Pharmacy **2014**, *2*, 276-286; doi:10.3390/pharmacy2040276

OPEN ACCESS

pharmacy

ISSN 2226-4787

www.mdpi.com/journal/pharmacy

Article

Antimicrobial Renal Injury in a Pediatric Intensive Care Unit: β-Lactams *vs.* Vancomycin

Jeffrey J. Cies [1,2,3,*], Wayne S. Moore II [3], Venkat Shankar [4] and Arun Chopra [5,6]

[1] St. Christopher's Hospital for Children, 160 East Erie Avenue, Philadelphia, PA 19134, USA

[2] Drexel University College of Medicine, Philadelphia, PA 19129, USA

[3] Alfred I duPont Hospital for Children, Wilmington, DE 19803, USA; E-Mail: Wayne.MooreII@nemours.org

[4] Children's National Medical Center, Washington, DC 20010, USA; E-Mail: VShankar@childrensnational.org

[5] NYU Langone Medical Center, New York, NY 10016, USA; E-Mail: arun.chopra@nyumc.org

[6] NYU School of Medicine, New York, NY 10016, USA

* Author to whom correspondence should be addressed; E-Mail: jeffrey.cies@gmail.com; Tel.: +215-427-5176.

External Editors: Sandra Benavides Caballero and Richard Parrish

Received: 9 September 2014; in revised form: 3 November 2014 / Accepted: 14 November 2014 / Published: 28 November 2014

Abstract: Vancomycin trough (Vt) concentrations of 15–20 mcg/mL have been associated with an increased rate of renal injury in adults. Current data in pediatrics suggests Vts of 15–20 mcg/mL do not increase the risk of renal injury in children admitted to a pediatric intensive care unit (PICU). The primary objective was to determine if a difference exists in the incidence of renal injury in PICU patients receiving a β-lactam as compared with vancomycin therapy with Vts of 15–20 mcg/mL. This was a retrospective cohort study conducted within a PICU within a freestanding tertiary care pediatric hospital. The records of children admitted to the PICU between 10/2008–6/2009 who received vancomycin for ≥48 h targeting higher Vt concentrations of ≥15 mcg/mL for pneumonia, bacteremia, and meningitis were reviewed. This cohort (V group) was compared to children admitted from July 2009–July 2013 who received cefepime or piperacillin/tazobactam for ≥72 h (B group). Serum creatinine values were collected from 48 h before until 48 h after discontinuation of therapy for calculation of estimated glomerular filtration rate. Renal injury was categorized according to pRIFLE. 57 and 112 patients were included in the V and B groups, respectively.

The mean (SD) therapeutic dose of vancomycin was 63.5(17.3) mg/kg/day and the mean (SD) trough was 17.8(3.1). The mean (SD) dose of cefepime was 51(26) mg/kg/dose with an every 8 h interval. The mean (SD) dose of piperacillin/tazobactam was 77(22) mg/kg/dose with an every 6 h interval. The mean (SD) PRISM scores were 10.9(10.2), 4.24(6.4) for the V and B groups, respectively ($p < 0.001$). Five of 57 and 10 of 112 patients in the V and B groups, respectively, were classified as having injury according to pRIFLE. No patient was classified as having a degree of renal injury greater than the pRIFLE injury. The incidence of renal injury was 8.8% in the V group and 8.9% in the B group, respectively ($p = 1$). Our observations suggest that maintaining Vt concentrations ≥15 mcg/mL is not associated with an increased rate of renal injury as compared with β-lactam monotherapy in a PICU population.

