Comparing Vancomycin Area Under the Curve With a Pharmacist Protocol that Incorporates Trough and Maximum Doses at a Children's Hospital

Betool O. Al-Mazraawy, PharmD and Jennifer E. Giroto, PharmD

OBJECTIVE Updated vancomycin guidelines suggest dose adjustment based on area under the curve in a 24-hour period (AUC_{24}). This study aims to determine whether a pharmacist managed vancomycin protocol that incorporates maximum dosing paired with trough monitoring can achieve appropriate vancomycin AUC_{24} exposures.

METHODS A retrospective review was performed evaluating vancomycin usage from October 2018 through September 2019 at a children's hospital. Patients with less than 4 doses or lack a trough concentration were excluded. Vancomycin AUC_{24} were estimated using 2 calculations: 1) the Le method, incorporating age and serum creatinine, and 2) the trapezoidal method based upon population data and patient-specific trough. Target AUC_{24} ranges were assessed. AUC_{24} goals were 400 to 600 mg•hr/L, but due to known variations between calculations, a variance of 20 mg•hr/L was allowed for each end of the goal. Secondary analyses included evaluations of efficacy and toxicity.

RESULTS Two-hundred twenty-three patients were included. Initial doses were estimated to meet AUC_{24} goals in only 63%. After trough-based dose modification, 81% achieved a therapeutic AUC_{24} . Using the trapezoidal method, therapeutic concentrations were found in 51% of patients based on the initial dose and 77% after dose modification. Only 6.3% of patients had kidney injury with only 1 of those patients having any calculated $AUC_{24} > 600$ mg•hr/L and none above 620 mg•hr/L. No clinical failures were identified.

CONCLUSIONS Increased initial dosing in infants and children is needed to result in AUC_{24} exposures recommended in the guidelines. Maximum dosing paired with trough monitoring may be an alternative to AUC_{24} monitoring in areas that are unable to perform AUC_{24} calculations. Prospective data are needed to validate these conclusions.

ABBREVIATIONS AKI, acute kidney injury; AUC_{24} , area under the curve over 24 hours; IQR, interquartile range; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*

KEYWORDS area under the curve; pharmacodynamic; therapeutic drug monitoring; trough serum concentration; vancomycin

J Pediatr Pharmacol Ther 2021;26(7):740–745

DOI: 10.5863/1551-6776-26.7.740

Introduction

Vancomycin is commonly used to treat infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). The 2020 vancomycin therapeutic monitoring guidelines suggest dose adjusting based on AUC over a 24-hour period (AUC_{24}) instead of trough monitoring alone, with an optimal AUC_{24} of 400 to 600 mg•hr/L for serious infections due to MRSA.¹ This target is based on literature that suggests it may provide similar clinical efficacy with decreased incidence of acute kidney injury (AKI). Specifically, the guidelines recommend doses of 60 to 80 mg/kg/day divided every 6 hours for patients 3 months to 12 years of age, and 60 to 70 mg/kg/day divided every 6 to 8 hours for those at least 12 years through the age of 18 years, with a suggested maximum

daily dose of 3000 to 3600 mg.¹

At a free-standing children's hospital in Connecticut, the vancomycin pharmacist-driven protocol has evolved due to continuous quality improvement through multiple plan-do-study-act cycles. The protocol recommends vancomycin doses per Neofax² for neonates and infants up to 44 weeks postmenstrual age. For all other age groups, the protocol recommends a dose of 15 mg/kg/dose every 6 to 8 hours up to 25 mg/kg/dose and 1000 mg/dose, except for adult patients with a central nervous system infection where the maximum dose is 1500 mg/dose (Table 1).

