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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Acute Kidney Injury: Finding a Pathway to Improved Patient Outcomes

Announcer:
Welcome to CME on ReachMD.

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Here’s your host, Dr. Ravindra Mehta.

Dr. Mehta:
Acute kidney injury, or AKI, is a rapid reduction in kidney function that takes place over the course of hours or even days. AKI occurs in upwards of 15 percent of patients who are admitted to the hospital with rates of AKI, often surpassing 50 percent of patients receiving intensive care. This is CME on ReachMD, and I'm Dr. Avinder Mehta. Joining me to discuss acute kidney injury is Dr. Rajit Basu, Associate Professor of Pediatrics at Emory School of Medicine and - and the Research Director of the Division of Pediatric Critical Care Medicine at Children's Healthcare of Atlanta. Dr. Basu, welcome to the program.

Dr. Basu:
Thank you for having me, Dr. Mehta, it's wonderful to be here with you.

Dr. Mehta:
Why don't you start, Dr. Basu, by telling us what AKI is and what it is not.

Dr. Basu:
I think we have so much evidence now in anywhere from basic science models all the way up to the bedside, that acute kidney injury is not a simple process. We have a lot of evidence that there are multiple mechanisms involved, ranging from the cellular to the macroscopic in the animal and in the human model. We have a lot of evidence that clinical signs of AKI have a lot of different manifestations. What we understand now more than we did 10, 20 years ago is that there is a complete heterogeneity of the AKI process.

Dr. Mehta:
And I think the bigger aspect for us to recognize is that the heterogeneity is very different in the developing world versus the developed world. While the common pathway of having a declined kidney function occurs in both, the etiologies are quite different. So, for example, in the developing world, environmental factors such as malaria, diarrhea are much more prevalent, whereas in the developed world is trauma, sepsis are more common to contribute to the disease. So maybe I can ask you, given that we have this basic problem of acute kidney injury and it's and - and it's progression overall, what would be an approach for us to start tackling this problem?

Dr. Basu:
I think the first step is to simply appreciate that there are patients at risk. And the 0X25 initiative for global AKI recognition and awareness is founded on the principle of the five R’s. And those R’s are risk, recognition, response, renal support, and rehabilitation. So

the first R is risk recognition and I think more than anything else, what our data shows us now at the bedside is that we should and could and have the possibility of identifying the patients that are at highest risk. The previous paradigm has been that we take a very diverse, heterogeneous population of patients and seemingly look at them all the same. But we have the ability now to narrow that population so that our - our intuition or clinical sense of who's at real risk and who's not at risk is more refined.

Dr. Mehta:
So what are the risk factors for acute kidney injury that are now recognized?

Dr. Basu:
I think as you mentioned, it really depends on the patient and, you know, the - if you break it down very simply in terms of developed nations and developing nations, the primary risk for all patients is one of - one of similar, uh, background of shock or infection states. We know in children, even though co-morbidities are somewhat lessened or different than in adults; we don't have as many patients with diabetes or heart disease, we have plenty of children who have a history of oncologic process or cancer. Transplants - we have plenty of kids who have overwhelming systemic infections that lead to other organ dysfunction.

Dr. Mehta:
Yeah, I think that in the adult world, one of the key factors comes in is the underlying co-morbidities. Uh, chronic kidney disease, heart failure, diabetes become key areas which are of concern and add in the risk. The other aspect we found with 0X25 was that dehydration and hypotension were common factors across the world. It didn't matter whether they were in the developed or the developing part of the world. So those become a key part. I guess the question then becomes is, given our current diagnostic criteria of creatinine changes and urine output, how do those play into us understanding the recognition of the disease, given that you could identify people who might be at higher risk?

Dr. Basu:
I think the issue with creatinine and urine output is that they are the absolute necessary foundations of how we understand kidney injury. I think creatinine and urine output are functional markers of what's happening in the kidney, but they are relatively generic. So in my sense, the way we are approaching this both in kids and adults, is the idea that we use creatine and urine output as the baseline. And we have new novel diagnostics that we use together with them, because I believe that the way forward in addressing the diagnostic paradigm is to start with creatinine and urine output and build upon them and become more precise in our understanding of AKI. As you are a part of the Acute Disease Quality Initiative in 2011 that talked about this idea of using creatinine and urine output together with other things, maybe you can address that.

Dr. Mehta:
As we have moved forward over the last 8 to 10 years is the recognition that there are different biomarkers which might be available to us. But if you think about them in terms of there's a group of biomarkers which reflect kidney damage and there's a group of biomarkers that affect kidney function, not too different from, say, the heart, where in the heart you have ejection fraction or a cardiac echo telling you the function of the heart and you have troponin or CPK as a biomarker telling you what's happening to the - to the damaged segments of the heart. And by combining them, you have a better profile. So to that point, I think what I'd like to ask you is there's this - over the last few years, there has been this concept which is emerging of acute kidney stress. And how- how do you envision that?

Dr. Basu:
To me, this - this concept of stress is no different than the way our whole body functions in individual organs. As an intensivist, one thing I'm always thinking about is this system of shock. And shock is really a supply-demand problem of oxygen balance.. So this idea of kidney stress is that same concept, that there is a supply-demand phenomenon. There's a biology that's happening in the kidney that is actually damage. That is actually this idea that the - the kidney is demanding more than is – than the supply is - is available to it. And so this idea of acute kidney stress is simply a - a parallel to the other organ systems that we have a more developed understanding at this point. And potentially what we're able to do is identify that that demand is greater than the supply phenomenon happening in the kidney.

