Vancomycin + Piperacillin/Tazobactam: Where Do We Stand?

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Grand Rounds

Norton Infectious Disease Institute

Objectives

- Describe the historical association of nephrotoxicity between vancomycin and piperacillin/tazobactam
- Identify methods to reduce the risk of nephrotoxicity when using vancomycin and piperacillin/tazobactam

Patient Case

68 y/o male (110 kg) with PMH CKD and CHF presents from home with shortness of breath and fever. Bedside CXR is suggestive of LLL infiltrates. Patient was emergently intubated, blood cultures were obtained, and due to hemodynamic instability, vasopressors were started. The team suspects pneumonia and elects to empirically start antibiotics.

- 101.4 F (38.6 C)
- HR 120
- Ventilated, FiO_2 50%
- 67/49 (phenylephrine started)
- WBC: 21.1
- Cr: 1.4 (EMR Calculated CrCl: 85 mL/min)
- Microbiology: MRSA in sputum 5 months ago

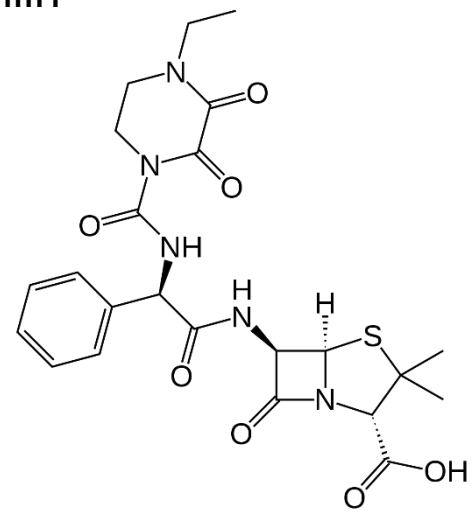
Antibiotic selection:

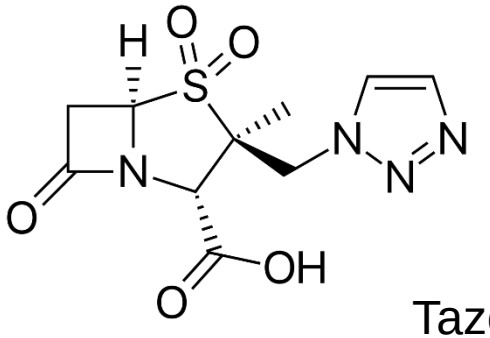
- Vancomycin 2 grams IV every 12 hours + meropenem 2 grams IV every 8 hours

Piperacillin/ Tazobactam

- Broad gram positive and gram negative (with anti-pseudomonal activity)
- Known to on very rare occasion lead to acute interstitial nephritis (AIN) resulting in acute kidney injury (AKI)
- Inhibits tubular secretion of creatinine (pseudo-elevation)

Piperacillin



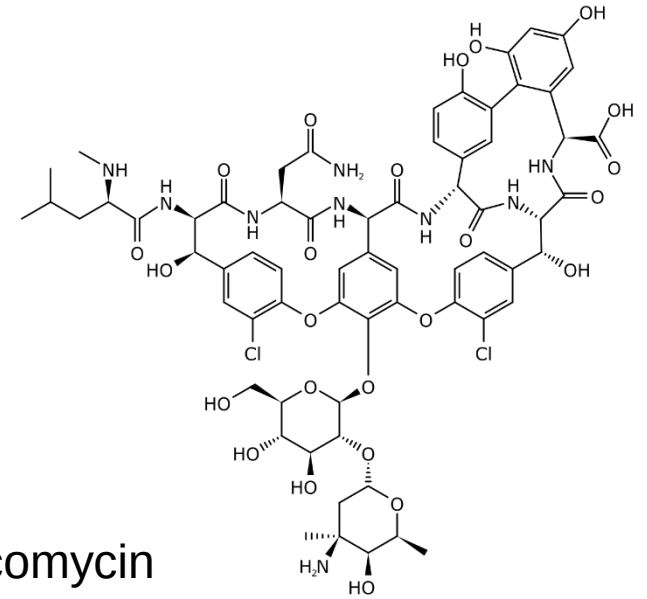


Tazobactam

Mandell et al. Principles of Practice of Infectious Disease. 2020

Vancomycin

- 1st line therapy for MRSA coverage and empiric gram positive coverage
- Commonly induces a reversible nephrotoxicity due to uncertain mechanisms (proximal tubule cell damage vs interstitial nephritis)
- Typically exposure related



Vancomycin

Mandell et al. Principles of Practice of Infectious Disease. 2020

Vancomycin Risk Factors for Nephrotoxicity

Trough >20 mg/L

Dose >4 grams/day

Duration >7 days

History of renal disease

Severity of illness (ICU)

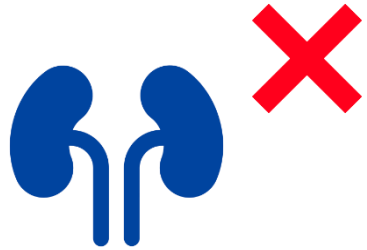
Concomitant nephrotoxic drugs

Watkins et al. Clin Infect Dis. 2017

So, why the fear?

