# Clinical Pharmacology & Toxicology Pearl of the Week

## ~ Renal Drug Dosing – Part 2 ~

**Case:** 62-year-old male has a prolonged hospital admission due to recurrent pseudomonal urinary infections, venous thromboembolism, and embolic strokes. Due to immobility, he is severely deconditioned with a recorded weight of 49 kg after losing 15kg over the course of his admission. He then develops suspected recurrent urosepsis with urine and blood cultures pending. The rounding physician plans to restart piperacillin-tazobactam at pseudomonal dosing given the patients history.

Below are various measures of this patient's kidney function estimates based on serum creatinine and serum cystatin C obtained on the same day:

| **Estimates using patients calculated BSA*** | **Creatinine Clearance** | **Creatinine-eGFR** | **Cystatin C-eGFR** | **Creatinine-Cystatin C eGFR** |
|---|---|---|---|---|
| | 57 ml/min | 87 ml/min | 19 ml/min | 38 ml/min |
| **Estimates using standard BSA of 1.73m$^2$** | | **Creatinine-eGFR** | **Cystatin C-eGFR** | **Creatinine-Cystatin C eGFR** |
| | | 93 ml/min/1.73m$^2$ | 21 ml/min/1.73$^2$ | 40 ml/min/1.73m |

*Estimates of GFR automatically assume an average body surface area (BSA) of 1.73m$^2$. Creatinine clearance does not incorporate BSA in the formula.

Drug nomogram for renal dosing of piperacillin-tazobactam is as follows:

| **Creatinine Clearance (ml/min)** | **Dose for Pseudomonal coverage** |
|---|---|
| ≥40 | 4.5g every 6 hours |
| 20 to < 40 | 4.5g every 8 hours **or** 3.75g every 6 hours |
| <20 | 4.5g every 12 hours **or** 2.25g every 6 hours |

How do you determine the appropriate dose of piperacillin-tazobactam for this patient?

1. When are creatinine-based kidney function estimates problematic?
    a. Serum creatinine has multiple non-GFR determinants including age, sex, muscle mass, nutritional status, and physical activity.[1-4]
    b. Many of the non-GFR determinants are dynamic and it can be difficult to estimate the degree to which they impact the serum creatinine measure.
    c. Non-GFR determinants that lead to a decrease in serum creatinine will overestimate an individual's creatinine-based eGFR and creatinine clearance. Using these measures to determine renal drug dosing in this setting could lead to inappropriately high drug doses and accumulation of drug and/or drug metabolites.
    d. Conversely, non-GFR determinants that lead to an increase in serum creatinine will underestimate an individual's eGFR and creatinine clearance potentially resulting in under-dosing and therefore undertreating medical conditions.

| Factors that increase serum creatinine (ie. underestimate eGFR) | Factors that decrease serum creatinine (ie. overestimate eGFR) |
|---|---|
| High muscle mass | Low muscle mass/cachexia |
| High protein diet | Low protein diets |
| Exogenous creatine intake | Cirrhosis / Liver dysfunction |
| Recent physical activity before blood work | Amputations |

