Retooling the Creatinine Clearance Equation to Estimate Kinetic GFR when the Plasma Creatinine Is Changing Acutely

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ABSTRACT
It is often desirable to estimate the GFR (eGFR) at the bedside to assess AKI or renal recovery. Current eGFR equations estimate kidney function when the plasma creatinine is stable, but do not work if the plasma creatinine is changing rapidly. To analyze kidney function in the acute setting, a simple formula is proposed that requires only a modest number of inputs that are readily obtainable from clinical laboratory data. The so-called kinetic eGFR (KeGFR) formula is derived from the initial creatinine content, volume of distribution, creatinine production rate, and the quantitative difference between consecutive plasma creatinines over a given time. For that period, the deciphered creatinine excretion then yields the creatinine clearance rate. The additional formula variables needed are any steady-state plasma creatinine, the corresponding eGFR by an empirical formula, and the maximum increase in creatinine per day if anuric. The kinetic formula complements clinical intuition but also adds a quantitative and visual dimension to the assessment of kidney function, demonstrated by its analysis of GFRs underlying the plasma creatinine fluctuations in several scenarios of AKI or renal recovery. Deduced from first principles regarding the physiology of creatinine balance, the KeGFR formula enhances the fundamental clearance equation with the power and versatility to estimate the kidney function when the plasma creatinine is varying acutely.


Assessing the GFR is problematic while the plasma creatinine is changing quickly. Physicians know that it is important to gauge the GFR accurately in AKI or renal recovery, but there is no widely accepted approach to guessimate kidney function in the acute setting. While the creatinine is fluctuating, most of us rely on our best guess about the underlying GFR, hoping to be close to the actual value that is calculable at last when the creatinine reaches a new steady state. In the interim, uncertainty reigns, partly due to a lack of familiarity with existing techniques that can extract a quantitative clearance from plasma creatinines in motion. In severe AKI, one often defaults to the assumption that the GFR is <10 ml/min. However, an actual GFR of 35 ml/min might alter the therapeutic management, or a GFR that was <10 ml/min but is now improving might avert the initiation of dialysis. Furthermore, no broad guidelines exist about approximating the GFR when the creatinine is declining, except to say kidney function is recovering.

One can do better than these qualitative generalizations by layering on a quantitative sophistication and charting the course of kidney function during an acute episode of injury. The evolution of GFR is not always obvious and our intuition may lead us astray. That is why we need to streamline the interpretation of creatinine kinetics and repopularize the lost art of estimating a kidney function to clarify our interpretation of AKI or renal recovery.

It has been in our power all along to assess the GFR when the creatinine is changing acutely. The venerable clearance equation remains valid even when the creatinine is not stable. Oddly, the absence of a steady state is often used to argue against the applicability of the clearance equation. This is not so if one realizes that the numerator (or urinary creatinine excretion) of the clearance equation does not have to be a constant, as is usually taught. In fact, the numerator has to be a dynamic parameter in order for the plasma creatinine to change. Creatinine excretion has to be less than steady state during AKI, allowing creatinine to accumulate in the body. Likewise, creatinine excretion has to be greater than steady state during renal recovery, thus removing net creatinine from the body. The trick is to quantify the
degree to which the creatinine excretion has decreased (AKI) or increased (recovery) relative to its steady-state value. Although kinetic estimated GFR (KeGFR) equations have previously been devised following the principle above, they have not been widely practiced or taught. This is unfortunate because we need to continue the favorable trend of interpreting kidney function not in terms of plasma creatinine but of clearance. The habit of translating creatinine into the estimated GFR (eGFR) is becoming more ingrained with the growing use of the Modification of Diet in Renal Disease (MDRD) formula and will only continue with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.\textsuperscript{1–4} In this regard, the clinical evaluation of CKD is more advanced, but the assessment of AKI and renal recovery can begin to catch up with the promulgation of creatinine kinetic formulae.

The earliest attempt at this was by Jelliffe and Jelliffe in 1972,\textsuperscript{5} followed by Chiou and Hsu in 1975,\textsuperscript{6} then Moran and Myers in 1985,\textsuperscript{7} and most recently Yashiro et al. in 2012.\textsuperscript{8} Each may differ in their mathematical approach, algebraic or calculus based, but they are all essentially rooted in first principles of creatinine mass balance that solves for the requisite creatinine excretion from a creatinine production rate and observed rate of change in the plasma creatinine. The creatinine excretion is then converted into a clearance rate. Despite being clinically validated in patients,\textsuperscript{6–10} the existing equations have not been adopted for routine clinical use by nephrologists or intensivists. Perhaps that has to do with their perceived complexities (arcane mathematical notation) or informational requirements such as knowing creatinine generation rate and volume of distribution.

To try to overcome the barriers to adoption, I have reformulated the core mathematical operations into a less intimidating and more pliable version at the bedside, a format that aligns well with typical laboratory reports and customary data gathering on rounds. In its most simplified form, the proposed KeGFR formula is reminiscent of the clearance equation in a way that makes the renal parameters more memorable and comprehensible as they are being manipulated in the math symbols. In promoting the current formula, I hope to revive the lost art of deciphering the eGFR patterns that are hidden within a panel of changing plasma creatinines. The exercise is both enlightening and empowering. What follows are case examples of the more illuminating revelations from using the formula (real-life examples are presented in the Supplemental Material), yielding conclusions about the GFR that may be missed despite the level of clinical experience.