Piperacillin/
Tazobactam

Vancomycin



Piperacillin/Tazobactam + Vancomycin

Commonly Avoided?

A Tale of Two Abstracts

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RETROSPECTIVE EVALUATION OF THE INCIDENCE OF VANCOMYCIN AND/OR PIPERACILLIN-TAZOBACTAM INDUCED ACUTE RENAL FAILURE

Thaddaus Hellwig, South Dakota State University/Sanford USD Medical Center, Rhonda Hammerquist, Beth Loecker, Jaime Shields, Sanford USD Medical Center

Introduction: Vancomycin and piperacillin-tazobactam are antibiotics used to treat a variety of infections. Acute renal failure (ARF) has historically been associated with vancomycin while incidence rates of ARF with piperacillin-tazobactam are limited. Anectdotal observations at our facility have demonstrated higher than expected rates of ARF with piperacillin-tazobactam. **Hypothesis:** The rate of ARF with piperacillin-tazobactam is equal to rates with vancomycin. **Methods:** Retrospective review of all patients 18 years and older admitted to Sanford USD Medical Center receiving either vancomycin and/or piperacillin-tazobactam for at least 48 hours over a 6 month period. ARF was defined as either an increase of serum creatinine (SCr) equal to ≥0.5 mg/dL or a μ 50% increase from baseline. Data collection included SCr, vancomycin levels, nephrotoxic medications, additional antibiotics, unit of hospital during initiation of therapy (floor or ICU), dialysis, and death. A p-value ($\alpha = 0.05$) was used for comparisons between treatment groups and development of ARF. The 95% confidence intervals and p-values were also computed for further analysis. **Results:** A total of 735 subjects were evaluated with an overall rate of 10.5% of subjects developing ARF in the groups of vancomycin, piperacillin-tazobactam, or combination therapy. The respective proportions of all patients developing ARF were 4.9%, 11.1%, and 18.6% (vancomycin vs. piperacillin-tazobactam, $p = 0.014$; vancomycin vs. combination, $p = 0.0001$); respective proportion of patients within the ICU developing ARF were 6.0%, 12.2%, and 21.2% (vancomcyin vs. piperacillin-tazobactam, $p = 0.279$; vancomycin vs. combination, $p = 0.005$). Significant characteristics leading to ARF included: unit of admission during initiation of antibiotics and total number of nephrotoxic medications. There was no statistical difference noted in baseline SCr or number/duration of additional antibiotics leading to ARF. **Conclusions:** Piperacillin-tazobactam demonstrated a significant increased rate of ARF compared to vancomycin in the overall population but not in the ICU population. Combination therapy showed an increased rate of developing ARF compared to vancomycin amongst both populations.

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ACUTE KIDNEY INJURY IN PATIENTS RECIEVING CONCOMITANT VANCOMYCIN AND PIPERACILLIN/TAZOBACTAM

Emily Min, Kevin Box, James Lane, Jose Sanchez, Raul Coimbra, Jay Doucet, Bruce Potenza, Lindsay Wargel, University of California San Diego Medical Center

