PEARLS OF LABORATORY MEDICINE

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TITLE: ACUTE KIDNEY INJURY

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Slide 1: Introduction

Hello, my name is **Rajeevan Selvaratnam**. I am a Clinical Biochemist at the University Health Network in the Laboratory Medicine Program and Assistant Professor at the University of Toronto. Welcome to this Pearl of Laboratory Medicine on Acute Kidney Injury.

Slide 2: Clinical Significance of AKI

Acute Kidney Injury (or AKI for short) is a common yet underrecognized syndrome, affecting up to 1.2 million people/year during hospital stays. AKI has been considered a syndrome with various factors that could underlie the severity and etiology of the disease. This heterogeneity of AKI ultimately contributes to adverse outcomes and increased cost to the healthcare system. The increased length of stay from AKI is on average by 3.5 days compared to those that do not incur AKI, which also translates to increased likelihood of death. Indeed, the death rate/year associated with AKI is more than breast cancer, prostate cancer, heart failure, and diabetes combined. When surviving AKI with complete or near complete recovery of kidney function, there is increased risk of developing chronic kidney disease (CKD), possibly at an accelerated rate of progression. Nonetheless, there is value in recognizing AKI in many instances for prevention and treatment.

Slide 3: Definition of Acute Kidney Injury

In simple terms, Acute Kidney Injury can be defined as a sudden deterioration of renal function. How do you define sudden? And what is deterioration? These questions have been addressed by various consensus guidelines, including RIFLE, which stands for RISK, INJURY, FAILURE, LOSS, and End stage renal disease. RIFLE was the first consensus definition developed by the Acute Quality Dialysis Initiative; RIFLE was subsequently updated to Acute Kidney Injury Network with the intention to replace the term acute renal failure with the more appropriate term, acute kidney injury since renal failure can be an outcome of AKI and to eliminate the use of estimated Glomerular Filtration Rates from the diagnostic criteria. The most recent guidelines are from KDIGO, Kidney Disease Improving Global Outcomes published in 2012.

Historically there has been a wide variation on what constitutes AKI which made it difficult to compare results across studies, validate new concepts such as biomarkers and overall hampered progress in understanding the syndrome of AKI. It is therefore important to have a universally accepted definition of what constitutes AKI and recognizing AKI in a consistent and familiar manner. This was the goal of Kidney Disease Improving Global Outcomes (KDIGO) guidelines on AKI that will be reviewed here.

Slide 4: Diagnostic Criteria of AKI

All consensus guidelines including KDIGO have relied on two important diagnostic criteria to define and stage AKI. These include the following:

1) Reduction in urinary output
2) Increased serum creatinine level

Either of these criteria can be used to define any of the 3 stages of AKI.

Slide 5: Urine Output - Diagnostic Criteria of AKI

Let's consider urinary output. Clinical Laboratories are not typically involved in monitoring or measuring urinary output, but the reduction in urinary output is an important criterion for the diagnosis of AKI. However, this diagnostic criterion based on urinary output is sometimes unreported in literature. There is also a wide variation and inconsistency on how one monitors and measures urinary output. In general, as evidenced from this table, lower rates of urinary output are associated with increased severity of AKI.

Slide 6: Serum Creatinine - Diagnostic Criteria of AKI

A common clinical criterion for evaluating AKI is that based on laboratory measurement of serum creatinine. The preferred method for creatinine measurement should be based on an enzymatic method and not the Jaffe method, which in general has known to have greater imprecision and interferences. Using the serum creatinine criteria, the three stages of Acute Kidney Injury are defined as follows.

Stage 1 is defined as a mild increase of serum creatinine by 50%. In other words, from baseline measurement, typically within 7 days or less, there is 1.5x increase in serum creatinine. Alternatively, an increase in serum creatinine by 0.3 mg/dL (26.5 µmol/L) or more within 48hrs is enough to define AKI stage 1.

Stage 2 is defined by evidence of serum creatinine increase by 2 times the baseline measurement.