Keywords: renal injury; vancomycin; pediatric; β-lactam; pRIFLE

1. Introduction

Current national guidelines recommend when vancomycin is used as empiric or definitive therapy for the treatment of methicillin resistant *Staphylococcus aureus* (MRSA) and in certain disease states (e.g., meningitis, pneumonia) a trough level of 15–20 mcg/mL and/or an area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio (e.g., AUC:MIC ratio) of ≥400:1 for adults and children should be attained to maximize efficacy [1–5]. Vancomycin has a long clinical history, some associated with an impure formulation that was termed "Mississippi Mud", which has included concerns for vancomycin induced renal injury [6–10]. As a result of the current recommendations for targeting higher vancomycin trough levels, concerns regarding vancomycin renal injury have re-emerged. The current adult literature suggests an increased incidence of renal injury with increasing vancomycin trough levels, especially when other risk factors are present including: intensive care unit admission, prolonged duration of vancomycin therapy, concurrent nephrotoxic medications, increased age, and obesity [6,11–13]. There is some level of disagreement in the pediatric literature evaluating risk factors for renal injury with higher vancomycin trough concentrations as compared with the adult literature [6,11–18].

The mechanism of renal injury associated with β-lactams is thought to be a result of acute proximal tubular necrosis [19]. Most investigations regarding β-lactam renal injury in the adult and pediatric literature have evaluated the incidence of renal injury of β-lactam therapy in conjunction with an aminoglycoside [20–22]. β-lactam monotherapy has consistently shown to have less renal injury as compared to the β-lactam/aminoglycoside combination. However, no investigation has sought to evaluate the incidence of β-lactam renal injury as compared with vancomycin therapy targeting troughs ≥15 mcg/mL in the general pediatric population or within a pediatric intensive care unit. Therefore, the purpose of this investigation was to compare the incidence of renal injury in pediatric intensive care unit patients receiving therapy with a β-lactam (cefepime or piperacillin/tazobactam) compared to those receiving vancomycin with a trough level ≥15 mcg/mL.

2. Materials and Methods

Study Design and Patient Population

This was a single-center, retrospective study that was conducted at a 189-bed freestanding children's tertiary care teaching hospital with 33 critical care beds that provide care for children with burns, trauma, congenital heart disease and children on extra corporeal life support (ECLS). This study protocol was approved by the Drexel University College of Medicine Institutional Review Board and this investigation was performed in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki.

The β-lactam cohort was comprised of children admitted from July 2009 through July 2013 that received either cefepime (CEF) or piperacillin/tazobactam (TZP) for ≥72 h (B cohort). The purpose of a 72 h inclusion criteria for the β-lactam cohort was chosen to allow for exclusion of individuals receiving concomitant vancomycin for empiric therapy. There were no restrictions related to age or dosing regimen received. The B cohort was compared to a previously described cohort of patients that received vancomycin for at least 48 h targeting higher vancomycin trough (Vt) concentrations of 15–20 mcg/mL for pneumonia, bacteremia, and meningitis [15]. There were no restrictions related to age or dosing regimen received. Concurrent use of non β-lactam antimicrobials was allowed in the B cohort (e.g., concurrent aminoglycoside therapy), excluding vancomycin.

Serum creatinine (SCr) values were collected from 48 h before the start of therapy, when available, until 48 h after the discontinuation of therapy. These values were used to calculate a baseline and daily estimated glomerular filtration rate (eGFR) using the updated Schwartz equation [23]. Patients with elevated baseline serum creatinine values were included if they met the criteria above regarding the duration of use for vancomycin or β-lactam therapy were met. Renal injury was defined and categorized utilizing the Pediatric-modified RIFLE (pRIFLE) criteria [24]. Utilizing the changes in eGFR, the pRIFLE criteria categorize the severity of renal injury as Risk, Injury, Failure, Loss, or End stage. Due to the high rate of diuretic use in both groups and since no patient in this study developed oliguria, we used changes in eGFR alone to define renal injury as has been validated in previous studies [25]. To be classified as having renal injury, patients had to have decreases in eGFR to meet the "risk", "injury", "failure", "loss", or "end-stage": criteria of pRIFLE For purposes of statistical analysis, renal injury was transformed into a "yes" or "no" binary outcome. Patients meeting pRIFLE criteria grading of "risk", "injury", "failure", "loss", or "end-stage" were classified as a "yes" for renal injury analysis as a binary outcome. All other patients were classified as "no" for renal injury analysis as a binary outcome.

