Medications and Kidney Function

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This FAQ covers dosing medications in patients with kidney impairment. Monitoring kidney function in patients taking potentially nephrotoxic drugs is briefly addressed.

eGFR calculators for adult and pediatric patients are available at: https://www.kidney.org/glomerular-filtration-rate-gfr

Question	Answer/Pertinent Information
How do you determine kidney function?	• **GFR** is the most accurate index of kidney function, but it cannot be measured directly.[2] GFR can be calculated by measuring the clearance of an agent that is exclusively excreted by filtration such as inulin (the gold standard), iothalamate, or iohexol.[12] However, this is clinically impractical, so the clearance of certain endogenous substances (e.g., **creatinine**, **cystatin-C**) is often used instead.[2] ◦ **Creatinine** is an imperfect indicator of GFR because SCr is not impacted until kidney function is significantly reduced; creatinine undergoes active tubular secretion as well as filtration; and SCr is influenced by factors other than glomerular filtration, including:[2] ▪ muscle mass (lower in the elderly, females, malnourished patients, amputees, spinal cord injury)[2] ▪ diet (cooked meats can transiently increase SCr; vegetarians have lower SCr)[2] ▪ medications (e.g., trimethoprim, cimetidine, piperacillin-tazobactam, dronedarone, dolutegravir, rilpivirine, cobicistat, olaparib, rucaparib, bosutinib, crizotinib, gefitinib, imatinib, pazopanib, sorafenib, sunitinib) reduce tubular creatinine secretion; cefoxitin and cefotetan [US] can falsely elevate SCr measured with the Jaffe [alkaline picrate] method.[2-5] Measure SCr at least two hours after cefoxitin dose.[4]) ▪ volume overload (reduced SCr).[1] ◦ **Cystatin C** is a protein produced all in cells with a nucleus (not only muscle cells, like creatinine).[2] After being excreted by filtration, it is broken down in the tubular epithelial cells. Only small amounts are eliminated in the urine.[2] Compared to creatinine, cystatin C production is more consistent and is not affected as much by age, sex, and diet. However, production may be increased with hyperthyroidism and steroid use. Higher levels are also associated with higher C-reactive protein levels, higher BMI, and cancer.[2,12] • The **CKD-EPI equation** is the equation recommended by the National Kidney Foundation and multiple US pharmacy organizations to estimate GFR for medication dosing decisions.[12,16] Variables in the equation are SCr and/or serum cystatin C, age, and sex.[11] Patient race is no longer used as a variable in the current CKD-EPI equations. Using **both** SCr and serum cystatin C in the equation increases accuracy.[2] **A calculator** is available at https://www.kidney.org/professionals/kdoqi/gfr_calculator. o This equation was developed and validated in a diverse population (i.e., Black and white adults 18 to 97 years of age, with GFR 2 to 200 mL/min/1.73 m^2, including solid organ transplant patients.).[2]

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Question	Answer/Pertinent Information
	The **Cockcroft-Gault equation** and **MDRD** equation are no longer recommended.[2] See footnote b for more information about these equations.
How do you choose a method to determine kidney function?	• **2021 CKD-EPI Creatinine**: consider for patients without comorbidities, medications, or body habitus that might affect SCr.[12] • **2012 CKD-EPI Cystatin C**: consider for patients with high muscle mass, eating disorders, above-knee amputation, spinal cord injury, meds affecting the clearance of creatinine[12] • **2021 CKD-EPI Creatinine-Cystatin C**: consider for patients with BMI >35 to 40 kg/m2, malnutrition, heart failure, cirrhosis, cancer, catabolic conditions (e.g., tuberculosis, AIDS), high-dose steroids[12] o Consider **measured GFR*** for patients in whom both creatinine and cystatin C may be significantly affected by non-GFR factors (e.g., serious infection or inflammation, rapidly dividing cancers, advanced cirrhosis, decompensated heart failure, extreme frailty).[12] • **Measured GFR:*** consider when high accuracy is needed (e.g., for dosing methotrexate [≥500 mg/m^2], carboplatin, or cisplatin, or other toxic drugs eliminated by the kidney), or kidney function is rapidly changing.[2,8,12] ***Measured urinary CrCl can be used if other methods are unavailable.[12]
What are some considerations for special populations?	• **Overweight or underweight**: o eGFR calculated using the CKD-EPI equation is standardized (indexed) to a "normal" BSA and is expressed in mL/min/1.73 m^2. This allows for a more accurate comparison of a patient's kidney function to normal values because kidney function is dependent in part on kidney size.[2] But for purposes of drug dosing, especially in patients with extremes of body weight, eGFR expressed in mL/min/1.73 m^2 should usually be multiplied by the patient's BSA (m^2) to get a BSA-adjusted (nonindexed) eGFR.[12,14] See **footnote a** for an example. The calculator at https://www.kidney.org/professionals/kdoqi/gfr_calculator can also do this for you. • **Elderly**: The common practice of substituting an SCr value of 1 mg/dL (88.4 umol/L) for elderly patients with SCr <1 mg/dL (88.4 umol/L) can underestimate kidney function.[7] Only input the actual SCr value when using CKD-EPI equations; do not round to 1 mg/dL, etc. • **Kidney transplant** patients: The CKD-EPI has been validated in these patients.[15] • **Critical care:** Kidney function estimates are inaccurate when kidney function is rapidly changing; changes in SCr or serum cystatin-C lags behind acute changes in kidney function.[2] If urine output is minimal, assume a GFR of <10 mL/min.[1]
How do you use kidney function estimation to dose drugs?	**Background:** • Most drug dosing recommendations have been based on CrCl calculated using the Cockcroft-Gault equation (often using total body weight) or other equations that are no longer used.[6] (See footnote b for more information.) • Since 2010, US labs have reported a standardized SCr.[2] But for most drugs FDA-approved before 2018, dosing recommendations are based on kidney function calculated using SCr measured using the old, nonstandardized method.[6,9]

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Question	Answer/Pertinent Information

Continued…
How do you use kidney function estimation to dose drugs, continued
	• **BSA-adjusted CKD-EPI equations (above) can be used for drug dosing**.[6,12] These equations are more accurate than Cockcroft-Gault for estimating GFR.[6] Use actual height and weight when calculating BSA-adjusted eGFR.
	