**FORMULA EXPLAINED**

The formula in its final state will be presented first. The complete derivation is available in the Supplemental Material, but when the mathematical simplification is done, the formula becomes more compact and intuitive. It should be relatively easy to memorize or reconstruct by clinical reasoning.

\[
\text{KeGFR} = \frac{\text{SSPCr} \times \text{CrCl}}{\text{MeanPCr}} \times \left(1 - \frac{24 \times \Delta P_{\text{Cr}}}{\Delta \text{Time}(h) \times \text{Max} \Delta P_{\text{Cr}} / \text{Day}}\right)
\]

Most of the variables are already recognizable as an alternative way to express the standard clearance equation. SSP\textsubscript{Cr} × CrCl means the product of any steady-state plasma creatinine and the corresponding creatinine clearance. SSP\textsubscript{Cr} × CrCl can substitute for U\textsubscript{Cr} × V in the numerator of the clearance equation, evident from the rearrangement of CrCl = \(\frac{U_{\text{Cr}} \times V}{P_{\text{Cr}}}\). SSP\textsubscript{Cr} × CrCl reflects creatinine production rate, which being a function of one’s muscle mass is mostly a constant. This allows physicians the freedom to use any plasma creatinine so long as it is multiplied by the corresponding steady-state creatinine clearance. Effectively, SSP\textsubscript{Cr} × CrCl can be calculated just once and the result used for a patient’s entire acute renal episode. Practically speaking, SSP\textsubscript{Cr} × CrCl is easiest to obtain from the laboratory report, because many institutions report the measured plasma creatinine next to the calculated eGFR from the four-variable MDRD equation.\textsuperscript{2}

The formula’s denominator, MeanPCr, is the equivalent of P\textsubscript{Cr} in the clearance equation. Because the kinetic situation deals with two creatinine endpoints, the starting and the ending values, the arithmetic mean yields a single halfway value that is suitable for use in the clearance equation. Of course, when the two creatinine endpoints are the same, in effect the steady state, the average is just that creatinine value. Technically, the creatinine average is an approximation but it is very close to the correct number when dealing with acute situations (creatinines <48–72 hours apart).

The most complex term is in the parentheses above, which is what I call the “1 minus subtracted ratio.” If it cannot be recalled, it can be deduced. Basically, the value of SSP\textsubscript{Cr} × CrCl is going to be increased or decreased by a multiplicative factor rationally determined by the patient’s particular set of kinetic parameters. Naturally, this multiplier factor centers around 1, the identity number for multiplication. From the value of 1, a ratio consisting of the patient’s relevant parameters will be subtracted or added (because the ratio can be negative, and subtracting a negative number is the same as adding that number’s absolute value).

\(
\Delta P_{\text{Cr}}\)

refers to the change in plasma creatinine. It is defined as the ending creatinine minus the starting creatinine or P\textsubscript{Cr} (end) – P\textsubscript{Cr} (start). Intuitively, the larger the excursion in the plasma creatinine, the greater the effect will be on the kidney function. For example, going from a creatinine of 1 to 2 mg/dl indicates a worse GFR than going from a creatinine of 1 to 1.5 mg/dl in the same amount of time. Thus, \(
\Delta P_{\text{Cr}}\) is proportional to how much the true GFR is impaired or improved versus the steady-state GFR. Direct proportionality places \(
\Delta P_{\text{Cr}}\) in the numerator of the ratio to be subtracted.
ΔTime(h) is the interval in hours between two consecutive creatinines. Intuitively, the shorter the amount of time in which a creatinine change occurs, the greater the effect will be on kidney function. Going from a creatinine of 1 to 2 mg/dl in 24 hours signifies a worse GFR than going from a creatinine of 1–2 mg/dl in 72 hours. Thus, time is inversely proportional to the adjustment ratio to be subtracted from 1, meaning that ΔTime(h) belongs in the denominator.

MaxΔPcr/Day refers to the maximal change (increase) in plasma creatinine that can occur per day if renal function is completely lost. In anuric ARF, the customary teaching is that the plasma creatinine can rise at most by 1.0–1.5 mg/dl per day. This rule does not hold true for all patients, so the numerical choice for MaxΔPcr/Day should be guided by actual individual patient data if possible. An opportunity arises, not uncommonly, when the patient needs to go on intermittent hemodialysis. The increase in creatinine from a nondialysis day to just before dialysis the following day (in effect, predialysis plasma creatinine minus the creatinine 24 hours earlier) may be safely considered to be the maximal rate of rise in the plasma creatinine with zero kidney function. Anecdotally, this usually ranges from 1.3 to 2.0 mg/dl per day in dialysis patients in the intensive care unit (ICU). One can usually default to a consistent MaxΔPcr/Day of 1.5 for most adult patients without risking too much inaccuracy. Because MaxΔPcr/Day must be greater than any observed ΔPcr indexed to a day, the subtracted ratio

\[
\frac{24 \times \Delta P_{cr}}{\Delta Time(h) \times Max \Delta P_{cr}/Day}
\]

can never exceed 1. The lowest possible value is zero, and the eGFR answers will never be negative. Because it represents the ceiling on how much the creatinine can increase in a day, MaxΔPcr/Day belongs in the denominator. Another way to recall its place is to realize that the units of MaxΔPcr/Day need to cancel with those of ΔPcr, already known to be in the numerator.

The ratio numerator constant of 24 refers to the number of hours in a day. The 24 is mandated by choosing to measure ΔTime in hours and to index the maximum Δ plasma creatinine increment in 1 day, hence the units of hours per day. Evidently, these choices of units are most convenient because the time stamps on creatinine laboratory results lend themselves to figuring the interval in hours and the clinical practice of getting laboratory results every morning attunes one’s sense of the greatest rise in creatinine to the scale of 1 day. The constant is designed for our convenience but does not have to be 24. If ΔTime were measured in minutes and MaxΔPcr were indexed to a half day, then the constant would become 720, the number of minutes in a half day. Note that the choice of scaling constant does not alter the calculation, because the necessary adjustments to ΔTime and MaxΔPcr automatically mitigate the change. To counterbalance ΔTime and MaxΔPcr/Day in the denominator, the constant factor belongs in the numerator so that the units cancel properly.

