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A Re[n]al Dilemma:
Estimating Renal Function Using Cockcroft-Gault Equation Versus Modification of Diet in Renal Disease Equation and Implications for Dosing Antibiotics in the Elderly

Introduction:

Glomerular filtration rate (GFR), which measures patients' renal function, is a critical lab value to have in the inpatient hospital setting. Knowing patients' GFR can assist both in terms of diagnosing kidney disease and determining doses of renally eliminated medications, including many antibiotics. In this particular case, a dosing discrepancy arose when the medical team ordered levofloxacin (Levaquin) 500 mg IV daily x 7 days to treat community-acquired pneumonia in BS, a 90-year-old, 5' female weighing 54 kg with SCr = 0.72 mg/dL, a CLcr = 31.5 mL/min (as calculated using the Cockcroft-Gault equation) and an eGFR of > 60 mL/min (as listed on UCare).[1] When a dosage change of 500 mg IV on Day 1 followed by 250 mg IV daily on Days 2 to 7 was recommended based on the patient's Cockcroft-Gault creatinine clearance and the UCSF/Mt. Zion Medical Center Adult Antimicrobial Dosing Guidelines, the team asked why the dose needed to be adjusted, especially given that the patient's eGFR was > 60 mL/min.[1] The team also asked how and why the drug was dosed based upon the Cockcroft-Gault equation and not the eGFR posted on UCare.

Question:

What has the literature shown as an effective method of estimating GFR for the purpose of recommending and adjusting doses of renally eliminated antibiotics like levofloxacin? What are the implications for clinical practice and drug dosing of antibiotics in elderly patients like BS?

Background:

Glomerular filtration rate (GFR) is of key physiologic interest in hospitalized patients, as GFR is used both to diagnose kidney disease and to dose adjust renally eliminated medications in order to prevent potential nephrotoxicity and other adverse drug reactions. Although measuring GFR directly is the most accurate method of evaluating a patient's kidney function, it is difficult, time-consuming, and expensive.[2,3,4] The high cost and lack of practicality in measuring GFR directly has, as a consequence, created a need to develop methods to find an estimated GFR (eGFR) that approaches a patient's true GFR – or one that at least estimates it accurately enough for use in clinical decision-making. Over the years, there have been many different eGFR equations that have been published in an attempt to find the most accurate GFR estimate possible without having to measure GFR directly. The most widely used and accepted eGFR equations consist of the Cockcroft-Gault (CG) equation, which was developed in 1976[5], and the Modification of Diet in Renal Disease (MDRD), which was developed in 1999.[6] Both of these estimations are used on a daily basis in the inpatient setting to evaluate patients' renal function.

The University of California, San Francisco, Medical Center joins many other institutions in posting a daily eGFR[1] as a part of patients' labs, and the Medical Center's Antibiotic Dosing Guidelines instruct providers to adjust doses of renally eliminated antibiotics based on patients' clearance creatinine (CLcr).[7] However, these two estimations of GFR are based on different equations and, therefore, provide estimations of

GFR that may not always correspond to each other. For instance, the daily eGFR posted on UCare is calculated using the four-variable MDRD method.[8] (A six-variable MDRD equation has also been developed. This discussion refers to the four-variable MDRD equation unless otherwise specified in the text.) The four-variable MDRD equation used at UCSF takes into account the variables of serum creatinine (SCr) level, age in years, gender, and race if the patient is African American:

$$eGFR = 186.3 * (SCr)^{-1.154} * age^{-0.203} * (0.742 \text{ if female}) * (1.21 \text{ if African American})^{8}$$

Like the MDRD, the CG equation's estimation of GFR accounts for serum creatinine (SCr), age in years, and gender, but it does not account for African American race:

$$CLcr\ (mL/min) = [(140-age)*(wt\ in\ kg)]/[72*SCr\ in\ mg/dL]*(0.85 \text{ if female})^{5}$$

The CG equation, however, does take into account the patient's body weight, using the patient's actual body weight in the equation unless the patient's ratio of actual body weight to ideal body weight is >1.2.[9,10,11] In this situation, the patient's ideal body weight – calculated based on the patient's height and gender – would be used in place of the actual body weight.[9,10,11] Furthermore, in using the CG equation, SCr < 1 mg/dL is typically rounded up to 1 mg/dL to yield a more accurate CLcr estimate that does not underestimate a patient's renal function due to low SCr levels, which may be more related to small muscle mass and a decreased production of creatinine than to a patient's renal function status.[9,11]

