Urea Based Measures of Dialysis Adequacy

SKC In-service Jan 2016

What does “Adequacy” mean?

- We consider dialysis adequate when it meets pre-specified cutoffs for urea clearance (spKt/V > 1.2, URR > 65)
- “Adequate” dialysis is not = optimal dialysis
- Optimal dialysis
  - Completely replaces native kidney function
  - Balances volume status
  - Corrects bone mineral metabolism derrangements
  - Corrects anemia of kidney failure
  - Results in the clearance of all uremic retention solutes
  - Rehabilitates patients so they can lead a normal life

Uremia / Toxins

- Historically the first solute recognized to be retained in persons with kidney failure was urea, hence the terms; uremia and uremic syndrome.
- Urea, easily measureable as blood urea nitrogen, has appropriately served as a surrogate marker for the uremic condition but it is important to note that urea itself is not responsible for the toxicity witnessed in kidney failure
- Scientific developments have revealed that numerous compounds of varying size and origin are progressively retained with decline in kidney function, many of these molecules having inherent properties quite different from urea.
- It is believed that the majority of uremic retention solutes are generated during the course of normal protein metabolism or by modifications of amino acids in the gastrointestinal tract by microbial flora, but it is also possible that toxins gain entry into the body via alternate pathways or metabolic processes.

Uremic Retention Solutes

- Small Molecules
- Middle Molecules
- Gut Derived
- Protein Bound

Table 6. C_{MAX}/C_U ratio: Highest scoring molecules

γ-Guanidinobutyric acid	52.55	Pseudouridine	6.61
2-Methoxyresorcinol	16.43	Oxalate	6.55
α-*N*-acetylarginine	13.95	Orotic acid	5.78
Indole-3-acetic acid	10.37	Threitol	5.75
Hyaluronic acid	8.57	Hydroquinone	5.65
Guanidinosuccinic acid	7.23	Guanidine	4.63
Benzylalcohol	6.96	Indoxyl sulfate	4.45
Interleukin-6	6.84	Erythreitol	4.11
Leptin	6.81	Thymine	4.00

Abbreviations are: C_{MAX}, maximal uremic concentration; C_U, mean/median uremic concentration.