Data pertaining to demographic, laboratory values, vancomycin dosing and pharmacokinetics, other nephrotoxic medications, and procedures were also collected (aminoglycosides, diuretics, acyclovir, amphotericin, vasopressors, contrast dye, ECLS). For the purpose of statistical analysis, use of aminoglycosides, acyclovir, or amphotericin was considered as a single categorical variable, concomitant nephrotoxic medications. Steady-state vancomycin serum trough concentrations were generally obtained, taking into consideration age, population pharmacokinetic estimates and SCr. All vancomycin concentrations (and their temporal relationship to the preceding or subsequent vancomycin dose) were collected, and the highest serum Vt concentration during the duration of vancomycin therapy was documented. Pediatric risk of mortality (PRISM-III) scores [26] were also collected to allow for comparison of criticality between the β-lactam and vancomycin cohorts to determine its potential impact or contribution

to renal dysfunction. For the purposes of statistical analysis, PRISM-III scores were considered a continuous variable.

Demographic and clinical characteristics were compared between the cohorts with a student's *t*-test for continuous variables and a chi-square, Fisher's exact test, or Mann-Whitney U test for non-continuous variables. A two-sided significance level with $\alpha = 0.05$ was used to determine statistical significance. Logistic regression was used to test the association between antimicrobial received and renal injury. Variables determined to be clinically or statistically significant ($p < 0.05$) were then included in a multivariable logistic regression analysis to determine clinical variables that represented potential predictors of renal injury. All analyses were performed using IBM SPSS Version 20 (SPSS Inc., Chicago, IL, USA).

3. Results

Overall, 177 children in the pediatric intensive care unit received vancomycin between November 2008 and June 2009 [15]. Of these, 120 were excluded: 91 for a non-study disease state and 29 who did not have a Vt concentration. Therefore, 57 patients met the inclusion criteria and were included in the V cohort. From July 2009 through July 2013, there were 928 courses of cefepime or piperacillin/tazobactam in the pediatric intensive care unit. Of these, 675 were excluded because the duration of therapy was <72 h and 141 were excluded for not having SCr values available for assessment allowing for enrollment of 112 patients in the β-lactam (B) cohort. Baseline demographics are presented in Table 1. The median age was 2 years in both cohorts. The gender distribution was 56% *vs.* 53% males comparing V and B cohorts, respectively ($p = 0.74$).

Dosing and interval selection for each antimicrobial is presented in Table 2. For the V cohort, interestingly, 19 of 57 (33.3%) patients received vancomycin on an every 4 h dosing interval in order to obtain a vancomycin trough ≥15 mcg/mL. The median duration of vancomycin therapy was five days (range two–22 days). Thirty-three of fifty-seven (57.8%) patients in the V cohort received concurrent nephrotoxic medications and 20 of 57 (35%) received vasoactive medications while on vancomycin therapy. Of note, five of 57 (8.7%) patients in the V cohort were on ECLS at the time they were receiving vancomycin. Sixty-one of one hundred and twelve (54.5%) patients in the B cohort received concurrent nephrotoxic medications, $p = 0.74$ for the comparison between the V and B cohorts for patients receiving concurrent nephrotoxic medications. Sixteen of one-hundred twelve (14.3%) patients received vasoactive medications while receiving β-lactams, $p = 0.003$ for the comparison between the V and B cohorts for patients receiving vasoactive medications.

The baseline SCr values between the two cohorts were 0.49 ± 0.48 and 0.38 ± 0.49 mg/dL for the V and B cohorts, respectively ($p = 0.29$). The mean (SD) PRISM (Table 3) scores were 11 (10.2) and 4.2 (6.4) ($p < 0.001$). Patients who developed renal injury were classified as meeting the definition of "injury" according to the pRIFLE criteria No patient developed a degree of renal injury higher than the pRIFLE "injury" classification. Five of fifty-seven (8.8%) and 10 of 112 (8.9%) patients developed renal injury in the V and B cohorts, respectively, demonstrating no statistical difference in the incidence of renal injury between groups ($p = 1$).