And Stage 3 is defined by an even faster rate of increase of serum creatinine. Specifically, an increase by three times or more in serum creatinine from the baseline measurement. Alternatively, an increase to 4.0 mg/dL (353.6 µmol/L) or more or initiation of Renal Replacement Therapy, abbreviated as RRT define the most severe stage of AKI. In pediatrics or those less than 18 years of age, an eGFR that is less than 35 mL/minute/1.73 m^2 defines the severe Stage 3.

Slide 7: Clinical Decision Support for AKI

Since AKI is not associated with any specific symptoms, and with the diagnosis dependent largely on the laboratory-based measurement of serum creatinine, electronic alerts or clinical decision support systems can be implemented to streamline and automate AKI recognition. This involves computerized detection of changes in serum creatinine and electronically alerting the caregivers, including primary care providers of the opportunity to respond proactively, possibly enabling early recognition, timely intervention, and effective follow-up.

For example, a study by Al-Jaghbeer et al, in 2017 at the University of Pittsburgh Medical Center has shown that implementing such an automated clinical decision support system, improved clinical outcomes that resulted in reduction of mortality by 0.8%, a reduction in length of stay by 0.3 days. Dialysis use was also reduced by 2.7% in patients with AKI, which was most notable in surgical patients. These numbers may seem modest, but given the frequency of AKI and by the study estimates, this translated to 1.2 billion dollars in savings, and more than 17 000 lives saved.

Slide 8: Clinical Management

Such an electronic alert system provides opportunities for optimizing and enabling prompt clinical management, which can be for example notifying the pharmacist and clinical team about discontinuation or dose-adjustment to minimize nephrotoxicity and renal elimination. Clinical management can also be directed toward treating the underlying disease as well treatment of electrolyte disturbances, including the optimization of fluid balance and hemodynamics.

Slide 9: Risk Factors for AKI

Several risk factors for AKI have been associated with exposures and/or susceptibilities. Susceptibilities are generally shared risk factors such as certain demographics and genetic predispositions, whereas exposures are specific patient-related risk factors. Notable exposures include sepsis, cardiac surgery, radiocontrast agents, and nephrotoxic drugs among others noted in the table.

Slide 10: The Problem with Serum Creatinine

To this point we have relied on serum creatinine, an ancient marker for evaluating kidney injury. There are limitations with using serum creatinine, which is known to be a delayed marker, requiring more than 50% loss of renal function. Therefore, while serum creatinine may be a good marker for epidemiological studies, its suitability at bedside for assessing AKI has been questioned. Also unclear are indications on frequency of serum creatinine measurements in general, although in passing the KDIGO guidelines does note that serum creatinine should be measured at least daily in high risk individuals. However, this may lead to missing the observation of smaller changes in serum creatinine.

Slide 11: Small Changes in Kidney Function

From current guidelines, we know that even small changes in kidney function are important as there is a strong association with significant short and long-term outcomes. But how small of a change is significant? A few studies have demonstrated that changes smaller than those recommended by the guidelines are important. For example, even a 0.1 mg/dL increase was associated with increased risk of AKI, as shown by Newsome et al in their 2008 study of cardiac surgery patients.

In another important study by Chu et al that evaluated retrospectively 303 patients with common histologic evidence of AKI, noted that using serum creatinine criteria alone, only 185 of the 303 patients had creatinine changes that met the guideline requirement. This improved slightly when urinary output was factored in, but approximately 1/3rd of the patients still did not meet the clinical criteria of AKI diagnosis despite histopathological evidence. The reason cited by the authors in majority of the discrepant cases were, a slower serum creatinine increase than that required by AKI definition from KDIGO.

These indications contribute to the notion that serum creatinine is not an ideal marker. However, the changes based on serum creatinine as indicated in the KDIGO guidelines enable a universal recognition of AKI in a familiar and consistent manner, while the search for novel markers that provide earlier indications are established.