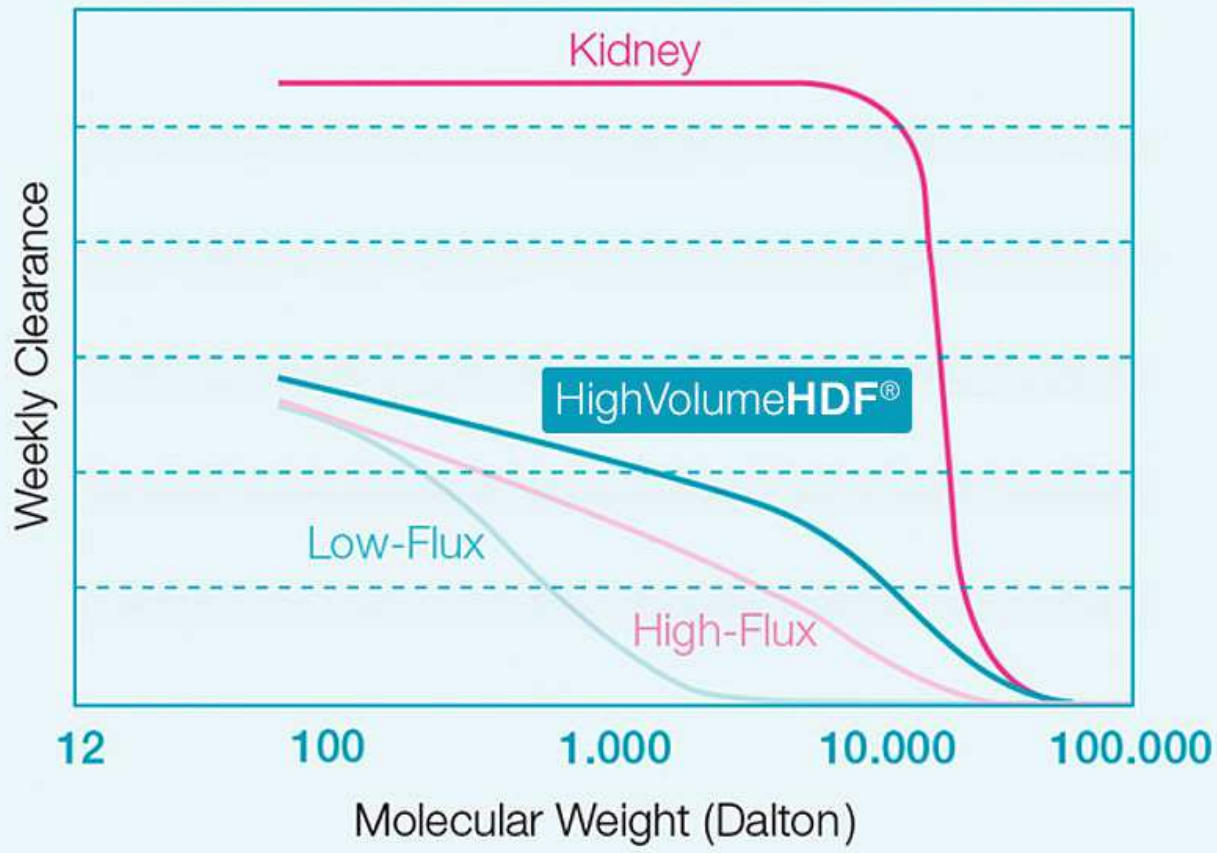
Small Molecules

- Molecular weight < 500 Da
- Urea, MW 60 Da
- Examples of some other small molecules that can accumulate during kidney failure are creatinine (MW 113), phosphates (MW ~95) and electrolytes such as sodium (MW 23) and potassium (MW 39).
- Movement of small molecules during dialysis is predominantly dependent upon diffusion; therefore, clearance of small molecules is governed largely by solute gradients established by the amount of blood (Qb) and dialysate (Qd) that is delivered to the dialysis membrane.

Middle Molecules

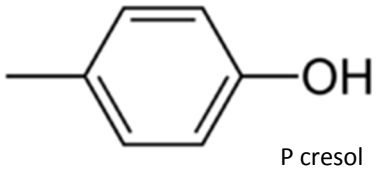
- Classically, middle molecules were described to have molecular weights in the range of 300-2,000 but more recent classifications have simplified the issue by adding all compounds of molecular weight 500-60,000, the upper number of this range being the approximate size barrier of the glomerular basement membrane.
- By nature of their size relative to the dialysis membrane pore size, middle molecules have a more limited dialysance than small molecules.
- The classic, prototypical surrogate middle molecule is vitamin B12 (MW 1470). Another larger middle molecule frequently measured for research purposes is beta-2-mircoglobuin (MW 12,000).
- Clearance of middle molecules is dependent upon membrane surface area, dialysis time and membrane pore size.
- Middle molecules are only removed during dialysis after passage through larger pores on the dialysis membrane. There are relatively few large pores in most standard dialyzers, thus, both surface area and time are seen as more important in middle molecule clearance.
- High flux dialyzers and convective methods of clearance provide better middle molecule clearances

Clearance by size/modality

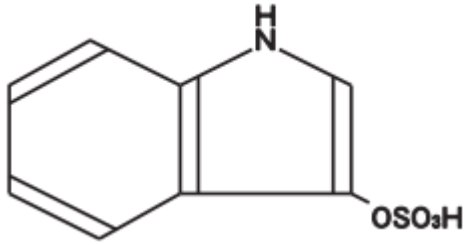


Protein Bound Toxins

- The binding of a uremic toxin to the predominant plasma protein, albumin (MW 66,000), effectively makes it relatively impermeable to the dialysis membrane when compared to free unbound solute.
- Examples of commonly studied protein bound uremic retention solutes include p-cresol and indoxl sulfate.
- Removal of protein bound uremic toxins during dialysis is typically slow and incomplete.
- Clearance of some protein bound uremic retention solutes has been shown to increase with increasing dialysate flow rate (800 ml/min).
- Large volume convective therapies (60L+) seem effective in increasing removal of protein bound uremic retention solutes
- Various exciting and unique strategies have been suggested to improve removal of protein bound substances during dialysis such as sorbent based therapies and albumin dialysis.

