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Nephrotoxicity of concomitant piperacillin/tazobactam and teicoplanin compared with monotherapy

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Objectives: Piperacillin/tazobactam combined with vancomycin has been associated with a decline in renal function when compared with monotherapy. Teicoplanin is a glycopeptide similar to vancomycin. We investigated whether piperacillin/tazobactam combined with teicoplanin is associated with a decline in renal function as well.

Methods: We conducted a single-centre retrospective cohort study with data from our electronic health records from 9 August 2013 to 15 November 2019, including all adult patients that received either piperacillin/tazobactam, teicoplanin or piperacillin/tazobactam + teicoplanin. The incidence of acute kidney injury (AKI) at 48–72 h served as the primary outcome, whereas change in serum creatinine served as a secondary outcome.

Results: Of the 4202 included patients, 3188 (75.9%) received piperacillin/tazobactam, 791 (18.8%) received teicoplanin and 223 (5.3%) received piperacillin/tazobactam + teicoplanin. The incidence of AKI at 48–72 h after commencement of antibiotic therapy was 5.4% for piperacillin/tazobactam, 3.4% for teicoplanin and 11.7% for piperacillin/tazobactam + teicoplanin ($P < 0.001$). However, mean serum creatinine at 48–72 h was slightly higher in the piperacillin/tazobactam + teicoplanin group therapy compared with baseline [$+1.61\%$ (95% CI -2.25 to 5.70)], indicating a slight decrease in renal function, and decreased for piperacillin/tazobactam [-1.98% (95% CI -2.73 to -1.22)] and teicoplanin [-8.01% (95% CI -9.54 to -6.45)]. After correcting for significant confounders in a multivariate linear regression analysis, these patterns remained.

Conclusions: Our study suggests that piperacillin/tazobactam + teicoplanin is associated with a higher prevalence of AKI compared with monotherapy. However, as the overall decline in renal function with piperacillin/tazobactam + teicoplanin is very small, its clinical relevance is likely limited. Therefore, piperacillin/tazobactam + teicoplanin can probably be safely combined.

Introduction

Healthcare-associated infections frequently require both *Pseudomonas* spp. and either MRSA, coagulase-negative *Staphylococcus* spp. or *Enterococcus faecium* coverage. Accordingly, a commonly used combination of antibiotics consists of piperacillin/tazobactam and vancomycin. The nephrotoxicity of vancomycin has been well recognized, occurring in up to 40% of patients depending on the dose.^{1,2} Though its mechanism is not completely understood, it is hypothesized that vancomycin causes oxidative

effects on the proximal renal tubule, resulting in renal tubular ischaemia. Risk factors for developing vancomycin-related nephrotoxicity include dose, duration of therapy, severity of illness and chronic kidney disease.³ Teicoplanin is a glycopeptide with chemical and microbiological properties similar to vancomycin.⁴ Teicoplanin is shown to be equally effective in terms of treatment outcomes when compared with vancomycin, but with significantly less nephrotoxicity.^{5–7} A Cochrane systematic review concluded that teicoplanin reduced the risk of nephrotoxicity

compared with vancomycin, with a relative risk of 0.66 (95% CI 0.48–0.90).⁸ Therefore, in our university medical centre, teicoplanin is currently preferred over vancomycin for the treatment of the above-mentioned diseases and pathogens.

The concomitant use of vancomycin with piperacillin/tazobactam was recently found to be associated with an even greater decline in renal function when compared with vancomycin monotherapy. Several meta-analyses show a 2- to 3-fold increase in acute kidney injury (AKI) when piperacillin/tazobactam is given simultaneously with vancomycin, compared with vancomycin alone.^{9–11} Furthermore, the incidence of AKI with concomitant piperacillin/tazobactam and vancomycin appears to be significantly increased when compared with vancomycin plus other antipseudomonal antibiotics such as cefepime and meropenem.^{11–17} This relationship has also been established in paediatric patients.^{18–20} In critically ill patients evidence is conflicting, with studies reporting a decline in renal function^{21–23} as well as stable renal function^{24–26} when concomitant piperacillin/tazobactam and vancomycin is compared with monotherapy. It is hypothesized that the decline in renal function seen with concomitant piperacillin/tazobactam and vancomycin may be due to a synergistic effect of these antibiotics. However, no additional histopathological kidney injury is seen with combination therapy in a rat model when compared with monotherapy, indicating that these results may still be the result of confounding.²⁷

