Supplemental Material

A. Online: Real-life patient cases

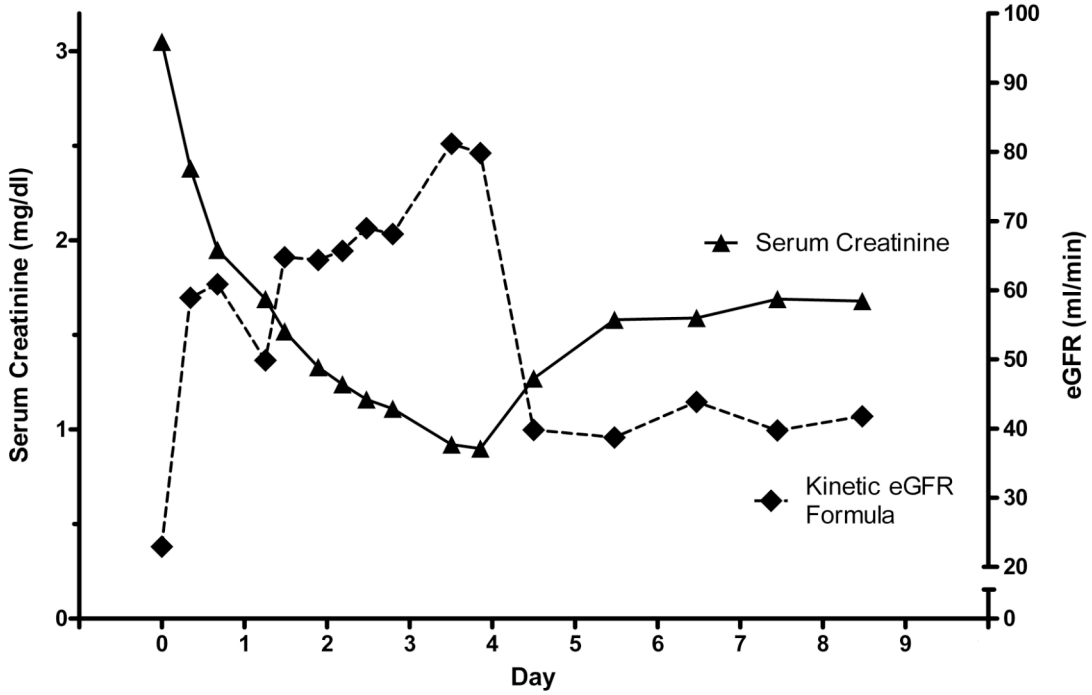
Real life is not quite as tidy as the idealized examples discussed in the manuscript; nevertheless, to show that the kinetic eGFR formula can be applied to actual patients and still uncover the stereotypical patterns of kidney function changes, below are three IRB-approved additional cases of real-life patients as analyzed by the kinetic formula and the lessons learned.

Case 1: CVVH initiation and withdrawal, overlapping with native kidney recovery

The first patient suffered acute kidney injury and stabilized at a serum creatinine in the low 3's when he was initiated on CVVH. As expected, the treatment immediately started to lower his serum creatinine, but was the decline solely due to the CVVH or was it also due to a concomitant gain in his native kidney function? As analyzed by the kinetic formula, the creatinine downtrend was indicative of a clearance rate that suddenly increased and then remained relatively constant. Since this step increment pattern of 'artificial recovery' is most consistent with the continuous nature of that renal replacement therapy, CVVH was probably providing all of the abruptly augmented clearance. The transient dip in eGFR between days 1 and 2 may have been due to a pause in CVVH. But overall, the patient had a steady combined GFR (CVVH plus native kidney function) that consistently averaged ~65 ml/min.