Table 1. Patient demographics and clinical characteristics.

Parameter	Vancomycin	B-lactam
Patients, n	57	112
Median age, years (IQR)	2 (0.33–8)	2 (0.5–9)
0–6 months, n	16	28
7 months–2 years, n	14	37
3–8 years, n	13	20
9–12 years, n	0	6
13–18 years, n	13	17
19–23 years, n	1	4
Males, n (%)	32 (56)	59 (53)
Median weight, kg (range)	13.5 (2–108)	12 (2–106)
Diagnosis		
Bacteremia/Sepsis *, n (%)	31 (54)	28 (25)
Fever/Neutropenia, n (%)	0	5(4.5)
Intra-Abdominal, n (%)	0	8 (7)
Meningitis **, n (%)	9 (15.7)	1 (0.9)
Pneumonia, n (%)	17 (29.8)	29 (26)
Pyelonephritis	0	3 (2.7)
Wound, n (%)	0	1(0.9)
Tracheitis ***, n (%)	0	37 (33)
Median baseline SCr (IQR)	0.3 (0.25–0.7)	0.28 (0.2–0.42)

* p-value = 0.02; ** p-value = 0.0003; *** p-value < 0.0001; SCr = serum creatinine; SD = standard deviation; IQR = interquartile range.

Table 2. β–lactam and vancomycin dosing and interval selection.

Parameter	Vancomycin	Cefepime	Piperacillin/Tazobactam
Patients, n	57	85	27
Starting dose (mean ± SD) mg/kg	51.8 ± 17.1/day	51 ± 26/dose	77 ± 22/dose
Median starting dose (IQR) mg/kg	60 (40–60)	50 (38–55)	80 (56–100)
Therapeutic dose (mean ± SD) mg/kg/day	63.5 ± 17.3	N/A	N/A
Serum trough level (Mean ± SD), mcg/mL	17.8 ± 3.1	N/A	N/A
Every 4 h dosing interval, n (%)	19 (33.3)	0	1 (3.7)
Every 6 h dosing interval, n (%)	33 (57.9)	38 (44.7)	23 (85.2)
Every 8 h dosing interval, n (%)	5 (8.8)	39 (45.9)	3 (11.1)
Every 12 h dosing interval, n (%)	0	8 (9.4)	0

SD = standard deviation; IQR = interquartile range.

Table 3. PRISM scores for the β-lactam and vancomycin pediatric intensive care unit cohorts.

Category	Vancomycin	β-Lactam
Mean	10.9 *	4.23 *
SD	10.2	6.45
Min	1	1
Max	37	34.1
Median	9	1.6

* p-value < 0.001 for the comparison of the mean PRISM scores between the vancomycin and β-lactam cohorts; SD = standard deviation; min=minimum; max=maximum.

The results of the regression analysis are presented in Table 4. For the V cohort, concurrent nephrotoxic medications were not found to be associated with an increased incidence of renal injury, odds ratio (OR) = 0.93, 95% confidence interval (CI) 0.88–1.06. There were three factors found to be associated with renal injury in the V cohort and they were duration of vancomycin (OR = 1.32, 95% CI 1.01–1.22), use of VA-ECLS (OR = 1.32, 95% CI 1.13–1.75), and the use of vasoactives (OR = 1.41, 95% CI 1.11–1.37). For the B cohort, none of the factors were found to be associated with renal injury (Table 4).

Table 4. Univariate regression analysis results.

Cohort	Variable	OR	CI
V	Concurrent nephrotoxin	0.93	0.88–1.06
V	Duration of therapy *	1.32	1.01–1.22
V	VA-ECLS *	1.32	1.13–1.75
V	Vasoactives *	1.41	1.11–1.37
V	PRISM score	1.01	0.97–1.12
B	Concurrent nephrotoxin	1.04	0.92–1.14
B	Duration of therapy	1.05	0.98–1.1
B	Vasoactives	1.05	0.85–1.2
B	PRISM score	1.06	0.991.01

V = vancomycin; B = β-lactam; CI = confidence interval; VA-ECLS = veno-arterial extracorporeal life support; OR = odds ratio; * = p-value < 0.05, statistically significant.

