NephMadness 2015

an online edutainment project

NephMadness 2015: Nephrology as a Cornerstone of Medicine

The specialty of nephrology is facing an identity[1,2] crisis. Applications to fellowship programs are declining, leaving even well-established programs unable to fill allotted positions.[3,4] Further threatening the specialty is loss of expertise as aspects of nephrology practice are being absorbed by hospitalists, intensivists, rheumatologists, interventional radiologists, and cardiologists. Challenging these trends will require creativity and new approaches. A goal of these new approaches should be highlighting the diversity and positive attributes of nephrology practice in order to stimulate interest in the field while teaching cutting-edge concepts, while having fun.

NephMadness began in March 2013 as a social media education project of the AJKD blog. Up to that point, nephrology-related social media forays had been limited to brief Twitter interactions and isolated posts on a few academically minded nephrology blogs that occasionally received comments. From the beginning, we envisioned NephMadness as an ambitious month- long social media campaign, featured in multiple AJKD blog posts that encouraged deep engagement.

What is NephMadness?

We modeled NephMadness after the National Collegiate Athletic Association (NCAA) Basketball Tournament, colloquially known as March Madness. NephMadness replaces the usual field of 64 basketball teams with 64 concepts in nephrology, arranged into a tournament bracket. During 6 rounds of knockout competition, the 64 teams/concepts are progressively narrowed to 32 teams, then the Sweet 16, the Elite 8, the Final Four, then 2, and ultimately a champion. As the tournament advances, our contingent of NephMadness bloggers play the role of tournament analysts, reviewing strengths and limitations of the winners and losers, explaining forthcoming topics, and generating enthusiasm.

Each of the 64 concepts is described in short, fully referenced, entries written by guest authors who are experts in the field. The posts are not meant to be comprehensive topic reviews, but rather casual summaries of the interesting aspects of a concept written in a conversational voice appropriate for social media. As concepts successfully survive early challenges and advance through the brackets, additional posts highlight nuances of the topic, newer data, and alternative view points.

The NephMadness material constitutes a type of learning module increasingly referred to as free open access medical education (FOAMed),5 which can take the form of blog posts, podcasts, online discussions, videos, or recorded presentations. FOAMed is gaining popularity in multiple medical specialties, in particular, emergency medicine and critical care. The NephMadness project was our impetus to produce hundreds of pages of nephrology-focused FOAMed. The prolonged nature of the campaign also invokes a concept called spaced education,6 defined by presenting information repeatedly over time instead of in isolated binges, thus hopefully increasing the uptake and durability of knowledge. Several randomized trials conducted among medical students and residents have demonstrated that the technique, which also includes repeated testing, boosts knowledge by up to 50%, with improved (up to 2 years) duration of retention.[6]

NephMadness focuses on topics from across the broad scope of nephrology. We emphasize emerging science and advances in the field to challenge any perception that nephrology is stagnating. In the past, we have drawn concepts from major randomized clinical trials, basic science research and techniques, and landmark initiatives such as KDIGO (Kidney Disease: Improving Global Outcomes) and the Medicare dialysis program.

The AJKD blog[7] is the primary mechanism to deliver the educational content,[8] and Twitter functions as a lively back channel between educators and learners. The size and scope of NephMadness continues to grow, with 2015 breaking new boundaries in how educational content is delivered and consumed in nephrology.

How is NephMadness played?

Participation in NephMadness mirrors how basketball fans participate in March Madness. Fans fill out brackets predicting which team/nephrology concept will win each matchup. NephMadness uses a dedicated tournament website in which participants can easily enter all their bracket predictions. When the tournament begins, each player can see every other player's brackets. Points are awarded for correct predictions, and scores are automatically tallied, ranked, and displayed. The results are published at about the same pace as the real basketball tournament, covering a 3-week period in March and April.