For most infections due to MRSA, the protocol recommends a target trough concentration of 10 to 15 mg/dL. For conditions where drug tissue penetration is a concern, including meningitis, endocarditis, osteomyeli-

Table 1. Initial Dosing Recommendations Per the Vancomycin Collaborative Practice Protocol

Creatinine Clearance	Dosage
CrCl > 50 mL/min/1.73 m ²	
Infants and children	15 mg/kg every 6 hr
Adolescents being treated for meningitis, endocarditis, pneumonia or osteomyelitis	15 mg/kg every 6 hr
Adolescents (indications not listed above) and all indications in adults	15 mg/kg every 8 hr
CrCl ≤ 50 mL/min/1.73 m ² *	
30–50	10 mg/kg every 12 hr
10–29	10 mg/kg every 18–24 hr
<10	10 mg/kg as a single dose; subsequent dosing determined by serum concentration obtained 24 hr after the dose

CrCl, creatinine clearance

* Estimated creatinine clearance using the modified Schwartz equation¹⁵ for those < 18 years and Cockcroft-Gault for those ≥ 18 years of age.

tis, and pneumonia, the protocol recommends a target trough of 15 to 20 mg/dL. For non-MRSA infections, empiric doses are the same and cases are reviewed individually by the infectious diseases and antimicrobial stewardship teams given the possibility of different pharmacodynamic goals. The primary outcome of this plan-do-study-act cycle was to determine if the protocol needs to be changed to result in vancomycin AUC₂₄ exposures that are recommended by the updated guidelines.

Materials and Methods

Patients who received vancomycin between October 1, 2018, and September 30, 2019, were included if they received at least 3 doses of vancomycin and had at least 1 steady-state trough level obtained prior to the fourth dose. Those who were on extracorporeal membrane oxygenation were excluded. AUC₂₄ exposures were estimated for each vancomycin trough concentration using 2 validated calculations: 1) the Le et al³ method, which takes into consideration patient age in days, weight, vancomycin dose, and serum creatinine levels to determine vancomycin clearance and incorporate in the AUC₂₄ equation, and 2) the trapezoidal method,⁴ which incorporates patient-specific weight, vancomycin dose, trough concentrations, and made assumptions from the literature for age-appropriate volume of distribution of vancomycin.^{5–7} The trough concentration was used to back extrapolate an estimated peak level⁴ to incorporate into the trapezoidal equation. AUC₂₄ goals were 400 to 600 mg•hr/L, but due to known variations between calculations, a vari-

ance of 20 mg•hr/L was allowed for each end of the goal. Therefore, therapeutic AUC₂₄ was deemed 380 to 620 mg•hr/L. Subtherapeutic was below 380 mg•hr/L and supratherapeutic > 620 mg•hr/L.

To assess potential kidney injury, individual patients' serum creatinine levels and urine outputs were reviewed prior to the start of vancomycin if this information was available, and within 48 hours of vancomycin exposures. Serum creatinine levels were obtained at least once daily while patients were on vancomycin, as per the pharmacist-driven vancomycin dosing protocol. The pediatric risk, injury, failure, loss, end stage renal disease criteria were used to classify injury through end stage renal disease.⁸ Concurrent nephrotoxins (e.g., vasopressors, aminoglycosides, non-steroidal anti-inflammatories, and diuretics) and AUC₂₄ were also estimated, recorded, and assessed for those with any degree of kidney injury. To ensure that the dosing and/or AUC₂₄ exposures did not result in poor clinical outcomes, patients with confirmed Gram-positive infections were determined to have either success or failure. Clinical success was defined as culture clearance, symptomatic improvement, and no documented infection recurrence and/or readmission due to the same infection. Descriptive statistics were used to analyze the results. For normally distributed data, means and standard deviations were reported and for non-normally distributed data, medians and interquartile ranges were reported.

Results

A total of 302 patients were identified as receiving vancomycin in the time period assessed. Seventy-nine patients were excluded (67 received less than 3 doses of vancomycin, 10 never received a steady-state trough, and 3 patients received extracorporeal membrane oxygenation). A total of 223 patients with a total of 429 vancomycin trough levels were included (Table 2).

Area Under the Curve. Sixty-four percent (n = 143) of the vancomycin trough concentrations based on the initial dose recommended in the institution's protocol were within therapeutic range. Thirty-four percent (n = 76) were subtherapeutic and 2% (n = 4) were supratherapeutic. The Le et al³ method resulted in an average estimated AUC₂₄ of 450 ± 131 mg•hr/L with 63% (n = 141) of patients within the goal of 380 to 620 mg•hr/L. Of those outside of the goal (n = 82), 76% (n = 62) were below 380 mg•hr/L. After dose adjusting based upon the trough serum concentration following the protocol, 81% (n = 180) of patients eventually achieved a therapeutic AUC₂₄. For each of the analyzed trough concentrations within therapeutic range, the percent agreement between troughs and the AUC₂₄ was 58%.