As teicoplanin appears to be less nephrotoxic than vancomycin, without compromising efficacy,⁸ we investigated whether or not teicoplanin combined with piperacillin/tazobactam is associated with a decline in renal function when compared with monotherapy.

Methods

Study design and setting

We performed a single-centre retrospective cohort analysis using patient data collected from the electronic medical records at Radboud University Medical Center (Radboudumc), a tertiary hospital in the Netherlands. As this study consisted of retrospective anonymized data, the need for formal ethics approval was waived by the Radboudumc Research Ethics Board according to the Dutch Law of Human Research.

Patients

Patients were selected when hospitalized between 9 August 2013 and 15 November 2019. Patients were included if they were at least 18 years of age, received piperacillin/tazobactam, teicoplanin or both simultaneously (piperacillin/tazobactam + teicoplanin) at any time during admission. Patients were excluded if no serum creatinine level was available from 7 days prior to admission until commencement of antibiotic treatment or at 48–72 h after commencement, if they had an estimated glomerular filtration rate (eGFR) of <30 mL/min before admission, if they were diagnosed with AKI at admission, or if they received renal replacement therapy before or during admission. Patients were also excluded if they received piperacillin/tazobactam and teicoplanin without overlap during admission. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.²⁸ AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, as an increase in serum creatinine by $\geq 26.5 \mu\text{mol/L}$ within 48 h or as an increase in serum creatinine level by $\geq 50\%$ from baseline.²⁹ We did not take urine output into account for the definition of AKI as these data were not available.

Standard care

Both piperacillin/tazobactam and teicoplanin were dosed according to national guidelines drafted by the Dutch Working Party on Antibiotic Policy (SWAB). Piperacillin/tazobactam was dosed at 4500 mg q8h for patients with normal renal function and q12h for patients with an eGFR of <30 mL/min. Patients on teicoplanin always received a loading regimen followed by a maintenance dose, abiding by local protocol. Until 2018, our local protocol consisted of a single loading dose of 800 mg followed by a maintenance dose of 400 mg q24h. From 2018 onwards, our local protocol has changed³⁰ to a loading regimen consisting of five consecutive doses of 12 mg/kg with a maximum of 800 mg per dose q12h, followed by a maintenance dose of 12 mg/kg with a maximum of 800 mg q24h. In patients with an eGFR <50 mL/min, the maintenance dose was halved.

Data and outcome variables

The data collected for each patient included demographic data, hospital length of stay, admission type (ICU or non-ICU), serum creatinine levels until 7 days pre-admission, at admission and at start of antibiotics, and consecutive creatinine levels every 24 h after start of antibiotic treatment. Furthermore, the number of nephrotoxic agents (see [Supplementary Information](#), available as [Supplementary data](#) at JAC Online) and the number of days on vasopressors were noted.³¹ Baseline serum creatinine was defined as serum creatinine levels either at start of antibiotics, at admission or up to 7 days pre-admission, depending on the available data. If multiple values were available, the one closest to the start of antibiotics was chosen. If multiple values per day were available, the earliest value was used.

Primary outcome

The incidence of AKI at 48–72 h after start of piperacillin/tazobactam, teicoplanin or piperacillin/tazobactam + teicoplanin served as the primary outcome variable.

