NIDDK VIRTUAL ACUTE KIDNEY INJURY TOWN HALL MEETING

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) hosted an Acute Kidney Injury (AKI) Town Hall Meeting to discuss strategies for the treatment and management of COVID-19 patients with kidney disease, especially those who develop AKI. NIDDK is interested in understanding the pathophysiology of COVID-19-related AKI, improving the care of patients, and identifying potential treatments that are ready to be tested in these patients. The virtual town hall, conducted via Zoom, had 108 attendees.

Summary

Dr. Ivonne Schulman described the current reports on COVID-19 patients with AKI, which had prompted this meeting. Physicians and health professionals observed that COVID-19 is causing a quite unusual form of AKI. The range of AKI incidence in patients with COVID-19 has been reported to be as low as 0.5% in hospitalized patients to as high as 23% in intensive care unit (ICU) patients. AKI was reported to develop at a median of 15 days in one study; another study reported that most AKI developed within 7 days of admission. The data on AKI in COVID-19 patients is limited to patients who are hospitalized and, in some studies, to critically ill patients in the ICU.

The purpose of the town hall meeting was to bring the research community together to design and execute meaningful studies and to enable new collaborations. Although NIDDK has not been given any special funds for COVID-19, this town hall meeting will serve as a catalyst for future research initiatives in other NIH funding opportunities. During this meeting, NIDDK and attendees explored the current challenges with COVID-19-associated AKI incidence, discussed information about what is known and unknown, detailed risks factors, and described how to obtain data that is needed to properly plan a clinical trial and any research proposals to treat COVID-19 in patients with kidney diseases.

The attendees discussed the variability of COVID-19 presentation and outcomes in their patients. Each site provided an estimated number of COVID-19 confirmed cases and patients with AKI. In addition, some sites reported on deaths, ICU admissions, and whether their AKI patients with COVID-19 exhibited some differences or no differences from other AKI patients. Other sites reported that their AKI patients are experiencing hypercoagulability, which has been addressed based on patient history and illness. Participants encouraged all sites to observe and track clotting complications.

Finally, the attendees discussed innovative proposals to address COVID-19, including a major nationwide epidemiological study to collect detailed clinical data on ICU patients with or without end-stage renal disease or AKI. Additionally, the attendees held a chat room discussion about various challenges, questions about COVID-19 in AKI patients, experiences using citrate for continuous renal replacement, COVID-19 mechanistic pathways, biospecimen collections, right ventricular function, troponin levels, equipment shortages, learning opportunities from Wuhan, and future directions.

Dr. Robert Star announced general guidance and resources from the National Institutes of Health and the U.S. Food and Drug Administration. There will be funding opportunities for research at the National Institute of Allergy and Infectious Diseases (NIAID) (infection, viral transmission), the National Center for Advancing Translational Sciences (screening platforms), National Primate Research Center, and the National Institute of Biomedical Imaging and Bioengineering (assay development). Dr. Tracy Rankin announced specific COVID-19 funding opportunities at NIAID, the National Institute of General Medical Sciences, the National Heart, Lung, and Blood Institute, and the National Institute on Drug Abuse. Dr. Danny Gossett announced small business funding opportunities conducting research in commercialization of new drugs and diagnostics that are relevant to COVID-19. The Biomedical Advanced Research and Development Authority (BARDA) issued a Broad Agency Announcement that it is accepting only submissions related to COVID-19 (see slide for specifics).

NIDDK is encouraging future virtual forums. Those who would like to lead a discussion in the future should contact Dr. Schulman.