When looking at the calculations from the trapezoidal method, the mean estimated initial AUC₂₄ was 410 ± 89 mg•hr/L with 51% (n = 114) of patients having a therapeutic AUC₂₄. All 109 (49%) of subjects that were

Table 2. Baseline Characteristics (N = 223)

Characteristics	Patients n (%)	Days of Therapy, median (IQR)	Baseline SCr, median (IQR), mg/dL	Abnormal SCr, median (%), mg/dL
Age group				
Neonate	14 (6.28)	2.1 (2.0–2.6)	0.3 (0.3–0.4)	0 (0)
Infant	48 (21.52)	2.3 (1.8–3.1)	0.1 (0.1–0.3)	0 (0)
Child	95 (42.60)	2.5 (1.9–3.9)	0.3 (0.1–0.3)	2 (2.1)
Adolescent	46 (20.63)	2.1 (1.7–4.9)	0.5 (0.4–0.7)	1 (2.2)
Adult	20 (8.97)	2.6 (2.0–4.9)	0.6 (0.5–0.7)	0 (0)
Sex, n (%), male	121 (54.26)			
Infectious Indication				
Bacteremia*	116 (52.02)	2.5 (1.9–3.9)		
Respiratory	38 (17.04)	2.1 (1.7–3.0)		
CNS	27 (12.11)	1.9 (1.6–2.7)		
Bone and joint	12 (5.38)	2.9 (1.9–3.9)		
Skin and soft tissue	17 (7.62)	2 (1.8–2.6)		
Other	13 (5.83)	4.5 (2.1–5.8)		

CNS, central nervous system; SCr, serum creatinine

* confirmed or suspected

determined to be outside of goal AUC_{24} range were subtherapeutic. Using protocol adjustments based on the trough level, 77% (n = 171) of cases were calculated to be within the goal AUC_{24} . The percent agreement between therapeutic trough concentration and the estimated AUC_{24} using the trapezoidal method was 71%.

As many of the initial doses resulted in subtherapeutic AUC_{24} exposures, a post hoc analysis was performed using the Le et al³ method to estimate the percent of patients who would have achieved optimal initial AUC_{24} using higher empiric doses suggested by the 2020 vancomycin guidelines. Specifically, doses between 60 and 80 mg/kg/day (3 months–12 years) and 60 to 70 mg/kg/day (12 years and older) at maximum doses of 3000 mg/day and 3600 mg/day were used to determine estimations. Table 3 shows the results of estimated AUC_{24} exposures at different doses within these ranges, and at each of the maximum suggested doses. For patients 3 months to 12 years of age, the highest dose that results in less than 10% of supratherapeutic levels was 70 mg/kg/day (with a maximum dose of either 3000 or 3600 mg/day). For those 12 years and older, 65 mg/kg/day (with a maximum dose of 3000 mg/day) is the highest dose that results in < 10% supratherapeutic exposures. Importantly, using a maximum of 3600 mg/day in the adolescents and adults was predicted to result in higher than target AUC_{24} > 10% for all doses evaluated.

Toxicity. The pediatric risk, injury, failure, loss, end stage renal disease criteria application identified 14 (6.3%) patients meeting criteria for at least kidney injury. Specifically, 11 (4.9%) patients had renal injury and 3 (1.3%) renal failure. None of the patients included in the study developed renal loss or end stage renal disease. Upon full evaluation, 2 of the injury patients and 1 of the failure patients had kidney insult prior to starting vanco-

mycin. Eleven of the 14 had received at least 1 concurrent nephrotoxin (e.g., vasopressors, aminoglycosides, non-steroidal anti-inflammatories, and diuretics). Only 1 of the patients with any degree of kidney insult had an estimated AUC_{24} using only the Le et al³ method of greater than 600 mg•hr/L, and this was less than our maximum of 620 mg•hr/L at 619 mg•hr/L. This subject was on multiple vasopressors and had developed AKI prior to initiation of vancomycin.