Secondary outcome

Secondary outcomes included change in serum creatinine at 48–72 h after start of piperacillin/tazobactam, teicoplanin or piperacillin/tazobactam + teicoplanin expressed as a percentage relative to baseline, absolute values of serum creatinine at baseline and 48–72 h after start of antibiotic treatment, changes in serum creatinine relative to baseline for the ICU and non-ICU population, and the impact of covariates (age, sex, hospital length of stay, ICU admission status during antibiotic treatment, the number of different nephrotoxic drugs received during admission and amount of days on vasopressors during admission) on change in serum creatinine. We also investigated whether there was a difference in outcome before and after the standard dose of teicoplanin was increased due to a change in local protocol. Furthermore, we compared the characteristics of the missing data with our study population.

Statistical analyses

Patient characteristics were described with basic descriptive statistics. Continuous variables were compared with a one-way analysis of variance (ANOVA) and categorical variables were compared with a Pearson's χ^2 test. To satisfy the assumption of underlying linearity, the log-transformed data were considered regarding serum creatinine. Data were analysed for the overall study population, and the ICU and non-ICU population separately. To gain insight into our data and be able to determine effect size, we investigated the association between a relative increase in serum creatinine at 48–72 h with regard to baseline and the antibiotic treatment with either piperacillin/tazobactam, teicoplanin or piperacillin/tazobactam + teicoplanin by using a linear regression model in addition to a logistic regression model. *Post hoc* comparisons were performed with a Tukey HSD test. Age, sex, hospital length of stay, ICU admission status during antibiotic

treatment, the number of different nephrotoxic drugs received during admission and number of days on vasopressors during admission served as covariates.³¹

The data were analysed using Python 3.7.3 with the Pandas package (version 0.25.1), Numpy (version 1.17.0), Matplotlib (version 3.1.1) and Seaborn (version 0.9.0). Statistical analyses were performed using the Statsmodels (version 0.10.1) and Pingouin (version 0.3.2) packages. Significance was defined as a *P* value <0.05.

Results

Of 8747 eligible patients, 4202 were included in the analysis (Figure 1). Of these, 3188 (75.9%) received piperacillin/tazobactam alone, 791 (18.8%) received teicoplanin alone and 223 (5.3%) received piperacillin/tazobactam + teicoplanin. Patient characteristics are described in Table 1. There are significant differences between groups with regard to age, sex, hospital length of stay, ICU admission, baseline eGFR and number of nephrotoxic drugs to the detriment of piperacillin/tazobactam + teicoplanin. Patients in the piperacillin/tazobactam + teicoplanin group, for instance, had a longer hospital length of stay [mean of 29.6 days (SD 26.2) versus 17.3 days (SD 17.8) for piperacillin/tazobactam and 22.5 days (SD 17.5) for teicoplanin, *P*<0.001] and a higher ICU admission status (31.8% versus 15.4% for piperacillin/tazobactam and 12.8% for teicoplanin, *P*<0.001). The medical subspecialty for which the patient was admitted for the non-ICU population is shown in Table 2.

Primary outcome

The incidence of AKI at 48–72 h after commencement of antibiotic therapy was 5.4% for piperacillin/tazobactam, 3.4% for teicoplanin and 11.7% for piperacillin/tazobactam + teicoplanin (*P*<0.001) (Table 3). Logistic regression indicated statistical significance for piperacillin/tazobactam + teicoplanin (*P*<0.001); significant confounders were increased age (*P*=0.010), male sex (*P*=0.025) and ICU admission status (*P*<0.001).

Secondary outcome

The change in serum creatinine from baseline to 48–72 h after commencement of antibiotic therapy was –1.98% (95% CI –2.73 to –1.22) for piperacillin/tazobactam, –8.01% (95% CI –9.54 to –6.45) for teicoplanin and +1.61% (95% CI –2.25 to 5.70) for piperacillin/tazobactam + teicoplanin, indicating an improvement in renal function for monotherapy and a decline with combination therapy [*F*=27.07, *P*<0.001] (Figure 2). *Post hoc* comparisons using the Tukey HSD test showed a mean difference between piperacillin/tazobactam + teicoplanin and teicoplanin of 9.6% (*P*=0.001) and a mean difference between piperacillin/tazobactam + teicoplanin and piperacillin/tazobactam of 3.6% (*P*=10.057), to the detriment of piperacillin/tazobactam + teicoplanin when compared with monotherapy. The mean difference between piperacillin/tazobactam and teicoplanin was 6.0% (*P*=0.001).

