Green Nephrology Proposal

The relation between health/health care and environment/climate change is bi-directional. On one hand environment/climate change has identifiable effects on various aspects of human health, while the health care sector, when globally considered, also has a clear effect on the environment. It is estimated that between 5-10% of the global greenhouse gas emissions come from health care related activities. This is in conflict with the general theme in medicine of “primum non nocere”. While attention of health professionals, policy-makers and politicians to environmental problems in general is on the rise, the issue that the health care sector itself is a contributor to the greenhouse gas emissions, that affects health of today’s and future generations in a negative way is still largely ignored by most health professionals and by the community at large.

Several bodies have initiated activities on a global level, including the WHO, the World Bank and others (1,2,3). The Lancet Countdown is a collaboration between 24 academic institutions and intergovernmental organizations with representations from a wide range of disciplines (4). In the title it calls for “a global transformation for public health”. It tracks progress on health and climate change and provides an independent assessment of the health effects of climate change and the actions that are developed to stop it. It states: “The health profession not only has the ability but the responsibility to act as public health advocates by communicating the threats and opportunities to the public and policy makers and ensuring climate change is understood as being central in human wellbeing.” In the 2018 version, the Lancet Countdown calls for “profound changes in the methods of delivery of healthcare” (5).

The general goals defined by the global institutions should be translated into concrete actions in nephrology. Health care workers in nephrology are often active in patient care, research and in medical education. In all three sectors the subject of sustainable health and sustainability of health care should be on the table. The ERA-EDTA has recently decided to put this on its agenda (6,7). In fact, it will be a specific topic during its annual meeting in 2020. Now the time is appropriate for KDIGO as a global organization to address these two big issues as well, i.e. how environment affects kidney health/disease and how we can reduce the environmental burden of the care for kidney patients. The goal of the conference is to address these two big subjects and to identify key relevant literature, areas of uncertainties, reviews existing activities, address controversial issues, outline a research agenda, identify relevant stakeholders, etc.

Peter J Blankestijn

August 30, 2019

Refs

1 World Health Organization. Healthy Hospitals, healthy planet, healthy people. 2009. Accessed through: http://www.who.int/globalchange/publications/healthcare_settings/en/

2 World Bank Group. Climate smart health care. 2017, accessed through: http://documents.worldbank.org/curated/en/322251495434571418/Climate-smart-healthcare-low-carbon-and-resilience-strategies-for-the-health-sector

3 http://www.euro.who.int/__data/assets/pdf_file/0007/341944/OstravaDeclaration_SIGNED.pdf?ua=1

4 Watts N et al. The Lancet Countdown on health and climate change: from 25 years of inaction to a global transformation for public health. Lancet 2018; 391: 581-630

5 Watts A, et al. The 2018 report of the Lancet Countdown on health and climate change: shaping the health of nations for centuries to come. The Lancet 2018; 392(10163): 2479-514

6 Blankestijn PJ, et al. ERA-EDTA invests in transformation to greener health care. Nephrol Dial Transplant. 2018 Jun 1;33(6):901-903.

7 Blankestijn PJ, Bruchfeld A, Capasso G, Fliser D, Fouque D, Goumenos D, Massy Z, et al. Lancet Countdown paper: what does it mean for nephrology? Nephrol Dial Transplant. 2019; 34(1): 4-6.

Measurement of urinary proteins in clinical trials and clinical practice: Albuminuria or Proteinuria?

Chairs: Hiddo JL Heerspink, Bengt Fellström,

Proposed planning committee: Sean Barbour, Jonathan Barratt, Lesley Inker, Hong Zhang, Masaomi Nangaku, Ron Gansevoort, Peter Rossing, Maria Tyden, Joseph Vasalotti

Analytical committee: Niels Jongs Hiddo JL Heerspink Lesley Inker Ron Gansevoort, Maria Tydén

Increased protein excretion predicts CKD and CV outcomes and reducing albuminuria is associated with a reduced risk in kidney outcomes. Albumin is the most abundant protein in most type of kidney disease and its measurement is standardized. Measurement of albumin is considered gold standard. However, in clinical trials and nephrology practice, traditionally, urinary proteins are quantified by using total protein assays. These methods are generally cheaper and may be used because of traditions or other considerations although they are probably less precise and may impact diagnosis and prognosis in clinical practice and statistical power of clinical trials. Total protein and albumin in urine are strongly correlated and conversion equations do exist, but it is unknown which proteinuria measure is best for prediction, monitoring and determination of treatment efficacy and whether this varies by CKD aetiology.

Overall Goal:

We propose to systematically assess and compare the optimal method to measure urinary proteins (albuminuria vs proteinuria) in patients with CKD with respect to CKD (1) *diagnosis*, (2) *prognosis*, (3) *monitoring* of disease progression and (4) *evaluating drug efficacy* of current and new treatments for CKD.