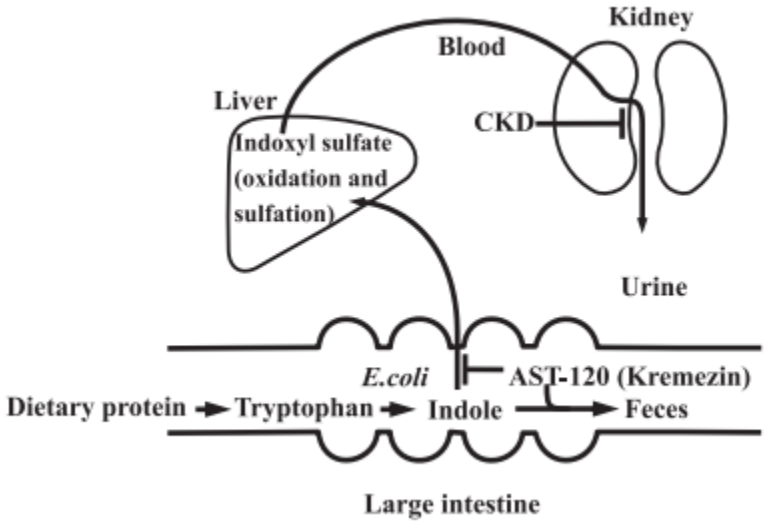


P cresol



Indoxyl sulfate

Gut Derived Uremic Toxins

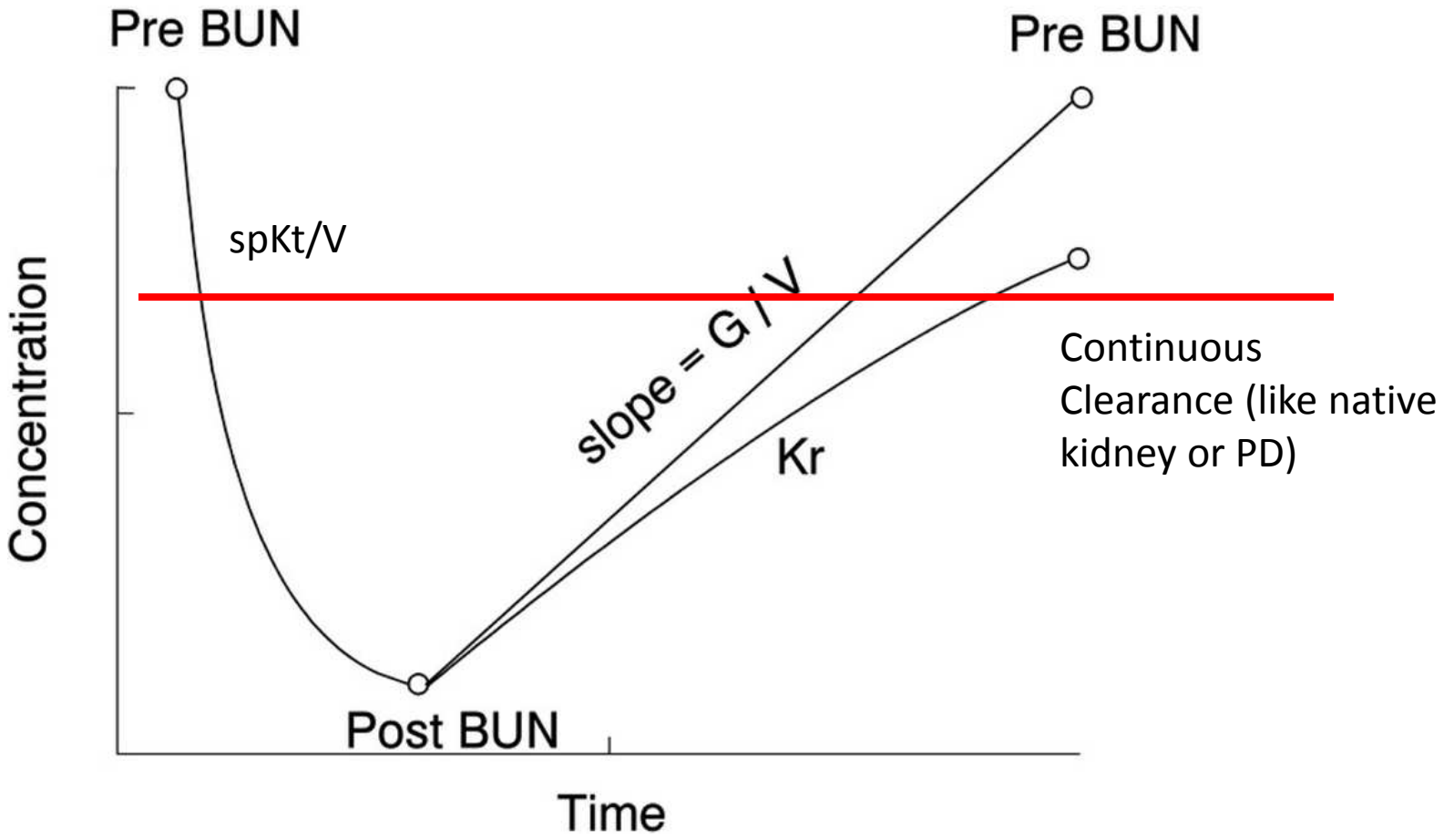


- Uremic retention solutes can be derived from exogenous intake, endogenous production or from gastrointestinal microbial metabolism.
- Examples of sources of exogenous intake include normal food nutrients, preservatives, known environmental toxins or drugs.
- Flora metabolism of various compounds such as amino acids and fermentation of various sugars is also likely to play a role in the production of uremic retention solutes.
- Previously mentioned protein bound uremic compounds p-cresol and indoxyl sulfate are, at least in part, produced as a result of microbial processing of amino acids in the colon.
- Indole is a product of metabolism of amino acid tryptophan and is later metabolized to indoxyl sulfate in the liver.
