

BACKGROUND

- Acute kidney injury (AKI) can significantly increase length of stay, healthcare cost, and mortality
- Several antibiotics have been linked to the risk for AKI
- Piperacillin-tazobactam in combination with vancomycin has a higher incidence than vancomycin with cefepime, or vancomycin alone^{1,2}
- It is unknown whether this effect is exclusive for piperacillin-tazobactam or if it also exists in other beta-lactam antibiotics
- The purpose of this study is to investigate the difference in nephrotoxicity between nafcillin and piperacillin-tazobactam in adult hospitalized patients

METHODS

Study Design: single-center, retrospective cohort

Setting: University of Kentucky Healthcare

Time: September 1, 2010 and September 1, 2014

Inclusion: Adult hospitalized patients treated with piperacillin-tazobactam or nafcillin

Exclusion: Past history of chronic kidney disease (CKD), structural kidney disease, dialysis, underlying renal dysfunction at initiation, vancomycin exposure in piperacillin-tazobactam, vancomycin exposure >5 days in nafcillin, length of stay <2 days, age <18 years, baseline creatinine clearance >4*SD+mean or <30 mL/min, days of antibiotic therapy <2 days, AKI prior to treatment index, within 48 hours of treatment index, or >7 days after treatment was discontinued, no serum creatinine values

Primary Endpoint: Difference in AKI as defined by the RIFLE criteria³

Secondary Endpoints:

- Time to AKI from initiation of antibiotic therapy
- Hospital length of stay
- Mortality (inpatient mortality or transfer to hospice service)

RIFLE Criteria

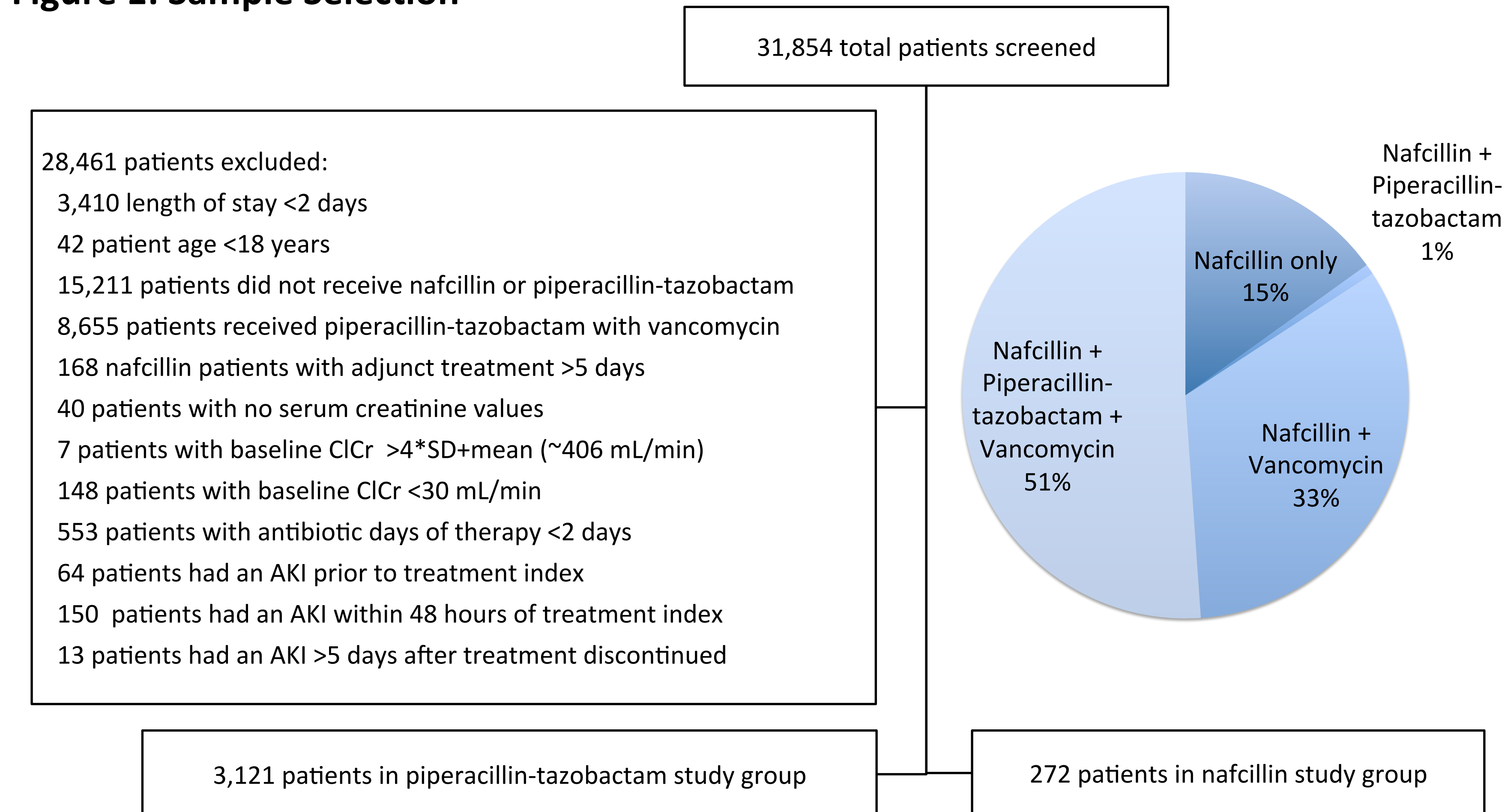
- Risk = 25% decrease GFR from baseline
- Injury = 50% decrease GFR from baseline
- Failure = 75% decrease GFR from baseline