Table 4 shows the median and IQRs for serum creatinine levels at baseline and at 48–72 h. Figure 2 shows the change in serum creatinine at 48–72 h after commencement of antibiotic treatment compared with baseline for the entire study population, the ICU population and the non-ICU population, with 95% CI. These results are also shown in Table 5.

To correct for differences in patient characteristics, age, sex, hospital length of stay, ICU admission and number of nephrotoxic drugs served as covariates in our multivariate linear regression. Our multivariate linear regression analysis showed a significant correlation between the antibiotic treatment (piperacillin/tazobactam, teicoplanin, piperacillin/tazobactam + teicoplanin) and change in serum creatinine at 48–72 h, with a *P* value of 0.0016. Statistically significant confounders were increased age (*P*<0.001) and ICU admission status (*P*<0.001). After correction for these confounders, the adjusted mean differences were 10.8% between piperacillin/tazobactam + teicoplanin and teicoplanin (*P*=0.010) and 7.7% between piperacillin/tazobactam + teicoplanin and piperacillin/tazobactam (*P*=0.047), to the detriment of piperacillin/tazobactam + teicoplanin when

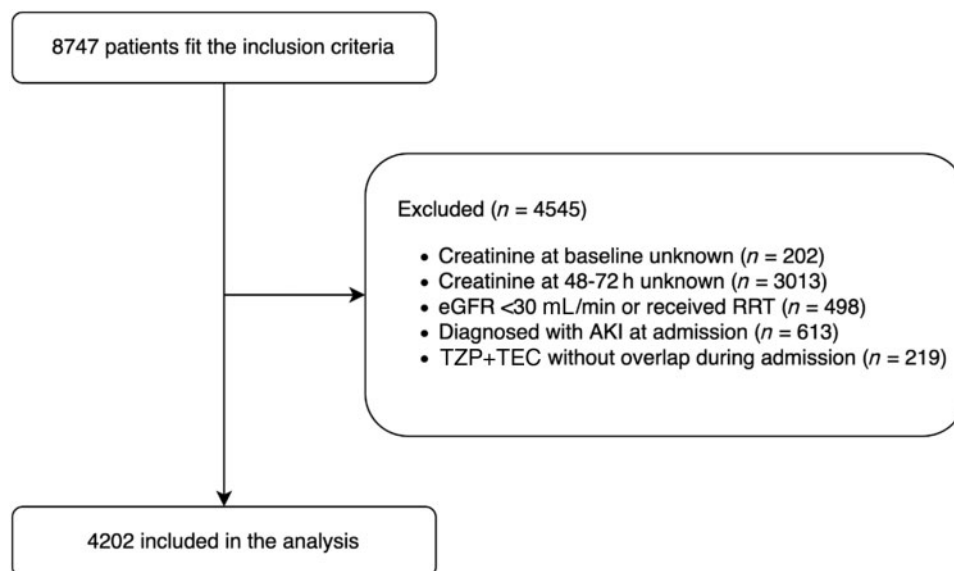


Figure 1. Flow diagram for patient inclusion and exclusion. RRT, renal replacement therapy; TZP+TEC, piperacillin/tazobactam + teicoplanin.