- Phenolic compounds such as p-cresol are a result of breakdown of phenylalanine.
- In a study of ESRD patients post colectomy compared with ESRD patients with a normal colon, composition of uremic retention compounds was different, suggesting a colonic contribution, some of which has yet to be characterized.
- Many of these seemingly gut derived uremic retention compounds are not easily removed during the dialysis process and therefore present a future target for improvement in dialytic therapy.
- Oral absorbents and agents to modify gastrointestinal bacterial flora or motility have also been proposed as a potential treatment strategy.

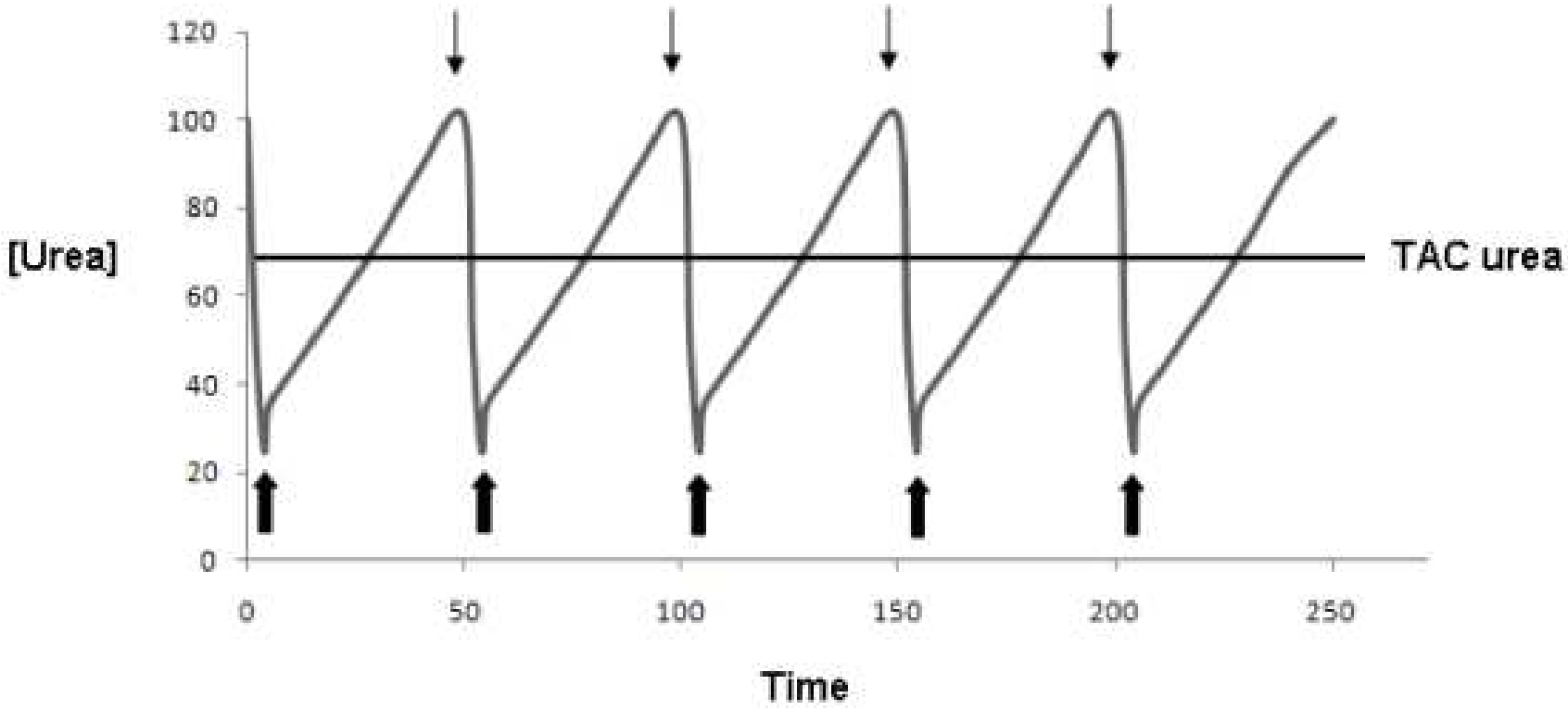
Urea Kinetics

- Time Averaged Urea Concentration (TAC urea)
- Urea Reduction Ratio
- Urea Kinetic Modeling
- Single Pool Kt/V
- Equilibrated Kt/V
- Standard Kt/V