Slide 12: Future of AKI Diagnosis: From Reactive to Pro-Active Approach

If we look at the current paradigm of how we diagnose AKI, it is at the late stage where the damage has already occurred, *i.e.* in a symptomatic state as evidenced by decline in eGFR and increased creatinine. Therefore, the current approach is reacting to manage the damage that has already been done.

A proactive approach may be one where biomarkers are present early in an asymptomatic state, reflecting not cellular damage, but instead impending damage or cell stress. Therefore, a pro-active approach to anticipate AKI occurs in the asymptomatic state, may involve new predictive markers in conjunction with risk stratifications, and possibly tailored to specific susceptibilities and exposures of AKI such as sepsis or cardiac surgery.

Slide 13: Other Markers of AKI

Several markers have been investigated as early indicators of AKI. On one hand, you have the classical or conventional serum markers that reflect decreased glomerular filtration such as creatinine and cystatin. On the other, you have urinary markers, that have recently been brought to light as early indicators of AKI and proposed to reflect renal tubular stress and injury leading to AKI. These urinary markers include Tissue Inhibitor of Metalloproteinases 2 (abbreviated as TIMP2), Insulin-like growth factor-binding protein (abbreviated as IGFBP7), Neutrophil Gelatinase-Associated Lipocalin (abbreviated NGAL), Urinary Albumin, Liver-type Fatty Acid Binding Protein (abbreviated as L-FABP), and Interlukein-18 (or IL-18).

The advantage of these markers would be their rise in the pre-injury phase leading to AKI which enables preventative and protective interventions such as reducing exposures to renal insults.

Slide 14: Kinetics of Urinary Markers of AKI

A few studies have indicated that these urinary markers of AKI are earlier reflections of renal damage than conventional serum markers. Note that typically, serum creatinine will take 24 to 36hrs to rise after a renal onslaught. The table below summarizes the kinetics of some of these novel markers for comparison. For example, KIM or kidney injury molecule-1 peaks within 48-72hrs post-injury, but is detected earlier at 12-24hrs. IL-18 peaks within 12-18 hours, but is detected as early as 6hrs. If these kinetics are slow, then consider that NGAL and L-FABP, both of which peak at 6hrs. Despite the earlier detectable presence of these markers in urine, what remains unclear is if serial sampling is necessary, much like in the diagnosis of acute myocardial infarction using troponin.

Slide 15: Impact of new markers of AKI

Several promising studies have explored the potential for these early urinary biomarkers of AKI, however additional studies are needed to define how they will be incorporated in to routine clinical practice. Currently, it's not clear at what time points and frequency the new markers will need to be measured. And are these markers personalized to a specific AKI exposure such as sepsis? Or are these markers independent of exposures and susceptibilities such as pre-existing chronic kidney disease? How the kinetics will change in the context of pre-existing chronic kidney disease is unknown. While many questions remain unanswered, new biomarkers are much needed for early detection and management of AKI.

Slide 16: Conclusion and Summary:

In summary, the universal criteria for diagnosing AKI is currently defined by changes in serum creatinine and by urinary output as recommended by the KDIGO guidelines. The intention of KDIGO guidelines was to raise clinical awareness and stimulate research to improve both clinical care and patient outcomes globally, which can be accomplished when AKI is recognized in a consistent and familiar manner. AKI is clinically heterogenous, as it is a syndrome that is highly variable in severity of presentation, etiology, and timing of the acute insult. This heterogeneity of AKI allows it to be under recognized, making it costly to the livelihood of the patient and financially to the health system. Therefore, the future of AKI diagnosis may rely on novel predictive markers that anticipate and prevent AKI to enable optimal management, as dictated by proven clinical outcomes.

Slide 17: References

Slide 18: Disclosures

Slide 19: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Acute Kidney Injury**."

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PEARLS OF LABORATORY MEDICINE

Acute Kidney Injury

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Clinical Significance of Acute Kidney Injury (AKI)[1]

- Common yet underrecognized syndrome (1.2 Million people/year)
- Heterogenous
- Costly
  - Increased length of stay
  - Increased risk of mortality
  - Increased risk of chronic kidney disease (CKD)

[1]Lewington AJ et al., 2013, Kidney international, 84(3):457-67

Definition of AKI

Sudden Deterioration of renal function

- What is sudden?
- What is deterioration?