On day 3–4, the clearance rate jumped into the 80's, without an attendant increase in the CVVH prescription. The kinetic formula was predicting a renal recovery on top of the clearance provided by CVVH, and as the serum creatinine was being driven below 1.00 mg/dl, the decision was made to stop CVVH. With the loss of the additional clearance from CVVH, a creatinine of 0.90 mg/dl was not sustainable, and sure enough the serum creatinine started to rise by the very next day after discontinuing CVVH. But is the rate of the creatinine rise worrisome? The creatinine uptrend was interpreted by the kinetic formula to represent a stable GFR of ~40 ml/min, his underlying native kidney function at the time. Nephrology consultants were able to reassure the ICU team that the patient was not developing a new episode of acute kidney injury and that the worsening numbers represented an expected effect of creatinine kinetics trying to equilibrate at a new steady-state serum creatinine, commensurate with the overall lower GFR. In fact, we predicted that if his GFR remained stable around 40 ml/min that the patient would plateau at a serum creatinine of ~1.7 mg/dl. Over the next few days, our prediction became reality.

Case 1



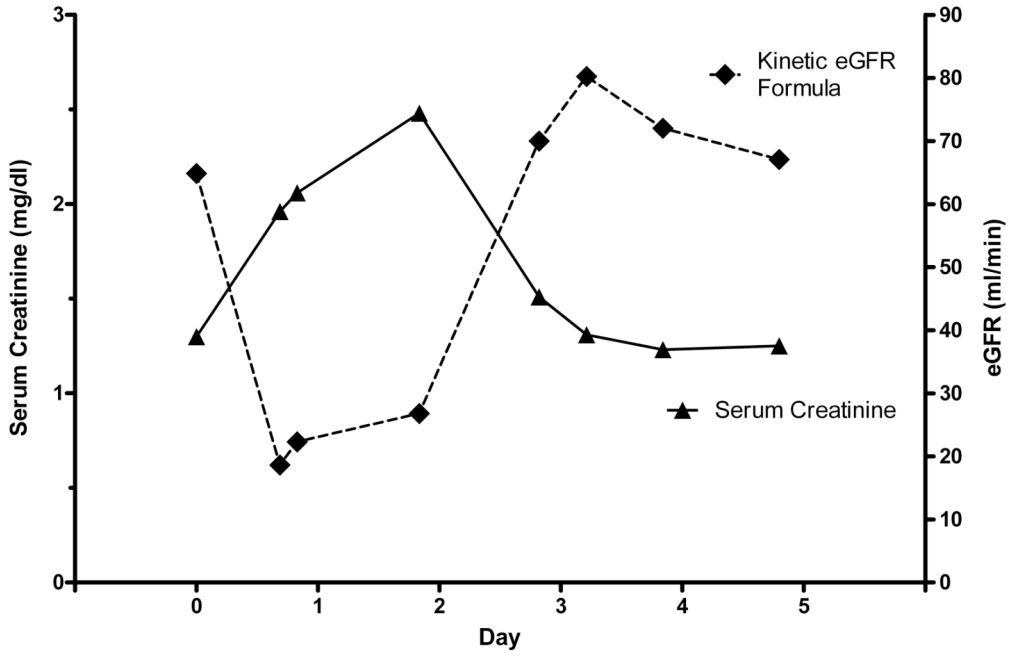
Case 2: Step decrement in renal function due to isolated kidney insult followed by ramp recovery

Starting off with a preoperative serum creatinine of 1.30 mg/dl, our patient undergoes surgical repair of an aortic coarctation, involving cardiopulmonary bypass and aortic cross-clamping. Although he does not suffer intraoperative hypotension, his first post-operative serum creatinine is already elevated to 1.96 mg/dl. The patient is non-oliguric and blood pressures are normal. Repeat serum creatinine 3.5 hours later is 2.06 mg/dl. Nephrology is consulted for acute on chronic kidney injury. 24 hours after the 2.06 value, the serum creatinine has risen to 2.48 mg/dl.

All can agree that the acute creatinine increase from 1.30 to 1.96 mg/dl represents acute renal dysfunction, likely due to hemodynamic changes during the surgery. But, perhaps surprisingly, the subsequent creatinine trends are analyzed by the kinetic eGFR formula to indicate a renal recovery that is already underway. Who would have suspected that the serum creatinine rise from 1.96 to 2.06 mg/dl in 3.5 hours meant that the eGFR is actually improving? Or that the next serum creatinine increment from 2.06 to 2.48 mg/dl in 24 hours represented further improvement still? The nephrology consultants initially suspect that dialysis might be imminent, but with the help of the kinetic formula, they realize that the patient is having a pattern of acute kidney injury step decrement followed by ramp recovery.

