affinity might be compensated by a high transport capacity [74,79], making this process sensitive to drug-drug interactions.

Various drugs (i.e., cobicistat, trimethoprim, and cimetidine) are potent inhibitors of these transporters, affecting the tubular secretion component of Cr clearance [76, 80] and can increase SCr levels by 0.2–0.4 mg/dL and decrease Cr clearance by 15–34 mL/min [76]. Both piperacillin and tazobactam are recognized substrates for OAT1 and OAT3 [81]. Although not confirmed in humans, vancomycin may also partly suppress messenger RNA and protein expression of OAT1 and OAT3 [82]. Together, these effects of piperacillin, tazobactam, and vancomycin could significantly diminish the number and activity of organic anion transporters on the basolateral membranes of proximal tubular cells and cause impaired Cr secretion and increased SCr, with apparent AKI. However, this phenomenon would be a form of pseudo-AKI termed *pseudo-nephrotoxicity* [62], because Cr secretion and Cr clearance are decreased, but GFR is unchanged [71], and there is no parenchymal renal tubular damage – in the absence of other causes of tubular injury (sepsis, nephrotoxins, etc.). If the apparent nephrotoxicity of the VPT combination is in fact a false AKI diagnosis caused

by drug-induced impairment of Cr secretion, concomitant BUN elevations should not occur (in the absence of other causes – diuretics, corticosteroids, and true tubular injury), and BUN/Cr ratios should be oddly low. Unfortunately, none of the case series of VPT-associated AKI have reported these data.

Indirectly, an interesting clinical study provided some evidence suggestive of an effect of PT on tubular Cr secretion [83]. Historically, PT has been considered as having low potential for nephrotoxicity. However, treatment with PT appears to delay renal function recovery after AKI. A post hoc analysis of the Procalcitonin and Survival Study (PASS) compared the change in eGFR with starting and stopping antibiotics in critically ill patients. PT was associated with delayed renal recovery compared to other beta-lactams, with steady SCr decreases occurring during treatment with meropenem (or cefuroxime, in a less ill group), but delayed SCr decreases occurring only in the 5 days following cessation of PT therapy [83]. Taken together with the absence of synergistic experimental model tubular damage [57], a strong case for the pseudo-nephrotoxicity phenomenon may be made. Although interesting, pseudo-nephrotoxicity is unlikely to be the sole explanation for the consistently observed increased incidence of AKI in VPT-treated patients, which may alternatively be caused by true nephrotoxic injury (vancomycin-induced ATN, or allergic interstitial nephritis caused by vancomycin or piperacillin exposure) or septic AKI (hypoperfusion, inflammatory cytokines, postinfectious glomerulonephritis, etc.) in patients with serious infections. This could explain the presence of higher levels of kidney stress biomarkers and AKI severity in patients treated with the VPT combination compared to either drug alone (although potentially confounded by bias in patient selection for combination therapy) [56], as previously described with kidney damage biomarkers in vancomycin-treated patients [84]. Finally, the effects of VPT on tubular Cr secretion could exaggerate the SCr increase and apparent GFR loss in cases of vancomycin-induced ATN, or AIN caused by vancomycin or piperacillin.

Prevention, Monitoring, and Management Strategies to Minimize the Risk of VPT-Associated AKI

Antimicrobial Stewardship

Antimicrobial stewardship (AMS) is the promotion of optimal drug regimens including choice of agent, dosing, duration of therapy, and route of administration [85].

Table 2. Take-home messages to minimize AKI risk associated with VPT combination therapy in hospitalized patients

(A) Initial diagnosis of sepsis and prescription of antimicrobials
Are both vancomycin and piperacillin-tazobactam required?
History or risk factors for MRSA?
Intravascular catheter/Prosthetic material infection suspected?
Other indication for vancomycin?
Review of antimicrobials with availability of diagnosis/microbiological investigations (usually after 24–48 h):
(a) Are both vancomycin and piperacillin-tazobactam required?
(b) Is there a more appropriate/narrower spectrum agent available to replace either or both?
(B) Identify patients at risk of AKI (i.e., obesity, previous drug-related AIN, infection requiring long-duration treatment, CKD?)
(C) Vancomycin dosage and monitoring
Use the appropriate trough level targeted
Monitor vancomycin level at least every fourth dose in hospitalized patient
Monitor vancomycin level more frequently if one of the following situations occurs:
Ongoing AKI
Acute conditions at risk of SCr variation: hemodynamic instability, major surgery
New initiation of piperacillin-tazobactam
Exposure to concomitant nephrotoxin or contrast agent
Dosage modification
(D) Minimize antibiotic duration
(E) Select less nephrotoxic antimicrobial combination
(F) Kidney function monitoring
Daily SCr and BUN
Consider monitoring serum cystatin C also, if available
(G) If SCr increases during antibiotic therapy
Assess the etiology using appropriate clinical and laboratory investigations
Monitor vancomycin level more frequently
Consider a switch of antibiotics
Consider nephrology consultation
Obtain urinalysis including microscopic sediment examination
<i>Novel tubular injury biomarkers may be useful</i>
VPT, vancomycin-piperacillin-tazobactam; AKI, acute kidney injury; SCr, serum creatinine.