We will use existing data from cohort studies and clinical trials to answer these four research questions.

Populations:

We will collect data from observational cohort studies and clinical trials including the following cohorts:

1) Patients with diabetes and CKD
2) Patients with glomerular nephropathies (IgA Nephropathy, FSGS Nephropathy, Membranous Nephropathy)
3) Patients with inflammatory diseases (e.g. Lupus Nephritis)
4) Patients with non-glomerular diseases such as ADPKD and hypertensive renal (a/o tubular-interstitial disease) disease

Diagnosis

The optimal method for assessing urine proteins should have minimal intra- and inter laboratory variability.

<u>Approach:</u>

We will send samples from patients with CKD (with and without type 2 diabetes) who collected urine (24-hour or first morning void urine samples) to different laboratories to measure urine albumin and

urine protein. We will use existing data from trials where patients collected three consecutive first morning voids and determine in the three consecutive urine samples albumin and protein. We will calculate coefficient of variations and calculate the number (%) of measurements outside 50% range of the geometric mean of each individual.

Prognosis

The optimal method for assessing urine proteins should predict clinical outcomes best

We will use cohort and clinical trial data to determine which method (albumin or total protein) can be used best to predict clinical outcomes (kidney failure, cardiovascular outcome). We will report the hazard ratios with clinical outcome per standard deviation albuminuria or proteinuria and compare C-statistics for predicting clinical outcomes (i.e. End-stage kidney disease). Analyses will be stratified by CKD aetiology (e.g. glomerular and non-glomerular disease) and CKD stage to assess impact of these variables on the prognostic performance.

Monitoring

The optimal method for monitoring of urine proteins over time should have the lowest within-individual variability over time

We will use cohort and clinical trial data to determine which method has the lowest within individual day-to-day variation. We will use measurements collected over a 3 to 6 months period and calculate for each individual the within-individual coefficient of variation. We will use data from patients with CKD with and without diabetes. Analyses will be stratified by CKD aetiology (e.g. glomerular / non-glomerular disease) and CKD stage to assess whether he within individual variability in urinary proteins varies by these variables.

Establishing treatment effects

The optimal method for demonstrating treatment effects with urinary proteins should have

1) *Minimal within-individual variability to increase statistical power*
2) *The early change in urinary proteins during treatment should show a strong association with clinical outcomes*
3) *Trial level analyses should show a strong correlation between the early treatment effect on urine proteins (either albuminuria or proteinuria) and treatment effect on clinical outcome*

Clinical trials (phase 2 and phase 3) with both proteinuria and albuminuria measurements potentially available for analyses are shown in the table below. We will compare effect sizes using urinary albumin:creatinine ratio and urinary protein:creatinine ratio for each intervention and in patients with glomerular/non-glomerular disease as currently proteinuria is often measured in patients with glomerular diseases whereas albuminuria often measured in diabetic kidney disease. However, empirical data systematically comparing with uniform analytical methods the magnitude and precision of treatment effects on these urinary protein methods is lacking.

Trial Acronym	Drug Class	Patient Population	Outcomes	N Patients	In-house data	PMID
RENAAL	ARB	Diabetic CKD	DS / ESKD	701	Yes	20634296
IDNT	ARB	Diabetic CKD	DS / ESKD	1715	Yes	11565517
PLANET	Statin	CKD with/wo diabetes	eGFR slope	Diabetic CKD: 325 Non-diabetic: 220	Yes	25660356

KDIGO Controversies Conference on Acute Interstitial Nephritis

Authors: Dennis G. Moledina, MD, PhD; Mark A. Perazella, MD
Department of Internal Medicine (Nephrology), Yale School of Medicine, New Haven, CT

Background

Acute interstitial nephritis (AIN) is a common and important cause of acute and chronic kidney disease (CKD) as well as end stage kidney disease (ESKD). AIN is a form of immune-mediated kidney injury triggered by use of certain medications (such as antibiotics, proton pump inhibitors, and immune checkpoint inhibitors) or by autoimmune diseases (such as sarcoidosis, Sjogren's syndrome, IgG4-related kidney disease, and tubulointerstitial nephritis with uveitis syndrome). Medications are the most common cause of AIN (>70%) in developed countries and cause AIN in up to 50% in developing countries. Infections are now a less common cause of AIN (except in developing countries). AIN is the cause of acute kidney injury in about 15% patients who undergo a kidney biopsy.[1-3] Clinical diagnosis is often quite challenging and a kidney biopsy is frequently required. Ongoing inflammation in AIN leads to interstitial fibrosis, tubular atrophy and permanent kidney damage, and 40-60% of patients develop CKD after an episode of AIN.[4,5] AIN is thought to be the cause of 2% of CKD, which is equivalent to 10 million prevalent cases in the world.[3] AIN is the primary cause of ESKD in 3-4% incident patients.[6]

