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Antimicrobial Dosing in Specific Populations and Novel Clinical Methodologies: Kidney Function

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Abstract

Kidney function is a common parameter used to define antimicrobial drug dosage and frequency of administration. Several methods exist to measure kidney function but for pragmatic reasons rely on estimated kidney function equations based on the endogenous biomarker serum creatinine and common clinical variables. Current regulatory guidance on the design of studies in patients with abnormal kidney function in the United States also recommend consideration of estimated kidney function for this reason. Over the past few decades, alternate endogenous biomarkers, administration of exogenous biomarkers for noninvasive measurement, use of probe substrates to characterize individual kidney drug clearance pathways, modifications to conventional equations to account for time-varying clearance, and improved clinical trial modeling and simulation to factor in these uncertainties have occurred. Furthermore, major changes to kidney replacement therapy delivery in the outpatient, inpatient, and at-home setting are occurring. Antimicrobial drug dose adjustment in this diverse population is complex and in a state of flux due to technical innovations. Over-reliance on kidney function estimates to guide drug dosing in patients with infectious diseases can bias underdosing especially among the acutely ill. A holistic approach to drug dose adjustment in patients with abnormal kidney function is necessary to optimize clinical outcomes.

Kidney function is a key quantitative figure used by clinicians to stage kidney disease and to inform drug dose selection.[1] Several antimicrobials are hydrophilic and eliminated in part as unchanged drug or as metabolites in urine.[1] Of the 41 antibiotics in global clinical development, ~ 40% will likely include recommendations for dose adjustment in patients with abnormal kidney function.[2] The regulatory framework on study designs to establish dose adjustments in patients with abnormal kidney function are currently therapeutic indication-agnostic and set from the perspective of achieving bioequivalence in patients with chronic kidney disease (CKD) relative to healthy patients.[3] Although patients with CKD constitute a significant portion of individuals with abnormal kidney function, they do not constitute the entire spectrum of potential cases that require antimicrobial therapy. Patients presenting with infectious diseases have a diverse and dynamic set of kidney

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CONFLICTS OF INTEREST

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function phenotypes that may be inadequately accounted for in our conventional approaches to antibiotic dose adjustment.[4]

When considering these phenotypes in clinical practice, patients with serious infections can have a transient augmentation of kidney function and drug clearance that may necessitate dose adjustment.[5,6] In one study, therapeutic failure was observed in 33.3%, 17.4%, and 12.9% when augmentation of kidney function lasted for more than a day, only 1 day, and not at all.[7] Alternatively, patients may have transient elevations in the principal biomarkers of kidney function (serum creatinine) that leads to a premature use of lower than standard initial doses.[4] Progression of infections to sepsis and septic shock can also lead to acute kidney injury (AKI) that may or may not require dose modifications.[8] These dynamic shifts are presently difficult to characterize with serum creatinine (S_{cr}) due to the lag time between the change in this biomarker and the actual improvement or impairment of kidney function.[9] The absence of fast turnaround therapeutic drug monitoring for specific antimicrobials exacerbates this uncertainty. Clinical reliance on rapid estimates of kidney function rather than measured kidney function is also driven by this pragmatic need for quick decision making. Our working hypothesis is that equivalent antibiotic pharmacodynamic target exposures in a population yield comparable outcomes.[10] However, patients with CKD likely have immunologic and physiologic aberrations from comorbidities that are distinct from patients with AKI.[11] Unfortunately, few data have explored these nuances and so this review is limited to the translation of kidney function estimates to drug clearance. In the past few decades, several strategies have advanced to better account for the discordance among estimated kidney function, measured kidney function, and drug clearance. These innovations include the use of alternate endogenous biomarkers, administration of exogenous biomarkers, modifications to conventional equations to account for time-varying clearance, and improved clinical trial modeling and simulation to factor in these uncertainties. The current review explores the uncertainties associated with kidney function estimation and novel clinical methodologies to improve antibiotic dosing in this specific population of patients with abnormal kidney function and augmentation. Nomenclature to harmonize our language and abbreviations surrounding kidney function has recently been detailed and are summarized in Table 1.[12] Patient-centered and precise terminology that align with guidelines are preferred and oblige us to move away from the use of the term “renal impairment” to “abnormal kidney function,” as one example.