The multivariable logistic regression analysis has been previously reported [15]. As none of the variables of interest were found to be statistically significant in univariable analysis, multivariable regression was not conducted for the B cohort.

4. Discussion

Multiple investigations have been conducted in an effort to elucidate the association and incidence of renal injury with vancomycin. In pediatric patients, some investigations have been undertaken. McKamy *et al.* evaluated the incidence and risk factors for vancomycin induced renal injury in children who were older than 1 week to 19 years [14]. The authors suggested that higher vancomycin troughs in addition to admission to the intensive care unit were potential risk factors for renal injury [15]. Similarly, Knoderer *et al.* suggest that ICU admission and initial vancomycin trough levels ≥15 mcg/mL were associated with renal injury [17]. However, these studies did not address the relationship between the vancomycin trough concentrations and the incidence of renal injury in critically ill children Cies *et al.* did attempt to quantify the incidence of vancomycin induced renal injury in a pediatric intensive care unit population between troughs ≥15 mcg/mL and troughs of 5–15 mcg/mL [15] and demonstrated there was not an increased incidence of vancomycin induced renal injury in a cohort of 113 patients that received vancomycin for at least 48 h [15]. Similarly, Moffett [18] and colleagues evaluated the incidence of renal injury in pediatric cardiac intensive care unit patients. The rate of renal injury in this population was estimated at 7%, which closely resembles the rate of 8.8% in the Cies [15] investigation. Further, Totapally [16] and colleagues did not observe a relationship between renal injury and the

total vancomycin dose, the peak vancomycin level or the trough vancomycin level in their pediatric ICU population.

β-lactam antimicrobials are also thought to be nephrotoxic in some capacity [19–22]. Most of the investigations to date have evaluated the incidence or association with renal injury in patients that received a β-lactam in conjunction with another class of antimicrobial, most commonly being an aminoglycoside. Tamma [20] and colleagues demonstrated that combination therapy with a β-lactam and aminoglycoside was common for definitive treatment of Gram-negative bacteremia and sought to determine whether there was any difference in efficacy and safety between combination therapy and monotherapy. Of the 879 patients with bacteremia, which included pediatric intensive care unit patients, 61% received combination therapy. While there was no difference in mortality between the combination and monotherapy treatment groups, 19% of patients in the combination group met their definition of acute kidney injury while the incidence of acute kidney injury in the monotherapy treatment group was 10% (OR = 2.15, 95% CI 2.09–2.21) [20]. Piperacillin/tazobactam was the most commonly prescribed β-lactam (37%) followed by ceftriaxone (30.8%) and cefepime (15%). The estimation of acute kidney injury of 10% with β-lactam monotherapy closely resembles the incidence of renal injury in our investigation of 8.9%. Interestingly, the investigation by Zengin [21] and colleagues in a non-pediatric intensive care unit population of children with febrile neutropenia treated with piperacillin/tazobactam, no patient receiving monotherapy experienced renal injury. There was 1 patient in the piperacillin/tazobactam plus amikacin group that experienced reversible renal injury that was attributed to the amikacin. Further, in the Cochrane Database review [22] of β-lactam monotherapy *versus* combination therapy in adult patients, the incidence of renal injury with β-lactam monotherapy is estimated at ~26%. This increased incidence of renal injury in adult patients can be explained by other physiologic and age-related factors.

