PHARMACY TO DOSE
THE CRITICAL CARE PODCAST

# Acute Kidney Injury (AKI)

Special Guest: Erin Barreto, PharmD, MSc, BCPS, BCCCP, FCCM

## How do you define and classify AKI?

- Before 2004, when RIFLE was proposed by the Acute Disease Quality Initiative group, we essentially had nothing to standardize the definition for what at the time we were calling acute renal failure
    - Think of this as sepsis before the BONE criteria or 2/4 SIRS criteria with a possible source of infection
- Lacked standardization in what we were calling short-term kidney dysfunction
- This led to problems with:
    - Consistency in epidemiologic studies of incidence, prevalence, and short/long-term outcomes assessment
    - Studying, evaluating, and implementing preventative and treatment strategies
- Can't study old or new therapeutics if we can't define the disease consistently
- RIFLE was a huge advancement as it created thresholds based on serum creatinine (SCr) and urine output (UOP).
- AKIN was an advancement in that even small changes in serum creatinine that occurred over a short period of time (0.3 mg/dL over 48 hours) would meaningfully alter the patients' prognosis
    - Big differences are in Stage R or Stage 1 (comparing RIFLE and AKIN criteria)
- KDIGO continued to build on this by combining the positives from RIFLE and AKIN which is described as the standard of care from their 2012 guidelines
    - A lot of features from RIFLE with the caveats (such as small SCr changes) added from AKIN
    - Stages 4 & 5 (L and E) are more long-term prognostication
    - Focuses on 3 stages
- This information is only 15 years old, more needs to be done
- The next guideline update likely will acknowledge the potential to include other functional biomarkers (in addition to SCr and UOP).
    - Also work on tailoring and talking about AKI based on subtypes

        - For example, we know sepsis-associated and cardiopulmonary bypass-associated AKI are not the same, but we currently refer to them as the same thing.
        - Referring to everything under the AKI umbrella is likely making it difficult to tailor medication treatment strategies and investigations/research
            - This is like saying all shock is the same and they should be treated the same when that is clearly not the case
- Moving forward will likely see an evolution in the staging system
    - Placing patients in the appropriate stage based on how the AKI occurred

**Are we moving towards the direction of sub-specifying the type of AKI?**

- Yes, we are moving in that direction
    - It is more present in electronic health record documentation
- Pre-clinical and translational models have been good at this for a long time because they study a specific type of AKI (e.g. toxin-mediated AKI)
- An example of contemporary research work is ARDS
    - Recognizing the hyperinflammatory endophenotype of ARDS that may be more responsive to corticosteroids rather than studying all types of ARDS as the same
    - We will likely move towards this eventually with AKI, just not there yet
- When we teach AKI is pre-renal, intra-renal, or post-renal that can be helpful to get them comfortable with what contributes to AKI
    - But it is a gross oversimplification
- Using the subtype of pre-renal AKI as an example, people historically thought "pre-renal AKI, give fluid, and prevent them from moving to intrarenal AKI"
    - This mindset needs to be re-framed
    - Pre-renal AKI is anything associated with a decrease in effective arterial blood volume
        - In acute decompensated heart failure (ADHF), giving fluids would make them worse even though they have a pre-renal AKI because they have a decrease in blood volume.
- This three bucket (pre-renal, intra-renal, or post-renal) general AKI umbrella strategy has us moving in the wrong direction

- Need to think more critically about how to tailor our interventions and what is included into each of the subtypes or classifications

**Do we know how often AKI occurs in the ICU?**

- Historically there are large ranges in the incidence of AKI
- This gets at the point Erin was making regarding the evolving definitions of AKI
  - Our treatment of other critical care diseases, such as sepsis, have evolved and improved
    - Our understanding has changed dramatically, and this changes the approach
- Contemporary estimates put the number around 20% in ICU patients developing some stage of acute kidney injury
  - Prevalence can be a higher depending on your patient population
  - Also, AKI historically higher in developing country
- The large range can lead to problems in research with estimating sample size or find the right patient population

**Does anything exist to help identify patients who are at risk for developing AKI?**

- Three categories of risk factors
  - Chronic conditions
    - Elderly age, CKD, CHF, liver disease, hypertension, diabetes mellitus
  - Acute factors
    - Sepsis, shock, respiratory failure, anemia, acidosis, surgery
  - Iatrogenic exposures
    - Nephrotoxin exposure
- We can't control the acute or chronic factors (such as whether someone needs surgery)
- We can look at nephrotoxin exposure, volume management, hemodynamic support among other things
  - Which could help limit the development of AKI or reduce the duration/severity