Introduction: Acute kidney injury (AKI) in critically ill patients has been associated with a two to six-fold increased risk of death over non-AKI patients. Nephrotoxic drugs can contribute to the development of AKI. Vancomycin and piperacillin/tazobactam (pip-tazo) are individually considered mildly nephrotoxic; however, the renal insult associated with their concomitant use is currently not described. **Hypothesis:** We hypothesize that concomitant use of vancomycin and pip-tazo is associated with higher rates of AKI than treatment with vancomycin or pip-tazo alone. **Methods:** Patients admitted to the surgical intensive care unit (SICU) during a one-year period who received vancomycin and/or pip-tazo for at least 48 hours were studied. The subset of treated patients developing AKI was then identified based on a serum creatinine (SCr) increase to greater than 1.5 times baseline during antibiotic therapy. Data collected from the electronic medical record included patient demographics; antibiotic indication, dose, and course; SCr; and concomitant use of other nephrotoxic agents. The primary endpoint was the incidence of AKI. **Results:** During the study period, 73 patients were treated concomitantly with vancomycin and pip-tazo, and 67 patients were treated with vancomycin alone. Due to the small sample size, the pip-tazo alone group ($N = 10$) was excluded from analysis. Baseline demographic data was well-matched between the groups. Factors potentially contributing to the development of AKI, such as severity of illness as measured by APACHE II score and concomitant use of other nephrotoxic agents, were controlled for in the analysis. The incidence of AKI was higher in the vancomycin/pip-tazo group (40.5%) compared to the vancomycin alone group (9.0%; $p<0.001$). **Conclusions:** Concomitant use of vancomycin and pip-tazo is associated with a higher incidence of AKI than treatment with vancomycin alone among SICU patients.

Hellwig et al. Crit Care Med. 2011
Min et al. Crit Care Med. 2011

Cascade of Retrospective Research

Nephrotoxicity during Vancom
Therapy in Combination with
Piperacillin-Tazobactam or Cefe

W. Cliff Rutter,[a,b] Jessica N. (
David S. Burgess[a]

Is the Combinati
Associated with
analysis

Christopher A. Giulia

Comparison of Acute Kidney Injury During Treatment with Vancomycin in Combination with Piperacillin-Tazobactam or Cefepime

Diane M. Gomes, Carmen Smotherman, Amy Birch, Lori Dupree, Bethany J. Della Vecchia,

Does Combination Therapy With Vancomycin and Piperacillin-Tazobactam Increase the Risk of Nephrotoxicity Versus Vancomycin Alone in Pediatric Patients?

Katherine E. McQueen, PharmD and Dana W. Clark, PharmD

Department of Pharmacy, Children's Healthcare of Atlanta, Atlanta, Georgia

Con
with vancomycin in combination with piperacillin–tazobactam or with meropenem

Majed S. Al Yami[a,b,*]

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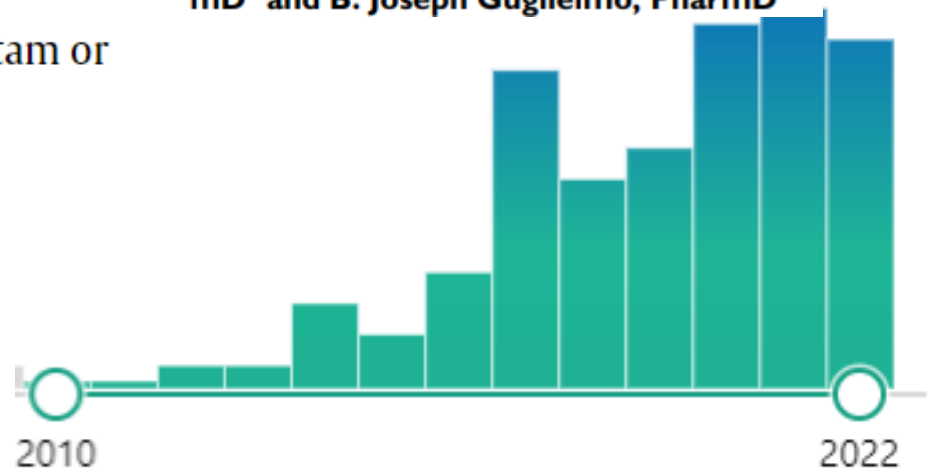


Figure available at: PubMed.ncbi.nih.gov

Research Findings

- Vancomycin vs. vancomycin + piperacillin/tazobactam combination and the frequency of nephrotoxicity or AKI
- Typically, data supported the combination led to more incidence of AKI
- Systematic Reviews conducted also came to similar conclusions*

Luther et al. Crit Care Med. 2018
Blair et al. Am J Nephrol. 2021

What have we done to mitigate the risk?

- Avoid the combination?
  - Select alternative gram positive agent
  - Select alternative beta-lactams

Avoid Vancomycin?

- Strategy to Prevent Nephrotoxicity in Patients With Multiple Risk Factors for Adverse Renal Outcomes (STOP-NT)
  - Objective
    - Evaluate early switch to less nephrotoxic antimicrobials to prevent AKI in high-risk patients receiving vancomycin
  - Design
    - Randomized Controlled Trial (n=103)
  - Primary Outcome
    - Nephrotoxicity
  - Secondary Outcome
    - Modified AKI definition

Carreno et al. Ann Pharmacotherapy. 2017

STOP-NT: Results and Implications

- Nephrotoxicity
  - 6.1% vs 9.8%, respectively, P = 0.72
- Modified AKI
  - 32.7% vs 31.4%, respectively, P = 0.89
- Conclusion
  - Vancomycin is not the influential factor to lead to AKI in this high-risk patient population and using a less-nephrotoxic agent led to similar rates of kidney insult

Take Away:
Alternative strategies, such as enhanced monitoring in patients at risk

Carreno et al. Ann Pharmacotherapy. 2017

Cefepime or Meropenem Instead?