**UNITS CHECK**

As a check of validity, algebra can be used to ensure that the final units of the eGFR formula are correctly in ml/min. Considering the subtracted ratio first, one can see that each and every unit cancels, leaving a unitless number to be subtracted from 1, which itself is unitless.

\[
1 - \frac{24 \times \Delta P_{cr}}{\Delta Time(h) \times Max \Delta P_{cr}/Day}
\]

Then, it is straightforward to see the remainder of the KeGFR formula yields units of ml/min.

\[
KeGFR (ml/min) = \frac{SSPCr (mg/dl) \times CrCl (ml/min)}{MeanP_{cr} (mg/dl)} \times (Unitless \ Number)
\]

The plasma creatinine above does not have to be in mg/dl. Physicians in many parts of the world express creatinine in μmol/L (multiply the mg/dl measure by 88.4). The formula accepts any units for creatinine as long as consistency is maintained. By the same token, CrCl does not have to be in ml/min. Whatever units of volume per time are chosen will dictate the final units of the eGFR. This flexibility in the units speaks to the fundamental nature of the kinetic clearance equation.

In contrast, most of the empirical equations fitted to patient data are rigid about the required units.

**ANALOGY**

The first half of the kinetic equation is an alternative form of the classic clearance equation. The expression

\[
\frac{SSPCr \times CrCl}{MeanP_{cr}}
\]

is what the GFR would be if the patient were in steady state at the midpoint creatinine (and then MeanPcr simply becomes Pcr). Whenever steady state is not true, the would-be GFR departs from its steady-state benchmark value, up or down, by an extent determined by the “1 minus subtracted ratio” term,

\[
1 - \frac{24 \times \Delta P_{cr}}{\Delta Time(h) \times Max \Delta P_{cr}/Day}
\]

working like a metaphorical amplifier knob, its value is centered at the neutral position of 1, representing steady state. When turned down from 1, it is because the creatinine has gone up, and the degree of the counterclockwise turn depends on the severity of the AKI. The knob cannot go below zero volume because MaxΔPcr/Day sets the lower bound there. Negative KeGFRs are thus avoided. When turned up from 1 because the creatinine has gone down, the knob dials in the adjustment to the steady-state benchmark according to the robustness of the renal recovery (or renal replacement therapy). In theory, there is no upper bound to how far the knob can be turned clockwise. The only limit comes from the constraints of kidney physiology or dialysis technology. In reality, the knob rarely gets above 2.
It is worth remembering that the knob being above 1 does not define renal recovery. A pivot into a clockwise turn, regardless of the position on the dial, can also signify renal recovery. When the knob has been turned relentlessly to the left but then suddenly turns to the right, even though the knob still resides between 0 and 1, the kidneys could be starting to recover, especially if the clockwise trend continues. This example describes the patient whose creatinine had been climbing quickly, but then the rise slows down more than expected. The deviation from the usual trajectory is hard to detect without training. Although the creatinine has not yet plateaued, renal recovery might be imminent. Likewise, the same logic holds for AKI in that the knob does not necessarily have to be below 1. It could start at a position >1 and be turning right (creatinine declining), but then a pivot to a counterclockwise turn is compatible with AKI. That example describes a renal recovery interrupted by another bout of AKI. Because the metaphorical knob can be turned however quickly or can abruptly reverse direction, the kinetic eGFR formula nimbly accommodates any amount of volatility in the kidney function. Hopefully, this analogy will help to conceptualize the inner workings of the mathematics.

MATCHES INTUITION

Finally, one can do a qualitative check to see whether the kinetic eGFR formula performs as expected. First, in steady state, does the kinetic formula revert to the regular clearance equation? When the plasma creatinine is unchanged, no matter how high or low the number, the $\frac{\Delta PCr}{\Delta Time(h)}$ is zero, making $24 \times \frac{\Delta PCr}{\Delta Time(h)}$ equal to 1. One time the results of the formula, $SSPCr \times CrCl - MeanPCr$, reduces to the classic clearance equation, because $SSPCr \times CrCl$ is equal to $UCr \times V$ in the steady state and the mean of a stable creatinine is simply the creatinine itself, $PCr$. Fittingly, when the creatinine is stable, $\Delta Time(h)$ becomes irrelevant. In a sense, the steady-state clearance equation is just a special case of a broader, more versatile kinetic clearance equation.

Second, in AKI, does the kinetic formula return a KeGFR that is lower than the would-be GFR if pretending to be in steady state? For example, when the plasma creatinine goes from 1 to 2 mg/dl, the actual GFR is close to zero, but a misapplied clearance equation would inform that at the creatinine of 2 mg/dl, the steady-state GFR would be approximately 50 ml/min. The egregious mismatch arises from the false assumption of steady state, which is clearly not the case in AKI. The more capable kinetic equation is needed and then the steady-state pretend value for CrCl will be reduced by a multiplicative factor that is sensibly derived according to the pertinent parameters: the measured rate of rise in creatinine, or $\frac{\Delta PCr}{\Delta Time(h)}$, and the maximum creatinine rate of rise, or $Max \Delta PCr/Day$. When creatinine is going up, $\Delta PCr$ is always positive, forcing $1 - \frac{\Delta Time(h) \times Max \Delta PCr/Day}{24 \times \Delta PCr}$ to become $<1$, because neither $\Delta Time(h)$ nor $Max \Delta PCr/Day$ can be negative. The greater the difference in creatinine, the more that gets subtracted from 1, causing the multiplier to reduce the eGFR all the more. Likewise, the more precipitous the rise in plasma creatinine [smaller value of $\Delta Time(h)$ in the denominator], the more that is subtracted from the identity multiplier 1. Thus, in AKI, both the magnitude and rapidity of the creatinine increase influence the eGFR in the ways that we expect.