Early forecasting of renal recovery, even in the midst of a worsening serum creatinine, was vindicated when the patient really starts to regain kidney function, exemplified by the creatinine declining from 2.48 (the peak) to 1.51 mg/dl in the next 23.5 hours. Then in going from a serum creatinine of 1.51 to 1.31 mg/dl, the patient achieves a supra-physiologic GFR, at least for him, of 80 ml/min, according to the kinetic eGFR formula. This is consistent with the observation that kidney function can momentarily exceed the usual GFR in order to lower the serum creatinine back to baseline. Once serum creatinine has stabilized again, the clearance drops down to the value appropriate for that creatinine (mid-60's to low-70's ml/min, in this case), the same renal function that would be calculated by the steady-state clearance equation.

Case 2



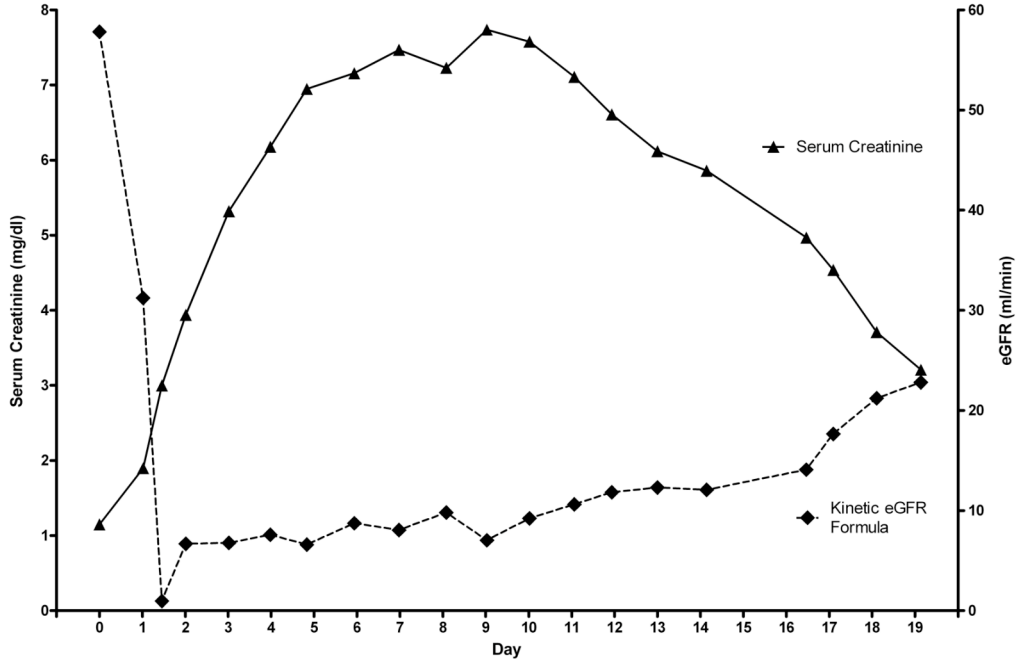
Case 3: Ramp/Step decrement in renal function followed by slow ramp recovery

A woman with chronic kidney disease and a baseline serum creatinine of 1.10 to 1.15 mg/dl develops nephrotoxic acute tubular necrosis. Over the first day and a half (36 hours) of the acute injury episode, the serum creatinine rises rapidly, going from 1.15 to 1.90 mg/dl in 24.4 hours and then from 1.90 to 3.00 mg/dl in the next 10.5 hours. The latter creatinine rise was especially rapid, such that the rate helped determine a setting for the $Max\Delta P_{Cr}$/Day (2.6 mg/dl/day) to avoid any negative values for the eGFR. The first two kinetic eGFR values hint at a ramp decrement pattern, albeit a very steep one, that could also be construed as an abrupt step decrement that happened to be measured during the evolution of injury. The kidney function goes from 58 ml/min (when the baseline creatinine was stable at 1.15 mg/dl) to 31 ml/min (when the creatinine increases from 1.15 to 1.90 mg/dl) and then to 1 ml/min (when the serum creatinine increases from 1.90 to 3.00 mg/dl).