ALTERNATE ENDOGENOUS BIOMARKERS FOR ESTIMATED GLOMERULAR FILTRATION RATE

Current approaches to determine estimated glomerular filtration rate (eGFR) in drug development rely almost exclusively on the endogenous biomarker S_{cr}. Routine S_{cr} assay methods had a bias of −0.06 to 0.31 mg/dL at a typical S_{cr} value of 0.90 mg/dL.[13] This bias led to a global effort to reduce interlaboratory variability using isotopic dilution mass spectrometry calibration standards.[13,14] However, this standardization does not correct the many limitations of S_{cr}.[15] The ideal endogenous biomarker should be produced at a constant rate, not be bound to plasma proteins, be freely filtered through the glomerulus, have no kidney tubular secretion or metabolism, and have no non-kidney metabolism.[16]

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Unfortunately, S_{cr} fails most of these criteria. The production or input of S_{cr} is not constant and depends on muscle mass and activity, diet, and is impaired in patients with cirrhosis.[15] Tubular secretion also accounts for 10–15% of S_{cr} elimination and is impacted by organic cation transporter-mediated drug interactions.[17] An almost 50% reduction in glomerular filtration rate (GFR) is necessary before a rise in S_{cr} is observed and the lag time between these events are dependent on the baseline GFR.[9] Although kinetic GFR equations have been developed to correct for these changes, they cannot overcome all of these flaws.[18] Reliance on S_{cr} has also led to the inclusion of a "race factor" in eGFR equations to correct for ethnic differences in average S_{cr} values.[19-21] A multitude of alternate equations have been developed to "fix" this bias but the generalizability of this approach between populations is unlikely.[22] Although alternatives exist to enhance translation of S_{cr} to eGFR are present, none are ideal and only cystatin C has been evaluated for drug dosing considerations.[16]

Serum cystatin C (S_{cys}) is a low molecular weight protein produced at a constant rate by all nucleated body cells that increases the precision of eGFR estimates based on S_{cr} in specific populations.[23-25] Although this low molecular weight protein biomarker was discovered over 35 years ago, the novelty of this biomarker exists because its adoption in practice remains slow.[23] Current guidelines recommend use of S_{cys} in patients with an eGFR between 45 and 59 mL/min/1.73 m_2 and urine albumin < 30 mg/g creatinine.[26] This recommendation overcomes the "creatinine-blind range," where S_{cr} values fail to rise due to the compensatory increase in tubular secretion of S_{cr}. Warnings for decreased efficacy of certain antibiotics in patients with creatinine clearance (CL_{cr}) estimates of 30–50 mL/minute begs the question of whether inclusion of S_{cys} in future antimicrobial phase III clinical trials could help resolve potential dose adjustment discrepancies.[4] Equations that transform S_{cys} measurements to eGFR do not require an adjustment of race as a factor compared with S_{cr} based equations.[27] Table 2 provides a summary of the key equations used to determine estimated CLcr (eCL_{cr}) and eGFR and illustrates this use and nonuse of race with adjustment for body surface area (BSA).[14,27-31]

Over the past few decades numerous studies have now compared the use of S_{cys} to S_{cr} and the combination of the two to estimate eGFR for drug dosing in acutely ill patients.[25,32-34] The use of eGFR using the combination of S_{cys} and S_{cr} improved target concentration achievement from 35% to 54% for vancomycin and the estimate of gentamicin clearance (CL; within 30%) from 77% to 82% when compared with S_{cr} alone.[34] Although this improvement is incremental, the use of these biomarkers in combination may be particularly useful in nonambulatory patients with reduced muscle mass.[35] Recently, use of the combination of S_{cys} and S_{cr} has been shown to improve antibiotic dosing for an agent (ceftriaxone) not traditionally adjusted for kidney impairment.[36] Sarcopenia or muscle mass loss as a function of aging can be estimated by the ratio of S_{cr} and S_{cys}.[37] Simulations demonstrate that the eGFR based on the combination of these biomarkers better predicts ceftriaxone exposures and doses than body weight.[36] Limitations do exist with use of S_{cys} due to underestimation of eGFR in patients with obesity, malignancy, high-dose corticosteroid use, kidney transplant recipients, and in patients that smoke.[38] Production of S_{cys} is dependent on cell turnover, which is disrupted in hypothyroidism and hyperthyroidism, which can lead to overestimation and underestimation of eGFR,

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respectively.[38] Despite these limitations, the international federation for clinical chemistry working group has established human serum certified reference materials and are advancing global standardization.[39] The next generation of eGFR based on endogenous biomarkers will require prospective evaluation of S_{cys} and the combination of S_{cys} with S_{cr}. Given the dynamic state of kidney function in patients with serious infectious diseases, eGFR is unlikely to completely close the gap in optimal dose selection in this population.