Third, in recovery, does the kinetic formula return a KeGFR that is higher than the would-be GFR if pretending to be in steady state? This also makes intuitive sense because if a certain GFR is needed to hold steady at a plasma creatinine, then an even greater GFR is required to get down to that creatinine. When the creatinine is going down, $\Delta PCr$ is always negative because ending creatinine $PCr(end)$ is less than the starting creatinine $PCr(start)$. Thus, $\frac{\Delta Time(h) \times Max \Delta PCr/Day}{24 \times \Delta PCr}$ becomes $>1$, which when multiplied by the steady-state CrCl ensures that the eGFR will increase by an amount depending on the magnitude and rapidity of the creatinine downtrend. Therefore, in all three situations, steady state, AKI, and renal recovery, the KeGFR formula behaves as expected and supplements our clinical instincts with a quantitative component.

FORMULA APPLIED

To show how the kinetic eGFR formula might work in practice, I will apply it to various hypothetical but realistic clinical scenarios to demonstrate its utility in ascertaining the GFR when the plasma creatinine is evolving rapidly; additional real-life examples are presented in the Supplemental Material.

Case 1A: AKI (Step Decrement)

A 50-year-old man has prolonged intraoperative hypotension and develops ischemic acute tubular necrosis that is compounded postoperatively by the administration of ketorolac tromethamine for analgesia and intravenous contrast for a computed tomography scan. Sepsis ensues and he becomes oliguric.

The patient weighs 80 kg and the baseline creatinine is 1.10 mg/dl. The plasma creatinine is now climbing rapidly, increasing by more than a point each day (Table 1).

By the Cockcroft–Gault formula, the initial eGFR is

$$eGFR = \frac{140 - age \times weight(kg)}{72 \times PCr} \times 1 \text{ for Male} = \frac{(140 - 50) \times 80}{72 \times 1.1} = 91 \text{ ml/min}$$

By the four-variable MDRD formula, the initial estimated GFR is

$$\frac{186}{PCr^{1.134 \times Age^{0.203}}} \times 1.212 \text{ for Black}$$

$$\times 1 \text{ for Male} = \frac{186}{1.11^{1.134} \times 50^{0.203}} \times 1.212 = 91 \text{ ml/min} \times 1.73 \text{ m}^2$$

The two steady-state GFR estimators do not always agree this closely, but given the choice, the MDRD-derived eGFR is easier
to use as the corresponding CrCl because most laboratories already report it. If MDRD underestimates the GFR at low creatinines,\textsuperscript{12} then the Cockcroft–Gault or Jelliffe or Wright equations may be used.\textsuperscript{13} Underestimation is less of a problem with the newer CKD-EPI formula that uses a separate spline/knot to handle the lower plasma creatinines.\textsuperscript{3,14} Whichever estimator equation is used, the same CrCl associated with a steady-state creatinine may be used throughout a patient’s entire acute renal episode in the hospital. The product of any SSPCr and CrCl pair is nearly constant, because it reflects the creatinine production rate of that individual (Supplemental Equation 1).

Running through the first calculation in Table 1 using the kinetic eGFR formula, going from a plasma creatinine of 1.10 to 2.29 mg/dl in 23 hours, using a MaxΔP\textsubscript{Cr}/Day of 1.5 mg/dl per day:

$$KeGFR = \frac{SSPCr \times CrCl}{\text{MeanP}_{Cr}} \times \left(1 - \frac{24 \times \Delta P_{Cr}}{\text{DeltaTime}(h) \times \text{MaxP}_{Cr}/\text{Day}} \right)$$

$$= \frac{1.10 \times 91}{2.57} \times \left(1 - \frac{24 \times 1.19}{23 \times 1.5} \right)$$

$$= 10.17 \frac{ml}{min}$$

The large jump in creatinine is worrisome and is checked 12 hours later; the creatinine has increased from 2.29 to 2.85 mg/dl. The 12-hour interval is slightly harder to intuit than a 24-hour period, but is the eGFR just as depressed as before? Yes, as shown below.

$$KeGFR = \frac{1.10 \times 91}{2.57} \times \left(1 - \frac{24 \times 0.56}{12 \times 1.5} \right)$$

$$= 9.87 \frac{ml}{min}$$

The other eGFR calculations between each pair of consecutive creatinines have been performed (Table 1). On the associated graph (Figure 1), the creatinine is seen to rise in a rapid, quasi-linear trajectory that will slow down toward a target creatinine, consistent with the known severe AKI. As interpreted by the KeGFR formula, kidney function is seen to plunge from the 91 ml/min when the creatinine was 1.10 mg/dl to approximately 10 ml/min and then to remain at approximately 10 ml/min for the remainder of the episode. This pattern has been termed a step decrement and it usually results from an acute insult that is sustained by continued unfavorable hemodynamics.\textsuperscript{7} Thus, renal assessment does not have to wait for the reaching of a new steady state, which may take a week or longer for the plasma creatinine to plateau.

In contrast to the sudden and persistent loss of GFR immediately and unambiguously disclosed by a kinetic formula, the clearance equation suggests a more gradual disappearance of kidney function (Figure 1). The latter is clearly an erroneous analysis that most physicians would know to ignore. However, unaware physicians may accept the analysis at face value when they see the laboratory report showing a gradual decline in the MDRD-derived eGFRs. The laboratory computer is trying to be helpful, but it is doing a disservice in the case of AKI. The MDRD and other CKD estimator equations are not equipped for the nonsteady state.