- The risk tools range from simple scores to complex AI-based algorithms
    - Will likely start putting indicators and prediction tool for AKI into the electronic health record
    - Need to improve clinical risk prediction models before getting to biomarkers
        - Good example is heparin-induced thrombocytopenia (HIT)
            - Don't send HIT lab tests on everyone, instead we use a clinical tool (4 T's) to identify the risk and then apply the diagnostic test (or biomarker) in high-risk patients
                - This is hopefully the future for AKI
    - Need to improve the clinical risk prediction, based on tools we already have
        - Then can talk about adding other tests on top of those

**Do you have any preferred tool/scale to use for acute kidney injury clinical risk prediction?**

- Unlike in cardiology, there isn't a validated score with a cool name for AKI risk prediction
- Erin prefers one that was developed with UCSD and Mayo Clinic and published by Dr. Rakesh Malhotra
    - PMID: 28402551

**What would make the perfect or ideal kidney biomarker?**

- Easy, rapid to test, and inexpensively measured
- Can detect kidney damage or decreased GFR
- Specific and unaffected by other disease
- Proportional response to disease severity
- Present early in the course of the disease
    - Kidney disease is a spectrum from no kidney disease, to being at risk for AKI, early evidence of kidney damage, loss of GFR, then kidney failure and its complications
- Ideally you would like something that is an upstream tool that picks up at-risk patients or early damage AKI patients before they move to loss of kidney function

**How does the ideal kidney biomarker compare to our current standard (serum creatinine and urine output)?**

- Our current biomarkers check some of the boxes but certainly not all of them
- Urine output is a good qualitative tool
    - Can't say UOP dropped by 50% so I need to dose reduce my medications by 50%
    - Also challenging to measure accurately when we are trying to reduce the use of foley catheters
    - Also heavily affected by things such as diuretic use and hypovolemia
- It is easy to measure, rapidly accessible but isn't perfect
- Serum creatinine has some benefits but also limitations
- SCr has been around 50+ years
- Lots of data regarding its use
- Quick turnaround, rapidly available in almost every lab worldwide
    - We're also more comfortable with using SCr
- SCr is the terminal byproduct of skeletal muscle catabolism
    - Anything that affects body composition could affect the observed value in the bloodstream independent of underlying kidney function
- Using SCr and UOP to analyze kidney function is like looking in the rearview mirror to see what the kidneys were doing 1-2 days ago
    - Makes it difficult to implement prevention strategies because of this delay
        - Don't want that when the patient is close to losing their GFR it should be when it is more upstream with early evidence of risk/damage
- Structural v. Functional biomarkers
    - Functional biomarkers (SCr/UOP) – indicate a loss of filtration function or the kidneys' ability to process fluid and solute
    - Structural/damage biomarkers – provide early evidence of risk or injury before GFR has deteriorated

**Do we have any "novel kidney biomarkers" that would be considered a structural biomarker? And how are they being used clinically?**

- Some are already doing this via Urinalysis
    - Renal tubular epithelial cells or cast cells

- There are many novel biomarkers that can be measured in the urine or blood being looked at and tested
- The two most common biomarkers are Nephrocheck (TIMP-2-IGFBP7) and NGAL
- These tools are the most helpful when being layered on top of a robust clinical risk prediction model (See HIT analogy earlier in the document)
- For example, if a cardiac surgery patient with a PMH significant for DM who comes out of the OR intubated and anemic, this patient is at high clinical risk for AKI
    - Some of them would develop AKI and some wouldn't
    - If you only use SCr, in two days you'll find out who develops it and who doesn't
        - There's data describing the use of a layered strategy
            - High clinical risk patients get a test such as Nephrocheck or NGAL
            - Find those who have both high clinical risk and high laboratory risk
            - Those would be the high value targets and you could more closely monitor nephrotoxic agents, hemodynamics, volume status, and maybe even obtain an early Nephrology consult
- These laboratory tests are best used in combination to prevent overtreating/monitoring patients who won't develop AKI
    - The PrevAKI trial took cardiac surgery patients (by definition are at a high clinical risk) in the post-op period and checked the urine biomarker
    - When the biomarker was high (high laboratory risk) they deployed the KDIGO prevention bundle
        - This staged approach for patients at risk of AKI
        - Allows the implementation of a simple prevention strategy to try and stave off AKI
        - Compared to usual care, they reduced the development of moderate-severe AKI (Stage 2/3)
            - Suggests that there may be treatment for acute kidney injury
            - Because we can prevent AKI to some degree, it's our responsibility to test future strategies
                - John Kellum, MD; PMID: 30546091