Consensus Guidelines

- RIFLE: **R**isk, **I**njury, **F**ailure, **L**oss, **E**SRD
- AKIN: Acute Kidney Injury Network
- KDIGO: **K**idney **D**isease **I**mproving **G**lobal **O**utcomes

Diagnostic Criteria of AKI

1) Reduction in urinary output
2) Increased serum creatinine

- Either of these criteria can be used to define the 3 stages of AKI

Urine Output - Diagnostic Criteria of AKI

AKI Stage[2]	Urine Output
1	< 0.5 mL/kg/h for 6–12 hours
2	< 0.5mL/kg/h for ≥ 12 hours
3	<0.3mL/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

[2]KDIGO 2012 Clinical Practice Guidelines for Acute Kidney Injury; Kidney International Supplements (2012)

Serum Creatinine - Diagnostic Criteria of AKI

Stage[2]	Serum Creatinine Criteria
1	Increased by x1.5 (within 7 days) OR ≥ 0.3 mg/dL (≥26.5 µmol/L) (within 48hrs)
2	Increased by x2
3	Increased by x3 or ≥ 4.0 mg/dL (≥353.6 µmol/L) or initiation of RRT Or <18 years, a decrease in eGFR < 35 mL/minute/1.73 m^2

[2]KDIGO 2012 Clinical Practice Guidelines for Acute Kidney Injury; Kidney International Supplements (2012)

Clinical Decision Support for AKI

Study by Al-Jaghbeer et al.[3]

- **Mortality:** 0.8% reduction
- **Length of stay:** 0.3 days reduction
- **Dialysis Use:** 2.7% reduction

[3]Al-Jaghbeer M et al., 2018; Journal of the American Society of Nephrology, 29(2):654-60

Clinical Management[2]

- Discontinue or dose-adjust nephrotoxic drugs
- Treat the underlying disease
- Treat electrolyte disturbances
- Optimize fluid balance and hemodynamics

[2]KDIGO 2012 Clinical Practice Guidelines for Acute Kidney Injury; Kidney International Supplements (2012)

Risk Factors for AKI[2]

Exposures	Susceptibilities
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female Gender
Burns	Black Race
Trauma	CKD
Cardiac surgery (especially with cardiopulmonary bypass)	Chronic diseases (heart, lung, liver)
Major noncardiac surgery	Diabetes Mellitus
Nephrotoxic Drugs	Cancer
Radiocontrast agents	Anemia
Poisonous plants and animals	

[2]KDIGO Clinical Practice Guidelines for Acute Kidney Injury; Kidney International Supplements (2012)

The Problem with Serum Creatinine

- Delayed Marker: >50% renal function loss for increase in creatinine[4]
- Good for epidemiological studies, difficult to apply at the bedside
- How often is serum creatinine measured in AKI evaluation?
  - High risk: Measure at least daily[2]