The methods of calculating these equations to estimate GFR are quite established, but the conflict lies in which estimation to use in drug dosing. Like UCSF, other institutions have documented conflicts between prescribers using the MDRD-derived eGFR posted in their patients' charts for drug dosing and clinical pharmacy policies of using the CG-obtained clearance creatinine to guide dosing of renally eliminated drugs.[3,6] This conflict is complicated by the National Kidney Disease Education Program (NKDEP), the American Society of Nephrology, and the National Kidney Foundation's recommendations that medical laboratories automatically report estimated GFR every time a serum creatinine level is ordered,[12,13] making this value incredibly accessible and perhaps more tempting to use than performing the Cockcroft-Gault calculation for each patient – a calculation that often is not automatically calculated or reported. Yet another matter complicating the situation is the conflicting recommendations found in the literature. For instance, after acknowledging the caveats of both the MDRD and Cockcroft-Gault equations in estimating renal function, especially in certain populations, the National Kidney Foundation concludes that using either the MDRD or the Cockcroft-Gault equation will not lead to differences in drug dosing for the majority of patients, also citing the NKEDP's recent endorsement of using either equation as a basis for drug dose selection.[8] This assertion, however, directly conflicts with numerous studies in the literature that examine situations in which individual patients would receive different drug doses when one equation is used to estimate their renal function over another.[2,3,6,14,15,16] So the real question becomes: Which equation should be used in drug dosing, and can the MDRD and CG equations be used interchangeably to determine what dose of a drug is given to a patient?

In terms of the ability to interchange the four-variable MDRD and CG equations in estimating renal function for drug dosing, several studies have found statistically significant discordance between MDRD- and CG-based dosing recommendations. These dosing discrepancies often involved antibiotics, including levofloxacin, as in this particular case. One observational study conducted by Wargo et al. analyzed 409 patients with chronic kidney disease and calculated an average GFR for all patients of 34.8 ± 12 mL/min using the Cockcroft-Gault method and an average GFR of 40.2 ± 12 mL/min using the MDRD method.[2] The study found that, although the MDRD and CG estimations for clearance had an 80% correlation among all patients in the study, the MDRD estimate ranged between 9.8 mL/min below the CG estimate to 20.6 mL/min above the CG estimate in 95% of instances.[2] This range is quite wide, and, when applied

to dose adjustments based on manufacturer dosing recommendations, it yielded a statistically significant discordance rate of 21% to 37%.[2] Other studies have also noted significant differences between renal estimates as calculated by the MDRD and CG equations. A study conducted by Pedone et al. found significant discrepancies between renal function estimations using CG and MDRD in a population composed of 7747 patients – all of whom were over the age of 65 (mean age of 77.8 years) – with 51.1% of these patients being female.[15] Although the CG and four-variable MDRD equations did agree in 71.2% of cases, the variability between the two equations ranged from 48% to 127%[15], which marks another rather wide range. A third study by Golik and Lawrence showed discordance rates of 22.8% to 36.3% when comparing CG-based dosing recommendations to MDRD-derived dosing recommendations[14] – discordance rates that approach and substantiate the discordance rates calculated by both Pedone et al. and Wargo et al.[2,15] For levofloxacin in particular, Golik and Lawrence found dosing discordance rates of 31%.[14]

Furthermore, the studies comparing MDRD and CG estimates of GFR have consistently found that using the MDRD in selecting drug doses tends to overdose patients when compared to the dosing chosen using Cockcroft-Gault in the same patients. The majority of these instances of discordance occurred when the MDRD-calculated GFR did not predict a need to adjust the dose, whereas the CG-calculated GFR did call for a dose adjustment.[2] Wargo et al.'s study found that the MDRD estimate often rendered dose adjustments of antimicrobials unnecessary, which would have resulted in overdosing patients an average of 21% of the time (with a range of 18% to 30%) when compared to doses chosen using CG.[2] For levofloxacin in particular, dose discrepancies occurred in 89 patients when CG indicated a need to dose adjust but MDRD did not.[2] Interestingly enough, however, when the MDRD equation called for dose adjustments but the CG equation did not, discrepancies only occurred in 18 patients receiving levofloxacin.[2] Hermsen et al. determined that MDRD estimations of renal function exceeded CG estimations by 0.84 to 1.98 times in 95% of cases, noting that 35.7% of patients in the study (116 patients) had different antimicrobial dosage changes recommended when using the MDRD equation versus Cockcroft-Gault, with 115 of these 116 patients receiving a higher dose of antimicrobial if the MDRD equation was used as the basis for dose adjustment.[3] In another study, only 37.2% of patients were classified in the same stage of CKD regardless of whether the CG or MDRD formula was used, and the MDRD consistently calculated higher GFR estimations than the Cockcroft-Gault equation, leading to a reclassification of CKD staging by one stage (i.e. from a CKD stage of 4 to a CKD stage of 3) in 59.8% of the 106 patients studied.[16]

