#60

EVALUATION OF OUTCOMES ASSOCIATED WITH INTERMITTENT VERSUS EXTENDED INFUSION OF PIPERACILLIN/TAZOBACTAM IN ACUTELY ILL VETERANS.

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Background

- Piperacillin/tazobactam is one of the most commonly used beta-lactams in the inpatient setting for empiric and targeted treatment of serious infections[1]
- The efficacy of beta-lactams is determined by $fT > MIC$, the amount of time that concentration of free drug exceeds the organism's MIC[1]
- Maximum bactericidal effect can be achieved when free drug concentrations exceed the MIC four-fold for 40-60% of the dosing interval, and studies indicate that extended infusion over three to four hours is the best strategy for reaching ≥ 50% T>MIC.[2,3]
- At the Veterans Affairs San Diego Health Care System, a protocol was implemented starting July 2018 for dosing extended infusion piperacillin/tazobactam in the medical/surgical and critical care wards
- Multiple studies raise increasing concerns about nephrotoxicity from combination therapy with piperacillin/tazobactam and vancomycin.[4-6]
- To date, there is limited data on the impact of piperacillin/tazobactam infusion strategy on incidence of nephrotoxicity in patients concurrently on vancomycin, or in patients with obesity

Objectives

- **Primary:** Evaluate the impact of an extended-infusion (EI) piperacillin/tazobactam dosing protocol on clinical outcomes in acutely ill veterans treated for infections.
- **Secondary:** Compare incidence of adverse effects between study groups, including subgroups for combination therapy with vancomycin and for veterans with obesity

Methods

- **Design**: Single-center, retrospective cohort study from 12/2017 to 02/2019 conducted via chart review
- **Inclusion criteria**: age ≥ 18, admitted to the medical/surgical unit at VA San Diego, at least 48 hours of continuous therapy with piperacillin/tazobactam; for subgroup analyses: ≥48 hours of combination therapy with vancomycin, BMI ≥30 for defining obesity
- **Exclusion criteria**: intermediate sensitivity or resistance to piperacillin/tazobactam, interruption in therapy, intermittent hemodialysis, peritoneal dialysis
- **Primary outcomes**: length of hospital stay, in-hospital mortality rate, 30-day mortality rate, 30-day readmission rate
- **Secondary outcomes**: incidence of adverse drug reactions including thrombocytopenia, acute kidney injury, hepatotoxicity, and *Clostridium difficile* infection
- **Statistical Analysis:** chi-square and Fisher's exact tests for unmatched bivariate analyses, Mann-Whitney U test for non-parametric continuous data, calculated using SPSS Statistics

Results

Table 1. Baseline Characteristics

Characteristic	Intermittent Infusion (N=130) n (%)	Extended Infusion (N=130) n (%)	P-value
Age in years, mean	63.9 ± 12.7	65.5 ± 13.4	0.190
Male gender	126 (97)	124 (95)	1.00
Race:			
• White	90 (69)	100 (77)	0.162
• Non-white	30 (23)	20 (15)	0.116
• Unknown	10 (8)	10 (8)	1.00
BMI, mean	28.8 ± 7.8	28.3 ± 7.2	0.642
Obese (BMI ≥ 30)	48 (37)	44 (34)	0.537
Creatinine Clearance			
• >40 mL/min	113 (87)	114 (88)	0.852
• 20-40 mL/min	14 (11)	14 (11)	1.00
• < 20 mL/min	3 (2)	2 (1)	0.652
≥2 SIRS Criteria	44 (34)	40 (31)	0.331
Culture-positive infection	77 (59)	72 (55)	0.531
Median days of therapy with piperacillin/tazobactam	3	4	0.341
Infection type:			
• SSTI	36 (28)	21 (16)	0.025
• Intraabdominal	18 (14)	29 (22)	0.076
• Pneumonia	20 (15)	24 (18)	0.617
• UTI	15 (11)	14 (11)	0.844
• Osteomyelitis	14 (11)	15 (11)	0.844
• Bacteremia	8 (6)	10 (8)	0.452
• Other	6 (5)	6 (5)	0.844
• Multiple	6 (5)	11 (8)	0.210
Concurrent use of another antibiotic	94 (72)	87 (67)	0.345
Other antibiotic used:			
• Vancomycin	81 (62)	80 (61)	0.174
• Other	13 (10)	7 (8)	0.519