Intermittent and continuous clearances are different



TAC Urea



URR

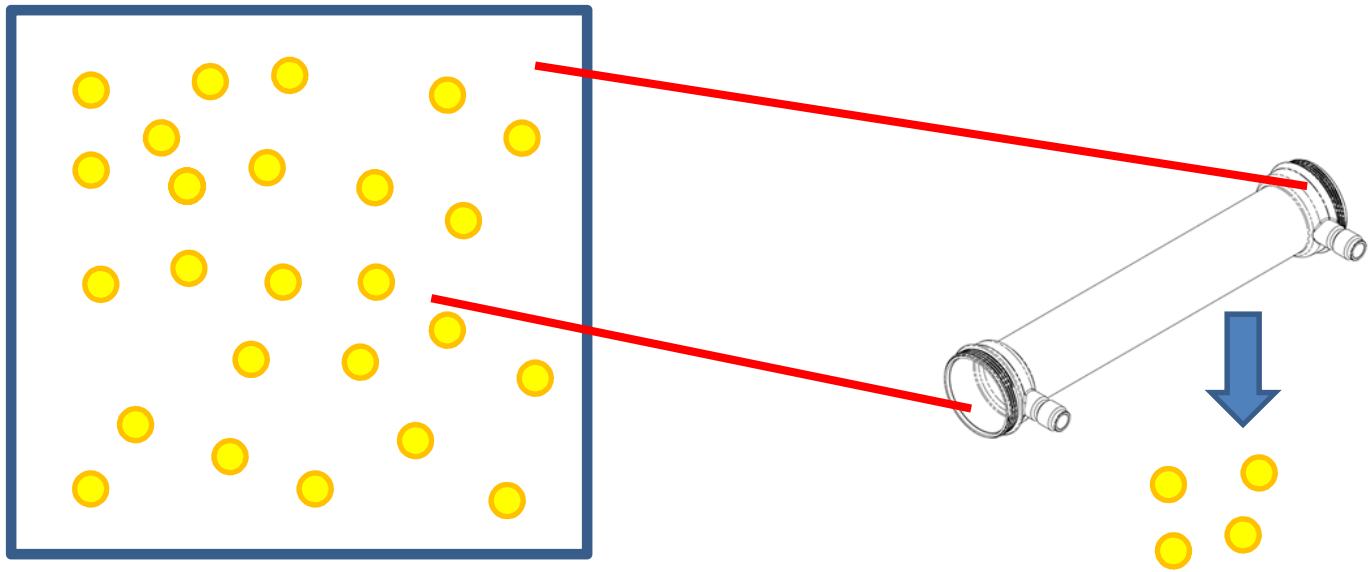
- Ratio, when multiplied by 100 = percent reduction of urea during dialysis session
- URR = Pre Dialysis BUN – Post Dialysis BUN / Pre Dialysis BUN
- Example: Pre BUN = 100, Post BUN = 50
  - 100 – 50 / 100 = 50/100 = 0.5 X 100 = 50% urea reduction
- Goal URR > 65

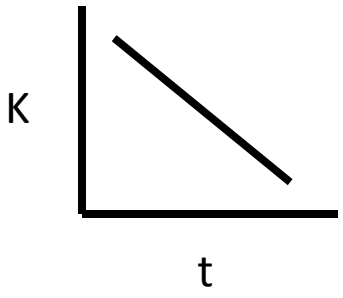
Urea Kinetic Modeling

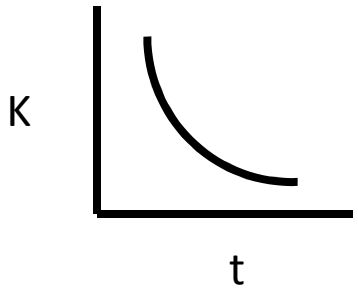
$$C = C_0 \left[\frac{V - B \cdot t}{V} \right]^{\left(\frac{K_r + K_d + B}{B} \right)} + \frac{G}{K_r + K_d + B} \left[1 - \left[\frac{V - B \cdot t}{V} \right]^{\left(\frac{K_r + K_d + B}{B} \right)} \right]$$