- Vancomycin + cefepime or meropenem versus vancomycin + piperacillin/tazobactam was significant for more AKI in those receiving piperacillin/tazobactam
  - No difference in critically ill populations*
- Has pushed many providers to pursue cefepime or meropenem as the beta-lactam backbone in patients

Is this a reasonable route to take?

Luther et al. Crit Care Med 2018

What can we take away from the data?

Vancomycin + Piperacillin/Tazobactam	
Well understood or reasonable pathophysiological explanation for additive nephrotoxicity/AKI?	✗
Using alternatives to vancomycin negates AKI?	✗
Using alternative to piperacillin/tazobactam negates AKI?	✓ / ✗

Possible conclusion:

Patients are likely to get nephrotoxicity or AKI regardless of exposure → focus on mitigating risk

Return to Risk Factors

Trough >20 mg/L

Dose >4 grams/day

Duration >7 days

History of renal disease

Severity of illness (ICU)

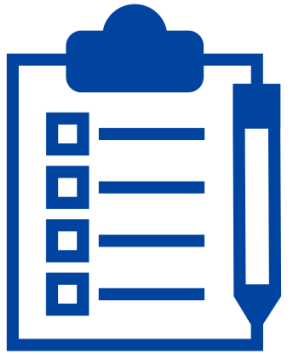
Concomitant nephrotoxic drugs

Implement Strategies on the Patient and System Level to Mitigate Kidney Injury and Exposure to Vancomycin

Watkins. Clin Infect Dis. 2017

Mitigate AKI on the Patient

- Assess appropriateness of empiric combination therapy
- Assess risk factors for AKI development
- Limit the exposure of vancomycin or combination therapy