Eventually, the clearance equation will agree with the kinetic formula. If the GFR stays at 10 ml/min, the patient is predicted by the clearance equation to stabilize at a plasma creatinine of 10.01 mg/dl:

$$10 \frac{ml}{min} = \frac{1.10 \times 91}{P_{Cr}},$$

solve for $P_{Cr}$. The exact same solution is found by the kinetic formula, knowing that in steady state the $\Delta P_{Cr}$ is zero:

$$10 \frac{ml}{min} = \frac{1.10 \times 91}{\text{MeanP}_{Cr}} \times \left(1 - \frac{24 \times 0}{\text{DeltaTime}(h) \times 1.5} \right);$$

solve for MeanP\textsubscript{Cr}, which is just the single creatinine when it is stable. As affirmed in this example and proved above, the kinetic formula reduces to the clearance equation in any steady state.

**Case 1B: AKI (Ramp Decrement)**

A case of AKI in which the above patient sustained a lesser but ongoing renal insult and was nonoliguric instead would be more challenging to analyze. The plasma creatinine might have risen slowly at first, not yet triggering a renal consultation. If the bedside physicians were habituated to the indolent rise in creatinine, consultation could be further delayed until the creatinine increase accelerated and became too obvious to ignore (Figure 2). Shortly afterward, the creatinine would start to level off, giving the overall creatinine trajectory a sigmoidal shape (Figure 2). By this time, the patient has suffered cumulative loss.

Table 1. Example of an increasing plasma creatinine in step decrement AKI

<table>
<thead>
<tr>
<th>Day</th>
<th>Hours between Creatinine Measurements</th>
<th>Plasma Creatinine (mg/dl)</th>
<th>Kinetic eGFR Formula (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>23</td>
<td>1.10</td>
<td>91</td>
</tr>
<tr>
<td>0.96</td>
<td>12</td>
<td>2.29</td>
<td>10.17</td>
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<tr>
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<td>6.39</td>
<td>10.04</td>
</tr>
</tbody>
</table>

The plasma creatinine rises precipitously in severe AKI, usually by >0.5 mg/dl per day. The differing numbers of hours between creatinine measurements are listed, resulting in fractional days, but 6 days of data are shown. Between successive pairs of creatinines, the eGFR by the kinetic formula has been calculated in the last column. The rate of creatinine rise starts to slow down eventually, but the abrupt drop in kidney function persists, reminiscent of the shape of a step, hence step decrement.
of GFR, and the opportunity to intervene earlier has passed. This not-atypical scenario describes the ramp decrement pattern of AKI in which GFR is lost gradually. Such a patient may have benefited from the continual evaluation of the creatinine trend by the kinetic formula. Despite the deceptively sluggish rise in creatinine, the very real and steady attrition of GFR that is immediately evident (Figure 2) would persuade the bedside physicians to consult a nephrologist in a timelier manner.

**Case 1C: AKI (Hyperbola Decrement)**

The patient above with a baseline creatinine of 1.10 mg/dl that equates to a CrCl of 91 ml/min instead suffers reduced contractility after cardiac surgery and is receiving vasopressor support in the ICU. The plasma creatinine is noted to increase by a consistent 0.4 mg/dl per day. Because of the relatively slow creatinine rise and nonoliguria, the anticipated feeling about the severity of renal injury is mild to moderate. Vancomycin dosing is not adjusted, and a nephrologist is not consulted until the creatinine reaches 2.70 mg/dl on postoperative day 4.

In this case, a rosy assessment of the kidney function is unwarranted. Although seemingly less worrisome, the linearity of a creatinine rise when analyzed by the KeGFR formula is seen to result from a GFR pattern in which the bulk of kidney function is lost quickly and then the remainder is lost gradually (Figure 3). The GFR varies inversely with time, more or less, and the shape is that of a hyperbola. The clearance equation produces a curve similar to that of the kinetic formula, but quantitatively the renal impairment is judged less severe (Figure 3). Ironically, paying heed to an erroneously applied clearance equation might have galvanized the bedside physician to take AKI more seriously, and the patient would not have experienced vancomycin toxicity.

**Case 2A: Renal Recovery (A Devious One)**

Our example patient undergoes surgery as in case 1A but avoids all postoperative nephrotoxic insults. The plasma creatinine rises briskly over the first 3 days, almost as rapidly as before (Figure 4), prompting a consultation for the initiation of dialysis. At face value, the creatinine trend seems to compel a therapeutic intervention. Instead, by applying the KeGFR formula, one discovers that the kidney function plunged right after surgery but has been improving since postoperative day 1 (Figure 4). The decision to postpone dialysis, so as to not hamper recovery, is vindicated on days 4 and 5, when the plasma creatinine levels off and then starts to decrease, while the eGFR continues to ramp up (Figure 4). The urine output is noticeably increased and by the following day, the creatinine has started to consistently decline (not shown).

The foregoing GFR pattern represents a step decrement followed by a ramp increment. This not uncommon scenario can unfold after surgery if the renal insult is isolated and the postoperative course is free of further hemodynamic compromise. Even as recovery is underway, the incremental gain in GFR is only sufficient to decelerate, at first, the creatinine rise versus a full-blown step decrement (case 1A). The resultant skewing of the creatinine curve to the right is difficult to recognize as an incipient renal recovery that is gaining momentum (Figure 4). However, this renal recovery posing as AKI is unmasked with the help of a KeGFR formula.

**Case 2B: Recovery with Continuous Venovenous Hemofiltration**

Reverting to case 1A as originally described, the patient has not shown any
improvement in his KeGFR as analyzed by the kinetic formula (Figure 1 and Table 1). The step decrement pattern of kidney injury does not appear like it will improve soon, so continuous venovenous hemofiltration (CVVH) is initiated shortly after the plasma creatinine gets above 6.0 mg/dl. Laboratory values are still monitored daily, and with the successful start of CVVH, the creatinine starts to decline. It decreases rapidly at first, but over the next few days the slope gradually flattens out toward horizontal. After more than a week, it becomes clear that the addition of CVVH will only lower the patient’s creatinine to approximately 4.00 mg/dl (Figure 5). This equates to a cumulative CrCl of approximately 25.0 ml/min, finally obtainable by the classic clearance equation now that steady state holds true: 

\[
CrCl = \frac{1.1 \times 91}{4.00} = 25.0 \text{ ml/min}
\]

Presumably, the 25.0 ml/min consists of the 10 ml/min that the injured kidneys can still muster and the 15 ml/min that the CVVH is providing.

