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Acute Kidney Injury in Sepsis and How We Can Predict It

Announcer:
Welcome to ReachMD.

This medical industry feature, titled “Acute Kidney Injury in Sepsis and How We Can Predict It,” is sponsored by bioMérieux, Inc.

Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I’m your host Dr. Jennifer Caudle. And joining me today to discuss how we can respond earlier to acute kidney injury, or AKI, in sepsis—potentially before it even occurs—are Dr. Devendra Amin and Dr. John Ofenloch. Dr. Amin is Medical Director of Critical Care Services at Morton Plant Hospital in Clearwater, Florida. Dr. Amin, welcome to the program.

Dr. Amin:
Thanks for having me.

Dr. Caudle:
And Dr. Ofenloch is a cardiothoracic surgeon at the Center for Advanced Structural Heart and Valve Care at Morton Plant Hospital in Clearwater, Florida. Dr. Ofenloch, thank you for joining us today.

Dr. Ofenloch:
It’s great to be here.

Dr. Caudle:
So let’s look at the big picture, Dr. Amin. Just how big of a problem are sepsis and AKI in the emergency department, or ED, and inpatient settings?

Dr. Amin:
So sepsis and AKI, both together and individually, have a huge impact on patient outcomes. AKI affects 3.2 million hospitalized patients a year, [1] and it tops the list of clinically addressable potential inpatient complications. [2]

Globally, about two million patients die as a result of AKI annually.[3] In fact, patients with AKI in the U.S. have a six to 13 times the risk of in-hospital mortality.[4]

Looking at the data from one European study, close to a quarter of patients with AKI end up needing renal replacement therapy, representing a significant health burden to both the patient and the overall health system.[5] In addition AKI costs the U.S. healthcare system between five and 24 billion dollars a year.[6]

When it comes to sepsis, the numbers are just as stark. Patients with sepsis account for 16 percent of those who die during an inpatient stay, and patients who develop sepsis are over eight times more likely to die as compared to those without it.[7]

I should also point out the connection between these two health threats as sepsis is a risk factor for AKI.[8-12] Data from a multicenter study in Australia showed that 42 percent of critically ill patients with sepsis develop AKI.[13]

One study conducted in a Belgian surgical ICU found that patients with both AKI and sepsis had double the in-hospital mortality rate, at 57 percent, compared to 28 percent for patients who had sepsis but no AKI.[14]

Dr. Caudle:
And turning to you now, Dr. Ofenloch, what are some of the gaps associated with how we conventionally track and diagnose AKI?

Dr. Ofenloch:
That's a really important question, Dr. Caudle, because failing to diagnose AKI in a timely manner can lead to irreversible kidney damage,[15] which can then both complicate a patient's clinical course during their immediate stay, and then go on to follow them for the rest of their life. But despite the urgent attention AKI demands, we're continuously falling short in our identification of it.

By some estimates, close to half of patients who die from hospital-acquired AKI have inadequate risk assessments performed and experience unacceptable delays in diagnosis.[12,16-18] Even worse, up to 79 percent of patients with moderate or severe AKI, in other words, those who need early intervention the most, are not identified in a timely manner.[19]

And so we need to get as good at managing AKI as we are at taking care of myocardial infarction, or MI. Because as research suggests, AKI is about twice as deadly. Just to illustrate the difference in outcomes, there's one study that followed over 73,000 U.S. veterans who had a hospital admission for AKI or MI over the course of several years.[20] At the one-year mark, it found that patients with a primary discharge diagnosis of MI had a 14 percent lower chance of survival, but those with AKI had a 30 percent lower likelihood of survival.[20] And even in my own experience, we've gotten really good at managing MI, in no small part with guidance from early markers of injury. And so, it would be great if we could do the same with AKI.