The incidence of renal injury associated with vancomycin across pediatric patients is 7%–14%, but could be lower based on recent investigations. The incidence of renal injury for β-lactams is estimated to be around 10%, which is consistent with the rates of renal injury in our investigation [20–22]. Although we did show that the duration of vancomycin therapy was associated with increasing renal injury, the overall rates were not different from patients treated with β-lactam antimicrobials. While there is much debate and perseveration regarding renal injury associated with vancomycin, our data from our previous [15] and current investigation suggests the incidence and risk is not greater than that associated with other β-lactam antimicrobials, which are commonly used in pediatric intensive care units and don't engender the same debate or concern for renal injury. As previously mentioned, there have been two investigations evaluating whether vancomycin trough levels are associated with renal injury across an entire pediatric population and three specifically evaluating varying pediatric ICU populations [14–18]. While ICU admission and vancomycin troughs ≥15 mcg/mL were identified as risk factors, thus far, none of the three investigations of pediatric ICU patients validate the finding of increased renal injury with vancomycin trough levels ≥15 mcg/mL [15,16,18]. The pediatric intensive care unit is a very dynamic setting and there are many factors that could be associated with and contribute to renal injury such as vasoactive medications, contrast dye, other nephrotoxic medications, reduced cardiac output, fluid restriction, and overall reduced body perfusion in pediatric patients that are critically ill. While the ability to measure vancomycin serum concentrations is readily available, elevated serum vancomycin concentrations may not be the sole cause of renal injury for each patient. A renal insult

could happen at any point during the pediatric intensive care unit admission and after that insult, the clearance and elimination of medications such as vancomycin and β-lactams will be reduced. Therefore, an elevated vancomycin level in the presence of renal injury may not represent renal injury in a cause and effect relationship. Since the ability to measure serum concentrations of other commonly used medications in the pediatric intensive care unit is limited, the clinician's ability to determine the cause of the true renal insult will be rather difficult. Since changes in serum creatinine are late markers of renal damage, other biomarkers may more useful in determining the true time course and reason for the renal insult such as cystatin C [25–27].

Based on the inclusion criteria for this investigation, there was a difference in the disease states included in this analysis. The inclusion criteria were limited with regard to the specific disease states for the vancomycin cohort for multiple reasons. First, in an effort to remove any potential unmeasurable confounders from other disease states, we tried to create a study population that was homogeneous. Second, pediatric IICU patients with pneumonia, meningitis, or bacteremia typically represent the more critically ill population that may need vancomycin, as opposed to patients with urinary tract infections, skin and soft tissue infections, or osteomyelitis, or when vancomycin is used as surgical prophylaxis, for example. Similarly, when evaluating patients receiving β-lactam monotherapy, there will naturally be a difference in disease states treated such as tracheitis, intra-abdominal infections, and fever with neutropenia. While attempting to make this investigation mirror clinical practice, this may have introduced unmeasurable confounders.

Our investigation was conducted at a single, academic, free-standing pediatric institution and, as such, causation cannot be inferred nor generalization to other pediatric hospitals or settings. The true determination of causality of an event such as renal injury can only truly be determined via a prospective investigation. Therefore, our findings could be a result of sample selection. While each of these limitations are valid, this investigation is the first attempt to quantitate the incidence of renal injury with vancomycin troughs ≥15 mcg/mL and commonly used β-lactam antimicrobials in the pediatric intensive care unit. Our data suggests all of unrest surrounding renal injury and vancomycin troughs ≥15 mcg/mL may not be warranted.

This data implies the rate of renal injury may be similar in patients treated with vancomycin as those treated with β-lactam antimicrobials. In this cohort, the patients treated with vancomycin seemed to represent a sicker patient population with higher PRISM scores, more use of vasoactives and ECLS. Despite this bias towards sicker patients, the rate of renal injury was similar further calling into question the hypothesis that vancomycin presents a higher risk of renal injury than other antimicrobials prescribed in the pediatric intensive care unit.

Renal injury is a relatively common occurrence in critically ill patients, and from this retrospective review we cannot determine whether the rate of renal injury was increased with the use of vancomycin over the degree of illness, yet we can infer that using other antimicrobials may be equally harmful. Targeting vancomycin trough levels ≥15 mcg/mL does not seem to increase the risk of renal injury over the use of other commonly used antimicrobials in critically ill pediatric patients. We would encourage all practitioners to follow both serum levels for medications as well as employing close monitoring for renal injury and be prepared to adjust medication doses and intervals frequently to maintain appropriate levels to minimize secondary renal injury from inadvertent overdosing in patients whose renal function is declining.