Participants are encouraged to tweet, blog, and promote their picks. In this way, NephMadness deviates from classic medical education with its bright line between teacher and pupil. For previous NephMadness tournaments, medical bloggers have written on their own blogs about the concepts and explained their selections. Twitter has hosted spirited exchanges on the strengths and weaknesses of many concepts. Some discussions were intellectual debates complete with links to the medical literature; others resembled the trash talking one would expect to find in a pick-up game of 3-on-3 basketball. In 2013 and 2014, during the month of March and April, the hashtag #NephMadness was the dominant

nephrology hashtag on Twitter. For 2014, participants who had the greatest number of correct picks, in addition to those who we thought produced the best original content on social media about NephMadness, won prizes.

How are the winners picked?

The glaring difference between the NCAA tournament and NephMadness is that there is no actual head-to-head competition to determine the winners of each matchup. We could use the wisdom of the crowd and have the teams with the most votes win each round. However, when we tried this strategy in the inaugural year, the concepts with the most name recognition won most of the votes. In our view, part of the mission of NephMadness is to cast light on less obvious and more obscure concepts that deserve more recognition.

For example, in last year's matchup of balanced solutions versus normal saline solution, the popular vote would have had normal saline solution winning in a landslide, but we handed the victory to balanced solutions because of their increasing acceptance and potential critical role in preventing acute kidney injury, as shown in a recent trial.[9] Basic science work has corroborated these findings and demonstrated that a chloride-rich fluid such as normal saline solution may result in more kidney injury.[10] Even a recent editorial purportedly supporting normal saline versus balanced solutions conceded:

> Although we have attempted to show 0.9% NaCl in a positive light, it must be accepted that it is a poor candidate for fluid resuscitation and that alternative crystalloid solutions, several of which have been developed over the last years, are indeed better.[11(p1,094)])

In the 2014 tournament, rituximab, which also has a high profile, exited early from the tournament. We believed that a drug with multiple noninferiority comparisons in which it failed to deliver the predicted reductions in side effects was not worthy of a win.[12, 13] The crowd did not agree with us, resulting in a spirited debate. However, we would argue that raising questions and challenging commonly held beliefs in a provocative manner forces the learner and the educator to think beyond conventional dogma. This year we are deputizing a blue ribbon panel including *AJKD* Deputy Editor Daniel Weiner and Education Editor Scott Gilbert to determine the winners. The identity of the remaining members of the panel will be revealed on the *AJKD* blog in March.

What is new for NephMadness 2015?

The theme for NephMadness 2015 is nephrology's connections with other specialties. The 8 topics (called regions in honor of the geographically organized contests in March Madness) are listed in Box 1. When interacting with other specialties, we as nephrologists need to broaden, not narrow, our scope of practice.[14] It is difficult to stake out one's turf without

being aware of other specialties' state-of-the-art issues. It is with that spirit that we seeded the field of this year's NephMadness. We encourage members of the nephrology community to show passion and enthusiasm for their chosen field by playing and interacting with NephMadness. Subscribers to *AJKD* will find a printed copy of the NephMadness 2015 brackets bundled with their March issue. Those angling for public glory or a prize should visit www.ajkdblog.org for links to the bracket site, more information on prizes, and the contest rules. Let's revive our specialty by sparking the interest of students and residents.

The 8 Regions and Selection Committee for NephMadness 2015

1. Obstetric Nephrology: Phyllis August, MD
2. Infectious Disease and Nephrology: Samir Gupta, MD
3. The Heart and Kidney Connection: Andrew A. House, MD
4. Nephrology and Nutrition: Allon Friedman, MD
5. Genetic Nephrology: Conall O'Seaghdha, MD
6. Critical Care Nephrology: Lakmir Chawla, MD
7. Nephrology and Vascular Surgery: Timmy Lee, MD
8. Onconephrology: Mitch Rosner, MD

Matthew A. Sparks, MD,[1] Edgar V. Lerma, MD[2] Warren Kupin, MD,[3] Paul J. Phelan, MD[4] Kenar D. Jhaveri, MD,[5] Joel Topf, MD[6]

1 Duke University and Durham VA Medical Centers, Durham, North Carolina

2 University of Illinois at Chicago College of Medicine/Advocate Christ Medical Center, Oak Lawn, Illinois

3 Miami Transplant Institute, University of Miami Miller School of Medicine, Miami, Florida

4 Royal Infirmary of Edinburgh, Edinburgh, Scotland

5 North Shore University Hospital and Long Island Jewish Medical Center, Hofstra North Shore LIJ School of Medicine, Great Neck, New York

6 St. John Hospital and Medical Center Detroit, Michigan

NephMadness 2015: Let the Madness Begin

What is NephMadness?