Clearly, several studies have shown that the discrepancies that often exist between MDRD- and CG-calculated renal function can significantly influence drug dosing recommendations and dose selection. Additionally, the magnitude of discrepancy between the two equations is strongly influenced by age[15], which could contribute to even more exaggerated dose discrepancies among the elderly in particular. Pedone et al. noted that using the six-variable version of the MDRD equation in older patients whose serum creatinines fell within the normal range could increase their calculated creatinine clearance by a maximum of 20 mL/min.[15] This 20 mL/min increase in calculated renal function, however, can certainly sort patients into different ranges of renal function. In several instances, the increase in estimated clearance associated with using the six-variable MDRD equation would lead to classifying patients as having normal renal function, whereas using the Cockcroft-Gault equation would classify them as having reduced GFR.[15] In the Gill et al. study findings, which involved an elderly multi-ethnic population, discordant estimations in renal function were obtained in over 60% of the study's elderly patients when comparing GFR estimations derived from the CG equation versus the MDRD equation.[16] In terms of drug dosing, Gill et al. also found – consistent with the previously mentioned findings – that 20% fewer of the elderly patients in the study (70% of patients when using MDRD versus 91.2% of

patients when using CG) would have qualified for a decrease in their amantadine dose.[16] This means that 20% of this patient population would have received higher total cumulative doses of the drug if the MDRD was used in place of CG to determine amantadine dose adjustments.[16] To further illustrate this, Golik and Lawrence highlight one patient in their study who, coincidentally, resembles BS. This particular patient was a 91-year-old, 4'9" female with an actual body weight of 55.7 kg and SCr of 0.77 mg/dL.[14] (Compare Golik and Lawrence's patient to BS, who is a 90-year-old 5' female with an actual body weight of 54 kg and SCr of 0.72 mg/dL.[1]) Like BS, her GFR varied radically when the MDRD and CG equations were used to estimate her renal function. The MDRD equation calculated an GFR of 67.2 mL/min, whereas CG calculated a GFR of 28.9 mL/min.[14] (BS' eGFR on UCare was listed as > 60 mL/min, whereas her CG-calculated GFR was 31.5 mL/min.[1]) Because estimated GFR heavily influences drug dose selection, such a variation between eGFRs can have potentially serious and clinically significant ramifications, especially if higher drug doses are inappropriately administered. Given the elderly's increased sensitivity to some renally eliminated drugs and active metabolites, this could certainly create some undesirable and potentially preventable adverse drug events.

Response:

Although, like any model, the Cockcroft-Gault and the Modification of Diet in Renal Disease equations may not always calculate an estimated glomerular filtration rate that is as accurate as a measured glomerular filtration rate, they both provide very useful methods of estimating renal function. In terms of drug dosing, however, the vast discrepancies that occur when comparing the two equations' recommendations for drug dosing do merit caution and discourage their interchangeable application in estimating GFR. In fact, several aforementioned studies state that these two formulas cannot – and should not – be used interchangeably, especially in the elderly[15,16], as the team caring for BS had suggested in its recommendation of levofloxacin (Levaquin) 500 mg IV daily x 7 days based on BS' MDRD-calculated eGFR. Furthermore, the Cockcroft-Gault equation has 30+ years of experience behind it and is still currently the basis for drug manufacturers' renal dosing recommendations.[3,5,9] Given the lack of studies that have assessed the clinical utility and outcomes of using the MDRD equation for dose adjusting renally-eliminated medications, clinicians should avoid using the Modification of Diet in Renal Disease in place of the Cockcroft-Gault equation in estimating glomerular filtration rate for the purposes of drug dosing and drug dosing adjustment.[2,6,14,16] Furthermore, more studies should explore the clinical ramifications of using the MDRD equation in drug dosing before clinicians can confidently abandon the historically accepted Cockcroft-Gault method of estimating renal function for the purpose of dosing renally-eliminated medications. In the meantime, clinicians should be reminded of the proven utility of the Cockcroft-Gault equation – albeit, like the MDRD, only an estimation of patient's renal function – in drug dosing and be discouraged from the temptation to use the readily available MDRD-calculated eGFR to dose drugs until studies documenting its safe application are published.

In conclusion, for the specific case situation introduced above, BS should not receive the levofloxacin 500 mg IV daily x 7 days, as no MDRD-specific dosing guidelines for levofloxacin have been developed. Instead, as dictated by her renal function calculated using the Cockcroft-Gault equation, BS should receive a dose of 500 mg IV on Day 1, followed by 250 mg IV daily on Days 2 to 7, which was the recommendation made to and followed by the team.[1]

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