Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized with Acute Infection (ACORN)

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Background and Overview

The Surviving Sepsis Campaign recommends timely administration of antibiotics targeted against MRSA or multidrug resistant gram-negative organisms when risk factors for these are present. At Vanderbilt University Medical Center, is it standard practice to administer vancomycin for MRSA coverage and either piperacillin-tazobactam (TZP) or cefepime (FEP) to patients admitted to the medical ICU with concerns of sepsis irrespective of risk factors. Considering the widespread use of these agents, tolerability of concomitant therapy is often discussed. Cefepime has been associated with neurotoxicity presenting as delirium, seizures, and even coma. This occurs with a median of 4 days of therapy in patients with renal dysfunction, older age, or a previous brain injury. When therapeutic drug monitoring is available, it is most commonly associated with cefepime trough concentrations greater than 20 mg/L. Overall incidence has been reported at 0.21% but has been reported up to 15% in the ICU setting. TZP's association with nephrotoxicity when combined with vancomycin is inconsistent through the literature (shown below). Available observational data indicates that acute kidney injury (AKI) can occur as early as 48 hours into therapy but occurs more commonly after 72 hours with an overall incidence of 22.2%. A regular conclusion found in these studies is that a randomized control trial is needed to assess the nephrotoxicity of Vancomycin and TZP.

Study	Design	Supports Increased AKI	Refutes Increased AKI
Luther et al, *CCM*, 2018; 46(1)	Meta-analysis (n=24,799)	X	
Guiliano et al, *Pharmacotherapy,* 2016; 36(12)	Meta-analysis (n=3,258)		
Moenster et al, *Clin Microbiol Infect*, 2014; 20(1)	Retrospective Cohort, Vanc + TZP vs Vanc + FEP x 72 hours (n=139)	X	
Gomes et al, *Pharmacotherapy,* 2014; 34(7)	Retrospective Cohort: Vanc + TZP vs Vanc + FEP ≥ 48 hours (n=224)	X	
Navalkele et al, *CID,* 2017; 64(2)	Retrospective Cohort: Vanc + TZP vs Vanc + FEP ≥ 48 hours (n=224)	X	
Karino et al, *AAC*, 2016; 60(6)	Retrospective Cohort: Vanc + TZP ≥ 48 hours (n=320)	X	
Chang et al *AAC*, 2023; 67(8)	Rat model comparing renal biomarkers when givening Vanc+TZP vs Vanc alone		X
Miano et al, *ICM,* 2022; 48(1)	Prospective Cohort ICU patients (n=739): Vanc + TZP vs Vanc + FEP ≥ 48 hours noted increase in Scr but no change in other biomarkers or outcomes		X
Blevins et al, *AAC,* 2019; 63(5)	Retrospective Cohort (n=2,492): Vanc + TZP vs Vanc + FEP vs Vanc + Mero≥ 48	X	
O'callaghan et al, *Int J Antimicrob Agents,* 2020; 56(1)	Retrospective cohort study ICU patients (n=260); Vanc + TZP vs Vanc + FEP vs Vanc + Mero≥ 48	X	
Wen et al, *Int J Pharm,* 2018; 537(1)	Rat Model indicating that TZP are substrates for OAT1/3		X
Pais et al, *J Antimicrob Chemother,* 2020 75(5)	Rat Model with histopathology indicated all vancomycin treated rats had AKI, addition of TZP did not worsen UOP or biomarkers.		X

Methods

Primary Objective: To compare the safety of cefepime(FEP) versus piperacillin-tazobactam (TZP)

Design: Pragmatic, open-label, parallel-group, randomized comparative safety trial between November 10th, 2021 and October 7th 2022.

Inclusion:

- ≥18 Years of age
- At least 1 dose of FEP or TZP ordered within 12 hours of presentation

Laboratory strategies:

- Allergy to cephalosporins or penicillin's
- Received > 1 dose of antipseudomonal B-lactam in prior 7 days
- Incarcerated
- If treating physician determined on option was better

Intervention/Follow up:

- Randomization 1:1 using CDS tool recommending dose based on GFR
  - TZP: 3.375g Bolus over 30 minutes followed by extended infusion over 4 hours Q8h
  - CEF: 2g IV push over 5 minutes Q8h
  - For 7 days after enrollment, CDS would remind/record a reason for change to alternative therapy
- Duration determined by treating physician
- Addition of vancomycin or metronidazole was determine by treating physician
- Therapeutic drug monitoring (TDM) was completed by clinical pharmacists for vancomycin, but not B-lactams.
- Frequency of laboratory assessment was determined by the treating physician
- RASS and GCS scores recorded every 12 hours
- CAM-ICU score recorded every 12 hours for ICU patients
- Trial personnel adjudicated:
  - Presence of sepsis using Sepsis-3 criteria
  - Presumed source of infection
  - Whether renal replacement had been received and indication

Primary End Point:

- Highest stage of acute kidney injury (AKI) or Death within 14 days of randomization
  - 5 level ordinal scale utilized for AKI
  - Baseline determine by pre-admission record when available
  - Patients already on RRT received a score of 0 for survival and 4 for death

Secondary Endpoints:

- Proprortion of patients experiencing a major adverse kidney event at day 14 defined as a composite of:
  - Death
  - Receipt of new RRT
  - Persistent Kidney dysfunction (final inpatient creatine was 2x bassline)
- Days of alive free of delirum or coma within 14 days
  - CAM-ICU + or a RASS of -4 or -5

Statistical analysis:

- Designed to enroll 2050 patients to provide 80% power to detect 0.65 primary analysis
  - Sample size target increased to 2500 due to 75% concomitant vancomycin therapy
  - 2500 patients would provide 92% power to detect an OR of 0.75 in primary analysis
- Odds regression model for the primary analysis
- Major AKI's compared using unadjusted logistic regression model
- Sensitivity analyses including:
  - All enrolled patients including those who did not receive FEP or TZP
  - > 48 hours of therapy
  - Restricted to patients with a measured creatinine prior to admission
  - Only preillness creatinine level as baseline creatinine level

Multivariable proportional odds regression model for primary outcome:

- Age
- Sex
- Baseline creatinine
- Prior RRT
- Presumed source of infection
- Location at enrollment
- Vasopressors
- Mechanical ventilation
- SOFA Score

Results

Baseline Characteristics (n=2511)	FEP (n=1,214)	TZP (n=1,297)
Average Age, median (IQR)	57 (42 to 68)	59 (44 to 69)
Sepsis	658 (54.2%)	704 (54.3%)
Suspected Source at enrollment (Top 3 listed)		
Intra-abdominal	319 (26.3%)	293 (22.6%)
Lung	257 (21.2%)	300 (23.1%)
Skin and Soft Tissue	201 (16.6%)	245 (18.9%)
Vancomycin on day of enrollment	942 (77.6%)	997 (76.9%)
Vancomycin with 14 days of enrollment	1004 (82.7%)	1049 (80.9%)
Vancomycin Median Duration (IQR)	2 days (1-4)	2 days (1-4)
Chronic Kidney Disease	243 (20.4%)	259 (20.3%)
Assessment at enrollment		
No AKI	623 (51.3%)	652 (50.3%)
Stage 1 AKI	231 (19%)	311 (24%)
Stage 2 AKI	134 (11%)	123 (9.5%)
Stage 3 AKI	148 (12.2%)	144 (11.1%)
Median creatinine level (IQR)		
Lowest in prior 12 months	0.7 (0.6-0.8)	0.8 (0.6 to 0.9)
At enrollment	1 (0.8 to 1.6)	1 (0.8 to 1.5)
RASS Score Median (IQR) (within 12 hours of enrollment)	0 (-1 to 0)	0
Coma	84 (6.9%)	77 (5.9%)
Delirium	62 (5.1%)	51 (3.9%)
Median Duration	3 days (1-4 days)	3 days (1-4 days)
Adjunctive GNR Coverage (aminoglycoside or carbapenem) within 14 days of enrollment	85 (7%)	92 (7.1%)

Outcomes	FEP (n=1,214)	TZP (n=1,297)	OR or ARR (95% CI)
Primary Outcome: AKI or death by day 14			OR: 0.95
No stage (survived)	910 (75%)	952 (73.4%)	(0.8-1.13)
Stage 1 (survived)	86 (7.1%)	100 (7.7%)	
Stage 2 (survived)	41 (3.4%)	70 (5.4%)	
Stage 3 (survived)	85 (7.0%)	97 (7.5%)	
Stage 4 (died)	92 (7.6%)	78 (6.0%)	
Secondary Outcome: Major adverse kidney at day 14	124 (10.2%)	114 (8.8%)	ARR: 1.4 (-1 to 3.8)
Secondary Outcome: Death	92 (7.6%)	78 (6.0%)	ARR: 1.6 (-0.5 to 3.6)
Delirium and coma free days within 14 days	Median IQR: 14 (14 to 14) Mean SD: 11.9 (4.6)	14 (14 to 14) 12.2 (4.3)	**OR: 0.79 (0.65 to 0.95)**
Delirium and coma free days within 28 days	28 (28 to 28) 24.4 (9.1%)	28 (28 to 28) 24.8 (8.2%)	**OR 0.8 (0.66 to 0.97)**
Delirium	200 (16.5%)	181 (14%)	ARR: 2.5 (-0.4 to 5.4)
Coma	164 (13.5%)	162 (12.5%)	ARR: 1 (-1.7 to 3.7)
Delirium or Coma	252 (20.8%)	225 (17.3%)	ARR: 3.4 (0.3 to 6.6)

All post hoc and subgroup analyses showed similar results (Figure 3)

Conclusions

Strengths:

- Randomization with a pragmatic strategy (EMR)
  - Increased external validity
  - Blinding until enrollment
  - Minimal exposure to pre-antibiotics
- Large sample size

Limitations:

- Unblinded after enrollment
- Lack of therapeutic drug monitoring
  - Vancomycin trough
  - Cefepime trough
- Duration of antimicrobials
- Dose of antimicrobials

		• Culture data • Cross-over
	Authors' Conclusions: "Treatment with piperacillin-tazobactam did not increase the incidence of AKI or death. Treatment with cefepime resulted in more neurological dysfunction."	
	Recommendations: This is very well designed trial and should serve as a template for future RCT's looking for a pragmatic approach. However, the author's conclusions may be more accurate written as "treatment with TZP did not increase the incidence of AKI or death after a short duration with concomitant vancomycin. Treatment with cefepime resulted in statistically significant increases in neurologic dysfunction, although this does not appear to be clinically significant." The median duration of vancomycin in this study prevents us from concluding that longer therapies of Vanc + TZP does not cause true AKI. Until stronger evidence is available, it is best to align with the many retrospective studies indicating that AKI can occur after 72 hours of therapy. Additional conclusions that can be drawn from this trial is that it is time for VUMC to update its antimicrobial dosing strategies and risk factor assessments for ICU patients.	

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