Putting the tenets of AMS into practice would reduce unnecessary prescriptions of all antimicrobials, as well as potentially nephrotoxic combinations such as PT and vancomycin (Table 2). PT remains a popular choice among clinicians for empiric antimicrobial therapy with broad gram-positive, gram-negative, (including antipseudomonal) and anaerobic activity. However, there are several alternatives with similar spectra, or occasions when such broad empiric cover is not required. Vancomycin is a glycopeptide antimicrobial with sole gram-positive activity and carries additional activity against resistant bacteria such as MRSA (methicillin-resistant *Staphylococcus aureus*), *Enterococcus faecium*, coagulase-negative staphylococci, etc., not otherwise covered by beta-lactam therapy.

Choice of agent(s) for empiric therapy is typically guided by site of infection and local pathogen susceptibility patterns, and thus guidelines may differ between hospitals and regions. Combination of PT with vancomycin is started empirically when (a) there is a suspicion of MRSA infection [86], (b) empiric cover for prosthetic material infection is required, for example, a possible infected vascular line [87] or prosthetic heart valve [88], or (c) when the patient is acutely septic and the source and/or history of the patient is not known [89]. AMS promotes de-escalation of antimicrobials, whereby antimicrobial therapy is rationalized when a clinical diagnosis or microbiological results are available for a patient [89, 90]. It is frequently advocated for to reduce the emergence of multidrug-resistant organisms [91] but can be

applied to reduce incidence and duration of co-prescribing of PT/vancomycin. For example, MRSA screening swabs have high negative predictive value and can be used to safely de-escalate patients from empiric vancomycin therapy [92] once the MRSA status of the patient is known to be negative.

Clinicians must be vigilant in prescribing in all patients but particularly in those at high risk of VPT toxicity. First, it should be considered if VPT combination cover is required, or if alternatives to PT and/or vancomycin are appropriate and/or available. In addition, it is important for patients receiving this combination to receive short courses as shorter duration has been shown to reduce risk of AKI [29].

Risk Assessment and Monitoring

As for all known nephrotoxic medication, monitoring kidney function with SCr assessment is standard practice. However, as shown in both pediatric and adult populations [93, 94], lack of adequate monitoring is associated with unrecognized nephrotoxic medication-associated AKI. Monitoring is effective and has been shown to reduce drug-related AKI. In the large multicenter pediatric trial named Nephrotoxic Injury Negated by Just-in time Action (NINJA), a screening tool to quickly identify hospitalized children exposed to high nephrotoxic medication was implemented. Several interventions were therefore applied, including daily SCr monitoring, pharmacist review, and substitution for less nephrotoxic agents. A significant 23.8% decrease in drug-associated AKI was observed [95], confirming the utility of monitoring at risk patients with the currently available tool to assess kidney function – SCr – and intervening appropriately. Correlation with other markers of kidney function is important in considering potential cases of VPT-induced AKI because of the impact of this drug combination on tubular creatinine secretion, in which case trends in BUN and (where available) serum cystatin C may be revealing.

In future, monitoring with markers of kidney stress [56] or kidney damage [82] may further improve the prediction, detection, and assessment of cases of nephrotoxic AKI. The FDA and EMA recently supported the use of 8 safety biomarkers for monitoring kidney injury in early drug development [96]. Other emerging biomarkers may prove useful to distinguish cases of AIN from other forms of AKI [96]. Clinicians should be cautious in dosing vancomycin to achieve troughs 15–20 µg/mL, noting that increasing trough levels may signal nephrotoxic injury with declining GFR and vancomycin clearance before SCr increases significant-

ly. Previous guidelines have recommended trough-guided dosing to ensure efficacy and reduce risk of toxicity. The 2020 IDSA guidelines recommend AUC-guided dosing of vancomycin instead of trough-guided dosing. Targeting an AUC level 400–600 mg h/L has been shown to reduce nephrotoxicity without compromising efficacy [97]; however, its implementation requires increased labor and cost.

Conclusion

The recently described phenomenon of VPT nephrotoxicity is becoming a major medication safety topic. Despite a limited understanding of the underlying pathogenetic mechanisms and biological plausibility, this combination is now regarded as increasing the incidence of AKI in patients, compared to vancomycin alone or in other combinations (apart from aminoglycosides). Further research is required to further elucidate the mechanisms of apparent VPT nephrotoxicity, including the likely impact of impaired tubular Cr secretion and pseudo-nephrotoxicity. By applying AMS principles, this combination should only be used when there is an indication and should be reviewed on an ongoing basis with the availability of a diagnostic and/or microbiological results. If the combination is indicated, it should be kept to the minimum required duration, with an increased awareness of therapeutic drug monitoring and early signs of AKI. Careful monitoring should include surveillance with a combination of kidney function markers (SCr and BUN trends, perhaps novel biomarkers as well), and early alterations of antibiotic regimen where AKI is developing, particularly when kidney damage is present.

Acknowledgement

All authors would like to thank the CHUM Medical Pathology Department (Montreal) for providing biopsy pictures used to develop the figures.

Conflict of Interest Statement

P.T.M. has received past research funding from Abbott Laboratories and from Alere, and is a scientific consultant for FAST Biomedical, Sphingotec, AM-Pharma, and Renibus Therapeutics. The other authors have no potential conflicts of interest to declare.

Funding Sources

No specific funding has been received for this work. J.M.-C. is partly funded by the Fonds de Recherche en Santé du Québec, Société Québécoise de Néphrologie and Fondation CHUM as part of his research training.

Author Contributions

M.B. drafted and revised the manuscript. J.M.-C. drafted and revised the manuscript and designed the tables/figures. A.C. drafted and revised the manuscript. B.L. drafted and revised the manuscript. L.R. drafted and revised the manuscript. P.T.M. initiated the collaboration, as well as directed, drafted, and revised the manuscript.

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