Relevance of the topic and the conference

AIN is one of the few potentially treatable causes of AKI if identified and treated early. However, there are three key challenges in the management of patients suspected or diagnosed with AIN. First, the clinical diagnosis of AIN is difficult, which often results in delayed or missed diagnosis. Most patients with AIN do not have any characteristic symptoms or signs (rash, fever, flank pain, etc.). Currently available diagnostic tests, including serum and urine eosinophils, urine sediment examination for leukocytes and leukocyte casts, and imaging tests, have poor sensitivity and specificity for AIN diagnosis.[2,7-10] Thus, the diagnosis of AIN currently relies entirely on maintaining a high index of clinical suspicion for this disease and often requires confirmation by a kidney biopsy. Kidney biopsy may not be feasible in some patients due to bleeding risk or delayed to optimize this risk.[11,12] The lack of a diagnostic biomarker for AIN and need for a kidney biopsy to establish AIN diagnosis leads to a delay in diagnosis, which is associated with permanent kidney damage. Delay in diagnosis and management of AIN is associated with increased interstitial fibrosis and lower recovery of kidney function.[4,13-15]

Second, in the absence of consensus guidelines regarding histological diagnosis of AIN, there is significant heterogeneity in reporting. Histological diagnosis of AIN is based on an interstitial infiltrate consisting of lymphocytes, monocytes, macrophages, plasma cells and often (but not always) eosinophils, as well as presence of tubulitis where the inflammatory infiltrate extends into tubules. However, there are issues that make even histological diagnosis less reliable. First, it is increasingly recognized that the reliability of biopsy reports by a single pathologist has limitations. In a prospective observational study, we noted that a majority of adjudicating pathologists re-classified clinically reported AIN cases into non-AIN controls in a third of cases. This reclassification was lower when AIN was listed as the first diagnosis (18%) than when it was listed as 2nd or later (41%).[16] Second and related is the issue of low inter-rater agreement among pathologists; we noted low kappa for agreement for AIN diagnosis (0.35), as well as interstitial features of interstitial infiltrate (0.22), tubulitis (0.20), and eosinophils (0.39). Third, AIN is commonly associated with other diagnoses on the biopsy including acute tubular injury (ATI), diabetic kidney disease, lupus nephritis, and ANCA-associated vasculitis. It is unclear when AIN is thought to be secondary to these associated diagnoses (and hence would not warrant management changes) or a separate diagnosis. This poses a significant challenge for treating clinicians in making management decisions particularly if a renal pathologist is not available on site for discussion as is increasingly common. Clinicians in our study seemed to understand the uncertainty in histological diagnosis. They reclassified 19% of AIN diagnoses as not AIN; this reclassification was lower when AIN was listed as first (8%) than when it was listed as second or later (29%).

There are a few solutions to the challenges with histopathological diagnosis of AIN. First, pathologists in the NEPTUNE study improved concordance on glomerular diagnoses through an iterative adjudication process using description based scoring system.[17] Thus, it might be possible to improve the agreement among pathologists by establishing consensus criteria for AIN. Second, reporting of interstitial features should be in a standardized manner; e.g., percentages or percentage ranges. Avoiding terms such as mild, moderate, minimal, etc. This would improve patient care and research by allowing comparison across centers, studies and pathologists, help develop models to diagnose AIN using interstitial features, and allow application of machine learning techniques to biopsy slides. Finally, identification of etiology specific subsets of immune cells involved in AIN may lead to improved histological diagnosis as well as guide treatment. For example, recent studies have shown involvement of mast cells and Th17 cells in AIN, which are not routinely tested in clinical histopathology.[18,19]

Third, there is no evidence-based guideline for management of patients with AIN resulting in substantial variation in practice. For example, while it is generally accepted that withdrawal of the offending drug is the best first step after diagnosis of drug-induced AIN, prescription of corticosteroid therapy is more controversial. Observational studies of corticosteroid use in AIN show conflicting results in terms of benefit for kidney function recovery potentially indicating heterogenous treatment effects.[13] It is possible that there are certain subgroups of patients with AIN who derive the most benefit from corticosteroids (e.g., those with highly active immune responses), whereas others gain little benefit and only experience treatment side effects.[14] However, there are currently no guidelines around which patients are best suited to this therapy. Recent data suggest that urine biomarkers may help select appropriate patients for therapy.[20] Duration of therapy and appropriate dose are also not clear. Thus, clinicians rely on expert opinion and local practices vary by center.