Thereafter, from days 1.5 to 10, the rises in the serum creatinine continue to seem impressive and may alarm a less experienced physician, who may wrongly believe that this is the time during which the kidney function is being lost at a prodigious rate. But more astute clinicians realize that most of the kidney function has already been lost in the first day-and-a-half, an assessment that is borne out quantitatively by the kinetic eGFR formula. The remainder of the creatinine arc increasing up to its peak at 7.74 mg/dl is merely the result of a GFR that stays persistently low (estimated by the formula to range from 6–10 ml/min). The serum creatinine is trying to reach a new steady-state as determined by the reduced GFR, but no further kidney function is being lost. If anything, the kidney function appears to be gaining, slowly but steadily. Feeling comfortable with this analysis, the team opts not to start dialysis.

Before the serum creatinine can plateau at a new steady-state, however, renal recovery intervenes and begins to drive the creatinine level downwards, in a glide path that almost mirrors the upward rise. The decreases in creatinine seem to be fairly significant, with levels dropping from 7.74 to 7.58 to 7.11 to 6.61 to 6.12 to 5.86 mg/dl, and so forth on a daily basis. But when these numbers are plugged into the kinetic formula, the eGFRs are not as robust as they might seem. So that the medical team is not lulled into a false sense of complacency, caution is still urged to avoid nephrotoxins and to adjust the dosing of medications. When the serum creatinine reaches 3.21 mg/dl, the patient is discharged from the hospital, to continue her recovery as an outpatient, hopefully.

Case 3



B. Derivation of KeGFR

Some terms are similar enough that they will be used interchangeably: 1) creatinine clearance ⇔ GFR, with the caveat that creatinine clearance slightly overestimates the true GFR[1] and 2) serum ⇔ plasma. Serum is the aqueous supernatant after centrifuging clotted blood, and plasma is the supernatant after centrifuging anticoagulated blood. The two fractions have nearly identical creatinine concentrations,[2] and either measure can be used in the proposed formula.

First, the creatinine production rate does not need to be measured coming out of the muscles but can be inferred from its equality in steady-state with the creatinine excretion rate, quantifiable in the urine. That $U_{Cr} \times V$ is nearly a constant for a given individual across the spectrum of plasma creatinines is a testament to the fact that creatinine production rate reflects one's muscle mass, which itself is a constant, more or less. Thus, any steady-state plasma creatinine can be multiplied by the corresponding creatinine clearance to arrive at the creatinine production rate. Or it can be found by an equation that estimates the creatinine excretion rate in steady-state.[3]

Scaling to one day, arbitrarily (though the scale does not matter), the creatinine production rate is

$$\text{Creatinine production rate}\left(\frac{mg}{day}\right) = SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times \frac{1{,}440\min}{1day} \times \frac{1dl}{100ml} \qquad (1)$$

which is simply any steady-state plasma creatinine × corresponding CrCl × 14.4 units conversion factor. (Units such as mg/dl are displayed to help verify that the proper units cancel and that the leftover units match on both sides of the equation.)

Second, the volume of distribution (V_D) for creatinine does not need to be equated with total body water but can be expressed as a function of the creatinine production rate. The amount by which a known creatinine production rate can raise the creatinine concentration if all

excretion has ceased, i.e., GFR=0, informs about the V_D. Since there is only addition of creatinine and no subtraction, this situation describes the maximum increment of plasma creatinine in one day, termed $Max\Delta P_{Cr}/Day$. It is equivalent to V_D as follows:

$$V_D(dl) = \frac{SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times \frac{1{,}440\min}{1day} \times \frac{1dl}{100ml}}{Max\Delta P_{Cr}/Day\left(\frac{mg}{dl \bullet day}\right)} \qquad (2)$$

Or, if starting with an estimate of V_D, it can be converted to $Max\Delta P_{Cr}/Day$ by

$$Max\Delta P_{Cr}/Day\left(\frac{mg}{dl \bullet day}\right) = \frac{SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times \frac{1{,}440\min}{1day} \times \frac{1dl}{100ml}}{V_D(dl)} \qquad (3)$$

($Max\Delta P_{Cr}$ can be enumerated over any duration of time, really, but clinicians are used to gauging the rate of anuric creatinine rise over one day.)

