

# ALTERNATIVE VIEWPOINTS

## Clinical Judgment: To Renal Dose Adjust Antimicrobials or Not

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I read with great interest the article by Golik and Lawrence in the September 2008 issue of *Pharmacotherapy*, entitled “Comparison of dosing recommendations for antimicrobial drugs based on two methods for assessing kidney function: Cockcroft-Gault and Modification of Diet in Renal Disease.”<sup>1</sup> As a clinician, researcher, speaker, and author on the topic, I was anxious to see what new findings these authors would be able to add to the growing body of literature available on this topic. As more laboratories begin reporting estimated glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) equation, more practitioners are prone to utilize the results when dose adjusting medications when any degree of renal impairment is present. The reliability and accuracy of the MDRD estimation of GFR for the staging of chronic kidney disease (CKD) is well known, however the ability to use this equation to make dosage adjustments to medications remains unclear.<sup>2,3</sup> The authors of this study sought to determine if selected antimicrobials would have been dosed similarly based upon equation selected to estimate renal function. In their study, the authors found that, approximately 23–35% of doses of antimicrobials would have been in discordance, based upon the equation selected to make renal dosage adjustments. Importantly, the authors noted if the MDRD equation was used to dose adjust the selected antimicrobials, it would

have resulted in doses that were too high for the level of renal impairment (based upon Cockcroft-Gault (CG) estimations).

We too studied this research question and had quite similar results, albeit in a slightly different patient population.<sup>4</sup> While the vast majority of our two populations were Caucasian, our patient population was 10 years older ( $63.6 \pm 15.9$  vs.  $73.4 \pm 12.5$  years). The biggest difference in our two patient populations was the level of renal dysfunction. As Golik and Lawrence pointed out, our patient population had a higher degree of renal dysfunction than theirs. However, they failed to address that this was the intent of our study, to include only patients with CKF stages 3 or higher. Golik and Lawrence go on to state their patients represent “more of a real-world scenario” than ours. While I don’t disagree, use of the results of the MDRD equation in patients without defined CKD has not been validated and opens their results up to questions of validity.

Regardless, this is not a debate about which study was better; every piece of literature that is added on this topic helps us understand more. After continuous research on the topic, I am coming to the conclusion that ultimately, the question shouldn’t be which equation we use to dose adjust the antimicrobials, the question should be, *is this the only tool we need to use in order to dose adjust antimicrobials?* Clearly, adverse effects can occur when we fail to make dosage adjustments due to renal insufficiency secondary to accumulation of drug. One has to look no further than failing to adjust the dose of imipenem-cilastatin and the consequences of increasing the seizure potential. However, what should a clinician do when faced with a critically ill patient, on mechanical ventilation who develops pneumonia, has an estimated creatinine clearance (CrCl) of 30 mL/min based upon CG

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estimations, but 45 mL/min based upon MDRD estimations, and the physician writes an order for piperacillin-tazobactam 4.5g IV q6h? Reviewing the dosage adjustment guidelines provided by the manufacturer, the dose should be reduced to 3.375 g IV q6h for CrCl of 20–40 mL/min. Should we adjust the dosage? Some clinicians would say yes, some would say no, yet many others like myself would ask for more information. The point is that many institutions have renal dosage adjustment programs, approved by the Pharmacy and Therapeutics committees, allowing pharmacists to make an adjustment of certain medications based upon their estimated creatinine clearance calculation. Not to take a step back in practice, away from the autonomy we have earned to do such things, but I feel we need to move away from this. It is my opinion that pharmacists should use more of their clinical/critical thinking skills before simply making the dosage adjustment. When on the fence, would it not be better to overdose the antibiotic in a critically ill patient, rather than underdose it? Therefore, I propose this six-step approach when deciding to dose adjust medications:

1. **Estimate their kidney function using the equations.** How else is one going to be led down the path of potentially dose adjusting a medication? Compare the estimations of the CG and MDRD equations. Remember, our studies showed up to 35% discordance rates, which means more than 65% of the time they will result in the same adjustment recommendation. When results are discordant, move to step two.
2. **Assess the patient.** Is the patient in acute renal failure, do they have chronic kidney disease, are they still producing urine, are they on dialysis? What is the patient's nutritional status? What is their extracellular volume status? Are they in an acutely decompensated heart failure or cirrhotic state? Are they on any other medications that can impair their renal function further? All these questions need to be answered in order to truly assess a patient's renal function.
3. **Assess the medication to be adjusted.** This may go without asking, but is this medication renally eliminated? Why take this exercise in futility if you don't need to? Then, consider the therapeutic index of the medication, is it narrow or wide? In the case of a medication

like digoxin, you may opt to dose adjust if in a "gray" area, where as in the case of piperacillin-tazobactam, you may opt not to adjust the dose, which takes us to step four.

4. **Weigh the risks versus the benefits of adjusting the medication.** Will I underdose this patient's infection if I make the dosage adjustment? Will I make them go into heart block if I don't adjust the digoxin? Again, it is crucial to assess the potential for adverse effects and the severity of those adverse effects when deciding to adjust a medication.
5. **Document.** Whatever your decision, document your thought process. Why did or didn't you adjust the dose? Unfortunately, we live in a very litigious society where lawyers can feast on any mistake we make. In addition, patients don't read the textbooks and they can have any reaction, to any medication, at any time. Therefore, it is crucial that you have the documentation to support your decisions.
6. **Follow-up.** Again, whatever your decision, follow that patient to ensure they are still receiving the most appropriate dose. I cannot tell you how many times I have come across a medication someone adjusted several days prior when the patient was admitted and had prerenal azotemia due to volume contraction. Upon hydration, the patient's creatinine and urine output came back to their baseline, yet no readjustment was made in their dose. We must always follow our patients on a daily basis to ensure we are optimizing their therapy.

Making the decision to dose adjust medications based upon renal impairment should ideally be done through a multidisciplinary approach. Pharmacists are in a unique position to make recommendations for renal dose adjusting medications due to their education in pharmacokinetics and pharmacodynamics of medications. Many institutions have renal dose adjustment guidelines in place, approved by the Pharmacy and Therapeutics Committee, whereby pharmacists automatically adjust medications based upon the level of creatinine clearance calculated. Unfortunately, it requires more than simply evaluating a level of serum creatinine and plugging it into an equation. In addition to the clinical knowledge of pharmacists, input from nurses, physicians, nurse practitioners, and physician assistants can add significantly to the evaluation of renal function. Using the stepwise

approach, outlined here, will help pharmacists when deciding to make renal dosage adjustments.

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### Authors' Reply

The authors declined to reply.