Conference Overview

We propose a KDIGO conference on AIN that gathers a global panel of multidisciplinary clinical and scientific expertise (e.g., nephrology, pathology, epidemiology, pharmacology, etc.) to identify key diagnostic and management issues relevant to patients with AIN. Where possible these experts will provide evidence-based guidelines or identify areas in need of further research.

This conference will focus on three key aspects of clinical management of patients suspected to have AIN (see attached scope of work document for details):

1. Etiology and clinical diagnostic challenges:

The experts will perform systematic review existing literature followed by discussion and creation of consensus clinical criteria that support AIN and make a kidney biopsy unnecessary. The expert consensus would include a position statement on use of currently available diagnostic tests for AIN. This will also include discussion on novel biomarkers and imaging studies, as well as emerging causes of AIN such as immune checkpoint inhibitors.

2. Histological diagnosis:

The experts will answer key questions on histology including generation of consensus histological criteria for diagnosis of AIN and addressing co-existing histological diagnoses such as ATI, DKD, ANCA and lupus.

3. Prognosis and management:

Experts will review current evidence of appropriate management of AIN and produce a consensus statement addressing issues of patient selection for immunosuppressive therapy, dose and duration of therapy, as well as predictors of prognosis.

REFERENCES

1. Haas M, Spargo BH, Wit EJ, Meehan SM. Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 259 cases. Am J Kidney Dis 2000;35:433-47.
2. Moledina DG, Perazella MA. PPIs and kidney disease: from AIN to CKD. J Nephrol 2016;29:611-6.
3. Nochaiwong S, Ruengorn C, Awiphan R, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. Nephrol Dial Transplant 2018;33:331-42.
4. Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993-2011: a case series. Am J Kidney Dis 2014;64:558-66.
5. Simpson IJ, Marshall MR, Pilmore H, et al. Proton pump inhibitors and acute interstitial nephritis: report and analysis of 15 cases. Nephrology (Carlton) 2006;11:381-5.
6. US renal data system 2019 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2020;75:A4.
7. Perazella MA. Diagnosing drug-induced AIN in the hospitalized patient: a challenge for the clinician. Clin Nephrol 2014;81:381-8.
8. Fogazzi GB, Ferrari B, Garigali G, Simonini P, Consonni D. Urinary sediment findings in acute interstitial nephritis. Am J Kidney Dis 2012;60:330-2.
9. Muriithi AK, Nasr SH, Leung N. Utility of urine eosinophils in the diagnosis of acute interstitial nephritis. Clin J Am Soc Nephrol 2013;8:1857-62.
10. Perazella MA, Bomback AS. Urinary eosinophils in AIN: farewell to an old biomarker? Clin J Am Soc Nephrol 2013;8:1841-3.
11. Moledina DG, Luciano RL, Kukova L, et al. Kidney Biopsy-Related Complications in Hospitalized Patients with Acute Kidney Disease. Clin J Am Soc Nephrol 2018;13:1633-40.
12. Korbet SM, Gashti CN, Evans JK, Whittier WL. Risk of percutaneous renal biopsy of native kidneys in the evaluation of acute kidney injury. Clin Kidney J 2018;11:610-5.
13. Moledina DG, Perazella MA. Drug-Induced Acute Interstitial Nephritis. Clin J Am Soc Nephrol 2017;12:2046-9.
14. Moledina DG, Perazella MA. Treatment of Drug-Induced Acute Tubulointerstitial Nephritis: The Search for Better Evidence. Clin J Am Soc Nephrol 2018;13:1785-7.
15. Fernandez-Juarez G, Perez JV, Caravaca-Fontan F, et al. Duration of Treatment with Corticosteroids and Recovery of Kidney Function in Acute Interstitial Nephritis. Clin J Am Soc Nephrol 2018;13:1851-8.
16. Moledina DG, Wilson FP, Pober JS, et al. Urine TNF-alpha and IL-9 for clinical diagnosis of acute interstitial nephritis. JCI Insight 2019;4.
17. Barisoni L, Troost JP, Nast C, et al. Reproducibility of the NEPTUNE descriptor-based scoring system on whole-slide images and histologic and ultrastructural digital images. Mod Pathol 2016;29:671-84.
18. Zand L, Monaghan M, Griffin BR, et al. The role of type I hypersensitivity reaction and IgE-mediated mast cell activation in acute interstitial nephritis. Clin Nephrol 2015;84:138-44.
19. Berney-Meyer L, Hung N, Slatter T, Schollum JB, Kitching AR, Walker RJ. Omeprazole-induced acute interstitial nephritis: a possible Th1-Th17-mediated injury? Nephrology (Carlton) 2014;19:359-65.
20. Moledina DG, Wilson FP, Kukova L, et al. Urine Interleukin-9 and Tumor Necrosis Factor-α for Prognosis of Human Acute Interstitial Nephritis (Accepted). Nephrol Dial Transplant 2020.