Clinical Efficacy. A total of 12 patients had a documented infection requiring vancomycin, noted by a positive culture (8 bloodstream infections, 1 central nervous system infection, 2 osteomyelitis, and 1 endocarditis). Four of the patients had infections due to MRSA, whereas 8 were due to non-MRSA organisms (i.e., *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Rothia mucilaginosa*, *Bacillus cereus*) that required continuation of vancomycin based on their sensitivities. No treatment failures were identified.

Discussion

This study shows that with the protocol's recommended initial dose, patients frequently had suboptimal vancomycin AUC_{24} estimated exposures. However, after adjusting the dose based on vancomycin trough concentrations and utilizing maximum recommended doses in the protocol, percent goal AUC_{24} exposures increased without going above the newly recommended AUC_{24} goal targets (400–600 mg•hr/L). Based on these results, using higher initial empiric dosing and a maximum dose approach will increase the likelihood of patients meeting AUC_{24} targets without requiring AUC_{24} calculations on all patients. The population-based pharmacokinetic study performed by Le et al³ and colleagues demonstrated that a dose of 70 mg/kg/day is likely needed to achieve

Table 3. Estimated AUC₂₄ Exposures If Implemented 2020 Vancomycin Empiric Pediatric Dosing With Maximums

Age	AUC ₂₄	Empiric Vancomycin Dosing, mg/kg/day									
		Maximum 3600 mg/day					Maximum 3000 mg/day				
		60	65	70	75	80	60	65	70	75	80
3 mo–12 yr (n = 123)	Therapeutic* AUC ₂₄ (%)	50.4	56.1	60.2	69.9	71.5	50.4	56.1	61.0	71.5	74.0
	Subtherapeutic† AUC ₂₄ (%)	46.3	39.8	30.1	15.4	4.9	46.3	39.8	30.9	16.3	5.7
	Suprathreshold‡ AUC ₂₄ (%)	2.4	4.1	7.3	13.8	23.6	2.4	4.1	5.7	11.4	20.3
≥ 12 yr (n = 66)	Therapeutic* AUC ₂₄ (%)	77.3	65.2	59.1	51.5	45.5	83.3	78.8	74.2	68.2	66.7
	Subtherapeutic† AUC ₂₄ (%)	4.5	4.5	4.5	3.0	1.5	12.1	12.1	12.1	10.6	9.1
	Suprathreshold‡ AUC ₂₄ (%)	18.2	30.3	36.4	45.5	53.0	4.5	9.1	13.6	21.2	24.2

AUC₂₄, AUC over a 24-hour period

* Therapeutic was considered 380–620 mg·hr/L

† Subtherapeutic was considered < 380 mg·hr/L

‡ Suprathreshold was considered > 620 mg·hr/L

target AUC/MIC in subjects < 12 years of age and a dose of 60 mg/kg/day in subjects 12 through 18 years of age.³ Abdel et al⁹ also had similar findings, where a dose of 60 mg/kg/day achieved an AUC/MIC ≥ 400 mg·hr/L in only 21.5% of children, hence suggesting larger doses are required in this age group to achieve target AUC/MIC exposures.⁹ Our analysis of AUC₂₄ levels at doses ranging from 60 to 80 mg/kg/day based on the Le et al³ method agree that pediatrics 3 months to 12 years of age likely require an initial vancomycin dose of ≥ 70 mg/kg/day to increase the chance of obtaining AUC₂₄ goals more quickly. Doses ≥ 65 mg/kg/day however were calculated to result in significant suprathreshold AUC₂₄ estimations in patients ≥ 12 years. For this reason, it is likely better to start these patients on a dose of 60 mg/kg/day. Additionally, in subjects 3 months to 12 years of age, the percent therapeutic AUC₂₄ exposure appeared similar when doses were maxed at a dose of 3000 mg/day and 3600 mg/day. Specifically, the percent of these infants and children calculated to have AUC₂₄ exposures within range at a dose of 70 mg/kg/day were 61% and 60.2% at maximums of 3000 mg and 3600 mg, respectively (Table 3). Further, for both maximum dosages in this age less than 10% of those at this dose would be exceeding AUC₂₄ maximum target of 600 mg·hr/L. In patients ≥ 12 years, the percent therapeutic AUC₂₄ at 60 mg/kg/day was significantly higher and the percent suprathreshold exposures was significantly lower when doses were maximized at 3000 mg/day compared with when doses were maximized at 3600 mg/day. This indicates that our patients likely do not need daily doses higher than 3000 mg, which reflects the new recommendation in the guidelines.¹ In addition, one can use the Le et al³ method when determining the appropriate initial dose, to increase the likelihood of achieving a therapeutic AUC₂₄ more quickly. Given that the only laboratory value the Le et al³ method requires is a serum creatinine level, one can calculate a more optimal vancomycin starting dose if a serum creatinine level is available. This would not be possible with the trapezoidal method using a