5. Conclusions

This investigation suggests the incidence of renal injury in pediatric ICU patients receiving therapy with a β-lactam (cefepime or piperacillin/tazobactam) and those receiving vancomycin with a trough level ≥15 mcg/mL is similar.

Author Contributions

Jeffrey J. Cies was involved in the planning and development of the project, collection, analysis of the data and writing of the manuscript.

Wayne S. Moore II was involved in the planning and development of the project, analysis of the data and writing of the manuscript.

Venkat Shankar was involved in the planning and development of the project and writing of the manuscript.

Arun Chopra was involved in the planning and development of the project, analysis of the data and writing of the manuscript.

Conflicts of Interest

This work, in part, was presented at the 43rd Society of Critical Care Medicine Annual Congress abstract number 939 San Francisco, CA, USA, January 2014.

References

1. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 388–416.
2. Tunkel, A.R.; Hartman, B.J.; Kaplan, S.L.; Kaufman, B.A.; Roos, K.L.; Scheld, W.M.; Whitley, R.J. Practice guidelines for the management of bacterial meningitis. *Clin. Infect. Dis.* **2004**, *39*, 1267–1284.
3. Rybak, M.; Lomaestro, B.; Rotschafer, J.C.; Moellering, R., Jr.; Craig, W.; Billeter, M.; Dalovisio, J.R.; Levine, D.P. Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am. J. Health Syst. Pharm.* **2009**, *66*, 82–98.
4. Liu, C.; Bayer, A.; Cosgrove, S.E.; Daum, R.S.; Fridkin, S.K.; Gorwitz, R.J.; Kaplan, S.L.; Karchmer, A.W.; Levine, D.P.; Murray, B.E.; *et al.* Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. *Clin. Infect. Dis.* **2011**, *52*, e18–e55.
5. Bradley, J.S.; Byington, C.L.; Shah, S.S.; Alverson, B.; Carter, E.R.; Harrison, C.; Kaplan, S.L.; Mace, S.E.; McCracken, G.H., Jr.; Moore, M.R.; *et al.* The Management of Community-Acquired Pneumonia in Infants and Children Older than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin. Infect. Dis*. **2011**, *53*, e25–e76.