- KDIGO Prevention Bundle includes:
    - Stopping nephrotoxin agents if possible
    - Volume status and hemodynamic monitoring
    - Close kidney monitoring via strict UOP/SCr
    - Prevent hyperglycemia
    - Explore different testing strategies to avoid contrast
    - Early nephrology consultation
- Historically, our approach to AKI treatment interventions had two strategies
    - Take everyone who is at risk for AKI (almost all ICU patients)
        - Dilutes effect so much that you can't see any treatment benefit
    - Take only patients who have demonstrated AKI (Stage 2+)
        - By that point we are too late, and we can't rescue their kidney function
- The hope is that novel biomarkers can enrich the patient populations included in treatment/prevention trials so hopefully we can identify patients who are upstream and likely could benefit from new or existing interventions

**Once we've identified those who may be at a higher risk, is there any recommendation for what we should do to help prevent AKI?**

- The first thing is to establish some baseline criteria
    - Define the incidence of AKI and the outcomes in those patients
        - Otherwise, won't demonstrate anything that you do is effective
        - Also, can't identify the full scope of the problem
- Look at areas of interest
    - Don't try to tackle the entire "network" of AKI development and management
    - Focus on something that is relevant in your ICU
        - Excess NSAID use
        - High incidence of hypotension
        - Lack of SCr/UOP monitoring
            - The published research suggests we are worse at this then we think

- Once you have helped one issue, repeat the same process again focusing on high impact, relevant interventions to your ICU
- Might be helpful to re-frame the way we think about nephrotoxicity
    - We generally think about nephrotoxicity from a single agent
    - Many ICU patients receive multiple nephrotoxic agents which can add to their cumulative nephrotoxin burden
        - Consider a therapeutic interchange for some of them to reduce the number of nephrotoxic agents these high-risk patients receive
        - Much credit goes to Sandra Kane-Gill for her work in this area
- Need a combination of nephrotoxin stewardship in combination with antimicrobial stewardship
    - If someone is very close to needing dialysis, maybe we shouldn't hold back a non-nephrotoxic restricted antibiotic
    - Might be prudent to try to individualize the approach and care we deliver

**There are so many existing equations to assess kidney function and guide drug dosing. When thinking about ICU inpatients, should we be preferentially using any of these equations/tools?**

- Thinking about the creatine clearance or eGFR equations in general
    - Before you can apply these equations in adult ICU inpatients, you have to understand how these equations were first studied and when they apply
        - Need to understand their objective
            - Similar to Marvel movies, you have to understand their origin stories
    - Measured GFR is the patient's actual kidney function (the truth)
        - Give an exogenous compound (iothalamte, iohexol, inulin) that is freely filtered and not secreted/reabsorbed and measure how much is eliminated in plasma/urine
    - Most of these equations take a criterion standard (measured GFR)
    - Develop equations used regression-based strategies to predict that criterion standard

- Using eGFR tools that were validated for measured GFR, for purposes of medication dosing, this would be a secondary intent
- CKD-EPI is the best predictive equation across patient populations in the outpatient setting for the prediction of measured GFR
    - But doesn't say anything about its role in drug dosing
- The best equation depends on the outcome you are evaluating
    - Predict mGFR, diagnose CKD in an outpatient clinic, predict risk of long-term dialysis dependence, or trying to dose medications
- When using equations to predict drug dosing:
- If there is a package insert recommendation for a certain equation, would use that
    - Not very common
- FDA draft pharmacokinetic guidance document approximately 10 years ago currently being revised
    - Clinical trial evaluations of new medications could evaluate renal dose thresholds via Cockcroft Gault or MDRD in PK/PD trials
        - Pre-dates published research with CKD-EPI equation so this may change the recommendation of using MDRD
            - MDRD doesn't perform very well in patients with an eGFR > 60 (normal renal function)
- In general, there is interoperability among the creatinine-based equations
    - Looking at recommended medication doses in the acute setting
    - 80-90% of the doses remain similar if you flip out different creatinine-based equations for one another (For example, using CKD-EPI instead of MDRD)
    - When in doubt, take advantage of the wide therapeutic windows of the medications in the ICU to prevent undertreatment
- The distinction is what your institutional recommendations are and what calculators are built in the electronic health record
    - Important to understand what you have, the cut-offs, and the units of measure
        - Newer equations use mL/min/1.73m$^2$ rather than mL/min or L/hr which is the units we generally use for drug dosing and clearance