APPENDIX: SCOPE OF WORK

Breakout Group 1: Etiology and clinical diagnostic challenges of AIN

- What are well established immune and drug-induced causes of AIN?
    - What are specific clinical features that can help determine the etiology of AIN?
    - What are specific features of emerging causes of AIN such as immune checkpoint inhibitors?
- What is the accuracy of currently available clinical features for AIN?
    - Fever, rash, arthralgias, myalgias, flank pain, etc.?
- What is the accuracy of currently available blood tests for AIN?
    - Blood eosinophils, C-reactive protein, erythrocyte sedimentation rate, liver function tests, etc.?
- What is the accuracy of currently available urinary tests for AIN?
    - Urinalysis, urine sediment examination, urine eosinophils, sterile pyuria, etc.?
- What is the role of imaging tests?
    - Ultrasonography, gallium scan, PET scan, etc.?
- What is the role of novel biomarkers?
    - Injury markers, cytokine markers, etc.?
- What combination of above features establishes the diagnosis of AIN and eliminates the need for kidney biopsy?
    - When is kidney biopsy absolutely essential?
    - When is kidney biopsy generally safe in evaluation of AKI?

Breakout Group 2: Histological diagnosis of AIN

The experts will answer key questions on histology

- Histological features:
    - What is the relative importance of histological features of AIN?
    - Can AIN be diagnosed without presence of tubulitis?
    - Which interstitial feature is essential to AIN diagnosis?
    - What percentage of infiltrate is needed to diagnose AIN? Does infiltrate in medulla qualify? Does infiltrate in areas of fibrosis quality?
    - How many tubules need to be affected to qualify as tubulitis?
    - Are eosinophils necessary? What about diagnoses such as NSAID-AIN? What about eosinophilic granuloma?
    - Can histology inform etiology of AIN?

- Associated diagnoses:
    - Acute tubular injury (ATI):
        - When should ATI be considered a separate diagnosis?
        - When is infiltrate thought to be secondary to ATI and not reported as AIN?
    - Glomerular diseases:
        - Does concomitant glomerular pathology eliminate AIN?
        - Necrotizing pauci-immune GN, lupus nephritis, diabetic kidney disease?
    - In what sequence should these be listed on the biopsy report?
- Which novel studies should be included on routine pathology? e.g., mast cells, T-cell subsets

Breakout Group 3: Prognosis and management of AIN

- Once the cause of AIN is established (infection, autoimmune, drug, etc.), how do we determine prognosis?
    - Laboratory tests (baseline/peak serum creatinine)?
    - Imaging test (kidney size and echotexture on ultrasound)?
    - Kidney histology (IFTA, acute infiltrate, etc.)?

- When drug-induced, how do we identify and safely discontinue offending drug?
- Should corticosteroids be used in the treatment of AIN?
    - If so, can we predict which patients will benefit from corticosteroids?
    - Are there patients in whom steroids should be avoided?
- Should high-dose intravenous corticosteroids be used to initially treat AIN?
    - If so, what dose and for how long?
- Should only oral corticosteroids be used to initially treat AIN?
    - Should a combination of intravenous and oral corticosteroids be used to treat AIN?
    - What dose of oral corticosteroids should be used to treat AIN?
- What is the appropriate duration of corticosteroid therapy for AIN?
- When should corticosteroids be discontinued and tapered prior to reaching the intended duration?
- Are other drugs appropriate for the treatment of AIN?
- When should other drugs be employed (initial therapy or after failure/intolerance to corticosteroids)?
- Which novel, targeted therapies should be investigated in AIN?
- What is the framework for conducting international multicenter trials in AIN?

Expert Participants

Nephrologists

Clinical:

U.S.-

Mohammed Atta (Johns Hopkins), Anthony Valeri (Columbia), Ladan Zand (U of Minnesota), Kristy Murray (Baylor), Shivani Shah (Johns Hopkins), Ziyad al-aly (Washington U-epidemiologist), Mitchell Rosner (Virginia)

Global-

Ben Sprangers (Leuven, Belgium), Manuel Praga (Madrid, Spain), Maria Prendecki (London, UK), Alexander Woywodt (Preston, UK), Alexandre Hertig (Paris, France), Giovanni Fogazzi (Milan, Italy), Gregory Wilson (Queensland, Australia), Guillaume Bollee (Montreal, Canada), Esther Gonzalez (Madrid, Spain), Li Yang (China), Magdalena Madero (Mexico)