Table 1. Patient characteristics

	TZP	TEC	TZP + TEC	P value	Total
n	3188	791	223		4202
Age, years, mean (SD)	63.4 (14.8)	56.5 (16.5)	60.7 (14.6)	<0.001	62.0 (15.4)
Sex, n (%)					
male	1957 (61.4)	455 (57.5)	156 (70.0)	0.003	2568 (61.1)
female	1231 (38.6)	336 (42.5)	67 (30.0)		1634 (38.9)
Hospital length of stay, days, mean (SD)	17.3 (17.8)	22.5 (17.5)	29.6 (26.2)	<0.001	19.0 (18.5)
ICU admission, n (%)					
no	2697 (84.6)	690 (87.2)	152 (68.2)	<0.001	3539 (84.2)
yes	491 (15.4)	101 (12.8)	71 (31.8)		1634 (38.9)
Baseline eGFR (mL/min), mean (SD)	89.3 (37.2)	92.2 (39.6)	83.2 (35.1)	0.006	89.6 (37.6)
Number of nephrotoxic drugs, mean (SD)	1.6 (1.6)	1.9 (1.7)	2.3 (1.8)	<0.001	1.7 (1.6)
Days on vasopressors, mean (SD)	3.9 (30.2)	3.1 (7.9)	3.4 (4.3)	0.890	3.7 (26.8)

TZP, piperacillin/tazobactam; TEC, teicoplanin; TZP + TEC, piperacillin/tazobactam + teicoplanin.

Table 2. Medical subspecialty for the non-ICU population

Medical subspecialty	n (%)
Internal medicine	1132 (32.0)
General surgery	757 (21.4)
Pulmonology	283 (8.0)
Cardiology	226 (6.4)
Medium care	209 (5.9)
Urology/gynaecology	170 (4.8)
Trauma/orthopaedics	163 (4.6)
Neurology/neurosurgery	152 (4.3)
Psychiatry	7 (0.2)
Other	442 (12.5)

Table 3. Incidence of AKI at 48–72 h after commencement of antibiotic treatment for piperacillin/tazobactam (TZP), teicoplanin (TEC) and piperacillin/tazobactam + teicoplanin (TZP + TEC)

	TZP	TEC	TZP + TEC
AKI, n (%)	173 (5.4)	27 (3.4)	26 (11.7)
No AKI, n (%)	3015 (94.6)	764 (96.6)	197 (88.3)

compared with monotherapy, and 3.1% between piperacillin/tazobactam and teicoplanin ($P=0.862$).

Table 6 shows the change in serum creatinine at 48–72 h after commencement of antibiotic treatment compared with baseline for the entire study population and for patients who received teicoplanin either before 2018 or from 2018 onwards, when the adjustment was made in our local protocol to increase the standard teicoplanin dose. These results are similar.

Table 7 shows the patient characteristics of the missing data compared with our study population. Notable differences are that the missing data include patients with a shorter hospital length of

stay (11.2 versus 19.0 days) and fewer ICU patients (3.3% versus 15.8%).

Discussion

Our study suggests that the combination of piperacillin/tazobactam with teicoplanin is associated with a higher prevalence of AKI at 48–72 h after commencement of antibiotic treatment compared with monotherapy. Interestingly, when comparing serum creatinine at 48–72 h with baseline, renal function appears to improve with either piperacillin/tazobactam or teicoplanin, indicating an improvement in clinical status of the patient, but shows a slight decline in renal function for piperacillin/tazobactam + teicoplanin. The difference in change in renal function was statistically significant when piperacillin/tazobactam + teicoplanin was compared with teicoplanin, but not when compared with piperacillin/tazobactam monotherapy. In our *post hoc* analysis, however, after correction for confounders there was a statistically significant decline in renal function for piperacillin/tazobactam + teicoplanin when compared with both piperacillin/tazobactam treatment and teicoplanin treatment.

This decline in renal function with piperacillin/tazobactam + teicoplanin when compared with monotherapy could imply that these patients did not improve in clinical status as they may have been a sicker population to begin with, contrary to the patients on either piperacillin/tazobactam or teicoplanin. This is illustrated by the fact that the ICU admission status was higher in the piperacillin/tazobactam + teicoplanin group than in either the piperacillin/tazobactam or teicoplanin groups. In our multivariate analysis we corrected for severity of illness by taking ICU admission status into account. Our results may therefore suggest that the decline in renal function with piperacillin/tazobactam + teicoplanin is due to a synergistic antibiotic effect. Though it would have been preferable to use a more specific marker for severity of illness than ICU admission status, these data unfortunately were not available.