    - To do this: multiply eGFR x BSA / 1.73
        - This would take newer equations to mL/min
        - Important for patients who have BSA much different than 1.73 (morbidly obese or underweight)
- When evaluating equations, the evidence supports using the patient's actual serum creatinine rather than a rounded number
    - Rounding can disadvantage patients that don't have collateral information to support impaired kidney function
    - In general, this is not recommended
- Should likely use actual body weight in these equations as well
    - In the context of obesity, Erin uses adjusted body weight
    - But this is a big discussion in of itself

**How do these equations help us assess acute kidney injury or renal recovery? Should we be using them in these settings?**

- If the biomarker that underlies the equation is flawed, it won't be effective
    - Serum creatinine lags behind and has a bad kinetic profile with dynamic or fluctuating kidney function
- There are not many great answers, but Erin has some suggestions:
    - Exploit wide therapeutic windows for medications whenever possible
        - Go big on dosing to prevent undertreating which can lead to bad outcomes
    - Monitor surrogates such as UOP/BUN
        - If you see any change that can be an early indicator of kidney damage
    - Monitor drug levels when possible
    - Kinetic eGFR
        - Not extensively studied
        - Shows promise in drug optimization
    - Functional biomarkers with better kinetic profiles to assist with drug dosing
        - Cystatin C

        - Real-time GFR technologies with fluorescent tracers
- These are some forward-thinking potential solutions

**Is Cystatin C a brand-new biomarker?**

- This is new in the acute care setting
- Cystatin C is a functional biomarker (similar to SCr or UOP)
    - More timely then serum creatinine
- Introduced in 1980, it was put in the spotlight in 2012 from the NEJM but the CKD-EPI paper showing that serum creatinine and cystatin C in combination in an eGFR equation better predicted mGFR than either marker alone
- Cystatin C is released from all nucleated cells
    - Compared to SCr which comes from skeletal muscle
    - It is freely filtered at the glomerulus and reabsorbed in the proximal convoluted tubule cells and then catabolized
- Can measure in blood/urine
    - Measuring cystatin c in the urine could be an indicator of AKI/cellular damage
        - If proximal convoluted tubular cells are damaged, that will cause back leaking of reabsorbed cystatin C into the urine
        - Changing the test from a functional biomarker to a structural/damage biomarker
    - We are trying to address the potential to detect a decrease in GFR to assist with drug dosing
        - So generally speaking, this is more of a blood test
- A survey of hospital labs in Minnesota found that 79% of labs had access to cystatin c testing, but only 3% of them were able to result the test within 1 day
    - The slow turnaround time effectively precludes its use in the inpatient setting for medication management
        - Majority of the tests were send outs or only run a few times per week

**Can cystatin C guide drug dosing?**

- There is quite a bit of evidence to support the use of cystatin c to inform drug dosing
    - A systematic review of ~3500 patients evaluated in PK studies found that cystatin c was at least as good as predicting drug clearance compared to serum creatinine equations and in many cases better
        - Medications were mainly antimicrobials (e.g. vancomycin and aminoglycosides) but also cardiovascular and chemotherapy
        - These were simulations rather than applied use
    - Since there is little evidence regarding practical use at the bedside using updated equations with the most up-to-date targets, they completed a study to see if this strategy should be used for inpatients
        - 173 hospitalized patients with a vancomycin trough level drawn at steady state
        - The study question was if there was more information available, could their empiric dosing regimens achieve their targets more frequently
            - Found that the best performing model was the model that included the CKD-EPI equation with cystatin C, SCr, and expressed in mL/min units
        - This model was converted into a simple nomogram and then studied as a quality improvement project completed for validation
            - Compared to historical controls, this updated nomogram statistically significantly increased target attainment in 3 ICU's

**Are there situations where we should avoid ordering or interpreting cystatin C?**

- Changing from something that is entrenched in practice, such as serum creatinine, can create problems