patient's trough level to determine an estimated peak and incorporate both in the AUC₂₄ equation, as a trough level would not be available when trying to determine the initial vancomycin dose.

Unlike previous studies that demonstrated a correlation between elevated vancomycin exposures and increased AKI risk,^{10,11} our analysis showed that by incorporating a maximum dose and limiting concurrent nephrotoxins, the risk of AKI was low at 6.3%, which may be due to lack of extended exposures above an AUC₂₄ of 600 mg·hr/L. The majority of subjects did not have any form of renal injury. Further, of those that had renal injury, only 1 patient with renal injury in our study had an AUC₂₄ > 600 mg·hr/L based only on the Le et al³ calculation, not the patient trough specific trapezoidal method. This suggests that an inappropriately high vancomycin dose was likely not resulting in renal dysfunction in the study patients. Many of these patients were on multiple nephrotoxic agents, which could have contributed to their AKI. These findings are likely due to the presence of maximum doses in the hospital's vancomycin dosing protocol, as well as the hospital's general practice of using an alternative MRSA covering agent that is less nephrotoxic, such as linezolid, in subjects with renal insufficiency.

All patients with a confirmed infection warranting continuation of vancomycin achieved clinical success. The study did not have a significant number of patients with confirmed Gram-positive infection treated with vancomycin and only a few of these were MRSA. For the non-MRSA infections, it is important to consider that specific AUC₂₄ goals have not been established. This provides support that the dosing to achieve these goals is reasonable for these infections.

This study did have several limitations. It was a retrospective analysis and AUC₂₄ concentrations were determined using estimated calculations. These calculations may not reflect the exact AUC₂₄ value for each subject and are not as precise as Bayesian estimations.^{12,13} Specifically, the volume of distribution values used to

calculate the estimated AUC_{24} using the trapezoidal method were strictly based on age group. This may have impacted the results given other patient-specific factors, such as being critically ill, can affect the volume of distribution. Given the high cost of available Bayesian programs,¹⁴ it was not feasible for our institution to purchase and utilize Bayesian estimations for this study. The results of the post hoc analysis that was performed after the updated guidelines were published are estimations for study subjects as well. Thus, dosing requirements need to be validated on future patients. In addition, very few patients in the study had clinical infection with MRSA that required vancomycin therapy. AUC_{24} goals have only been validated for serious MRSA infections and primarily in adults. Although there were no clinical failures in the study, it is unclear if the estimated AUC_{24} values in subjects infected with non-MRSA organisms are what is needed to eradicate such organisms. The study included all patients, rather than MRSA-infected patients only, as exposures and toxicity can be better analyzed with a larger patient population.

Conclusion

The data in our study demonstrate that the starting dose the hospital's protocol recommends often did not result in goal AUC_{24} exposures, and percent AUC_{24} goal exposures did increase eventually after doses were adjusted based on the vancomycin trough and recommended maximum dose per the protocol. Only 6.3% of patients had AKI, and of these, only 1 had a calculated AUC_{24} just above 600 mg•hr/L. This study provides initial evidence that with a larger initial vancomycin dose, a hospital protocol using trough monitoring paired with maximum dosing may result in goal AUC_{24} exposures for most patients in a children's hospital. For institutions with budget constraints that cannot purchase a Bayesian software, this approach of using larger initial doses and maximum doses in conjunction with trough monitoring to meet AUC_{24} goals and minimize toxicity may be an appropriate alternative that is not cost prohibitive. Future prospective studies are needed to confirm these results and evaluate clinical outcomes in pediatrics with MRSA infections.