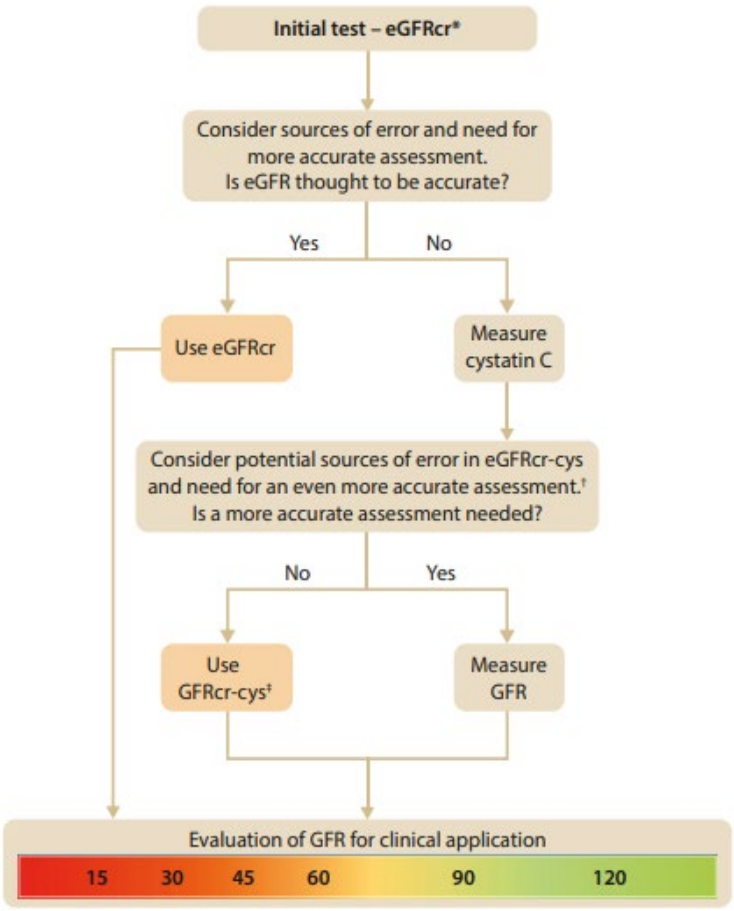
2. Alternative serum measures for estimating glomerular filtration rate
    a. Serum cystatin C (Cys)
        i. Cystatin C is a 13 kDa cysteine protease inhibitor protein that is produced by all nucleated cells in the body at a steady state
        ii. This is an available test in Alberta
        iii. Two important considerations include higher cost of cystatin C test, and it often takes 2-7 days for results to be available.
        iv. Cystatin-C eGFR is not calculated automatically by the lab but can be determined using the 2012 CKD-EPI Cystatin-C calculator on the National Kidney Foundation website or MD-Calc app.
        v. Our understanding of potential non-eGFR determinants of cystatin C is evolving however studies have shown that in the setting of muscle wasting it can provide a more accurate estimate of kidney function.[3]
    b. Combined creatinine and cystatin C estimation method
        i. Our understanding on factors that bias cystatin C or creatinine-based kidney function estimates is evolving.[3-5]
        ii. There are clinical instances where use of either cystatin C or creatinine alone can lead to biased estimates of kidney function.[3,4]
        iii. KDIGO 2024 guideline[3] for chronic kidney disease, recommends using the combined 2021 Cr-Cys eGFR calculator in instances where Cr-eGFR is felt to be inaccurate.

3. Summary of recommendations for considering a cystatin-C based method for kidney function estimation in renal dosing:

    a. The majority of individuals do not require a cystatin-C based estimate and creatinine estimates are reasonable and safe.

    b. For individuals with significant muscle wasting, advanced age, or liver failure, cystatin C based methods should be considered. KDIGO recommends the use of combined Cr-Cys eGFR in these circumstances.[6]

    c. For drugs that have narrow therapeutic windows or high potential for adverse outcomes with drug accumulation, clinicals should be mindful of factors that could lead to inaccurate estimates of an individuals Cr-eGFR.




Source: KDIGO 2024 adapted from Adingwupu et al. 2023.

**Case resolution:**

Given the patient's tenuous clinical state and the risk associated with undertreating pseudomonal urosepsis, the decision was made to renally dose piperacillin-tazobactam using the combined Cr-Cys eGFR of 38ml/min using the patients BSA. The patient was monitored closely for signs of drug accumulation or toxicity and there were no adverse outcomes.

**References:**


1. 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.
2. 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.
3. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease: Kidney Int. 2024;105(4S): S117–S314, DOI: 10.1016/j.kint.2023.10.018

4. Adingwupu, O.M., Barbosa, E.R., Palevsky, P.M., et al. (2023). Cystatin C as a GFR estimation marker in acute and chronic illness: A systematic review. Kidney Med, 5(12), 100727. DOI: 10.1016/j.xkme.2023.100727
5. 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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