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How to Integrate AKI Risk Assessments into Clinical Workflows

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by bioMérieux. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Clinician's Roundtab*le on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss how we can incorporate acute kidney injury risk assessments into our clinical workflows are Drs. Javier Neyra and Jonathan Himmelfarb. Not only is Dr. Neyra an Associate Professor of Medicine, but he's also the Co-Director of Critical Care Nephrology and the Associate Director of the Nephrology Research and Training Center at the University of Alabama at Birmingham. Dr. Neyra, welcome to the program.

Dr. Neyra:
Thank you very much for having me here. I'm looking forward to the conversation.

Dr Turck:
And Dr. Himmelfarb is the Founding Director of the Kidney Research Institute and a Professor of Medicine and Adjunct Professor of Bioengineering and Pharmaceutics, as well as Co-Director of the Center for Dialysis Innovation at the University of Washington. Dr. Himmelfarb, it's great to have you with us as well.

Dr. Himmelfarb:
Thanks. It's a pleasure to be here.

Dr. Turck:
So let's just dive right in, starting with you, Dr. Neyra. Would you tell us about the role that emerging biomarkers play in stratifying a patient's risk of developing acute kidney injury?

Dr. Neyra:
When we talk about biomarkers of acute kidney injury, we can first picture a little bit of the timeline of acute kidney injury. So we want to have biomarkers that can help us identify patients at high risk before they are exposed to the stressors. We also want biomarkers that can help us identify early cellular stress or kidney injury before there is a clinically evident episode. And also, once the acute kidney injury occurs and is clinically evident, we want biomarkers that help us to prognosticate the progression of acute kidney injury into acute kidney disease. And also, we want to have long-term prognosis of kidney function in these patients. And not only kidney function, also the comorbidities associated with kidney disease like, very importantly, cardiovascular disease. So that's how we should frame the continuum of acute kidney injury, acute kidney disease, and sometimes, in some patients, risk of chronic kidney disease.

Dr. Turck:
And turning to you now, Dr. Himmelfarb, how can those biomarker test results guide next steps and help us make proactive treatment decisions?

Dr. Himmelfarb:
So what we're hoping is that by developing biomarkers that are more proximal to the injury process in the kidneys, they will point us towards what's causing the injury, what's the best therapeutic approach to attenuating or mitigating that injury, and how we can improve the outcomes for patients. So that's the promise of biomarkers in this field. And there's been a lot of work in this field and a lot of effort to perhaps replace the definitions we use today with biomarker-based definitions, which many studies show actually correlate better with clinical outcomes than the current definitions that we have for acute kidney injury. So that's one area where as time goes on, I think

we're going to see dramatic changes in clinical practice, where we'll be defining the incidence and prevalence of acute kidney injury by biomarkers as opposed to by simply a change in the serum creatinine.

Dr. Turck:
And Dr. Himmelfarb, what are some of the biomarkers that you think presently hold the most promise for optimizing our acute kidney injury risk assessments?

Dr. Himmelfarb:
That's a great question. It's a work in progress, but there are some, what I would call, prototypical biomarkers. One of the first to be developed is called the KIM-1, or kidney injury molecule-1. And as its name implies, it really measures tubular injury, so it's a nice measure of tubular injury. There's another called NGAL, which has also been time tested, which stands for neutrophil gelatinase-associated lipocalin. It reflects both injury in a different segment of the kidney, but also, to a certain degree, inflammation. And so those are very useful for assessing tubular injury. And they have been proposed as perhaps being part of the definition for acute kidney injury in the future, in addition to changes in serum creatinine and urine output.

There are other biomarkers that measure specific processes that are, again, mostly now in the research realm. There is a biomarker combination called TIMP2-IGFBP7 that we think measures cell cycle arrest, which is part of the process by which tubular cells that have been injured respond to injury, and that may turn out to be very useful. That one is commercially available right now.

And then there are some new biomarkers coming along. There's one called CCL14, which measures a particular chemokine that seems to be associated with really persistent severe injury that has a bad clinical outcome. So that may become a marker for clinicians that they really have to jump into action because the patient is not doing all that well.

And then there are other markers that are coming along that are not yet readily available that measure epidermal growth factor or uromodulin, which tend to reflect, as a whole, the state of tubular health and tubular function in the kidney.