Article Information

Affiliations. Department of Pharmacy Practice (BA, JG) and Pediatrics (JG), University of Connecticut, Storrs/Farmington, CT; Department of Pharmacy (BA, JG), Divisions of Quality and Infectious Diseases and Immunology (JG), Connecticut Children's, Hartford, CT.

Correspondence. Jennifer Giroto, PharmD; jgiroto@connecticutchildrens.org

Disclosures. Dr Al-Mazraawy declares no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. Dr Giroto is a consultant for Lexi-Comp. Drs

Al-Mazraawy and Giroto had full access to all data and take responsibility for the integrity and accuracy of data analysis.

Ethical Approval and Informed Consent. This evaluation was deemed by the Institutional Review Board to be quality improvement and not require full review. It was exempt from patient assent and informed consent.

Acknowledgments. Preliminary results were presented at the Pediatric Pharmacy Association Annual Meeting virtually on May 1, 2020.

Submitted. July 9, 2020

Accepted. January 21, 2021

Copyright. Pediatric Pharmacy Association. All rights reserved. For permissions, email: mhelms@pediatricpharmacy.org

References

1. Rybak M, Le J, Lodice T, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2020;77(11):835–864.
2. Vancomycin: Drug Information. 2020. In NeoFax (Columbia Basin College Library ed.) [Electronic version]. Greenwood Village, CO: Truven Health Analytics. Accessed July 2020. <http://www.neofax.micromedexsolutions.com/>
3. Le J, Bradley JS, Murray W, et al. Improved vancomycin dosing in children using area under the curve exposure. *Pediatr Infect Dis J.* 2013;32(4):e155–e163.
4. Winter M. *Basic Clinical Pharmacokinetics*. 3rd ed. Vancouver, WA: Applied Therapeutics; 1994.
5. de Hoog M, Mounton JW, van den Anker JN. Vancomycin: pharmacokinetics and administration regimens in neonates. *Clin Pharmacokinet.* 2004;43(7):417–440.
6. Marsot A, Boulamery A, Bruguerolle B, Simon N. Vancomycin: a review of population pharmacokinetic analysis. *Clin Pharmacokinet.* 2012;51(1):1–13.
7. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. 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(1):82–98.
8. Akcan-Arikan A, Zappitelli M, Loftis L, et al. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int.* 2007;71(10):1028–1035.
9. Abdel Hadi O, Al Omar S, Nazer LH, et al. Vancomycin pharmacokinetics and predicted dosage requirements in pediatric cancer patients. *J Oncol Pharm Pract.* 2016;22(3):448–453.
10. Fiorito TM, Luther MK, Dennehy PH, et al. Nephrotoxicity with vancomycin in the pediatric population: a systemic review and meta-analysis. *Pediatr Infect Dis J.* 2018;37(7):654–661.

11. McKamy S, Hernandez E, Jahng M, et al. Incidence and risk factors influencing the development of vancomycin nephrotoxicity in children. *J Pediatr*. 2011;158(3):422–426.
12. Bayard DS, Jelliffe RW. A Bayesian approach to tracking patients having changing pharmacokinetic parameters. *J Pharmacokinet Pharmacodyn*. 2004;31(1):75–107.
13. Fuchs A, Csajka C, Thoma Y, et al. Benchmarking therapeutic drug monitoring software: a review of available computer tools. *Clin Pharmacokinet*. 2013;52(1):9–22.
14. Turner RB, Kojiro K, Shephard EA, et al. Review and validation of Bayesian dose-optimizing software and equations for calculation of the vancomycin area under the curve in critically ill patients. *Pharmacotherapy*. 2018;38(12):1174–1183.
15. Schwartz G, Munoz A, Schneider M, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629–637.