- Uses iterative mathematics (requires computer)
- Not used at NKC

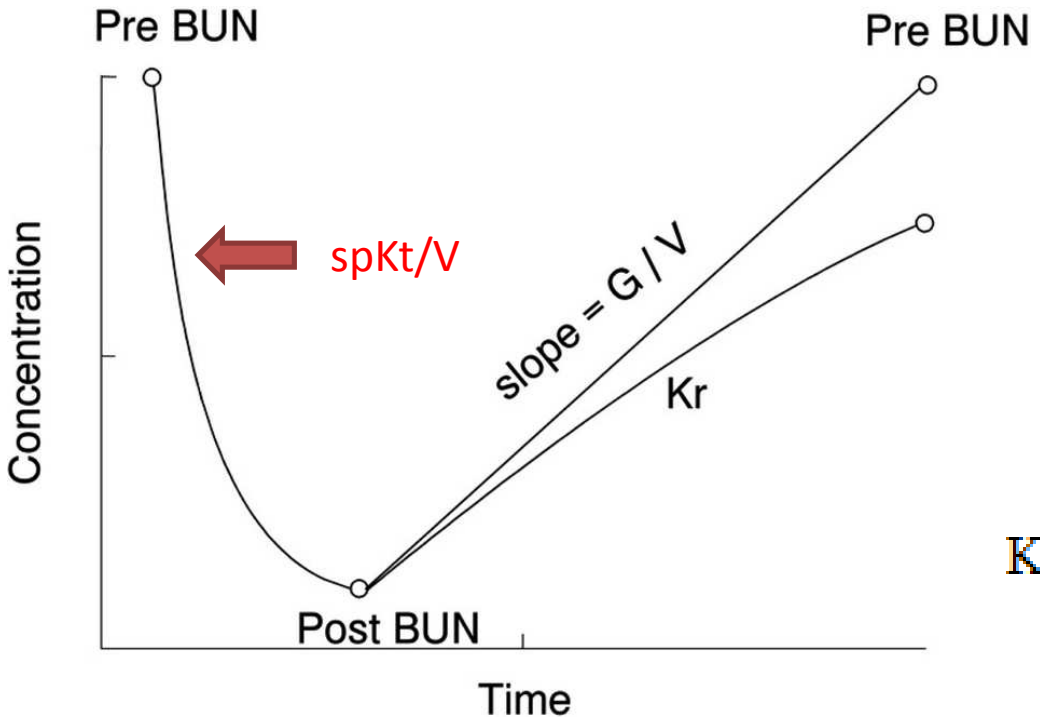
Single Pool Kt/V (spKt/V)







spKt/V



$$C = C_0 e^{-Kt/V}$$

$$Kt/V = -\ln\left(C/C_0\right)$$

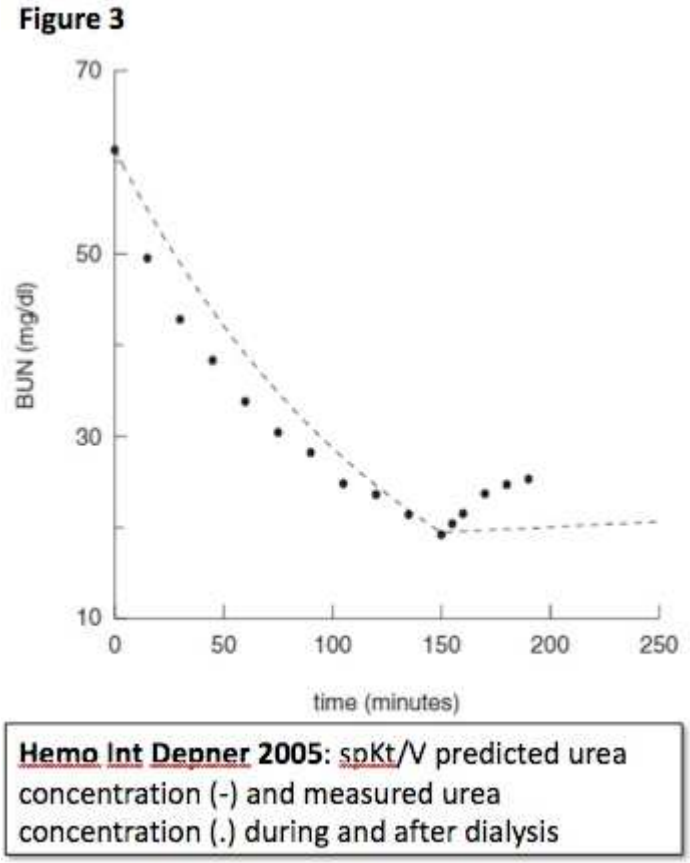
- K = Clearance (volume, L or mL per unit time)
- t = Time
- V = Volume of distribution of urea

