Clinical Pharmacology & Toxicology Pearl of the Week

~ Renal Drug Dosing – Part 1 ~

Case:

60-year-old male with a left prosthetic knee is admitted with recurrent left leg cellulitis. He has a known history of stage G3b CKD and his kidney function is at his pre-admission baseline during admission. He was initially started on cefazolin however subsequent workup showed positive MRSA swabs. The rounding physician plans to change his antimicrobials to vancomycin. His height, weight, and creatinine are as follows:

Height 170 cm
Weight 95 kg
BMI: 32.9 kg/m^2
Creatinine: 170 mmol/L

Below are various estimates of this patient's kidney function estimates based on serum creatinine:

CrCl (Actual Body Weight)	CrCl (Ideal Body Weight – 66kg)	CrCl (Adjusted Body Weight – 78kg)	Cr-eGFR (Assumed BSA* of 1.73m^2)	Cr-eGFR (Actual BSA** of 2.12m^2)
55 ml/min	38 ml/min	45 ml/min	39 ml/min/1.73m^2	48 ml/min

*Estimates of GFR automatically assume an average body surface area (BSA) of 1.73m^2. Creatinine clearance does not incorporate BSA in the formula.
*Body surface area (BSA) determined using the recommended Mosteller estimation

Drug nomogram for renal dosing of vancomycin is as follows:

Creatinine Clearance (ml/min)	**Loading Dose***	**Maintenance Dose**
>90 to <130	25-30mg/kg	15-20mg/kg every 8-12 hours
50 to 90	20-25mg/kg	15-20mg/kg every 12 hours
15 to <50	20-25mg/kg	10-15mg/kg every 24 hours
< 15	20-25mg/kg	10-15mg/kg

*Maximum recommended loading dose is 3g

How do you determine the appropriate vancomycin loading and maintenance dose for this individual?

1. Why do we consider renal drug dosing?
    a. The kidney is one of the main routes of drug elimination
    b. Drugs differ in the degree to which they are eliminated by the kidney
    c. Drugs can be eliminated as unchanged active drug, active metabolites, or inactive metabolites
    d. For drugs that utilize the renal elimination pathway, reduced kidney function can lead to accumulation of drug and/or drug metabolites, leading to toxicity and adverse drug effects

2. What **estimates** of kidney function are used for renal drug dosing recommendations?
    a. Most nomograms provide renal drug dosing recommendations using creatinine-based estimates of kidney function.
        i. Cockcroft-Gault Creatinine Clearance (CrCl)
            1. CrCl is not automatically calculated and reported on lab results but can be determined using the Creatinine Clearance calculator on available apps such as MD-Calc.
            2. CrCl estimates can vary significantly depending on what weight physicians use in the formula (ie. adjusted body weight, ideal body weight, lean body weight).[1]
        ii. CKD-EPI Creatinine Equation 2021 (Cr-eGFR)
            1. In Canada, eGFR results are automatically calculated and reported using this estimation method and the result is based on serum creatinine values.
            2. The formula that is used to calculate the reported eGFR incorporates an assumed body surface area (BSA) of 1.73m^2. This BSA value is somewhat arbitrary and is based on historical average weight and height range of 58.5-69kg and 162.5-172.7cm, respectively.[2]
            3. For individuals whose weight and height fall outside these ranges, physicians can attempt to correct for this variation using the following formula[3]:

$$Adjusted\ eGFR = \frac{(eGFR_{reported}\ x\ BSA_{patient})}{1.73m^2}$$

3. Is there a clinically relevant difference between CrCl and Cr-eGFR?
    a. In individuals with higher weights, CrCl will have higher kidney function estimates compared to Cr-eGFR particularly when actual body weight is used in the calculation. Some of the discordance between estimates in this setting will improve when ideal or adjusted body weights are used instead.[3,4]
    b. Discordance rates between these two kidney function estimates have been reported as high as 40%.[1,4-6]
    c. Differences in CrCl and Cr-eGFR measures do not always lead to differences in the recommendations for renal dosing. Discordance rates between the recommended renal adjusted dosing have been reported between 10-48%.[3-6]

4. Which creatinine-based kidney function estimate should be used?
    a. It is important to keep in mind that renal dosing recommendations assume that an individuals' serum creatinine is at steady state. In the setting of acute kidney injury or acute illness, estimates of creatine-based kidney function such as CrCl or Cr-eGFR may be inaccurate.[7]
    b. For most individuals, creatinine-based estimates obtained at steady-state are safe to use when determining renal dosing.
    c. Depending on when a drug was approved and when the nomogram was formulated, the reported renal dosing recommendations will either be based on CrCl or Cr-eGFR. Clinicians should use the kidney function measure that corresponds to the measure used on the nomogram for renal drug dosing.
    d. The FDA currently recommends the following[5]
        i. Cr-eGFR is recommended over CrCl for estimating renal dosing given its widespread availability however both are reasonable for use.

ii. In overweight or obese individuals, CrCl measures should be determined using ideal body weight (IBW) or adjusted body weight (ABW).

Case Resolution:

This patient received vancomycin with renal dosing corresponding to a CrCl between 15 to < 50 ml/min given the relatively concordant values obtained for CrCl and eGFR. This included a loading dose of 2g (~22 mg/kg) and subsequent maintenance dose initially at 1.5g (~15mg/kg) every 24 hours. Given there are multiple patient factors that influence vancomycin dosing including body habitus, vancomycin trough levels were monitored closely for necessary dose adjustments to target a trough level between 15-20mg/L.

References:

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2. Heaf, J.G. (2007). The origin of the 1.73m^2 body surface area normalization: problems and implications. Clinical Physiology and Functional Imaging, 27(3), 135-137.
3. Fernandez-Prado, R., Castillo-Rodriguez, E., Valez-Arribas, F.J., et al. (2016). Creatinine clearance is not equal to glomerular filtration rate and Cockcroft-gault equation is not equal to CKD-EPI collaboration equation. The American Journal of Medicine, 129(12), 1259-1263.
4. Parsh, J., Seth, M, Aronow, H., et al. (2015). Choice of estimated glomerular filtration rate equation impacts drug-dosing recommendations and risk stratification in patients with chronic kidney disease undergoing percutaneous coronary interventions. JACC, 65(25), 2714-2723.
5. U.S. Department of Health and Human Services Food and Drug Administration. (2024). Pharmacokinetics in patients with impaired renal function – study design, data analysis, and impact on dosing: Guidance for Industry. Clinical Pharmacology.
6. Paglialunga, S., Offman, E., Ichhpurani, N., Marbury, T.C, & Morimoto, B.H. (2017). Update and trends on pharmacokinetic studies in patients with impaired renal function: Practical insight into application of the FDA and EMA guidelines. Expert Review of Clinical Pharmacology, 10(3), 273-283.
7. Roy, R., MacDonald, J., Dark, P., Kalra, P.A., & Green, D. (2023). The estimation of glomerular filtration in acute and critical illness: Challenges and opportunities. Clinical Biochemistry, 118, 11068.

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The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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