With V_D coded as a function of creatinine production rate, the two creatinine concentrations that the patient is transitioning between can now be converted into their respective creatinine masses. The difference in masses represents how much creatinine was gained (AKI) or lost (recovery).

$$NetCreatinineDifference(mg) = V_D(dl) \times \left[P_{Cr}(2) - P_{Cr}(1)\right]\left(\frac{mg}{dl}\right) = V_D(dl) \times \Delta P_{Cr}\left(\frac{mg}{dl}\right) \qquad (4)$$

Third, the creatinine excretion in the urine will be found by its relationship to the two knowns: the creatinine production and the net creatinine difference above. Any change in plasma creatinine is brought about by an imbalance between creatinine production and excretion. Which is to say that the creatinine difference (mg) = creatinine production (mg) – creatinine excretion (mg). Logically, this just asserts conservation of mass. In steady-state when the delta creatinine is zero, the creatinine excretion matches production so that their difference also equals zero. In

AKI when the delta creatinine is positive, excretion lags behind production so that their difference is also positive, equaling the delta creatinine mass (mg). In renal recovery when the delta creatinine is negative, excretion exceeds production so that their difference is also negative, again equal to the change in creatinine mass (now a decrement). Solving for creatinine excretion amount so that it can later be converted into creatinine clearance,

$$CreatExcretion(mg) = Creat\,\mathrm{Pr}oduction(mg) - CreatDifference(mg) \qquad (5)$$

Fourth, the time needs to be incorporated to express Equation (5) in terms of a rate, the basis for clearance. For convenience, the time interval between plasma creatinine measurements is denoted in units of hours, the time scale of most acute renal situations. Divide the amount of creatinine (mg) that represents the difference between starting and ending plasma creatinines, Equation (4), by ΔTime(h) to get the rate in mg/hour.

$$CreatDifferenceRate\left(\frac{mg}{hr}\right) = \frac{V_D(dl) \times \Delta P_{Cr}\left(\frac{mg}{dl}\right)}{\Delta Time(hr)} \qquad (6)$$

Substituting Equation (2) for V_D above,

$$CreatDifferenceRate\left(\frac{mg}{hr}\right) = \frac{SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times \frac{1{,}440\min}{1day} \times \frac{1dl}{100ml} \times \Delta P_{Cr}\left(\frac{mg}{dl}\right)}{Max\Delta P_{Cr}/Day\left(\frac{mg}{dl \bullet day}\right) \times \Delta Time(hr)} \qquad (7)$$

Next, the creatinine production rate, Equation (1), is converted from mg/day to mg/hour.

$$Creat\,\mathrm{Pr}oductionRate\left(\frac{mg}{hr}\right) = SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times \frac{60\min}{1hr} \times \frac{1dl}{100ml} \qquad (8)$$

To determine the creatinine excretion rate, substitute Equations (7) and (8) into Equation (5).

$$CreatExcretionRate\left(\frac{mg}{hr}\right) = SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times \frac{60\min}{1hr} \times \frac{1dl}{100ml} -$$

$$\frac{SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times \frac{1{,}440\min}{1day} \times \frac{1dl}{100ml} \times \frac{1day}{24hr} \times \Delta P_{Cr}\left(\frac{mg}{dl}\right)}{Max\Delta P_{Cr}/Day\left(\frac{mg}{dl \bullet day}\right) \times \Delta Time(hr)} \quad (9)$$

(All units except for mg/hour will eventually cancel, but the cancellation in the denominator, $Max\Delta P_{Cr}/Day \times \Delta Time(h)$, will be handled separately, because it engenders one last conversion factor with the value 24 that remains in the final formula.)