The way many of us have been taught and continue to practice is by using changes in serum creatinine, glomerular filtration rate, creatinine clearance, and urine output to alert us to kidney injury. And it's true, they do just that. The problem is that these functional biomarkers are lagging indicators that are non-diagnostic in value until two to three days after AKI begins. So, they don't clue us into the problem until after damage has already begun to occur.[9,21]

Dr. Caudle:
So then it seems that the way we currently approach AKI leaves something to be desired. From your vantage point, Dr. Ofenloch, are there any ways we could work to close these gaps?

Dr. Ofenloch:
Yes, there are. Two biomarkers have been identified that the kidney begins to express as soon as it starts to undergo duress—and this is important to note here—*before* damage occurs. These are tissue inhibitor of metalloproteinase-2, or TIMP-2, and insulin-like growth factor binding protein-7, or IGFBP-7. They both promote the arrest of cellular division in the G1 step of the cell cycle.[17,22]

The thought is that by inhibiting cellular division of those renal tubular cells with DNA damage until the damage can be repaired, the biomarkers prevent the creation of new cells that already have DNA damage and are more likely to die. In two observational clinical trials that looked at over 300 potential biomarkers in 1,200 critically ill patients, including those with sepsis, two biomarkers stood out.[17,22]

That's why TIMP-2 and IGFBP-7 have been incorporated into the VIDAS® NEPHROCHECK® assay, which is an FDA cleared risk assessment test for critically ill patients aged 21 years and older who have acute cardiovascular or respiratory compromise.[17] The two biomarkers are assessed from a urine sample and sent to the lab within 24 hours of suspected compromise following a cardiovascular or respiratory event, and their concentrations are used to calculate what's called an AKIRISK™ Score. With a score above 0.3, the test identifies patients who are at increased risk of developing moderate to severe AKI in the next 12 hours with a sensitivity of over 82 percent.[17]

It has a negative predictive value of over 88 percent, meaning that those who test negative likely will not develop AKI in the next 12 hours. And importantly, it's not elevated for chronic kidney disease unless there's an acute-on-chronic injury. Similarly, it's not elevated in acute non-AKI conditions.[17] So what this has the potential to do is enable early triage and AKI risk stratification in a wide range of critically ill patients.[23]

Dr. Caudle:
And before we move on, let's take a moment to review some Important Safety Information on the VIDAS® NEPHROCHECK® assay.

Announcer:
VIDAS® NEPHROCHECK® is an automated test for use on the VIDAS 3 instrument for the immunoenzymatic quantitative determination of Tissue Inhibitor Metalloproteinase-2, or TIMP-2, and Insulin-like Growth Factor-Binding Protein 7, or IGFBP-7, proteins in human urine using the Enzyme Linked Fluorescent Assay, ELFA, technique for calculation of the AKIRISK Score.[17]

The VIDAS® NEPHROCHECK® assay is intended to be used in conjunction with clinical evaluation in patients who currently have or have had within the past 24 hours acute cardiovascular and or respiratory compromise and are ICU patients as an aid in the risk assessment for moderate or severe acute kidney injury within 12 hours of patient assessment. The VIDAS® NEPHROCHECK® test is intended to be used in patients 21 years of age or older.[17]

Dr. Caudle:
For those just tuning in, you're listening to ReachMD. I'm Dr. Jennifer Caudle, and today I'm speaking with Dr. Devendra Amin and Dr. John Ofenloch about how we can detect acute kidney injury, or AKI, earlier in sepsis.

So turning back to you, Dr. Amin, what are some ways we could practically implement the VIDAS NEPHROCHECK test when caring for a patient with a change in renal function?

Dr. Amin:
Well, probably the best way I could think of to address that question would be with hypothetical patient cases.

Let's start with an example of a typical post-operative cardiothoracic surgical patient. The patient is a 74-year-old female with severe aortic stenosis, aortic incompetence, and mitral regurgitation with a well-maintained ejection fraction of 55 to 60 percent. Her baseline creatinine is 0.9 milligrams per deciliter. She undergoes aortic valve replacement. The patient's renal stresses during the surgery are from the anesthesia, pump time, hypotension, and atrial fibrillation which complicates the post-op course.