NEW METHODS FOR MEASUREMENT OF GLOMERULAR FILTRATION RATE

The classic method for measured GFR (mGFR) includes administration of a continuous infusion of inulin followed by blood and urine collection at specified time points.[40,41] The advantage with administration of an exogenous compound as a kidney function biomarker is the certainty of the input function. However, the requirement for multiple sample collections and analysis makes this approach cumbersome and not practical for day-to-day clinical use. A systematic review of these methods suggests general agreement between these methods but also bias across the range of GFR.[42] This discrepancy between methods suggests that mGFR should not blindly be assumed to be the standard to benchmark drug dosing. From a practical perspective, repeated determination of mGFR may be needed across the duration of antimicrobial therapy because the knowledge gained on the first day of therapy may not be relevant later in the therapy if shifts in kidney biomarkers are observed. Alternatives, such as 8-hour measured CL_{cr}, have been used to determine kidney function but are generally useful in stable patients with indwelling urinary catheters.[43] Despite these limitations and complexities, novel techniques have been developed to get real-time mGFR that could support drug dosing decisions among critically ill patients.

A novel bedside approach in clinical development includes the use of visible fluorescent injectate that relies on two fluorescently tagged dextrans that are 5 and 150 kD, respectively.[44] After demonstration of safety in health volunteers, a phase IIb clinical trial has been performed with this method.[44] The method includes bolus injection (for 30 seconds) of the VFI with blood sampling at 15, 60, and 170 minutes, analysis by standard fluorimeter, and fit by a compartmental model to estimate clearance. Near perfect correlation of mGFR was documented with this technique in this study ($n = 32$) compared with iohexol mGFR. Use of the dual marker permits calculation of the volume of vascular space (150 kD dextran) while simultaneously capturing information of the freely filtered marker (5 kD). Although this approach may not necessarily be ready for day-to-day clinical application, it affords a potentially useful technique to ensure appropriate participant allocation in kidney function groups. Previous studies have demonstrated that participants can, on occasion, be miscategorized by eGFR impacting the interpretation of full design kidney impairment studies.[45] Although this approach is being advanced for mGFR determination in chronic heart failure, the potential application of this technology in critically ill patients could be particularly meaningful to qualify augmentation or abnormal kidney function that are not well qualified by endogenous biomarkers.

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More sophisticated noninvasive technologies are currently in development that may potentially eliminate the need for blood and urine collections to establish mGFR.[46] One such technology is transdermal GFR measurement that includes attachment of a sensor to the skin (sternum/manubrium preferred), followed by intravenous administration of a fluorescent tracer that is detected by the sensor. The sensor has been designed to calibrate to the individual patient's skin color and can continuously monitor GFR in a manner that is akin to current pulse oximeters. A phase I trial has been completed with this device but tolerability results have not been made public (NCT03810833). Current and future technologies being developed for mGFR could provide an incremental step toward precision drug dosing in acutely ill patients with infectious diseases. Nonetheless, drug clearance may not be fully characterized by GFR alone. Kidney tubular secretion, reabsorption, and metabolism play variable roles in clearance based on the drug in question. Although innovations have occurred to measure these processes, cost and feasibility have made their practical application difficult. Thus, the translation of kidney function to individual drug CL carries uncertainties that should be recognized by clinicians.

REBRANDING KIDNEY FUNCTION ESTIMATION

The complexity of kidney function measurement leads to oversimplification by estimation methods. A plethora of equations, modifications to these equations, and caveats exist when estimating kidney function for drug dosing using S_{cr}.[28-30,47-51] These citations include adjustments for body size, unstable S_{cr}, race, and disease conditions, and are by no means a comprehensive list. The jargon surrounding these estimates also leads to their imprecise application and will require action from multiple stakeholders to educate the end user that these estimates are guideposts.[12] The two predominant equations presently in product labels are the Cockcroft-Gault (C-G) equation and the modification of diet in kidney disease (MDRD) equation.[45] A recent update to the draft guidance for industry includes the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[3] All three dominant equations rely on S_{cr} and so suffer from the aforementioned limitations of this biomarker.