Topics Discussed

1. The NIAID trial is designed very well. It is a design that allows local standard of care. (Participant prefers not to use anti-IL-6.) Patients can be on observational studies but not on other interventional trials. There is much discussion on gaps and what to be added in the trial.
2. This disease does not affect children. How does ACE2 express in children versus adults?
3. Is anyone researching viral shedding in the urine?
4. There is a lot of hypercoagulability, and patients on continuous renal replacement therapy (CRRT) experience blood clots rapidly, and D-dimer levels are above 100,000. There is a strong correlation with mortality. Has anyone seen vascular/coagulopathy involvement in these cases?
5. Early outcomes: Has anyone seen anyone stop dialysis and survive? *No.*
6. What would be some good measures for more detailed phenotyping?
7. The ACE2 receptor has a lot of bulky amino acids (none in binding site) but could be titrated by changing pH (impractical for blood). Could alkalinizing the urine change the way in which the receptor allows the virus to enter? It probably is impractical if we cannot change the pH in the urine.
8. In Boston: Launch an open-label treatment protocol with high dose vitamin B3. The idea is to be able to try something that is safe, has a good clinical track record, is already on formulary, can be started quickly, and can be prescribed without blocking patients in other trials. In addition to participating in observation studies, there is progress in Institutional Review Boards (IRBs) to get approval for this as a quality improvement project. The name of the project is STOP COVID: Study of Treatment and Outcomes in Critically Ill Patients with COVID. The project is mostly nephrologists who are collaborating with critical care departments at their institutions. They are using REDCap that they are finalizing and detailed clinical data including AKI.

9. Virus gets through the kidney by filtration.
10. Regarding using stem cells: When investigators gave an intravenous infusion, the stem cells were getting stuck in the lung. We could repurpose this and observe the side effects.
11. Launching global snapshot point prevalence study, which can capture important information and enhance other projects on long-term follow up. There is opportunity for collaboration and to get a clear clinical picture. Knowing how the process of care is being done and gathering the information systematically would be helpful.
12. Is there any interest in molecules? Drug targets? Multiple targets? *The mouse models are showing promise. Will share some data set in the future.*
13. What is the current availability of pathology specimens? Can the examination be centralized? *Yes, examinations are being centralized at NIH Department of Pathology.*

Chat Comments

Participant 1: I am at Children's Hospital of Philadelphia. We have only had one child requiring ICU-level of care, no AKI. Single organ failure (respiratory). A handful of others admitted to the general floor; not sure of presence of AKI in that group.

Participant 2: At Kidney International, we have been receiving a lot of data from the Chinese experience. While we are publishing a paper showing a high incidence of AKI from one of the Wuhan systems, there have been several other papers showing a much lower incidence of AKI. So, there is a lot of variability, and at this point I cannot determine the characteristics of patients who develop AKI.

Participant 3: We are seeing a lot of clotting of our filters, as well requiring increasing citrate use.

Participant 4: Anybody have echo data on AKI patients? There is likely right ventricular failure (due to Pulmonary HTN type 3), which could increase risk for kidney failure.

Participant 5: Is the virus found in urine prior to AKI and the development of tubular necrosis?

Participant 6: Reports from China suggest proteinuria and hematuria are common, at least in admitted patients. How do these relate to the AKI seen? Do these urine findings precede AKI?

Participant 7: Is AKI occurring in the context of hemodynamic instability?

Participant 8: Presence of virus in urine has not been definitively demonstrated. This is the largest study I found—no virus in urine. jamanetwork.com/journals/jama/fullarticle/2762997

Participant 7: Given that ACE2 is highly expressed in the proximal tubule, is anyone seeing proximal tubular dysfunction like phosphate wasting/II RTA?

Participant 3: We are using citrate for CRRT.

Participant 9: We are also using citrate.

Participant 10: While ACE2 is highly expressed in proximal tubule, in mice kidneys TMPRSS2 is mainly expressed in distal tubules. Are there any different mechanisms for the virus to enter the renal tubules?

Participant 10: Reports from Italy suggest clotting, not clogging. Also, the D-dimers would suggest thrombosis.

Participant 11: Some MERS publications suggest that the coronavirus that causes MERS does directly enter renal tubule cells via DPP4.