Her immediate post-op creatinine is within the normal range at 1 milligram per deciliter. But, if we look at the signal from the VIDAS NEPHROCHECK, her AKIRISK score is already elevated at one signaling renal stress. So, our standard procedure is to give fluids to improve renal function.

By day two post-op, the patient's creatinine has gone up to 1.3 milligrams per deciliter, and there is a noted weight gain of 8 kg. Even though her creatinine is still within normal range, it is up from up to 1.3 from a baseline of 0.9 and meets the criteria for acute renal injury. So, the algorithm at that point is to give fluids and maintain intravascular volume and a reasonable mean arterial pressure. The patient was reassessed with VIDAS NEPHROCHECK and her AKIRISK Score had increased to 3.5. Given these findings, we would hold off on diuresing the patient to prevent further stressing the kidneys even though there's significant weight gain and oxygen requirement. As a result, the patient's oxygen requirement peaks on the second post-op day, going up to eight liters per minute high flow oxygen.

By the following morning, the patient's creatinine level comes down. But more importantly, she was reassessed with the VIDAS NEPHROCHECK and her AKIRISK score came back down to just over one. The patient is still at risk of developing AKI, however, because of significant fluid weight gain, we decide to start diuresing. And as diuresis kicks in over the next two or three days, oxygen requirement comes down.

As you can see for this post-cardiothoracic surgical patient, assessing for AKIRISK Score helped us support this patient's recovery without further injury to the kidneys. With only a creatinine measurement, this patient might have had diuresis during a time of kidney stress.

Dr. Caudle:
Wonderful insight, Dr. Amin. Now, could you provide us with an example involving the application of the VIDAS NEPHROCHECK for a septic patient?

Dr. Amin:
Absolutely. So here, we have a patient, a 68-year-old female who was diagnosed with colorectal cancer a year ago and has a past medical history significant for COPD. At baseline, her serum creatinine is 0.4 milligrams per deciliter. She undergoes abdominoperineal resection, and on post-op day two in the ICU, she develops sepsis and respiratory distress that requires intubation. Her creatinine inches up slightly, and she's placed on empiric antibiotic therapy with aztreonam, metronidazole, and vancomycin.

By post-op day four, she's on pressors to maintain a systolic blood pressure above 100 millimeters of mercury; her serum creatinine has jumped half a point above baseline; and her urine output has fallen to 30 milliliters per hour. The ICU team responds with a number of nephroprotective measures, but at this point, she's already developed AKI.

So the question is, could anything be done differently to mitigate the real injury?

Let's say the team had run the VIDAS NEPHROCHECK test within 24 hours of the patient's respiratory compromise and had an AKIRISK score of 3.4. At that point, they would have had a head-start on interventions such as:[24]

- discontinuing nephrotoxic medications like non-steroidal anti-inflammatory drugs, and
- considering a change in antimicrobial therapy, such as prospectively adjusting the vancomycin dose based on blood levels, or switching to a less nephrotoxic agent, as well as
- potentially getting a nephrology consult.

In critically ill patients, it's also important to pay careful attention to, and avoid when possible, hypotension, with an early goal-directed approach to fluid and diuretic management using dynamic parameters such as straight leg raise, or change in stroke volume index with a volume bolus.[24] That kind of course correction early on can avoid costly complications.[8,25]

On the other hand, let's say an alternate scenario, where the patient's AKIRISK score on day two was in the normal range at 0.1 and they determined that they can continue with normal management . As a result, her treatment course might have been fast-tracked. Her test result could even factor into whether she's appropriate for transfer to a stepdown unit or the floor.