Multiplying the fixed numbers arising from conversion factors, the right-hand side of Equation (9) simplifies to

$$SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times 0.6\left(\frac{\min \bullet dl}{hr \bullet ml}\right) - \frac{SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times 0.6\left(\frac{\min \bullet dl}{hr \bullet ml}\right) \times \Delta P_{Cr}\left(\frac{mg}{dl}\right)}{Max\Delta P_{Cr}/Day\left(\frac{mg}{dl \bullet day}\right) \times \Delta Time(hr)} \quad (10)$$

Factoring out the common terms, $SSP_{Cr} \times CrCl \times 0.6$, along with their concomitant units,

$$SSP_{Cr}\left(\frac{mg}{dl}\right) \times CrCl\left(\frac{ml}{\min}\right) \times 0.6\left(\frac{\min \bullet dl}{hr \bullet ml}\right) \bullet \left[1 - \frac{\Delta P_{Cr}\left(\frac{mg}{dl}\right)}{Max\Delta P_{Cr}/Day\left(\frac{mg}{dl \bullet day}\right) \times \Delta Time(hr)}\right] \quad (11)$$

In the denominator of the subtracted ratio, the conversion factor between *hr* and *day* makes it clear that the ratio is a dimensionless number. Multiplying by 1, in effect 24 hours per day, in the numerator causes all of the units in the ratio to cancel, leaving only a pure number.

$$SSP_{Cr}\left(\frac{mg}{dl}\right)\times CrCl\left(\frac{ml}{\min}\right)\times 0.6\left(\frac{\min\bullet dl}{hr\bullet ml}\right)\bullet\left[1-\frac{\Delta P_{Cr}\left(\frac{mg}{dl}\right)\times\frac{24hr}{1day}}{Max\Delta P_{Cr}/Day\left(\frac{mg}{dl\bullet day}\right)\times\Delta Time(hr)}\right] \qquad (12)$$

Fifth, the plasma creatinine concentration is used to turn the creatinine excretion amount into its equivalent volume, a virtual quantity of plasma from which all creatinine has been eliminated. The inclusion of time then turns this into a rate of volume cleared, the very definition of clearance. The creatinine excretion rate (mg/hr), term (12), is divided by the prevailing P_{Cr} (mg/dl) to get the creatinine clearance rate (currently in dl/hr). Prevailing P_{Cr} in steady-state is straightforward, simply the one creatinine. In the kinetic state with two creatinines, the prevailing P_{Cr} is approximately midway between the starting and ending plasma creatinines, as if the plasma volume being purged by the creatinine excretion had that average creatinine concentration the whole time, so (12) is divided by $MeanP_{Cr}$. (Note: the "true average" creatinine needs to be found by calculus and will not be elaborated upon here. But in acute situations, the mean is a good enough approximation. Creatinines obtained more than 72 hours apart will cause increasing inaccuracies in the kinetic formula.)

$$\frac{SSP_{Cr}\left(\frac{mg}{dl}\right)\times CrCl\left(\frac{ml}{\min}\right)\times 0.6\left(\frac{\min\bullet dl}{hr\bullet ml}\right)\bullet\left(1-\frac{\Delta P_{Cr}\times 24}{Max\Delta P_{Cr}/Day\times\Delta Time(h)}\right)}{MeanP_{Cr}\left(\frac{mg}{dl}\right)} \qquad (13)$$

To convert this creatinine clearance rate in dl/hr to the standard units of ml/min,

$$\frac{SSP_{Cr}\left(\frac{mg}{dl}\right)\times CrCl\left(\frac{ml}{\min}\right)\times 0.6\left(\frac{\min\bullet dl}{hr\bullet ml}\right)\times\frac{1hr}{60\min}\bullet\left(1-\frac{\Delta P_{Cr}\times 24}{Max\Delta P_{Cr}/Day\times\Delta Time(h)}\right)}{MeanP_{Cr}\left(\frac{mg}{dl}\right)\times\frac{1dl}{100ml}} \qquad (14)$$

Fortuitously, all of the constants arising from the conversion factors cancel out in the arithmetic:

$\frac{0.6 \times \frac{1}{60}}{\frac{1}{100}} = 1$. Most of the units above also cancel, leaving only the desired units of ml/min.