Statistical Analysis:

- Continuous variables: Student's T Test or the Wilcoxon Rank Sum test
- Categorical variables: χ^2 Test or Fisher's Exact Test
- Adjusted analysis: logistic regression

RESULTS

Figure 1: Sample Selection



Baseline Characteristics

- Patients in the piperacillin-tazobactam group had a larger mean age and Charlson Comorbidity Index than patients in the nafcillin group
- Nafcillin had a higher mean baseline creatinine clearance, hypotension, and number of concomitant nephrotoxins, as well as a longer duration of therapy

Table 1: Cumulative Incidence of Acute Kidney Injury (Unadjusted)

Nafcillin with Concomitant Antibiotics ≤5 days vs. Piperacillin-tazobactam						
Characteristic	Overall n=3,393	Nafcillin group n=272	Piperacillin-tazobactam group n=3,121	p-value		
Acute Kidney Injury, overall	294 (8.66)	53 (19.49)	241 (7.72)	<0.0001 ^a		
Risk	230 (6.78)	38 (13.97)	192 (6.15)			
Injury	47 (1.39)	10 (3.68)	37 (1.19)			
Failure	17 (0.50)	5 (1.84)	12 (0.38)			
Nafcillin only vs. Piperacillin-tazobactam						
Characteristic	NAF n=41	NP n=2	NV n=90	NPV n=139	PTZ n=3121	p-value
Acute Kidney Injury, overall	9 (21.95)	0 (0.00)	16 (17.78)	28 (20.14)	241 (7.72)	<0.0001 ^b
Risk	7 (17.07)	0 (0.00)	11 (12.22)	20 (14.39)	192 (6.15)	
Injury	1 (2.44)	0 (0.00)	4 (4.44)	5 (3.60)	37 (1.19)	
Failure	1 (2.44)	0 (0.00)	1 (1.11)	3 (2.16)	12 (0.38)	

Data are number (percentage) unless otherwise indicated. NAF = nafcillin only; NP = nafcillin + piperacillin-tazobactam; NV = nafcillin + vancomycin; NPV = nafcillin + piperacillin-tazobactam + vancomycin.
^aChi-Square Test
^bFisher's Exact Test

Table 2: Adjusted Odds Ratio for Acute Kidney Injury for Nafcillin as compared to Piperacillin-tazobactam

Nafcillin with Concomitant Antibiotics ≤5 days vs. Piperacillin-tazobactam			
Primary Outcome	Odds Ratio (OR)	95% Confidence Interval	
Acute Kidney Injury, overall	2.002	1.357	2.953
Risk	1.799	1.162	2.786
Injury	2.246	0.958	5.264
Failure	2.357	0.685	8.113
Nafcillin only vs. Piperacillin-tazobactam			
Primary Outcome	Odds Ratio (OR)	95% Confidence Interval	
Acute Kidney Injury, overall	2.634	1.154	6.016

Data analyzed using logistic regression. Adjusted for age, sex, Charlson Comorbidity Index, baseline creatinine clearance, hypotension, number of concomitant nephrotoxins, and duration of therapy.

Table 3: Time to Acute Kidney Injury, Hospital Length of Stay, and Mortality

	Overall n=294	Nafcillin group n=53	Piperacillin-tazobactam group n=241	p-value
Time to Acute Kidney Injury ^{a,b}	4.93 ± 3.80 4 (4)	6.00 ± 5.14 5 (4)	4.69 ± 3.41 4 (4)	0.0458 ^c
	Overall n=3,393	Nafcillin group n=272	Piperacillin-tazobactam group n=3,121	p-value
Hospital Length of Stay ^{a,b}	8.00 ± 8.30 5 (6)	14.38 ± 12.69 10 (11)	7.44 ± 7.55 5 (6)	<0.0001 ^c
Mortality	135 (3.98)	23 (8.46)	112 (3.59)	<0.0001 ^d

Data are number (percentage) unless otherwise indicated.
^aMean ± Standard Deviation, ^bMedian (Interquartile Range), ^cWilcoxon Rank Sum Test, ^dChi-Square Test

DISCUSSION

- The nafcillin group had 2 (95% CI 1.36-2.95) times the odds of AKI compared to the piperacillin-tazobactam group after adjusting for important confounders
- This difference persisted in the risk category, although not statistically significant in the injury and failure categories
- A similar result was seen when limiting comparison to those who received nafcillin only. The mean time to AKI and hospital length of stay were longer in nafcillin patients, and the incidence of mortality was also higher in the nafcillin group

CONCLUSIONS

- Beta-lactam antibiotics overall may contribute to nephrotoxicity in adult hospitalized patients, with nafcillin carrying a significantly greater potential for AKI than piperacillin-tazobactam
- Further analysis should be done to assess the impact of risk factors in contributing to this rate of nephrotoxicity, including time and duration of exposure to concomitant nephrotoxins, hypotension, and dehydration in relation to AKI
- Larger population, site and type of infection, dosing schemes, and other beta-lactam antibiotics should also be evaluated

1. Cox J, Rutter WC, Martin C, Burgess, DR, Zephyr, D, Burgess, DS. Acute Kidney Injury during Therapy with Vancomycin in Combination with Beta-Lactams. Acute Kidney Injury during Therapy with Vancomycin in Combination with Beta-Lactams. *Unpublished Data*. 2015.
2. Burgess LD, Drew RH. Comparison of the Incidence of Vancomycin-Induced Nephrotoxicity in Hospitalized Patients with and without Concomitant Piperacillin-Tazobactam. *Pharmacotherapy*. 2014;34(7):670-676.
3. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative w. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-212.