Participant 12: At sites that don't have enough CRRT machines and are doing accelerated "AVVH" for 8-12h per day at high flow rates, citrate would be challenging, no?

Participant 8: This preprint suggests proximal tubules and podocytes express both ACE2 and TMPRSS. Thus, virus could enter tubular cells. www.preprints.org/manuscript/202002.0331/v1

Participant 13: We made some interesting observations with a polyphenol, Urolithin A in rat and mouse models of AKI and CKD. We are currently analyzing RNA-Seq data in a CKD model of autoimmune disease.

Participant 13: In continuation, we formulated Urolithin A to improve oral bioavailability in canine model, the idea is to test in canine model of AKI.

Participant 14: It seems like one unmet need is characterization of COVID-AKI. Particularly urine markers of proximal tubule function like phosphorus, I am wondering about urine measurements of megalin and endogenous lithium clearance as clinical correlates. Traditional urine biomarkers may also be helpful. This data and time course seem important to designing a trial.

Participant 10: IL-6 NOT that impressive—much lower than bacterial sepsis.

Participant 14: I agree with Participant 10 regarding the IL-6 levels.

Participant 15: Are we allowed to spin urine without BSL-2 precaution?

Participant 15: Does absence or low IL-6 levels in urine argue against a cytokine storm as the pathogenesis of AKI?

Participant 10: Lowish IL-6 also fits with low levels of shock and MSOF. HOWEVER, some patients do seem to have more aggressive disease. Is it macrophage activation syndrome (MAS)? Is it glomerular?

Participant 12: The NHLBI PETAL Network is launching a biobanking study but I'm not sure about urine.

Participant 11: Do we know if viremia is closely associated with severity?

Participant 12: I am in PETAL and have asked to collect urine. Probably only from most severe patients.

Participant 16: We have an IRB approved to collect urine at UCSD. Any other recommendations regarding sample collection and storage?

Participant 17: Is there interest in expanding the Remdesivir trial to patients with eGFR < 50 mL/min/m^2?

Participant 18: To Participant 10 comment: Normalizing blood pH may decrease pulmonary vasoconstriction induced by hypoxemia and thus mitigate right ventricular (RV) failure and risk of AKI. Regardless, if this becomes a protocol, we should keep an eye on RV function and troponin levels.

Participant 12: You could alkalinize the urine with a drug like acetazolamide and thereby not have a major effect on blood pH.

Participant 18: Acidifying blood could be detrimental to pulmonary pressure, though.

Participant 19: With regard to chloroquine use: I do not know if I want to inhibit autophagy once the patients have multiorgan failure, but perhaps in non-sick patients it would kill the virus.

Participant 10: There are several approaches to alkalinize the urine without risking arterial acidosis—including sodium bicarbonate.

Participant 20: Is there a need to collect samples and clinical information and create a registry for AKI-COVID to perform enhanced clinical phenotyping and have samples for testing?

Participant 18: What I meant was that bicarbonate could be beneficial from other aspects.

Participant 21: Re: the alkalinizing the urine to prevent viral entry, are the receptors on the luminal side or basolateral?

Participant 18: While on acidemic patients acetazolamide may not be appropriate.

Participant 22: Agree, when it gets to the stage of AKI, there is a concern that chloroquine would block the protective response of kidney tubule cells of autophagy.

Participant 18: University of Minnesota has a hydroxychloroquine randomized clinical trial for prophylaxis of COVID-19 on those who were exposed.

Participant 17: We already have a kidney disease registry established to collect reliable curated EHR data across the Providence Healthcare system that covers five Western states, including Washington and California. We can ascertain AKI among both inpatients and outpatients, along with key longitudinal outcomes including death, hospitalization, ICU admission, dialysis, etc. Would be interested in contributing to observational studies, too.

Meeting summary prepared by: Ivonne Schulman, M.D. and Shannon Givens, M.P.H.