Primary Outcomes

Figure 1. Median Length of Stay

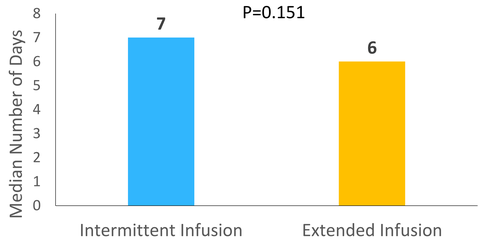
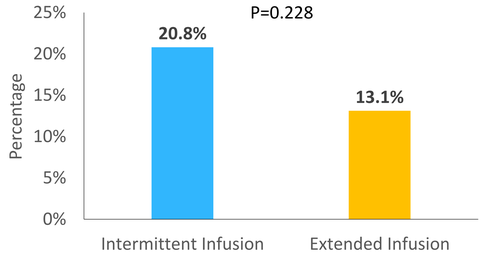


Table 2. Mortality Outcomes

	Intermittent Infusion (N=130) n (%)	Extended Infusion (N=130) n (%)
In-Hospital Mortality	1 (0.8)	0 (0)
30-Day Mortality	5 (3.8)	5 (3.8)

Figure 2. 30-Day Readmission Rates



Secondary Outcomes

Figure 3. Adverse Effects

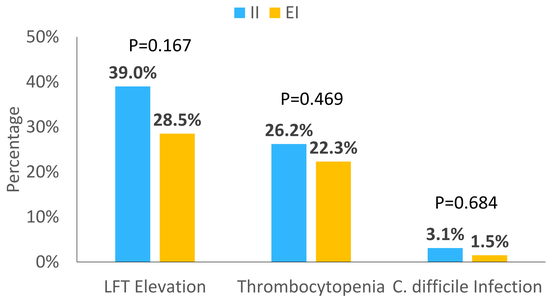
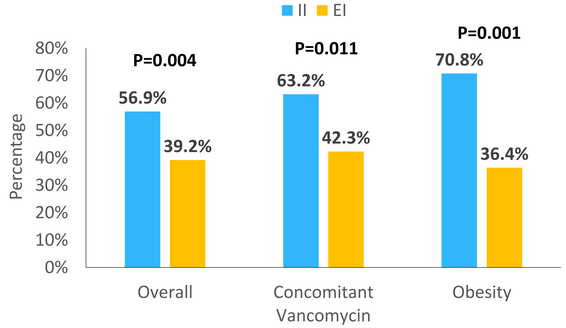


Figure 4. Acute Kidney Injury Rates including Subgroup Analyses



Discussion

- Results showed trends consistent with previous studies in acutely ill patients including lower 30-day readmission rates and reduced rates of adverse effects
- The study demonstrated the novel finding that extended infusion dosing is associated with significantly lower rates of acute kidney injury overall, as well as in subgroup analyses for veterans concurrently on vancomycin therapy as well as those with obesity. This is in contrast with previous studies that found no difference based on infusion strategies.[7-9]
- Reduced AKI rates with extended infusion dosing are likely related to diminished drug exposure or decreased peak drug concentration
- **Limitations**: retrospective cohort design, single center, limited assessment of other potential contributory factors to AKI including role of vancomycin dosing and concurrent administration of other nephrotoxic medications

Conclusion

- There were no statistically significant differences in primary clinical outcomes of length of stay, in-hospital mortality, 30-day mortality, and 30-day readmission rates between acutely ill veterans who received intermittent versus extended infusion dosing of piperacillin/tazobactam
- Extended infusion dosing was associated with absolute rate reductions of 30-day readmissions and incidence of adverse effects such as liver enzyme elevation, thrombocytopenia, and *C. difficile* infections
- Demonstrated significantly lower rate of acute kidney injury with extended infusion dosing which supports enhanced patient safety
- Extended infusion may be the preferred method of administration for obese patients and/or those receiving vancomycin concurrently
- This highlights the need to reduce risk of AKI using a multimodal approach including judicious use of broad spectrum empiric antimicrobial therapy, duration of therapy, and pharmacokinetic/pharmacodynamic optimization of antimicrobial dosing

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Disclosure

Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.