Basic Scientists

U.S.-

Lloyd Cantley (Yale), Richard Johnson (University of Colorado), Marc Scheetz (Midwestern University - Pharm D.), Rebecca Fischer (Texas A&M – epidemiologist)

Global-

Felix Knauf (Berlin, Germany), Stephen Walsh (London, UK), Samira Bell (Dundee, Scotland), Bernardo Rodriguez-Iturbe (Venezuela)

Pathologists

U.S.-

Glen Markowitz (Columbia), Samih Nasr (Mayo Clinic), Leal Herlitz (Cleveland Clinic), Cynthia Nast (Cedar-Sinai), Lynn Cornell (Mayo Clinic)

Global-

Peter Boor (Aachen, Germany)

Conference Co-Chairs
Mark A. Perazella (US)
Dennis G. Moledina (US)

Breakout Group Co-Chairs
Mitchell Rosner (US)
Cynthia Nast (US)
Felix Knauf (Germany)
Ben Sprangers (Belgium)
Ladan Zand (US)
Giovanni Fogazzi (Italy)

Breakout Group Members
Mohammed Atta (US),
Anthony Valeri (Columbia)
Kristy Murray (US)
Shivani Shah (US)
Ziyad al-aly (US)
Manuel Praga (Spain)
Maria Prendecki (UK),
Alexander Woywodt (UK)
Alexandre Hertig (France)
Gregory Wilson (Australia)
Guillaume Bollee (Canada)
Samih Nasr (US)
Esther Gonzalez (Spain)
Li Yang (China)
Lloyd Cantley (US)
Richard Johnson (US)
Marc Scheetz (US)
Rebecca Fischer (US)
Stephen Walsh (UK)
Samira Bell (Scotland)
Bernardo Rodriguez-Iturbe (Venezuela)
Glen Markowitz (US)
Leal Herlitz (US)
Peter Boor (Germany)
Lynn Cornell (US)
Magdalena Madero (Mexico)

KDIGO Controversies Conference on Acute Interstitial Nephritis

Dennis Moledina – Conference Co-Chair

Mark A. Perazella - Conference Co-Chair

Etiology and clinical diagnostic challenges of AIN	Histological diagnosis of AIN	Prognosis and management of AIN
	Breakout Group Co-Chairs	
Mitchell Rosner (US)	Cynthia Nast (US)	Ladan Zand (US)
Giovanni Fogazzi (Italy)	Felix Knauf (Germany)	Ben Sprangers (Belgium)
	Breakout Group Members	
Mohammed Atta (US)	Lloyd Cantley (US)	Stephen Walsh (UK)
Maria Prendecki (UK)	Glen Markowitz (US)	Marc Scheetz (US)
Esther Gonzalez (Spain),	Peter Boor (Germany)	Manuel Praga (Spain)
Rebecca Fischer (US)	Leal Herlitz (US)	Anthony Valeri (US)
Guillaume Bollee (Canada)	Richard Johnson (US)	Alexandre Hertig (France)
Ziyad al-aly	Samira Bell (Scotland)	Shivani Shah (US)
Gregory Wilson (Australia)	Samih Nasr (US)	Li Yang (China)
Kristy Murray (US)	Alexander Woywodt (UK)	Bernardo Rodriguez-Iturbe (Venezuela)
Magdalena Madero (Mexico)	Lynn Cornell (US)	

Preliminary Concept

KDIGO Controversies Conference on Managing the Impact of Widespread Communicable Disease in CKD, Dialysis and Transplant Patients

4th Quarter, 2020

KDIGO will utilize its highly respected Controversies Conference format to assemble a group of global experts who will debate, discuss and issue observations on the unique problems faced by CKD, dialysis and transplant patients living in serious outbreaks of communicable diseases. During 2020, the kidney community has faced such a dilemma because these patients are at significant higher risk yet require on-going medical care, frequently in settings with more than six people. This Controversies Conference will examine strategies for challenges like early testing, diagnosis, isolation, staffing, emergency planning and unique aspects of CKD and its treatments under the threat of communicable diseases.

CKD patients are at high risk especially in later stages. They frequently have cardiovascular issues and other co-morbidities that make serious infection a major challenge to their health and life. They are susceptible to such infections which may be more severe. Care must be taken with any drugs they take, and this may be true of new therapeutics for infectious disease as well as vaccines.

Dialysis patients are particularly vulnerable since they have all the risk factors of CKD as well as the need to be at a dialysis clinic three times a week. There may be numerous other patients dialyzing with them in relatively close quarters. Isolation poses a challenge to the dialysis providers in logistics, staffing and additional costs. Travel to and from a dialysis unit is also problematic in that it frequently involves other people. Home dialysis will be a very useful preventative strategy for many patients. However, training is usually done in a dialysis unit with all the same risks. Hospitalization is a risk for all dialysis patients, even those at home.

