Incidence of acute kidney injury in pediatric patients receiving vancomycin with concomitant piperacillin-tazobactam or anti-pseudomonal cephalosporin

Andrew T. Wright, PharmD, MSCR; Travis Heath, PharmD, BCPS, BCPPS; Beiyu Liu, PhD, MS
Duke University Hospital; Durham, North Carolina

Background
• When determining an empirical antibiotic regimen, factors such as potential pathogens, resistance patterns, organ function, and medication interactions must be considered. It is well known vancomycin is associated with dose-dependent nephrotoxicity in adults.1

• Vancomycin daily doses of >4 g/day, duration >7 days, trough concentrations >35 mcg/ml, and history of kidney disease are examples of risk factors that can potentiate nephrotoxicity.2 In contrast, the common anti-pseudomonal β-lactam piperacillin-tazobactam has not been shown to be associated with nephrotoxicity when used as a single agent.3

• Previous studies have shown the combination of vancomycin plus piperacillin-tazobactam was associated with a higher incidence of acute kidney injury (AKI) than with vancomycin alone.4,5 These initial retrospective studies have led to further investigations to evaluate the potential additive nephrotoxic effects of vancomycin combined with an anti-pseudomonal β-lactam.6,7

• Previous studies may not be generalizable to all patient populations; therefore there is an opportunity to evaluate therapy in the previously unstudied pediatric population.

Objectives

Primary Objective
• To determine the relative incidence of nephrotoxicity with vancomycin combination therapy with piperacillin-tazobactam as compared to vancomycin combination therapy with an anti-pseudomonal cephalosporin in the pediatric population

Secondary Objectives
• To determine if a difference exists between the relative incidence of AKI with vancomycin-/piperacillin-tazobactam as compared to vancomycin-/anti-pseudomonal cephalosporin in the following: Days to development of AKI
• Duration of AKI
• Vancomycin trough concentrations
• Hospital length of stay
• ICU length of stay
• Need for renal replacement therapy (RRT)
• Proportion of patients in each classification of pRIFLE
• Requirement of vasopressor agents, ICU stay, or mechanical ventilation at any time during admission

Study Design
• IRB-approved, single-center, propensity score-matched, observational retrospective cohort study

Methods

Inclusion Criteria
Pediatric patients age <18 admitted to the Duke Children’s Hospital between July 1, 2013 – August 1, 2016
Received at least 48 hours of vancomycin plus piperacillin-tazobactam OR vancomycin plus either ceftazime/tazidime
Had a baseline Scr recorded within 48 hours of admission and prior to antibiotic administration

Exclusion Criteria
Previously received renal replacement therapy prior to antibiotic initiation
Already received piperacillin-tazobactam or cephalosporin/tazobactam without the addition of vancomycin during their admission
Incomplete medical record
Documented Stage IV (GFR of 15-29 mL/min per 1.73 m²) or Stage V (GFR <15 mL/min per 1.73 m² or on dialysis) renal failure at baseline

Primary Endpoint
Incidence of AKI as determined by the “risk,” “injury,” or “failure” according to the published pRIFLE criteria during combination therapy or within 72 hours after completion of combination therapy in the vancomycin/piperacillin-tazobactam group vs. vancomycin/anti-pseudomonal cephalosporin group

Secondary Endpoints
Incidence of the following factors in patients that received vancomycin plus piperacillin-tazobactam vs. vancomycin plus an anti-pseudomonal cephalosporin:
Development of AKI (days) from initiation of combination antibiotic therapy
Duration of AKI according to pRIFLE injury or failure classifications (Days)
Hospital length of stay (days)
ICU length of stay (days)
Need for renal replacement therapy (RRT) after antibiotic initiation
Receipt of a vasopressor agent at any time during admission
Requiring ICU stay at any time during admission
Requiring mechanical ventilation at any time during admission
Proportion of patients stratified by pRIFLE classification between the two antibiotic regimen groups for risk, injury, and failure category

Table 1: Patient Population

Table 2: Pediatric Risk, Injury, Failure, Loss, End-stage renal disease (pRIFLE) Scaleα

Classification Estimated creatinine clearance (eCCL) Urine output
Risk eCCL decrease by 25% < 0.5 ml/kg/hr for 8 hours
Injury eCCL decrease by 50% < 0.5 ml/kg/hr for 16 hours
Failure eCCL decrease by 75% or <35 ml/min/1.73m² < 0.5 ml/kg/hr for 24 hours or anuric
Loss Persistent failure >4 weeks
End-stage End stage renal disease Persistent failure >3 months

Statistical Analysis
• Continuous variables will be summarized with mean/medians, standard deviation and ranges. Depending on whether the continuous variables are normally or non-normally distributed, two-sample t test or Wilcoxon-Mann-Whitney test respectively, will be used to compare the variables between the two cohorts. Categorical variables will be summarized with frequency counts and percentages. Chi-squared test/Fishers exact test will be used to determine if there is a difference between cohorts. Significance of the tests will be assessed at alpha = 0.05. Since the patients are not randomly assigned to one of these two treatment regimens, potential confounding effects of vancomycin combination therapy consisting of piperacillin-tazobactam or an anti-pseudomonal β-lactam will be assessed and inversely proportionate to treatment weighted (IPTW) approach will be used to make the sample more representative of the overall population

References

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