There are multiple unsettling characteristics of the C-G equation that include the decision to rely on weight and an uninformed adjustment for female gender as a surrogate for S_{cr} production differences due to muscle mass.[28] The C-G equation also predates S_{cr} standardization barring universal re-expression of this equation. Likewise, the MDRD equation and CKD-EPI yield values that require conversion to individual BSA estimates and have an adjustment for race that is divisive.[3,20,21] The eGFR equations have historically quantified BSA using the Dubois and Dubois method, whereas the predominant clinically used method is based on Mosteller's adaptation.[31,52,53] Race is a social construct that is a "lazy" population level variable that may imprecisely inform individual level drug dosing decisions.[54] Petitions for change, have led some institutions to eliminate this African American (MDRD) or Black (CKD-EPI) race factor.[20,55] Arguments about introduction of bias to eGFR estimation with elimination of this factor has been presented.[56] Race is not a factor when S_{cys} is used alone or when calculating eGFR using S_{cr} in children, which begs the question of its relevance as a factor in adulthood. If a decision is made to eliminate the race factor, then a revision to the entire MDRD or CKD-EPI equation is necessary (not just deletion of the race factor). Ultimately, too many modifications exist to these eCL_{cr}

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and eGFR that highlight their imprecision.[57] Serious concerns about these equations will expand discordance between labeled dosing recommendations and actual clinical practice.[58] Healthcare systems cannot easily integrate drug specific kidney dose modifications and more likely set institutional standards to either use eCL_{cr} or eGFR for all drugs on their formulary. The safety of this clinical decision has not been determined systematically. New methods for reporting these estimates and relaying the uncertainty of these values are critically necessary to inform the dose decision maker.

From an antimicrobial dosing perspective, the outputs from these equations are snapshots in time that may be useful in stable patients with CKD but not in AKI.[59] Acutely ill patients with infectious diseases have dynamic shifts in kidney function that warrant further modeling and simulation considerations. Equations have been developed to define eCL_{cr} and eGFR in these cases but have been included in drug labels.[18,47,60] Approximately 20% of patients with an infectious disease condition, such as pneumonia, intrabdominal, and urinary tract infections, have some degree of AKI at clinical presentation.[4] Almost half of these individuals can have recovery of kidney function within the first 2–3 days of admission.[4] Reductions in the S_{cr} lag behind this recovery, and so antibiotic dosing recommendations may be incorrectly lowered early in therapy.[9] The bacterial load is expected to be higher at treatment initiation than a few days into therapy. Therefore, ensuring adequate exposures are achieved during this early phase of therapy is paramount. Modeling and simulations to evaluate the risk-benefit of not modifying the antimicrobial dosing regimen during the early phase of therapy should be considered especially given that antibiotics (with few exceptions) tend to have a wide therapeutic index relative to other drug classes.

From a prescriber perspective, the medico-legal implications of not abiding by the product label designated cutoff values for dose modifications (e.g., reduce dose by 50% if $CL_{cr} < 30$ mL/min) force the hand of clinicians in some instances to use these values in unconditional terms. Laboratory values are simply an aid that require thoughtful interpretation.[61] Caution on the reporting and considerations for inclusion of percentile charts by age and sex has been suggested.[62] Consensus on whether eGFR or eCL_{cr} is the “best” approach to drug dose selection is unlikely and irrelevant in the long-term as new biomarkers and measurement methods develop. Therefore, increased transparency on the population pharmacokinetic models used to generate these drug dosing recommendations are necessary so that adjustments can be made to keep pace with technological and medical advancements. Development and application of physiology-based pharmacokinetic models offer discrete opportunities to help bridge these advancements.[63] Ultimately, kidney function is just one of several covariates that should drive decisions on dose adjustment. The complexity of multiple source information integration will likely lead us in the medium term to a path that is informed by machine learning and emerging artificial intelligence methods.[64] In the interim, broader education on the nuances of kidney function estimation are necessary along with systems to manage case scenarios where no information is available. This is often the case in patients with kidney failure. A wide array of kidney replacement therapies exist that make it difficult to deliver precise recommendations in current drug labels and beyond the scope of the present review.

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FUTURE DIRECTIONS

Patients with kidney disease are a complex specific population that are mathematically reduced to a single value, such as eGFR and eCL_{cr} to inform drug dosing. Although this simplification is necessary to ensure exposure matching in this population relative to patients without abnormal kidney function, it can bias under dosing of antimicrobials in this population. This is especially true because clear distinctions between patients with CKD and AKI are unaccounted when dosing antimicrobials. Techniques that improve the precision of kidney function estimation through measurement, such as transdermal GFR, are emerging and may better detect shifts in kidney function to improve antibiotic dosing. Likewise, newer biomarkers, such as S_{cys}, have the potential to be adopted and create an incremental improvement over S_{cr} alone in the near term. Ultimately, increased education of clinicians that uncertainty exists with these estimates coupled with better integration of information sources can help to improve antimicrobial dosing. Increased data transparency and creation of information warehouses within this space will allow researchers an opportunity to create newer user-friendly drug dosing models adaptive to kidney function.