Transplanted individuals are at very high risk in this circumstance since they are all immunosuppressed to some degree. After a transplant, many people lead very active lives and do things they did before they got sick. Being with other people and living a “normal” life is one of the motivators for seeking a transplant. The medicine they take to support their graft may bring them more risk since their immune system may face challenges in fighting off infection.

The Conference will deal with these issues from a scientific and global perspective. Medical considerations of the care provided to CKD, dialysis and transplant patients will be a major focus of the meeting. There are other issues such as global variation in response to disease outbreaks, discrimination in the provision of care when resources are scarce, extra cost and staffing considerations, as well as health policy considerations are all issues this Conference will address.

DIAMOND	SGLT2i	Non-diabetic CKD	Proteinuria	51	Yes	32559474
SONAR	ERA	Diabetic CKD	DS / ESKD	3668 Pts / 344 Events	Yes	30995972
NEFIGAN	Corticosteroid	IgA Nephropathy	UPCR	149 Pts	Pharma	28363480
TESTING	Corticosteroid	IgA Nephropathy	>40% eGFR decline / ESKD	503 Pts	Academia	34731857
APPLAUSE	Iptacopan	IgA Nephropathy	UPCR/eGFR	450 ongoing	Pharma	NCT04578834
PROTECT	ERA	IgA Nephropathy	UPCR/eGFR	380 ongoing	Pharma	NCT03762850
ALIGN	ERA	IgA Nephropathy	UPCR/eGFR	320 ongoing	Pharma	NCT04573478
DUET	ERA	FSGS	UPCR	109	Pharma	30361325
DUPLEX	ERA	FSGS	UPCR/eGFR	280	Pharma	NCT03493685
Goldfinch-Ph2	**TRPC5 Channel inhibitor**	diabetic CKD, ,FSGS, treatment- resistant MCD	UPCR and UACR change	125 Pts /ongoing	Pharma	NCT04387448

DS; doubling of serum creatinine; ESKD end-stage kidney disease

Expected outputs

The results of this research program will be presented at an international conference supported by KDIGO and ideally co-sponsored by FDA/EMA with the aim to reach consensus of measurements of urinary protein in clinical practice and future trials

Proposal of Controversies Conference: “Chronic Kidney Disease of Unknown etiology”

Framework

An epidemic of chronic kidney disease (CKD) is posing a serious public health in some areas of the world. Over the last two decades, Central America has reported as much as a 10-fold increase in the number of cases of people suffering from CKD. Among these cases, there have been reports of a type of CKD whose etiology is not related to traditional risk factors for CKD, such as diabetes and hypertension, and that constitutes what has been defined as “chronic kidney disease of nontraditional causes” (CKDnT), "chronic kidney disease of unknown origin"(CKDu), "Mesoamerican Nephropathy" and many other denominations.

In Central America, the age-standardized mortality rate attributable to CKD is higher than that observed in the rest of the Region of the Americas. Exhibiting an upward trend over time, the rate in some Central American countries has reached as high as 89.1 per 100 000 population. Over the past 20 years there have been many published reports describing an increase prevalence in CKD in Central America—up to five times higher than the expected frequency for the age distribution. This increased frequency has been reported mainly in rural Pacific coast areas of the Central American countries of Costa Rica, El Salvador, Guatemala, and Nicaragua. The disease has primarily affected young men living in agricultural communities, but women and children have also had an increased prevalence of CKD, although to a much lesser extent.

In addition, a similar clinical and epidemiological profile has been described in Egypt, India, and Tunisia, as well as extensively in the central-northern region of Sri Lanka, and some areas in Mexico. All of these areas share similar sociodemographic and climatic characteristics.

The increased frequency of CKD in some these populations does not seem to be associated with a rise in the frequency of traditional risk factors for kidney disease, but to date, many possible causes of CKDu such as heat stress and recurrent episodes of dehydration amongst many others have been proposed.

The most frequent clinical presentation is a slowly but steadily evolving deterioration in kidney function which begins in the second or third decade of life and involves minimal changes in urinalysis, normal blood pressure, an absence of peripheral edema, and no or low-grade proteinuria. Mild anemia, hypokalemia, and hyperuricemia are common. Renal biopsy samples from patients with CKDnT have shown a pattern of predominant tubulointerstitial damage associated with glomerulosclerosis and, in some cases, signs of glomerular ischemia.

At the moment, there is not a unique clinical consensus definition for this entity. Nevertheless, some important efforts have been made by the Latin American and the Sri Lanka nephrology groups for implementing a definition that would allow public health decisionmakers to know the real impact and dimension of the CKDu epidemic and to plan actions according to the distribution and causes of the disease. Much less advances have been made on the best practices to screen for and treat this entity in different stages of the disease.