$$\frac{SSP_{Cr} \times CrCl \bullet \left(1 - \frac{\Delta P_{Cr} \times 24}{Max\Delta P_{Cr}/Day \times \Delta Time(h)}\right)}{MeanP_{Cr}} in\left(\frac{ml}{\min}\right) \qquad (15)$$

Further simplifying and rearranging slightly, the KeGFR formula finally appears as

$$KeGFR = \frac{SSP_{Cr} \times CrCl}{MeanP_{Cr}} \times \left(1 - \frac{24 \times \Delta P_{Cr}}{\Delta Time(h) \times Max\Delta P_{Cr}/Day}\right) \qquad (16)$$

At this point, it is evident that only the corresponding CrCl will determine the units of the KeGFR output. Since SSP_{Cr} and $MeanP_{Cr}$ have the same units, they will cancel. And the term, 1 minus a ratio, is already unitless. Thus, whatever units are chosen for CrCl must then be the units of the KeGFR.

Practical tips

For a new patient, establish that person's baseline characteristics by obtaining any plasma creatinine and the associated CrCl or eGFR (MDRD often calculated for you by the lab). The product of SSP_{Cr} and CrCl is a surrogate of the patient's muscle mass. The $Max\Delta P_{Cr}$/Day is an inverse surrogate of the creatinine volume of distribution. Ideally, the value of $Max\Delta P_{Cr}$/Day should come from the individual patient, but not all patients with AKI go on to develop anuria. Reportedly, an anephric rate of creatinine rise is about 1.0-1.5 mg/dl per day.[4] Defaulting to 1.5

for the MaxΔP_{Cr}/Day in the absence of patient data is usually safe. However, the telltale sign that MaxΔP_{Cr}/Day needs to be increased from 1.5 is the output of negative KeGFRs by the kinetic formula. Another way that actual patient data can guide the choice of MaxΔP_{Cr}/Day is the subset of anuric patients who are placed on intermittent dialysis. The pre-hemodialysis creatinine minus the plasma creatinine 24 hours earlier should then be used for the MaxΔP_{Cr}/Day. Once the three parameters SSP_{Cr} and CrCl and MaxΔP_{Cr}/Day have been assigned for a patient, these values should be used consistently throughout all of the calculations of KeGFR for that person's acute renal episode. Exceptions may be made for MaxΔP_{Cr}/Day if it is known how the V_D or TBW is varying with time. [Use Equation (3) to convert the adjusted V_D to a new MaxΔP_{Cr}/Day.]

If the preceding three parameters are fixed and define the initial conditions, the next three parameters are dynamic and describe the kinetics of creatinine change. They are, of course, the starting and ending plasma creatinines and the time that it took to transition between the two values. A set of three numbers ΔP_{Cr} and ΔTime(h) and MeanP_{Cr} is inputted directly from the lab report for each round of KeGFR calculations.

The kinetic eGFR numbers should be plotted *versus* time, because a graph is better than a litany of raw numbers at conveying the true amplitude and volatility of changes and the evolution and possible trends in the kidney function (for example, by forecasting a renal recovery). Since the graph keeps a timeline, clinical setbacks (e.g., sepsis) and therapeutic interventions (e.g., trial of fluids) and biomarker levels can be superimposed when they occur. Temporal correlations between these events and the instantaneous KeGFR of the acute situation could yield insights regarding cause-and-effect relationships.

REFERENCES

1. Stevens LA, Coresh J, Greene T, Levey AS: Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med* 354: 2473-2483, 2006
2. Hrubec TC, Whichard JM, Larsen CT, Pierson FW: Plasma Versus Serum: Specific Differences in Biochemical Analyte Values. *J Avian Med Surg* 16: 101-105, 2002
3. Ix JH, Wassel CL, Stevens LA, Beck GJ, Froissart M, Navis G, Rodby R, Torres VE, Zhang YL, Greene T, Levey AS: Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. *Clin J Am Soc Nephrol* 6: 184-191, 2011
4. Foster C: The Washington Manual of Medical Therapeutics, Philadelphia, Wolters Kluwer 2010.