By using the kinetic formula immediately, one can accurately calculate the overall CrCl at the onset of CVVH, many days in advance of and without having to wait for steady state. Even as CVVH was lowering the plasma creatinine, the creatinine glide path was already indicative of a certain CrCl, uncovered by the kinetic formula. Without the help of the formula, most physicians would be hard-pressed to discern in the varying slopes of the creatinine trajectory the near-constancy of the underlying CrCl.

The kinetic formula’s consistent output of approximately 25 ml/min in this case attests to the continuous and steady nature of the CVVH therapy. Plugging the 25 ml/min into the clearance equation, one might predict that the patient’s plasma creatinine would eventually drift down to approximately 4.0 mg/dl:

\[
\frac{25 \text{ ml/min}}{P_{Cr}} = \frac{1.1 \times 91}{P_{Cr}}; \text{ solve for } P_{Cr}.
\]

In summary, the above examples showcase some of the applications of the KeGFR formula. It can be deployed at the bedside using clinical data that are readily accessible or easily obtainable. The KeGFR outputs can be tracked serially on a graph, providing a spatial representation of how the kidney function is evolving over time. The presentation of data in a visual format plays to our strengths and facilitates our perception of trends, comparisons, and relationships that might be missed from poring over a sequence of raw numbers. Sure, the information is all there, encrypted in the changes of creatinine over time, but it resembles a foreign language in which we are not quite fluent. Why not translate all creatinine measurements into KeGFR? Then we will have a direct handle on kidney function and perhaps meaningfully answer questions such as how is GFR changing over time? Plume met or gradual loss? Just how severe is the AKI and how should drug dosing be modified? Is the course of AKI being improved by our therapies? When is renal recovery happening?

VOLUME OF DISTRIBUTION

The volume of distribution (V_D) of creatinine requires more detailed consideration. It does not overtly appear in this version of the KeGFR formula, but it is very much there, being necessary to multiply by the plasma creatinine concentrations to get the absolute creatinine amounts which can be manipulated according to the principles of mass balance. V_D has been re-expressed, for good reason, in terms of how much the creatinine production rate can increase creatinine concentration in an arbitrary volume if all of the creatinine is added and none of it is subtracted. This is the strategy of adding a known quantity of dye to a bucket of water, measuring the concentration of dye after mixing, and then being able to back-calculate the bucket’s volume. An analogous situation occurs in patients when they become anuric and approximate an intact bucket that cannot leak. The muscles continue to add creatinine to the body at a known rate, the laboratory measures how much the plasma creatinine goes up in 1 day, and then one can infer the V_D of creatinine;
Figure 3. Graph of hyperbola decrement AKI. Plotted are the plasma creatinine (▼) and the formula-derived eGFR (●), along with the value that would be obtained by the clearance equation ( ■ ). When the plasma creatinine rises at a linear rate, the underlying GFR is actually decreasing in the shape of a hyperbola, i.e., the GFR varies inversely with time. Because of this, most of the kidney function is lost early on, and only minor additional amounts are lost later on. The gradual rise in creatinine can be misleading, so it is important to realize the rapidity and gravity of the renal impairment.

note that a patient’s starting creatinine does not matter, for one is only interested in the Δ creatinine. The absence of excretion not only simplifies the calculation, but it also re-frames the problem of finding VD in terms of a not-unfamiliar clinical scenario, anuric renal failure. Logically, creatinine being added to a smaller volume (VD) will raise the concentration more quickly (Max ΔPCr/Day); the same addition to a larger volume will raise the creatinine concentration more slowly. This inverse relationship between VD and Max ΔPCr/Day is helpful, because some prefer to think in terms of VD rather than Max ΔPCr/Day.

A dilemma arises because separate determinations of VD and Max ΔPCr/Day do not necessarily agree with each other. In experimental models, the apparent VD of creatinine is measured to be close to total body water (TBW), with some studies utilizing the strategy above of injecting radiolabeled creatinine and measuring its concentration to infer VD.15–18 Although TBW is not routinely measured in the ICU, it can be estimated from existing anthropometric equations, the simplest one being TBW (L) = 0.6 × weight (kg) for men. For women, 0.5 may be used. More complex formulas that deliver a more accurate estimate of TBW include the Watson formula, Hume–Weyers formula, Cher-tox’s bioimpedance, and Mellits–Cheek formula (for children).19–23

Returning to our 50-year-old, 80-kg man (see the cases above) to do a thought experiment, the patient has an estimated TBW ranging from 44 L (by Watson and Hume–Weyers) to 48 L (60% of body weight). His calculated creatinine production rate of 1441.44 mg/dl [i.e., 1.1 (mg/dl) × 91(100 ml × 1440 min = 1 day)] would be expected to raise his plasma creatinine by 3.00–3.28 mg/dl per day if GFR = 0

\[
\text{GFR (ml/min) } = \frac{1441.44 \text{ mg/dl}}{44 \text{ or } 48 \text{L}} \times \frac{1 \text{L}}{10 \text{dl}}.
\]