Dr. Caudle:
Thank you for walking us through those patient cases, Dr. Amin. Now we're just about out of time for today, so to bring this all home before we come to a close, I'd like to get some final thoughts from each of you about the early detection of AKI in patients with sepsis. Dr. Amin, what key takeaways would you like to leave with our audience?

Dr. Amin:
I'd like to remind our audience that urinary concentrations of TIMP-2 and IGFBP7 correlate with the risk of AKI, and they serve as early alarms to get the sense of where the patient's kidneys are heading.[23] They've been incorporated into a diagnostic test that has been validated in critically ill patients with acute cardiovascular or respiratory compromise, including those with sepsis.[17]

Dr. Caudle:
Thank you for sharing, Dr. Amin. And you get the final word, Dr. Ofenloch.

Dr. Ofenloch:
I agree with what Dr. Amin said, and I think it's just worth reiterating a point that deserves special emphasis. Some clinicians out there might reasonably be asking, "Is this really going to make a difference when I already change my patients' treatment courses immediately as soon as I see bumps in serum creatinine or drops in urine output?" And that's a fair question.

But I'd argue that we can't predict the severity of kidney injury when we see these initial changes in serum creatinine, for example, and so it's unclear which interventions are necessary and impactful at this stage.

Responding to serum creatinine, glomerular filtration rate, creatinine clearance, and urine output is the standard of care. So I'd respond with another question, "What impact might we have on a patient's life if we employed the same interventions, except days earlier? What if we had taken *pro*active measures rather than *re*act after we're already behind the eight-ball and kidney damage that could possibly be permanent has already been going on for several hours or days?"

The VIDAS NEPHROCHECK assay gives us that opportunity by identifying patients who are at increased risk of developing moderate to severe AKI in the next 12 hours.[17] That could give us the chance to adopt kidney-sparing strategies early and mitigate the worst effects of AKI—if not avoid it entirely—as we continue to monitor test results until the biomarkers decline.

Dr. Caudle:
Those are some compelling considerations and a great way to round out our discussion on responding earlier to AKI in sepsis. And I'd like to thank my guests, Dr. Devendra Amin and Dr. John Ofenloch, for sharing their insights with us.

Dr. Amin and Dr. Ofenloch, it was great speaking with you both today.

Dr. Amin:
Thank you for the opportunity, Dr. Caudle.

Dr. Ofenloch:
Thank you for having me today.

Dr. Caudle:
For ReachMD, I'm Dr. Jennifer Caudle. Please stay tuned to hear some additional Important Safety Information.

Announcer:
IMPORTANT INFORMATION

This medical industry feature was sponsored by bioMérieux, Inc. If you missed any part of this discussion, visit ReachMD.com, where you can Be Part of the Knowledge.

References:

1. Brown JR, Rezaee ME, Marshall EJ, Matheny ME. Hospital mortality in the United States following acute kidney injury. *BioMed Res Int*. 2016;2016:1-6. doi:10.1155/2016/4278579
2. Premier, Inc. Identifying hospital-wide harm associated with increased cost, length of stay and mortality in U.S. hospitals. *Complications Research*. Accessed July 24, 2020. http://ftpcontent4.worldnow.com/wtoc/web/Complications-Whitepaper-6-11-14.pdf
3. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: An integrated clinical syndrome. *Kidney Int*. 2012;82(5):516-524. doi:10.1038/ki.2012.208
4. Dasta JF, Kane-Gill SL, Durtschi AJ, et al. Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. *Nephrol Dial Transplant*. 2008;23(6):1970-1974. doi:10.1093/ndt/gfm908
5. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. *Intensive Care Med*. 2015;41(8):1411-1423. doi:10.1007/s00134-015-3934-7
6. Silver SA, Long J, Zheng Y, Chertow GM. Cost of acute kidney injury in hospitalized patients. *J Hosp Med*. 2017;12(2):70-76. doi:10.12788/jhm.2683
7. Elixhauser A, Friedman B, Stranges E. Statistical brief #122: Septicemia in U.S. hospitals, 2009. In:*Healthcare Cost and Utilization Project (HCUP) Statistical Briefs*. Agency for Healthcare Research and Quality; October 2011. Accessed January 25, 2024. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb122.pdf
8. Kidney Disease: Improving Global Outcomes (KDIGO). Clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2(1):1-138. doi:10.1038/kisup.2012.7
9. Mehta RL, Pascual MT, Soroko S, et al. Spectrum of acute renal failure in the intensive care unit: The PICARD experience. *Kidney Int*. 2004;66(4):1613-1621. doi:10.1111/j.1523-1755.2004.00927.x
10. Murugan R, Karajala-Subramanyam V, Lee M, et al. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. *Kidney Int*. 2010;77(6):527-535. doi:10.1038/ki.2009.502
11. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients. A multinational, multicenter study. *JAMA*. 2005;294(7):813-818. doi:10.1001/jama.294.7.813
12. Stewart J, Findlay G, Smith N, et al; National Confidential Enquiries into Patient Outcome and Death (NCEPOD). Adding insult to injury: A review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury. NCEPOD; 2009. Accessed January 26, 2024. https://www.ncepod.org.uk/2009report1/Downloads/AKI_report.pdf
13. Bagshaw SM, George C, Bellomo R. Early acute kidney injury and sepsis: A multicentre evaluation. *Crit Care*. 2008;12(2):R47. doi:10.1186/cc6863
14. Hoste EA, Lameire NH, Vanholder RC, et al. Acute renal failure in patients with sepsis in a surgical ICU: Predictive factors, incidence, comorbidity, and outcome. *J Am Soc Nephrol*. 2003;14(4):1022-1030. doi:10.1097/01.asn.0000059863.48590.e9
15. Lewington AJP, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: A global perspective of a silent killer. *Kidney Int*. 2013;84(3):457-467. doi:10.1038/ki.2013.153
16. Ronco C, Ricci Z. The concept of risk and the value of novel markers of acute kidney injury. *Crit Care*. 2013;17(1):117. doi:10.1186/cc12488
17. VIDAS® NEPHROCHECK® [TIMP-2 • IGFBP-7] Test Kit Package Insert US - 057209 - 01 - 2022-07. bioMérieux; 2022.

18. Meersch M, Volmering S, Zarbock A. Prevention of acute kidney injury. *Best Pract Res Clin Anaesthesiol*. 2017;31(3):361-370. doi:https://doi.org/10.1016/j.bpa.2017.08.002
19. Massicote-Azarniouch D, Magder S, Goldberg P, Alam A. AKI in the ICU: Risk factors and outcomes of physician recognition compared with KDIGO. *Crit Care Med*. 2015;43(12):245. Published Dec 2015. doi:10.1097/01.ccm.0000474802.32862.df
20. Chawla LS, Amdur RL, Shaw AD, et al. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin J Am Soc Nephrol*. 2014;9(3):448-456. doi:10.2215/cjn.02440213
21. Mårtensson J, Martling CR, Bell M. Novel biomarkers of acute kidney injury and failure: Clinical applicability. *Br J Anaesth*. 2012;109(6):843-850. doi:10.1093/bja/aes357
22. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17(1):R25. doi:10.1186/cc12503
23. Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: The light and the dark sides. *Nephrol Dial Transplant*. 2016;31(1):16-22. doi:10.1093/ndt/gfv130
24. Guzzi LM, Bergler T, Binnall B, et al. Clinical use of [TIMP-2]•[IGFBP7] biomarker testing to assess risk of acute kidney injury in critical care: Guidance from an expert panel. *Crit Care*. 2019;23:225. doi:10.1186/s13054-019-2504-8
25. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, et al. Cost and mortality associated with postoperative acute kidney injury. *Ann Surg*. 2015;261(6):1207-1214. doi:10.1097/sla.0000000000000732