spKt/V

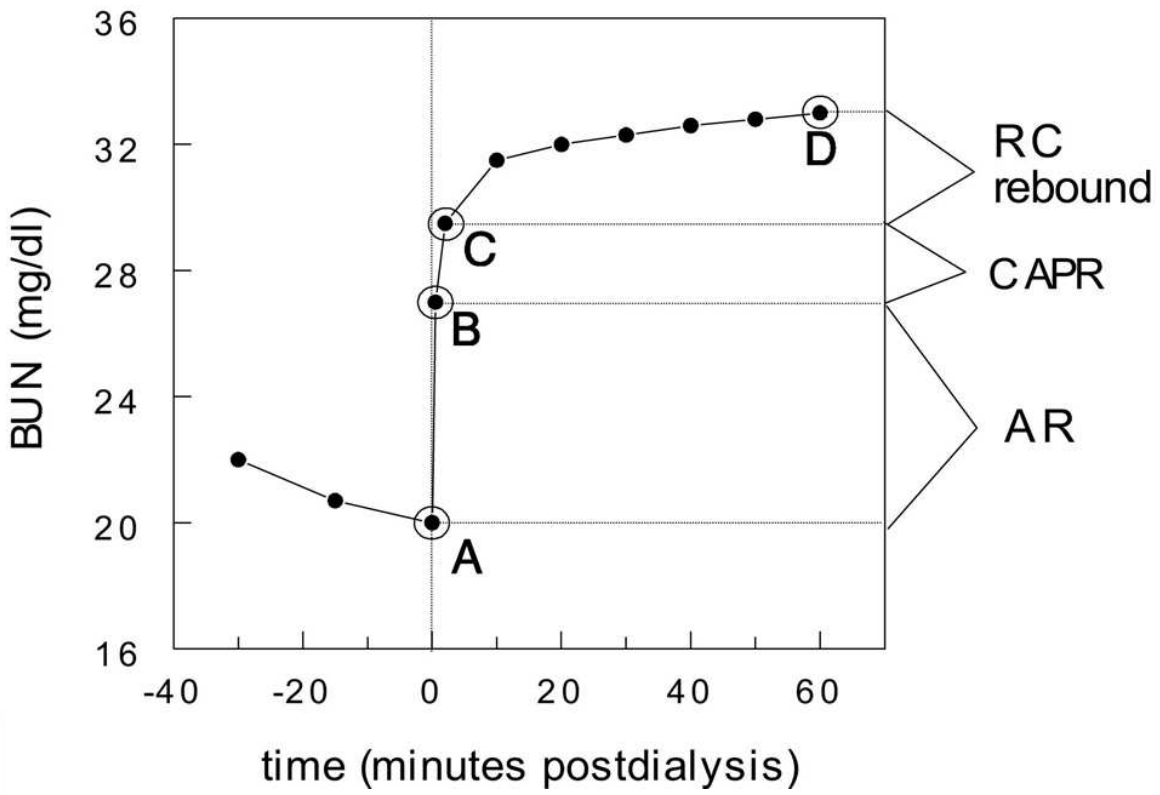
$$spKt/V = -\ln(R - 0.008 * t) + (4 - 3.5 * R) * UF / W$$

- Daugirdas II equation
- R = post dialysis BUN /pre dialysis BUN
- Accounts for UF (changing V)
- Used by NKC
- Goal spKt/V > 1.2

Equilibrated Kt/V



Hemo Int Depner 2005: spKt/V predicted urea concentration (-) and measured urea concentration (.) during and after dialysis