So there are whole families of these, and there may one day be panels that combine these in a way that, again, identify specific phenotypes in terms of what's the nature of the injury and what should be the response from a therapeutic perspective. But that is very much still work in progress.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Javier Neyra and Jonathan Himmelfarb about integrating acute kidney injury risk assessments into our clinical workflows.

Now, Dr. Neyra, using biomarkers to optimize our risk assessments could play a critical role in managing our patients' risks of acute kidney injury. But what are some obstacles that keep us from integrating them into our workflows?

Dr. Neyra:
Where we have failed as a field is in testing with optimal and feasible tools, the implementation of these biomarkers. So when we should measure the biomarkers and what window of interventions we have to actionate that can either help us mitigate the risk or mitigate the progression of acute kidney injury if the exposures already occur. So I think that is a challenge.

And the challenge is, of course, these biomarkers are not widely utilized in our healthcare systems. So we don't have real-world data with these biomarkers to assess actionable interventions. Right? So a lot of these biomarker data come from specific research cohorts that have identified their utility in a specific subset of patients, for example, cardiac surgery patients, ICU patients, sometimes more heterogeneous patients where sepsis predominates. But in those studies, a lot of the time these biomarkers are measured with collections of a specific sample and a specific time point. And then sometimes that biases our ability to interpret their utility because we are creating different types of biases in this type of research.

I think what can move the field forward is developing real-world data with biomarkers that can be useful and complementary. And it doesn't need to be one or two biomarkers; it could be a panel of biomarkers that can phenotype either the level of stress, can differentiate certain etiologies of AKI, and can also identify different levels of risk according to the patient baseline characteristics and the concept of their renal reserve.

So I think if we combine all these aspects in a pragmatic way, we may be able to actionate in specific windows, where we can certainly impact the AKI continuum in these patients.

Dr. Turck:
Now before we close, I'd like to hear some best practices from each of you for assessing and managing the risk of acute kidney injury. Dr. Neyra, let's hear from you first.

Dr. Neyra:
My advice is don't be a skeptic about the utility of biomarkers; let's collectively work together into how to incorporate this additional information into our workflow. Because the field has significantly evolved in two aspects in acute kidney injury that I think are very state of the art in my view. One is the need to subphenotype acute kidney injury. And with this, we're talking about endophenotypes as well as incorporate the genetic predisposition of the patient and the phenotypic characteristics of the AKI to create a risk profile of acute kidney injury onset and also prognosis after it occurs. So I think this is a very exciting field because it does not only involve biomarkers that are currently in use or in research phase, but it also involves all the information of these patients in their clinical record and also environmental information in these patients like social determinants of health and different exposures they may have had during their life that can predispose their kidneys to respond differently to different levels of stress.

So when we talk about how we're going to treat AKI in the future, it's going to be hopefully more personalized by incorporating all these factors that can certainly affect the risk and response to AKI in the various heterogeneous patient populations that we serve.

Dr. Turck:
Thanks, Dr. Neyra. And Dr. Himmelfarb, I'll give you the final word.

Dr. Himmelfarb:
Well, I think the final word is that while the whole field of acute kidney injury biomarkers is in evolution, there is a lot that clinicians can do to recognize when acute kidney injury is present and to then implement conservative steps to do no harm and to minimize consequences from acute kidney injury. And I think it's important for clinicians to recognize that even small changes in the serum creatinine concentration can reflect large changes in how the kidney is functioning, especially when the serum creatinine is not in a steady state, but it's continuing to rise. And that has a big impact both on prognosis for the patient, but also in terms of how the kidney eliminates drugs and how drugs should be dosed in kidney disease.

And it's important for clinicians to recognize that with any increase in the serum creatinine, this is a sign to pay more attention because it has a large impact on prognosis. And it becomes very important to do everything you can to protect kidney function from further injury, whether that means avoiding the use of nephrotoxic drugs or dosing drugs effectively, maximizing renal blood flow through hemodynamic changes in patient care.

There are a lot of things that can be done in this setting now to impact patient outcomes with care and with really being conservative and trying to do no harm in that setting.

Dr. Turck:
Well, given the importance of timely intervention for our patients with acute kidney injury, I want to thank my guests, Drs. Javier Neyra and Jonathan Himmelfarb, for sharing their perspectives and incorporating related risk assessments into our clinical workflows. Dr. Neyra, Dr. Himmelfarb, it was great having you both on the program.

Dr. Himmelfarb:
Thank you very much. And I very much enjoyed this conversation.

Dr. Neyra:
Thank you very much. I really enjoyed the time here.

Announcer:
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