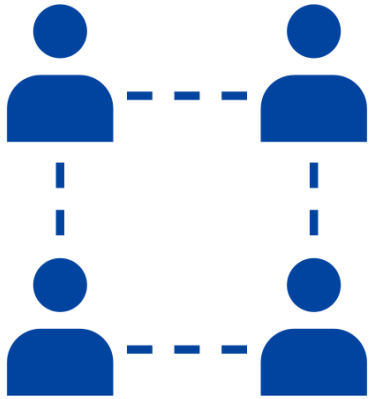


Patient Specific Approaches: Improve Assessment

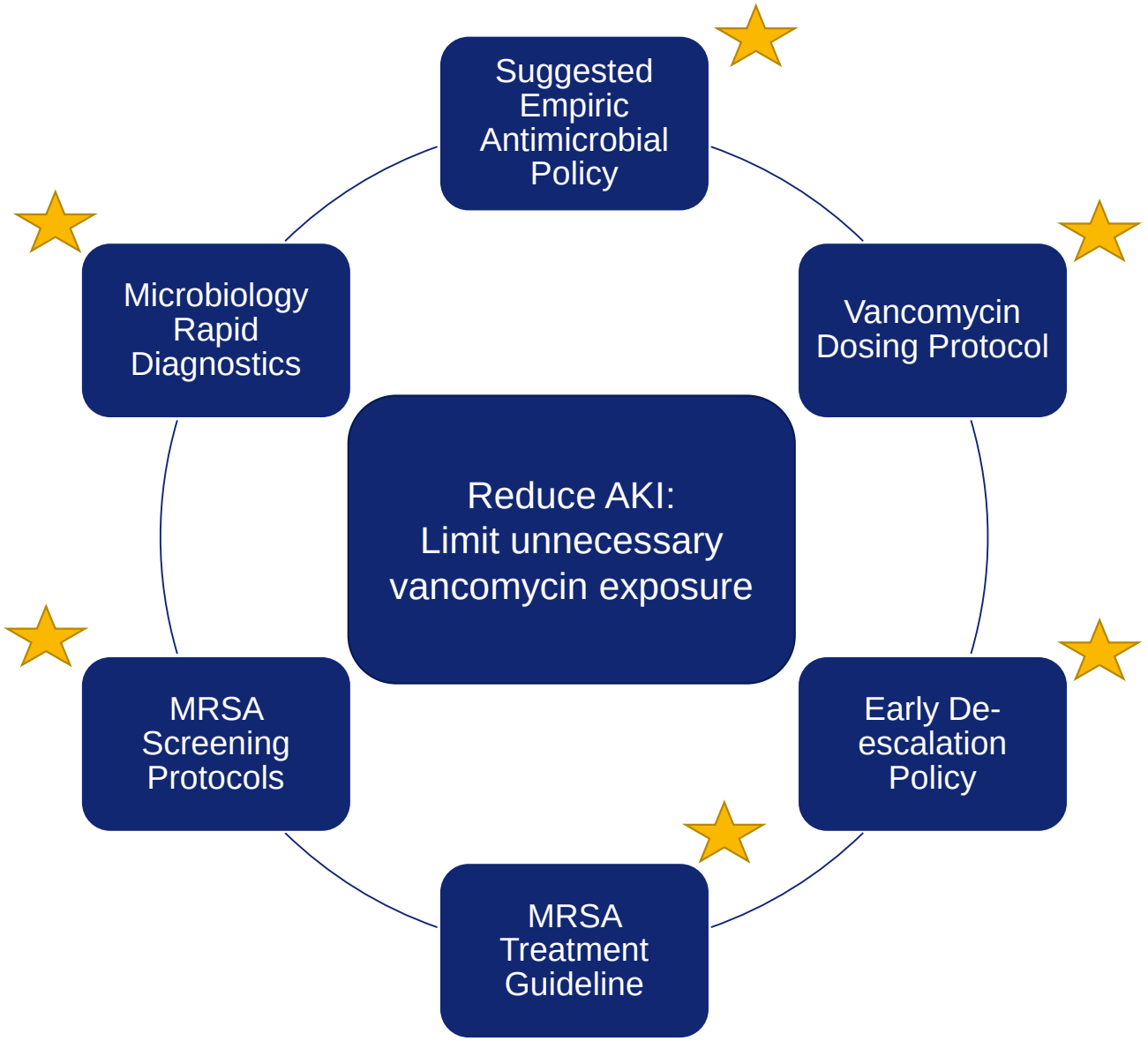
- Patients presenting in critical illness are likely going to develop an AKI/are already in AKI despite lab values
  - Creatinine is a lagging factor
- Large patients will require larger doses which will increase risk
- Not all patients require vancomycin + piperacillin/tazobactam
- Not all indications require broad or combination vancomycin + piperacillin/tazobactam
- Follow-up with microbiology and de-escalate/discontinue to limit vancomycin duration and exposure

Mitigating AKI on the System Level

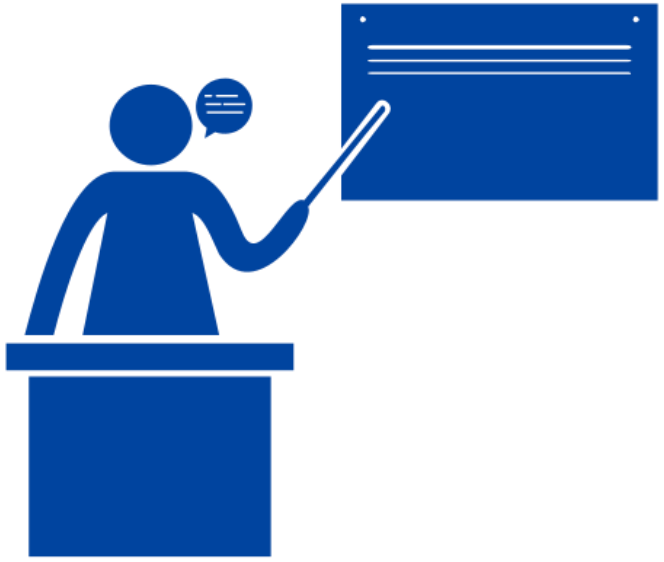
- Implementation of Stewardship Policies and Protocols to standardize practice
- Cooperation with the interdisciplinary team is key



System Level Stewardship Examples



Maintain Standardized Stewardship Practices



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Main Points

- Vancomycin+ piperacillin/tazobactam may contribute additional risk to developing AKI
  - Likely additional factors contributing the risk of AKI in these patients and vancomycin may be the driving force
- Identification of risk factors for AKI with vancomycin may be the strongest action we can take on the individual patient to mitigate risk
- Implementation of stewardship policies can standardize practice and mitigate AKI development with vancomycin on a system scale
- Use of vancomycin + piperacillin/tazobactam can still be an appropriate empiric regimen

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