Diagnosis Criteria

The topic would be on consensus criteria to assign the most common diagnosis of causes of CKD. "Officially", hypertension is the second most common cause of CKD requiring KRT. However, diagnostic criteria for hypertensive CKD (e.g. UpToDate) are obsolete, as they were developed in the 20th century, well before the current KDIGO CKD concept was born.

In the 20th century, hypertension had to precede kidney insufficiency (usually defined by higher serum creatinine values than those that would lead to a diagnosis of CKD by KDIGO standards) and proteinuria (which occurs later than the current concept of albuminuria >30 mg/g as diagnostic criterion for CKD). If the diagnosis of CKD occurs earlier in time (as per KDIGO instead of as per the outdated criteria outlined e.g., in UpToDate), then hypertension may no longer precede kidney disease, but occurs as a consequence of CKD. Reading the latest ESC CPG on hypertension there is no clear identification of criteria to consider CKD as cause or consequence of CKD.

Another item to diagnose hypertensive nephropathy is that there should be no other obvious cause (besides hypertension) for CKD. However, how "obvious" a cause is will depend on which diagnostic tests were performed.

As a result of these outdated diagnostic criteria, it is likely that hypertensive nephropathy is being overdiagnosed. The main problem I see resulting from overdiagnosis is that it conveys the notion that there is no need to do research on causes of CKD since it is clearly established that DM and hypertension account for a majority of cases of CKD.

The controversies conference would address:
1. what should be 21st century consensus diagnostic criteria for hypertensive nephropathy
2. to what extent there is evidence that it is being overdiagnosed (e.g., most African American patients labeled as hypertensive nephropathy have a genetic variant that predisposes to CKD triggered by different insults)
3. what tests would be necessary (e.g., genetic tests) to exclude other causes of CKD. One possibility is that hypertensive nephropathy is diagnosed when these tests were performed and came back negative for other causes. If, however, these tests were not performed, then other causes were not excluded, and the cause should be labeled as unknown, as the cause was not explored.
4. In this regard, another item in the agenda would be consensus diagnostic criteria for CKD of unknown cause (e.g., what etiologic diagnostic workup should be necessary to conclude that the cause is unknown)

I attach a manuscript that summarizes some of these concerns
Alberto Ortiz

We believe a Controversies Conference on "Chronic Kidney Disease of Unknown etiology" is required to address much of the unresolved issues related with this epidemic.

AGENDA
Proposed date and place: November- December 2020, Ciudad de Panama

Coordinators:
1. Latin America.
2. South Asia

Plenary sessions:
1. Climate change and CKD
2. Exposures and CKD
3. Clinical case definition.
4. Pathology
5. Pathogenesis of CKDu
6. Public Policies

Working group Topics:
1. Pathophysiology of CKDu
2. Clinical Case Definition and Detection
3. Prevention and treatment of cases
4. Surveillance and Public Policies

References
1. García-Trabanino R, Jarquín E, Wesseling C, Johnson RJ, González-Quiroz M, Weiss I, et al. Heat stress, dehydration, and kidney function in sugarcane cutters in El Salvador--A cross-shift study of workers at risk of Mesoamerican nephropathy. Environ Res. 2015 Oct;142:746–55.
2. Peraza S, Wesseling C, Aragon A, Leiva R, García-Trabanino RA, Torres C, et al. Decreased Kidney Function Among Agricultural Workers in El Salvador. Am J Kidney Dis. 2012 Apr;59(4):531–40.
3. Wesseling C, van Wendel de Joode B, Crowe J, Rittner R, Jakobsson K. 0204 Mesoamerican nephropathy in Costa Rica: Geographical distribution and time trends of chronic kidney
4. Chronic kidney diseases in agricultural communities: report from a workshop. Mendley SR, Levin A, Correa-Rotter R, Joubert BR, Whelan EA, Curwin B, Koritzinsky EH, Gaughan DM, Kimmel PL, Anand S, Ordunez P, Reveiz L, Rohlman DS, Scammell MK, Wright RO, Star RA.
Kidney Int. 2019 Aug 2
5.The International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology: report of the working group on approaches to population-level detection strategies and recommendations for a minimum dataset.
Caplin B, Yang CW, Anand S, Levin A, **Madero M**, Saran R, Jayasinghe S, De Broe M, Yeates K, Tonelli M, Jakobsson K, Strani L, Ruggiero A, Glaser J, Martin E, Pearce N, Wijewickrama E; International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology (i3C). Kidney Int. 2019 Jan;95(1):4-10.