Several mechanisms have been proposed for possible synergy between piperacillin/tazobactam and vancomycin. One such hypothesis is that the addition of the β -lactamase inhibitor

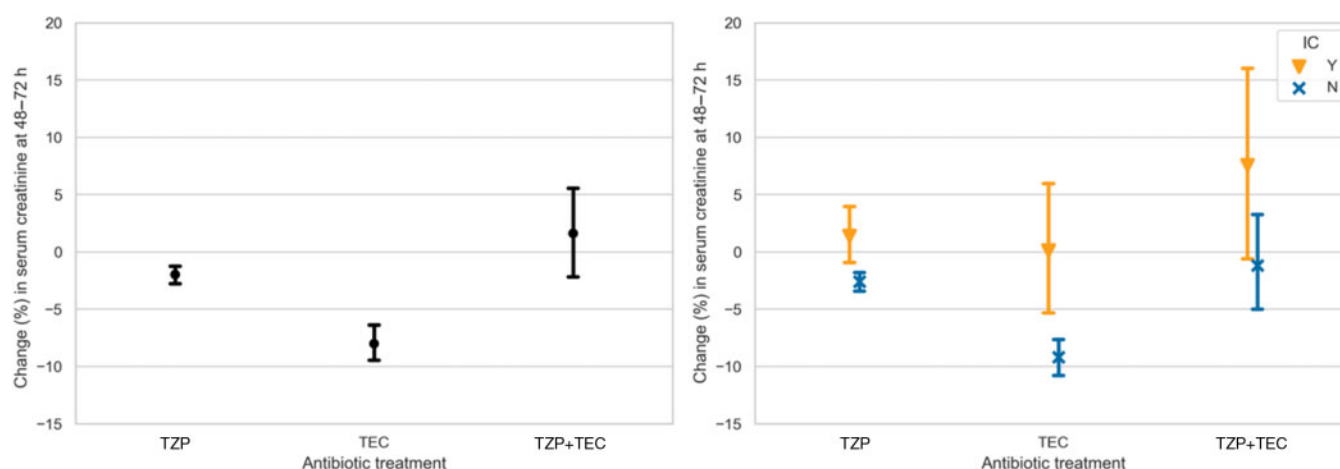


Figure 2. Change (%) in serum creatinine with regard to baseline for (left) the overall population and (right) the ICU (orange triangles) and non-ICU (blue crosses) patients separately for piperacillin/tazobactam (TZP), teicoplanin (TEC) and piperacillin/tazobactam + teicoplanin (TZP+TEC). This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 4. Median and IQRs for serum creatinine at baseline and 48-72 h

	TZP	TEC	TZP + TEC
Baseline serum creatinine ($\mu\text{mol/L}$), median (IQR)	74 (58-96)	71 (58-96)	82 (62-107)
Serum creatinine ($\mu\text{mol/L}$) at 48-72 h, median (IQR)	71 (56-94)	66 (52-87)	79 (59-109)

TZP, piperacillin/tazobactam; TEC, teicoplanin; TZP + TEC, piperacillin/tazobactam + teicoplanin.

Table 5. Change in serum creatinine with 95% CIs at 48-72 h after commencement of antibiotic treatment compared with baseline for the entire study population, the ICU population and the non-ICU population

	Entire study population	ICU population	Non-ICU population
TZP	-1.98% (-2.73 to -1.22)	1.41% (-0.91 to 3.75)	-2.59% (-3.37 to -1.78)
TEC	-8.01% (-9.54 to -6.45)	0.13% (-5.32 to 6.01)	-9.20% (-10.76 to -7.60)
TZP + TEC	1.61% (-2.25 to 5.70)	7.59% (-0.68 to 16.78)	-1.18% (-5.27 to 3.06)

TZP, piperacillin/tazobactam; TEC, teicoplanin; TZP + TEC, piperacillin/tazobactam + teicoplanin.