Accounts for urea rebound as it equilibrates from other areas in the body

eKt/V

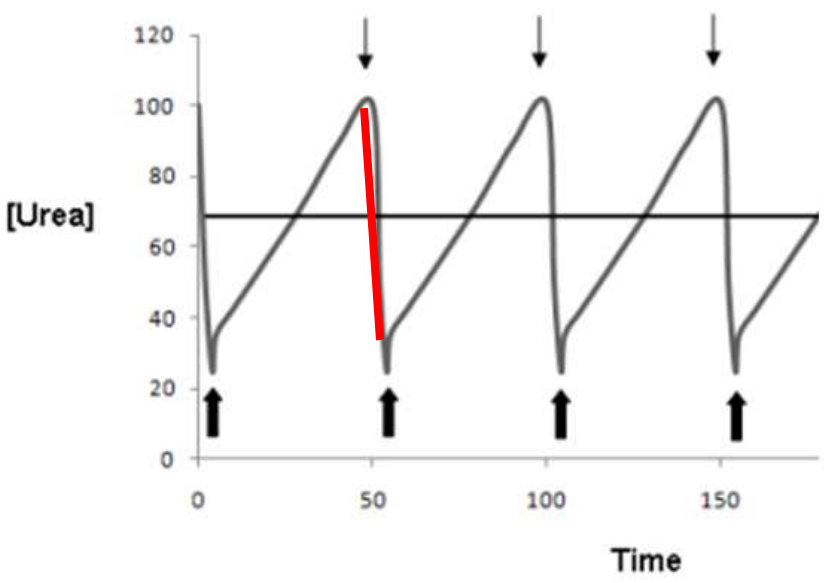
$$eKt/V = spKtV - 0.6\left(spKtV/T\right) + 0.03$$ AV Access

$$eKt/V = spKtV - 0.47\left(spKtV/T\right) + 0.02$$ Catheter

- spKt/V calculated and entered into above equations to adjust for estimated rebound
- In order to really know the eKt/V patient would have to stay for 60 min after dialysis to have the post BUN drawn

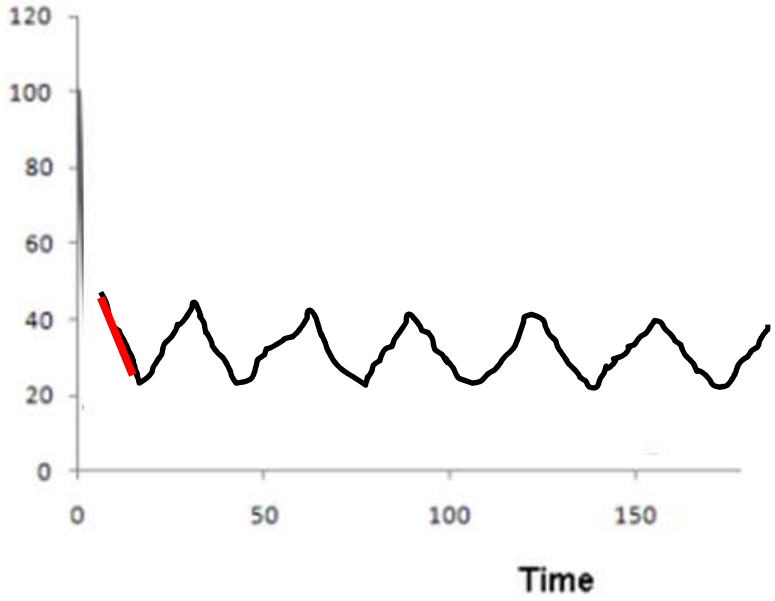
Standard Kt/V

Intermittent and clearances vary based on frequency



Thrice Weekly

spKt/V high



Daily

spKt/V low

Daily option is more close to native kidney function and more “adequate” than the thrice weekly. Therefore with more frequent or continuous dialysis spKt/V does not describe adequacy well. The two cannot be compared, thus the stdKt/V to allow comparision.

Standard Kt/V

$$\mathrm{stdKt}/V = \frac{10{,}080\dfrac{1-e^{-\mathrm{eKt}/V}}{t}}{\dfrac{1-e^{-\mathrm{eKt}/V}}{\mathrm{eKt}/V}+\dfrac{10{,}080}{\mathrm{Ft}}-1}$$

$$\mathrm{stdKt/V} = \mathrm{S}/\left(1-\left(0.74/\mathrm{F}\right)*\mathrm{UFw}/\mathrm{V}\right)+\mathrm{Kru}*\left(0.974/\left(\mathrm{spKtV}+1.62\right)+0.4\right)*10080/\mathrm{V}$$

More useful for patients running frequent in center, home dialysis or nocturnal dialysis.

Goal stdKt/V > 2.2

Limitations of urea kinetics

- Only drawn once monthly, does not account for other runs which may be suboptimal
- Does not include any information about other uremic toxins (?middle molecules)
- Sampling of BUN can be prone to error
- Urea generation dependent upon dietary intake of protein, can confound adequacy assessment
- Based on a fixed V, V can have mortality implications that are independent of urea clearance (e.g. large patients do better)

Take Home Points

- Measurement of adequacy by urea kinetics provides only a sliver of information about the dialysis treatments we provide.
- Adequate dialysis is not enough for our patients. Quality care demands that we strive towards optimal dialysis or replacement of native kidney function while balancing quality of life concerns.
- Regulatory agencies have placed significant weight on urea based measures of adequacy so it is important that we work to optimize them.