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Table 1

Summary of current and preferred terminology along with suggested abbreviations pertinent for clinical pharmacology use

Current terms	Preferred term	Suggested abbreviation
Renal	Kidney	Not specified
Renal impairment, dysfunction, insufficiency	Abnormal kidney function	Not specified
Residual renal function	Residual kidney function	RKF
Acute renal failure	Acute kidney injury	AKI
Renal replacement therapy	Kidney replacement therapy	KRT
Chronic renal disease	Chronic kidney disease	CKD
End-stage renal disease, dialysis-dependent CKD	Kidney failure	KF
	Dialysis	CKD G5D
	Hemodialysis	HD
	Peritoneal dialysis	PD
	Frequency: Continuous, intermittent (short or prolonged)	
Glomerular filtration rate (GFR)	Measured GFR	mGFR
	Estimated GFR	eGFR
	Estimated GFR using creatinine	e^{GFR}_{cr}
	Estimated GFR using cystatin C	e^{GFR}_{cys}
	Estimated GFR using creatinine and cystatin C	$^{eGFR}_{cr\text{-}cys}$
Clearance (CL)	Measured CL	mCL
	Measured CL using creatinine	m^{CL}_{cr}
	Estimated CL	eCL
	Estimated CL using creatinine	e^{CL}_{cr}
Tubular function	Tubular secretion	TS
	Tubular reabsorption	TR

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Table 2

Most common equations used for eCL_{cr} and eGFR based on S_{cr} and cys for drug dosing considerations

Name	Equation
Cockcroft-Gault[28] (eCL_{cr} in mL/minute)	(140 - age) x weight/(72 x S_{cr}) *note, this equation predates standardized S_{cr}
MDRD[49] ($eGFR_{cr}$ in mL/minute)	175 x $(S_{cr})^{-1.154}$ x $(age)^{-0.203}$ x (0.742 if female) x (1.212 if African American) x BSA/1.73
CKD-EPI[30] ($eGFR_{cr}$ in mL/minute)	141 x min (S_{cr}/K, 1)“ × max(S_{cr} /κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if Black] × BSA/1.73 κ = 0.7 (females) or 0.9 (males) α = −0.329 (females) or −0.411 (males) min = indicates the minimum of S_{cr}/K or 1 max = indicates the maximum of S_{cr}/K or 1
CKD-EPI[27] ($eGFR_{cr\text{-}cys}$ in mL/minute)	135 x min (S_{cr}/K, 1)$^{\alpha}$ x max (S_{cr}/K, 1)$^{-0.601}$ x min (S_{cys}/0.8, 1)$^{-0.375}$ x max (S_{cys}/0.8, 1)$^{-a711}$ × 0.995^{Age} x 0.969 [if female] x 1.08 [if Black] x BSA/1.73 K = 0.7 (females) or 0.9 (males) α = −0.248 (females) or −0.207 (males) min (S_{cr}/K or 1) = indicates the minimum of S_{cr}/K or 1 max (S_{cr}/K or 1) = indicates the maximum of S_{cr}/K or 1 min (S_{cys}/0.8, 1) = indicates the minimum of S_{cys}/0.8 or 1 max (S_{cys}/0.8, 1) = indicates the maximum of S_{cys}/0.8 or 1
CKD-EPI[27] ($eGFR_{cys}$ in mL/min)	133 x min (S_{cys}/0.8, 1)$^{-0.499}$ x max (S_{cys}/0.8, 1)$^{-1.328}$ × 0.996^{Age} x 0.932 [if female] x BSA/1.73 Min (S_{cys}/0.8, 1) = indicates the minimum of S_{cys}/0.8 or 1 Max (S_{cys}/0.8, 1) = indicates the maximum of S_{cys}/0.8 or 1
Schwartz Bedside[29] (eGFR in mL/minute/1.73 m^2)	(0.41 x Height)/S_{cr}
BSA[31]	BSA using Mosteller’s adaptation = $((Height \times Weight)/3{,}600)^{0.5}$

Age in years, weight in kg, S_{cr} (standardized) in mg/dL, S_{cys} (standardized) in mg/L, Height in cm, BSA in m^2.

BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cys, cystatin C; MDRD, modification of diet in kidney disease; eCLcr, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; Scr, serum creatinine.

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