	Practice Tips:
	• When choosing a dose, use clinical judgement; kidney function calculations are only estimation, even with BSA-adjustment.[6]
	• There is no way to "adjust" CKD-EPI equation results to compare them to Cockcroft-Gault-calculated CrCl in part due to variances in how the latter was calculated (e.g., use of IBW vs ABW, rounding-up of SCr, use of unstandardized SCr), and in part due to the population in which it was developed.[6]
	• For drugs with dosing recommendations based on Cockcroft-Gaultor standardized eGFR (mL/min/1.73 m^2), BSA-adjusted CKD-EPI equation results can still be generally used for most medication dosing decisions.[17] Another approach may include comparing CrCl and BSA-adjusted eGFR results to dosing cut-offs. If the results differ, consider the patient's illness severity and drug toxicities when choosing a dose.[6] The National Kidney Foundation provides additional guidance to help with decision-making when dosing adjustments in drug labeling and compendia are not based on BSA-adjusted eGFR: https://www.kidney.org/professionals/ckdintercept/race-agnostic-egfr-medication-related-decisions/faq.
	• In cases where kidney function is in question, consider the risk/benefit of:
	  o choosing an alternative drug (e.g., less toxic and/or not cleared by kidney)
	  o waiting to start the drug or dosing conservatively pending more information (e.g., send-out cystatin C, measured clearance) or kidney function stabilizes
	  o choosing a drug for which therapeutic drug monitoring is meaningful

What common medications need dosing adjustment for kidney function?	**Common examples** and related resources include:
	• Antibiotics
	  o See our FAQ, *Vancomycin Dosing and Monitoring for Adults*.
	• Anticoagulants
	  o See our chart, *Comparison of Oral Anticoagulants*, and our toolbox, *Appropriate Use of Anticoagulants*.
	• Antihypertensives
	  o See our charts, *Comparison of Oral Beta-Blockers* and *Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors*.
	• Diabetes drugs
	  o See our infographic, *Drugs for Type 2 Diabetes*.

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Question	Answer/Pertinent Information
What is a clinically worrisome change in kidney function in a patient receiving a potentially nephrotoxic drug?	• No general guidance exists, but based on definitions of acute kidney injury from various consensus groups, consider the following concerning: urine output <0.5 mL/kg/h; SCr increase of ≥0.3 mg/dL (26.5 umol/L); **or** SCr increase of ≥1.5 times baseline.[1] • For potentially nephrotoxic drugs, unless specific recommendations are available, consider checking SCr at baseline, after starting or increasing the dose, when the patient condition changes, and periodically. Also consider setting a reminder in the electronic medical record to watch kidney function trajectory. • Our algorithm, *Monitoring ACEIs and ARBs*, provides information to guide action based on increases in SCr and potassium.

a. **To change eGFR** expressed as mL/min/1.73 m^2 to mL/min, multiply by BSA. BSA can be estimated as follows:

BSA (m^2) = 0.007184 x $W^{0.425}$ x $H^{0.725}$, where height is in centimeters and weight is in kilograms.[2]

OR

BSA (m^2) = square root of: [(height x weight)/3131], where height is in inches and weight is in pounds.[10]

Values will be similar for average-size patients, but they can be very different for very large or very small patients. For example, in an average-size patient with a BSA of 1.75 m^2, with a calculated standardized eGFR of 40 mL/min/1.73 m^2, the BSA-adjusted (nonindexed) value will be 40 mL/min:

40 mL/min/1.73 m^2 x (1.75 m^2) = 40 mL/min.

But for a large patient with a BSA of 2.7 m^2 with a calculated standardized eGFR of 40 mL/min/1.73m^2:

40 mL/min/1.73 m^2 x (2.7 m^2) = 62 mL/min

b. The **Cockcroft-Gault equation** was developed to estimate CrCl (mL/min).[2] It was determined using data from white men with CrCl ~30 mL/min to 130 mL/min.[2] This equation factors in SCr, age, sex, and weight.[2] It was developed using unstandardized serum creatinine values.[13]

The **MDRD equation** is more accurate than a timed 24-hour urine collection or the Cockcroft-Gault equation.[2] It estimates GFR adjusted for body surface area using SCr, age, sex, and race.[2] It was determined using data from adults ≤70 years of age with CKD.[2] Most were nondiabetic white patients with eGFR 5 to 90 mL/min/1.73m^2.[2] It is most accurate for patients with GFR <60 mL/min./1.73m^2 (i.e., with stage III chronic kidney disease).[2]

Abbreviations: ABW = adjusted body weight; BSA = body surface area; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; eGFR = estimated GFR; GFR = glomerular filtration rate; IBW = ideal body weight; MDRD = Modification of Diet in Renal Disease; SCr = serum creatinine

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