Therein lies uncertainty. We typically do not see such a high rate of Max ΔPCr/Day even in the worst of anuric kidney failure. The rule of thumb taught at the bedside is that plasma creatinine can uptick at most by about 1.0–1.5 mg/dl per day, less than half of what was just calculated. In fact, approximately 1 mg/dl per day is said to be an anephric rate of creatinine rise, which may be a conservative estimate.24 The value is also determinable from another clinical situation that commonly arises, which is that of an anuric patient who gets placed on intermittent dialysis. Then the prehemodialysis creatinine minus the plasma creatinine 24 hours earlier, or as close to it, informs about the Max ΔPCr/Day. Anecdotally, the values for most patients on intermittent dialysis seem to range from 1.3 to 2.0 mg/dl per day. Finally, one scenario in which the Max ΔPCr/Day can climb as high as 3 mg/dl per day is rhabdomyolysis. However, rhabdomyolysis may entail more than just anuric AKI. Some believe that the resultant muscle damage releases creatinine into the TBW, causing the creatinine production rate to become supraphysiologic, accounting for an unusually high rate of creatinine rise. On the other hand, some believe that rhabdomyolysis does not release much creatinine at all and that the seemingly faster rate of creatinine rise is wholly explained by the mathematical
logic exemplified by the thought experiment above or by an overrepresentation of young, muscular men with an above-average creatinine production rate.\textsuperscript{25,26} Overall, the considerable sum of empirical observations on Max$\Delta$PCr/Day does not seem to concur with the experimental determinations of V\textsubscript{D}, even though they are strictly related to each other and both are reproducible measurements.

**FIXED CREATININE PRODUCTION RATE?**

What might reconcile the discrepancy? Maybe most forms of severe AKI have some degree of residual renal function. Maybe the creatinine production rate decreases during a critical illness, limiting the Max$\Delta$PCr/Day despite the total loss of GFR. The kinetic formula uses a creatinine production rate that is constant, based on GFR estimators like the MDRD or Cockcroft–Gault equation.\textsuperscript{1,2,11} These studies enrolled patients who had CKD and a stable plasma creatinine. Aside from having kidney disease, these patients were relatively healthy and had a reasonably normal muscle mass. However, the lessons of their creatinine production rates may or may not be transferable to the critically ill patient. The issue has not received much attention, but two studies have utilized continuous renal replacement therapy to put ICU patients into steady state, causing the CVVH(-dialfiltration)-supplied creatinine clearance rate to parallel the creatinine production rate.\textsuperscript{27,28} The clearance was found to average 15 ml/min,\textsuperscript{27} which is on par with the value used in case 2B. From clearance, the measured index of creatinine production was found to be lower than the same index that would be predicted by the Cockcroft–Gault equation, by almost half.\textsuperscript{11,27} Another study found a wide distribution of results for continuous renal replacement therapy–inferred creatinine production rates; however, in most cases, the measured rates were less than the calculated rates by the Cockcroft–Gault equation.\textsuperscript{28}

These data suggest that critically ill patients with AKI have a substantial somatic protein depletion that is only worsened by a malnourished state before the development of AKI.\textsuperscript{27} Not surprisingly then, about a third of ICU patients can have a timed urine collection that only seems inadequate (creatinine excretion $<10$ mg/kg per day instead of the usual 15–25 mg/kg per day) because of their reduced creatinine production rates.\textsuperscript{29} Not all critical illnesses are equal in their effects on creatinine generation. One mouse study suggests that septic AKI may lower the creatinine production rate by more than other etiologies of AKI.\textsuperscript{30}

By how much the creatinine production rate is reduced (or possibly increased) during acute disease states is mostly unknown. The extent will have to be determined empirically from a clinical trial, because the modification to creatinine production rate does not seem to be governed by any fundamental principle. The kinetic formula, being a fundamental equation itself, should remain uncluttered in mathematical elegance by assuming a constant rate of creatinine input. When empirical equations are finally found, their rules for altering the creatinine production rate can be incorporated into the KeGFR formula. Currently, the assumption of constancy is represented by the number 1 (times the product of SSP\textsubscript{Cr} and CrCl). The 1 will then be replaced by the patient characteristic–derived multiplicative factor (likely $<1$) that changes the SSP\textsubscript{Cr} $\times$ CrCl proxy for creatinine production rate. The subtracted ratio representing

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**Figure 4.** Graph of a transient step decrement followed by ramp increment recovery. Plotted are the plasma creatinine (▲) and the formula-derived eGFR (◆), along with the value that would be obtained by the clearance equation (●). The plasma creatinine is rising at an alarming pace, seemingly consistent with a sudden, severe, and persistent drop in the GFR (step decrement AKI). However, that is only part of the story according to the kinetic eGFR formula. The renal injury is temporary, and the kidney function is gaining steadily, even as the plasma creatinine continues to rise. In these cases, the steady-state clearance equation performs quite poorly.
the net Δ creatinine over ΔTime should remain the same.

Looking to the future, cystatin C may supplant plasma creatinine as the preferred inverse correlate of kidney function. Both measures are governed by the same principle that the dynamic balance between production and excretion determines their concentration at any instant. Thus, the kinetic formula will work just as well with cystatin C as creatinine, with trivial modifications. In fact, the formula could be bolstered by the use of cystatin C because it has a number of inherent advantages over creatinine. As a housekeeping gene, cystatin C is produced at a constant rate by all nucleated cells, not just by the muscle (mostly) as with creatinine. Reportedly, its production rate is not influenced by an acute phase reaction; thus, if cystatin C generation is not plagued by alterations due to acute illness, which remains to be proved, it will outperform creatinine for AKI. Perhaps the equivalent of a MaxΔP_{Cr}/Day rise of approximately 3 mg/dl in 1 day, albeit in mg/L, will routinely be observed with cystatin C in place of creatinine.

**AMBIGUITY OF MAX\(\Delta P_{Cr}/\text{Day}\)**

What value should be used for the Max\(\Delta P_{Cr}/\text{Day}\) in the KeGFR formula? Ideally, the value should come from the individual patient, but not all patients with AKI go on to develop anuria or are then started on intermittent hemodialysis. Without actual patient data to guide the choice, most physicians default to 1.5 mg/dl per day for the Max\(\Delta P_{Cr}/\text{Day}\). For most patients, this will satisfy the pivotal criterion of disallowing the generation of a negative KeGFR, assuming such an entity does not exist. If negative-value KeGFRs start to appear in the formula’s output, then the Max\(\Delta P_{Cr}/\text{Day}\) needs to be increased from 1.5 mg/dl per day.