  - We use creatinine on a daily basis and develop a comfort despite all of the limitations
  - Switching to something else has some real risks if people aren't ready or prepared for the switch
- As with any test, it should only be used if it's going to help your decision making
  - If someone is anuric, uremic, or their current SCr > 4x baseline, a cystatin c level likely won't change their current management
    - Can contribute to waste or confusion
- There are other ways cystatin c can be beneficial, but if people don't feel comfortable or understand, it can take people down the wrong path
  - Some say cystatin C is more accurate than serum creatinine because they know how many limitations serum creatinine has
    - This has not been shown in the literature
    - If you use a test without understanding its limitations it can be risky
- Cystatin C is produced from all nucleated cells
  - Anything that affects cell turnover like a rapidly proliferating malignancy or uncontrolled hyperthyroidism could increase production of cystatin C
    - That in turn would make cystatin C blood levels higher with a calculated eGFR lower than the actual kidney function
    - Using that to dose medications, patients would be underdosed
- Cystatin C is also part of the inflammatory cascade
  - Anything that interferes with those pathways could impact the observed serum concentration of cystatin C
    - For example, high pulse dose corticosteroids
- Just because cystatin c has limitations in the circumstances does not mean that it is not beneficial or inherently worse than SCr
  - This just means you need to look at it with intention and interpret the value carefully
- When interchanging creatinine-based strategies, going from Cockcroft Gault to MDRD to CKD EPI, the doses were similar 80-90% of the time
- This is NOT the case when talking about cystatin C estimates of GFR

    - If someone changed from SCr-based eGFR equations to cystatin c-based eGFR equations to guide drug dosing, about 50% of the recommended doses would change
        - Which is dramatically more than 10-20%
    - More importantly, the majority of these dose changes heavily favor dose reductions
        - Similar with combination or single biomarker equations
- There is so much opportunity with this test, but need to be careful with widespread use before the field is ready

**What should you do if your health system doesn't utilize these novel kidney biomarkers?**

- Try to understand what the primary barriers are
    - Concern about laboratory test volume
    - Place in therapy
    - Level of evidence
    - Awareness
    - Cost
- Could develop multidisciplinary group of people to help determine when the test would be run and in which patients
- There are a large amount of stakeholders regarding kidney assessment
    - Pharmacists, Intensivists, and Infectious Diseases colleagues are of course in the discussion
    - Don't forget about lab, IT, and other personnel that will be directly affected
- Want to make sure you that you secure buy in and input before moving forward to ensure appropriate use
    - Protocolized approach may assist with this as well

**What is your favorite website or mobile application to calculate these equations or clinical risk predictor scales?**

- National Kidney Foundation online GFR calculator for the CKD EPI equation
  - Publicly available free resource
  - Can do single biomarker, modify the units
- Also uses a vancomycin dosing nomogram that is available via QxMD that can be downloaded a smart phone.

## AKI Potpourri

*Vancomycin and Piperacillin/Tazobactam-Induced AKI*

- In critically ill patients, when used short-term, it is probably low risk
  - After adjusting for all the factors that would predispose these patients to AKI, there was no difference seen
- Dr. Scheetz used a robust rat and cellular model to reinforce that this is less of a problem than we previously thought
  - Need more data on long-term use

*Diuretics and Albumin*

- It's an intervention Erin doesn't love, but she rarely stands in the way if someone recommends it
  - Some blinded RCT data on the use of this in hypoproteinemic patients
- Prefers a strategy with a thiazide and a loop diuretic

*Contrast-Associated AKI*

- Not as common as we once thought
- Shifting nomenclature from contrast-induced nephropathy to contrast-associated AKI
- In the critically ill populations, it is substantially less likely than we previously thought

- The outcomes associated with it are much more infrequent than we previously thought
    - High potential for recovery if the AKI truly is contrast-associated

*"Renal dose" Dopamine*

- Please no. Let's let this go to the grave.

**What is the big picture takeaway when thinking about preventing or managing AKI in critically ill patients?**

- It's about caring about AKI and prioritizing its care
    - Easy to see people thinking about the kidney as a natural sacrifice while we prioritize on other organ systems
    - We do have a responsibility to pay attention to the kidneys and try to preserve its function
- Use QI tips that have been covered throughout the episode
    - Measure baseline epidemiology or characteristics in your center
    - Look at KDIGO bundle for what to introduce based on your findings
    - Things that Pharmacists can focus on:
        - Nephrotoxin burden and stewardship
        - Fluid management
        - Hemodynamics
        - Glycemic control
- Could be easy to get overwhelmed, focus on improving or implementing one step at a time