6. Lodise, T.P.; Patel, N.; Lomaestro, B.M.; Rodvold, K.A.; Drusano, G.L. Relationship between initial vancomycin concentration time profile and nephrotoxicity among hospitalized patients. *Clin. Infect. Dis.* **2009**, *49*, 507–514.
7. Moellering, R.C., Jr. Vancomycin: A 50-year reassessment. *Clin. Infect. Dis.* **2006**, *42*, S3–S4.
8. Rybak, M.J. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin. Infect. Dis.* **2006**, *42*, S35–S39.
9. Levine, D.P. Vancomycin: A history. *Clin. Infect. Dis.* **2006**, *42*, S5–S12.
10. Aronoff, G.R.; Sloan, R.S.; Dinwiddie, C.B., Jr.; Glant, M.D.; Fineberg, N.S.; Luft, F.C. Effects of vancomycin on renal function in rats. *Antimicrob. Agents Chemother.* **1981**, *19*, 306–308.
11. Lodise, T.P.; Lomaestro, B.; Graves, J.; Drusano, G.L. Larger vancomycin doses (atleast 4 grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob. Agents Chemother.* **2008**, *52*, 1330–1336.
12. Ingram, P.R.; Lye, D.C.; Tambyah, P.A.; Goh, W.P.; Tam, V.H.; Fisher, D.A. Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy. *J. Antimicrob. Chemother.* **2008**, *62*, 168–171.
13. Munsch, J.; Ellison, J.; Nguyen, N.; Christensen, C.; Halilovic, J. Association of vancomycin trough concentrations and nephrotoxicity. *Pharmacotherapy* **2009**, *29*, 182e–291e.
14. McKamy, S.; Hernandez, E.; Jahng, M.; Moriwaki, T.; Deveikis, A.; Le, J. Incidence and risk factors influencing the development of vancomycin nephrotoxicity in children. *J. Pediatr.* **2011**, *158*, 422–426.
15. Cies, J.J.; Shankar, V.S. Nephrotoxicity in Patients with Vancomycin Trough Concentrations of 15–20 μg/mL in a Pediatric Intensive Care Unit. *Pharamcotherapy* **2013**, *33*, 392–400.
16. Totapally, B.R.; Machado, J.; Lee, H.; Paredes, A.; Raszynski, A. Acute kidney injury during vancomycin therapy in critically ill children. *Pharmacotherapy* **2013**, *33*, 598–602.
17. Knoderer, C.A.; Nichols, K.R.; Lyon, K.; Veverka, M.M.; Wilson, A.C. Are elevated vancomycin serum trough concentrations achieved within the first 7 days of therapy associated with acute kidney injury in children? *J. Pediatr. Infect. Dis. Soc.* **2014**, *3*, 127–131.
18. Moffett, B.S.; HIlvers, P.S.; Dinh, K.; Arikan, A.A.; Checchia, P.; Bronicki, R. Vancomycin associated acute kidney injury in pediatric cardiac intensive care patients. *Congenit. Heart Dis.* **2014**, doi:10.1111/chd.12187.
19. Tune, B.M. Nephrotoxicity of beta-lactam antibiotics: Mechanisms and strategies for prevention. *Pediatr. Nephrol.* **1997**, *11*, 768–772.
20. Tamma, P.D.; Turnbull, A.E.; Harris, A.D.; Milstone, A.M.; Hsu, A.J.; Cosgrove, S.E. Less is more: combination antibiotic therapy for the treatment of gram-negative bacteremia in pediatric patients. *JAMA Pediatr.* **2013**, doi:10.1001/jamapediatrics.2013.196.
21. Zengin, E.; Sarper, N.; Kılıç, S.C. Piperacillin/tazobactam monotherapy *vs.* piperacillin/tazobactam plus amikacin as initial empirical therapy for febrile neutropenia in children with acute leukemia. *Pediatr. Hematol. Oncol.* **2011**, doi:10.3109/08880018.2011.557144.
22. Paul, M.; Dickstein, Y.; Schlesinger, A.; Grozinsky-Glasberg, S.; Soares-Weiser, K.; Leibovici, L. Beta-lactam *versus* beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. *Cochrane Database Syst. Rev.* **2013**, doi:10.1002/14651858.CD003038.pub2.

23. Schwartz, G.J.; Munoz, A.; Schneider, M.F.; Mak, R.H.; Kaskel, F.; Warady, B.A.; Furth, S.L. New equations to estimate GFR in children with CKD. *J. Am. Soc. Nephrol.* **2009**, *20*, 629–637.
24. Akcan-Arikan, A.; Zappitelli, M.; Loftis, L.L.; Washburn, K.K.; Jefferson, L.S.; Goldstein, S.L. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int.* **2007**, *71*, 1028–1035.
25. Hassinger, A.B.; Backer, C.L.; Lane, J.C.; Haymond, S.; Wang, D.; Wald, E.L. Predictive power of serum cystatin C to detect acute kidney injury and pediatric-modified RIFLE class in children undergoing cardiac surgery. *Pediatr. Crit. Care Med.* **2012**, doi:10.1097/PCC.0b013e318238b43c.
26. Krawczeski, C.D.; Vandevoorde, R.G.; Kathman, T.; Bennett, M.R.; Woo, J.G.; Wang, Y.; Griffiths, R.E.; Devarajan, P. Serum cystatin C is an early predictive biomarker of acute kidney injury after pediatric cardiopulmonary bypass. *Clin. J. Am. Soc. Nephrol.* **2010**, doi:10.2215/CJN.02040310.
27. Kandasamy, Y.; Smith, R.; Wright, I.M. Measuring cystatin C to determine renal function in neonates. *Pediatr. Crit. Care Med.* **2013**, doi:10.1097/PCC.0b013e318271f4a5.