Why not use an estimate of TBW as the V_D for creatinine and then convert it to Max\(\Delta P_{Cr}/\text{Day}\)? (Use Supplemental Equation 3 in the Supplemental Material.) For typical adult values of TBW around 40–70 L, the corresponding values for Max\(\Delta P_{Cr}/\text{Day}\) range from 3.6 to 2 mg/dl per day, respectively, with a creatinine production rate, for instance, of 100 mg × ml/ min × dl (from the product of SSP_{Cr} and CrCl). In practice, however, a single-day rise in the plasma creatinine of > 3 mg/dl is hardly ever observed. Nevertheless, the effect of using a Max\(\Delta P_{Cr}/\text{Day}\) of 3.0–3.6 mg/dl per day is to dampen the responsiveness of the kinetic formula. The eGFRs tend to be higher in AKI and lower in renal recovery. For example, for the creatinine to go from 2.0 to 2.9 mg/dl in 24 hours, the KeGFR would be 16.34 ml/min when the Max\(\Delta P_{Cr}/\text{Day}\) is 1.5 (V_D of 96 L) versus 28.60 ml/min when the Max\(\Delta P_{Cr}/\text{Day}\) is 3 (V_D of 48 L). To note, 16.34 versus 28.60 ml/min is a not-insignificant difference for the KeGFR. At least for AKI, it is probably better to err on the side of a lower-than-true GFR. On the other hand, the vigor of renal recovery may be overestimated, but a lower Max\(\Delta P_{Cr}/\text{Day}\) will make the kinetic formula more sensitive to forecasting a sustained recovery, which may be an advantageous feature if it stalls the initiation of unnecessary dialysis.

Overall, the Max\(\Delta P_{Cr}/\text{Day}\) regulates the volatility of the KeGFR output. Too low a Max\(\Delta P_{Cr}/\text{Day}\) risks excessive swings in the tracking of kidney function and too high a Max\(\Delta P_{Cr}/\text{Day}\) flattens out the KeGFR curve. This makes sense because a low Max\(\Delta P_{Cr}/\text{Day}\) translates into a high V_D and vice versa. A larger volume requires more creatinine flux to change the concentration. Therefore, a
given \( \Delta \) in the plasma creatinine must be the result of a more substantial swing in the kidney function than if the \( V_D \) were smaller. Is there an optimal point for the \( \text{Max} \Delta P_{Cr}/\text{Day} \), one that will work well for most patients? Future studies may be done to try to calibrate the \( \text{Max} \Delta P_{Cr}/\text{Day} \) to the closest match between the kinetic formula and actual measured GFR.

Should the same value of \( \text{Max} \Delta P_{Cr}/\text{Day} \) be used in all KeGFR calculations for a patient’s acute renal episode? It can be, but sometimes it may be prudent to adjust for the diluting effect that intravenous fluid administration has on plasma creatinine. Vigorous volume resuscitation may decelerate the creatinine rise that would have occurred, especially in the ICU, masking the true severity of AKI. Over time, the cumulative effect of a daily fluid balance that is usually or always positive can drastically increase the plasma creatinine. Vigorous volume re-flu can be, but sometimes it may be prudent to adjust the TBW in lump-sum fashion, after an admission weight mostly re.

-2 L of fluid (In – Out) to weigh 82 kg the next day, he gained 2 L of TBW, not 60% of that or 1.2 L. The TBW went from 48 L (0.6 \( \times \) 80 kg) to 50 L, not 49.2 L (0.6 \( \times \) 82 kg), and now represents 61% of his body weight (50 \( \div \) 82). Then the revised TBW, assumed to be the \( V_D \) for creatinine, can be converted back to \( \text{Max} \Delta P_{Cr}/\text{Day} \) for use in the KeGFR formula. (See Supplemental Equation 3 in the Supplemental Material.)

**CHOICE OF GFR ESTIMATOR**

Without wading into a controversy about which of the many eGFR equations is superior, I prefer the MDRD at present, because it is usually calculated by the laboratory computer; this saves time and cuts down on computational and clerical errors. Choosing the MDRD formula implies that the kinetic formula will generate values for the kidney function that are more indicative of glomerular filtration only, since it and similar equations are derived from clearances of iothalamate, which presumably is a true filtration marker. Inasmuch as tubular secretion of creatinine elevates the CrCl above GFR, so too is the urinary creatinine excretion rate increased above an MDRD-based creatinine production rate in steady state. The other issue with MDRD is the indexing to a body surface area of 1.73 m\(^2\). Larger individuals will thus have their eGFRs underestimated. Is the underestimation fixed by using Cockcroft–Gault or other equations derived from creatinine data? Perhaps. However, for bedside medicine, it may be better to assess the kidney function more conservatively when it comes to both AKI and renal recovery. The kinetic formula’s end-user has a choice to make, but whichever steady-state GFR estimator provides the corresponding CrCl should be the system to use consistently throughout a patient’s spell of renal function changes.

In CKD, the creatinine data already make it difficult enough to appreciate the GFR by expressing kidney function as its reciprocal. However, in AKI/recovery, discerning the GFR is made all the more challenging by the number of inputs we would need to consider (magnitude and direction of the change in creatinine, rapidity of the change, creatinine production rate, volume of distribution, etc.). Until we develop a proficiency at assimilating and appropriately weighting so much information simultaneously, I propose that we give the task to a KeGFR formula that can distill the myriad pieces of data into a single, meaningful eGFR number.

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**DISCLOSURES**

None.

**REFERENCES**

9. Jelliffe R: Estimation of creatinine clearance in patients with unstable renal function,

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