Table 6. Change in serum creatinine with 95% CIs at 48-72 h after commencement of antibiotic treatment compared with baseline for the entire study population, patients who received teicoplanin before 2018 (lower dose) and from 2018 onwards (higher dose)

	Entire study population	Lower dose TEC <2018	Higher dose TEC ≥ 2018
TZP	-1.98% (-2.73 to -1.22)	-1.69% (-2.61 to -0.75)	-2.63% (-3.94 to -1.32)
TEC	-8.01% (-9.54 to -6.45)	-7.30% (-9.15 to -5.39)	-9.34% (-12.02 to -6.62)
TZP + TEC	1.61% (-2.25 to 5.70)	3.05% (-1.50 to 8.03)	-2.30% (-9.01 to 4.84)

TZP, piperacillin/tazobactam; TEC, teicoplanin; TZP + TEC, piperacillin/tazobactam + teicoplanin.

tazobactam may induce nephrotoxicity, as a decline in renal function is not seen with the combined use of vancomycin with other β -lactam antibiotics such as cefepime and meropenem.¹²⁻¹⁶ There are no studies comparing piperacillin and piperacillin/

tazobactam with regard to nephrotoxicity. A matched-cohort study performed by Rutter and Burgess,³² in which patients were stratified according to vancomycin exposure, compared piperacillin/tazobactam with ampicillin/sulbactam with regard to renal

Table 7. Patient characteristics of missing data compared with the study population

	Study population	Missing data
<i>n</i>	4202	3013
Age, years, mean (SD)	62.0 (15.4)	62.0 (16.3)
Sex, <i>n</i> (%)		
male	2568 (61.1)	1803 (59.8)
female	1634 (38.9)	1210 (40.2)
Hospital length of stay, days, mean (SD)	19.0 (18.5)	11.2 (13.4)
ICU admission, <i>n</i> (%)		
no	3539 (84.2)	2914 (96.7)
yes	663 (15.8)	99 (3.3)
Antibiotic treatment		
TZP	3188 (75.9)	2433 (80.8)
TEC	791 (18.8)	526 (17.5)
TZP + TEC	223 (5.3)	54 (1.8)
Baseline eGFR (mL/min), mean (SD)	89.6 (37.6)	92.5 (34.2)
Number of nephrotoxic drugs, mean (SD)	1.7 (1.6)	1.0 (1.1)
Days on vasopressors, mean (SD)	3.8 (26.8)	3.1 (39.1)

TZP, piperacillin/tazobactam; TEC, teicoplanin; TZP + TEC, piperacillin/tazobactam + teicoplanin.

function. Results showed that the likelihood of AKI increased with the addition of vancomycin to piperacillin/tazobactam compared with piperacillin/tazobactam alone, but not when vancomycin was added to ampicillin/sulbactam. The authors conclude that the addition of a β -lactamase inhibitor is not responsible for the increased rates of AKI observed in patients treated with piperacillin/tazobactam + vancomycin.³² Another hypothesis suggests that the concomitant occurrence of interstitial nephritis (caused by piperacillin/tazobactam) and oxidative stress (caused by vancomycin) may lead to a stronger decline in renal function compared with monotherapy. However, a recent experimental study using a rat model showed no additional histopathological kidney injury with combination therapy when compared with monotherapy.²⁷ They did observe an increase in serum creatinine for both vancomycin and piperacillin/tazobactam + vancomycin, which they explain by proposing that there might be an interaction at the level of tubular secretion of creatinine. These proposed mechanisms have not been investigated for piperacillin/tazobactam + teicoplanin. Additionally, though vancomycin nephrotoxicity is dose dependent,¹ when comparing patients with lower-dose teicoplanin from before 2018 with higher-dose teicoplanin from 2018 onwards, our results do not suggest a relationship between teicoplanin dose and decline in renal function. Due to their wide CIs these results should be interpreted with caution.