Dr. Mehta:
You know, I think that's an excellent point. And I think just to re-emphasize that, is I - I think that we - we have always felt that we could rely on one set of tools. But it appears to me that now with the appearance of a variety of different biomarkers, we can actually start looking at our patient profiles in much more systematic and definitive way. So maybe you could tell us about the portfolio biomarkers which have emerged and what has been the data and evidence to their utilization so far.

Dr. Basu:
The - the biggest, let's say, the most prominent biomarkers that are coming out are a collection of damaged biomarkers that are specific to the tubular epithelium in the kidney. The biomarkers such as NGAL and IL18 and KIM-1 and L-FABP, mechanistic biomarkers like the cell cycle arrest biomarkers, TIMP-2 and IGFBP7. There are other interstitial biomarkers that are in NAG and pi-GST, and these markers

that tell us not only the mechanistics of what's happening, but also the location within the kidney.

And I think that the strongest evidence comes from the idea that we can use biomarkers to do a form of population enrichment. So there have been a series of studies now looking at the TIMP-2, IGFBP7 marker where patients after cardiac surgery or general surgery are tested in this way for the biomarker. And if that level is above a certain threshold, they are enrolled in a - in a series of kind of supportive care measures. Nothing out of the ordinary, nothing that we wouldn't say that we're doing. But the data show us that those patients that have this marker that's elevated, theoretically telling us that the demand is greater than the supply in that kidney. And they're systematically checklist driven toward the supportive care measures. We do a prognostic enrichment using kind of a biomarker-driven phenomenon. We also have evidence that in preliminary study in kids, we can take patients that are identified by a risk prodrome that we call renal angina, and they get tested for a damage biomarker. And those patients that are positive for renal angina and have a positive biomarker in that sense for a positive damage biomarker, they do better when they get early initiation of fluid management such as continuous renal - renal replacement therapy. So in a sense, what we're seeing now is rather than have a blanket approach to all patients with “AKI,” we potentially have a more refined approach to understanding, well, this is damage associated AKI.

Dr. Mehta:
That's - that's a - that's a fascinating area. And I think it would you - would you to think that these biomarkers have also a prognostic ability?

Dr. Basu:
To me, it is one of those that there are - the biomarkers don't predict anything. The biomarkers identified the damage that we previously were not able to recognize.

Dr. Mehta:
And so I think the question becomes is what is the biomarker being utilized for? Is it to - to recognize that a disease process has occurred? To define what the course of the disease is going to be? Define the intervention points? Or to suggest what the prognostic – prognosis is going to be?

Dr. Mehta:
I think that, uh, for those of you just tuning in, you're listening to CME from ReachMD. I’m Dr. Avinder Mehta, and I’m speaking to Dr. Rajit Basu about acute kidney injury. So, Dr. Basu, if you go back to the idea of identifying AKI early on the biomarkers with these specific ones, TIMP-2 and IGF binding protein, where do you see their future?

Dr. Basu:
I think they're part of the story. We have early evidence that I had mentioned earlier of the importance of using biomarkers such TIMP-2 and IGFBP7 to narrow down those populations at risk.

Dr. Mehta:
And I think to add, just to emphasize one other point that you - you were mentioning is essentially if you have a high-risk population, you add a biomarker and you identify the course of disease, which is early enough that it might lend itself to an intervention to prevent all the downstream things happening.
Could you comment on - I know that in the pediatric world, a lot of emphasis has been on electronic alerting and the NINJA project in terms of drug nephrotoxicity.

Dr. Basu:
So NINJA is nephrotoxic injury negated by just-in-time action. It's a - it's a very simple premise with the idea that you utilize the electronic medical record to identify patients that are exposed to nephrotoxins. And in that system, the compounding pharmacist or the team member, uh, is alerted that the patient's at risk for nephrotoxin associated AKI. So at certain centers now, a urine panel will be sent for a urine damage biomarker to assess what degree of AKI do we have with the creatinine that's changing. And I would actually ask you, Dr. Mehta, in the global sense in the world as we talk about the developing nations, uh, and the signal that's coming from there, what are the points of intervention that are possible in that in the rest of the world, really?

Dr. Mehta:
I think our - our study, which we did with the 0X25, which we did in Bolivia, , and Nepal, we actually took the point of care creatinine to a health care centers out in the community where there were no doctors and with a urine dipstick. So just with a combination of a point of care creatinine urine dipstick, we were able to identify patients at high risk for acute kidney injury, and then those who actually develop acute kidney injury.

Dr. Basu:
So what I hear you saying is there's still a role for creatinine and urine output.

Dr. Mehta:
And I think absolutely. I think that creatinine and urine output are going to be the basis against which we judge and actually combine other biomarkers. I don't think that they can be - they are going to go away in any way. On the contrary, I would take them as being very informative. Maybe not as early as some of the other biomarkers, but they are certainly going to be of great utility as we go forward.

Dr. Mehta:
Well, as this has been a very valuable discussion.

Dr. Basu:
I think it's a very exciting time for acute kidney injury.

Dr. Mehta:
Dr. Basu, it was great speaking with you today.

Dr. Basu:
It was wonderful to be here. Dr. Mehta, thank you for having me.

Announcer:
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