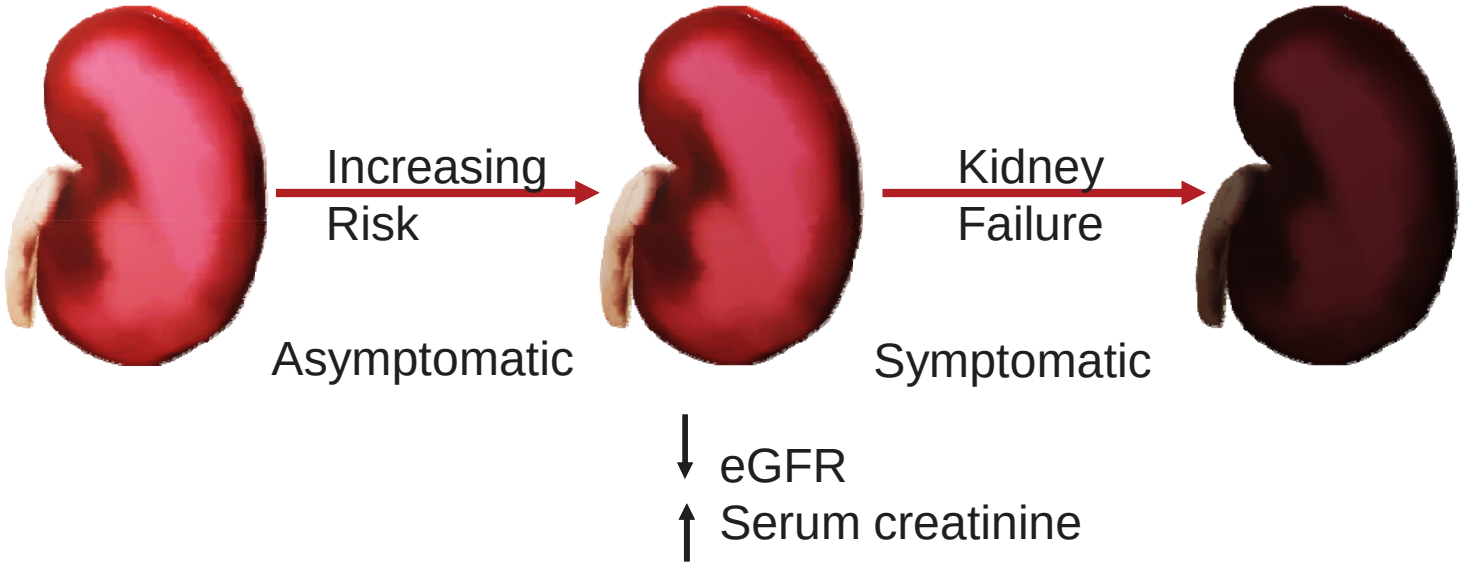
[4]Najafi M et al., 2014, World journal of cardiology, 6(9):1006
[2]KDIGO Clinical Practice Guidelines for Acute Kidney Injury; Kidney International Supplements (2012)

Small Changes in Kidney Function

- Associated with significant short & long-term outcomes
  - An increase of 0.1 mg/dL is associated with increased risk[5]
  - In patients with histopathologic evidence, 1/3 of patients could not diagnosed based on KIDGO criteria[6]

[5]Newsome BB et al., 2008, Archives of internal medicine, 168(6):609-16
[6]Chu R et al, 2014; Clinical Journal of the American Society of Nephrology, CJN-06150613

Future of AKI Diagnosis: From Reactive to Proactive



Proactive Measures → Reacting to Manage the Damage

Other Markers of AKI

Tubular Stress/Injury

- TIMP2
- IGFBP-7
- NGAL
- L-FABP
- IL-18

Decreased Glomerular Filtration

- Creatinine, Serum
- Cystatin, Serum

Kinetics of Urinary Markers of AKI[7]

Biomarker	Kinetics
KIM-1	Detected within 12-24h post injury, peaks at 48-72h
IL-18	Detected within 6h post injury, peaks at 12-18h
TIMP-2 + IGFBP-7	Detected within 12h post injury
NGAL	Detected within 3h post injury, peaks at 6h
L-FABP	Detected within 1h post injury, peaks within 6h

[7]Hertzberg D et al., 2017, Clinical Kidney Journal, 10(3):323-31

Impact of New AKI Markers

1. Promising Research
   - Need more clinical outcomes
2. Timing and frequency for biomarker measurements is unclear
   - Exposure specific?
3. How will AKI be addressed in the context of pre-existing chronic kidney disease?

Conclusion/Summary

- A syndrome that is highly variable in severity, etiology, and timing of the acute insult
- AKI is defined by changes in serum creatinine and urinary output – KDIGO Guidelines
- Early indications of AKI by novel markers to enable optimal management

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Disclosures/Potential Conflicts of Interest

Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:

- **Employment or Leadership**:
- **Consultant or Advisory Role:**
- **Stock Ownership:**
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