The occurrence of AKI with piperacillin/tazobactam + teicoplanin appears to be lower (11.7%) than reported in studies investigating piperacillin/tazobactam + vancomycin (11%–48.8% with an average of 27.4%).⁹ However, as studies investigating piperacillin/tazobactam + vancomycin used different definitions for AKI and methodologies different from those used in this study, this comparison should be made with great caution and no definitive conclusions should be drawn. Contrary to the studies

that investigated the nephrotoxicity of concomitant piperacillin/tazobactam + vancomycin, we used a linear regression model, using the change in serum creatinine as a continuous variable, in addition to a logistic regression model, in which AKI was dichotomously defined, in order to preserve information such as the ability to calculate the degree of effect.³³ The degree to which renal function declined with piperacillin/tazobactam + teicoplanin compared with monotherapy after correction for confounders was small: 10.8% when compared with teicoplanin and 7.7% when compared with piperacillin/tazobactam monotherapy. So even though our results appear to match the results of studies that investigated concomitant piperacillin/tazobactam + vancomycin with regard to renal function, our results indicate that the overall size of effect is much lower. The clinical relevance of these findings can therefore be questioned, as this effect seems to be small. The findings in this study should be weighed against the clinical indication for the combination of an antipseudomonal β -lactam antibiotic combined with a glycopeptide.

Our missing data consisted of patients with a shorter hospital length of stay and fewer ICU admissions, indicating that this group of patients was probably less severely ill than the patients in our study population. This can be expected as serum creatinine is less often determined in a healthier population compared with a sicker (or ICU) population. If these data had not been missing, however, the minor effect found in our study would probably have been even smaller.

Our study has several limitations that could interfere with these results. As the data were collected retrospectively from our electronic medical records, they are subject to potential biases and limited in completeness. Furthermore, there was no information available for several risk factors for kidney injury, such as the presence and duration of hypotension and volume depletion. Information on infection type, infecting organisms and susceptibility was also not available. When interpreting our results it should therefore be taken into account that residual confounding may play a role. This is especially so as the patient characteristics showed significant differences in various parameters. Additionally, as it is thought that nephrotoxicity of a glycopeptide might be dose dependent, nephrotoxicity could occur later than at the 48–72 h mark used in this study. Future studies should therefore consider taking the cumulative dose of teicoplanin and piperacillin/tazobactam into account with regard to renal function.

To our knowledge, this is the first study to investigate the nephrotoxicity of concomitant piperacillin/tazobactam and teicoplanin. The findings of our study suggest that even though piperacillin/tazobactam + teicoplanin is associated with an increase in AKI when compared with monotherapy, overall there is only a slight decline in renal function. Consequently, the clinical relevance is likely limited and these findings should be weighed against the clinical indication for the combination of an antipseudomonal β -lactam antibiotic combined with a glycopeptide. For clinical practice, our study suggests that with regard to renal function the combination of piperacillin/tazobactam and teicoplanin can probably be safely prescribed. Considering the limitations of our study, however, a propensity-matched study or a prospective study with a larger sample size are warranted to confirm these results.

Conclusions

To our knowledge, this is the first study to examine whether or not concomitant use of piperacillin/tazobactam and teicoplanin is associated with a decline in renal function when compared with monotherapy. Our study suggests that piperacillin/tazobactam + teicoplanin is associated with an increase in AKI compared with monotherapy. However, as the overall decline in renal function with piperacillin/tazobactam + teicoplanin is very small, its clinical relevance is likely limited. Our data therefore suggest that piperacillin/tazobactam and teicoplanin can probably be safely combined, though propensity-matched or prospective studies are warranted to further investigate these results.

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Supplementary data

[Supplementary Information](#) is available as [Supplementary data](#) at JAC Online.

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