NephMadness is an homage to the NCAA Basketball Tournament, March Madness, but while the basketball tournament seeds the top ranked basketball teams, we use some of the most important, newest, and controversial concepts in nephrology. This is not nephrology 101, You won't find hypokalemia, loop of Henle, or Winter's formula here. We expect that some of the concepts will be novel, even to academically minded nephrologists, so we provide deep, fully referenced, guides to each of the concepts. Please make sure you explore the entire field of 64 concepts which are divided into 8 regions. Each region is a bespoke collection of the finest topics curated by world-renowned experts:

1. Obstetric Nephrology: Phyllis August, MD
2. Infectious Disease and Nephrology: Samir Gupta, MD
3. The Heart and Kidney Connection: Andrew A. House, MD
4. Nephrology and Nutrition: Allon Friedman, MD
5. Genetic Nephrology: Conall O'Seaghdha, MD
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7. Nephrology and Vascular Surgery: Timmy Lee, MD
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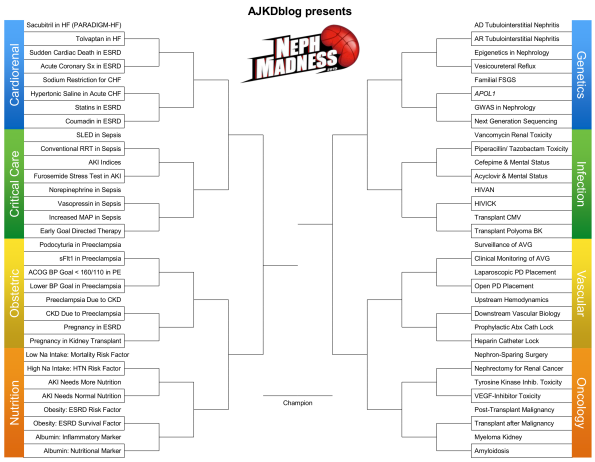


Click to download a PDF of the brackets

How do I participate in NephMadness?

Anyone can participate in NephMadness by predicting the outcomes of each head-to-head match up. This is called filling out your brackets. Once you are familiar with the field, go to the **NephMadness Bracket Submission Site** and make your predictions. You will need to register with an e-mail address and a user name. We also ask a few other questions, just so we have an idea of who the players are. These are optional. We think best part of NephMadness is when people take to social media to cheer their teams on. If you have a blog, write about your choices, if you are on Twitter, use #NephMadness to tweet about the game. Take a moment to check out the best tweets from NephMadness 2014. The winners of each match are determined by a Blue Ribbon Panel of judges. It is a mixture of training program directors, renal physiology/pathophysiology instructors, and journal editors.

- **Dan Weiner**, Deputy Editor, American Journal of Kidney Diseases
- **Scott Gilbert**, Education Editor, American Journal of Kidney Diseases
- **Melanie Hoenig**, Assistant Professor, Harvard Medical School
- **Nancy Adams**, Chair, American Society of Nephrology (ASN) Training Program Directors Executive Committee
- **Roger Rodby**, Fellowship Program Director, Rush University Medical Center; ASN Board Review Instructor
- **David S. Goldfarb**, Chief of Nephrology at the New York Harbor VA Medical Center and the Clinical Chief of Nephrology at the New York University Langone Medical Center
- **Jeffrey Berns**, Professor of Medicine, University of Pennsylvania; Editor-in-Chief, Medscape Nephrology; oh yes, and President of the National Kidney Foundation

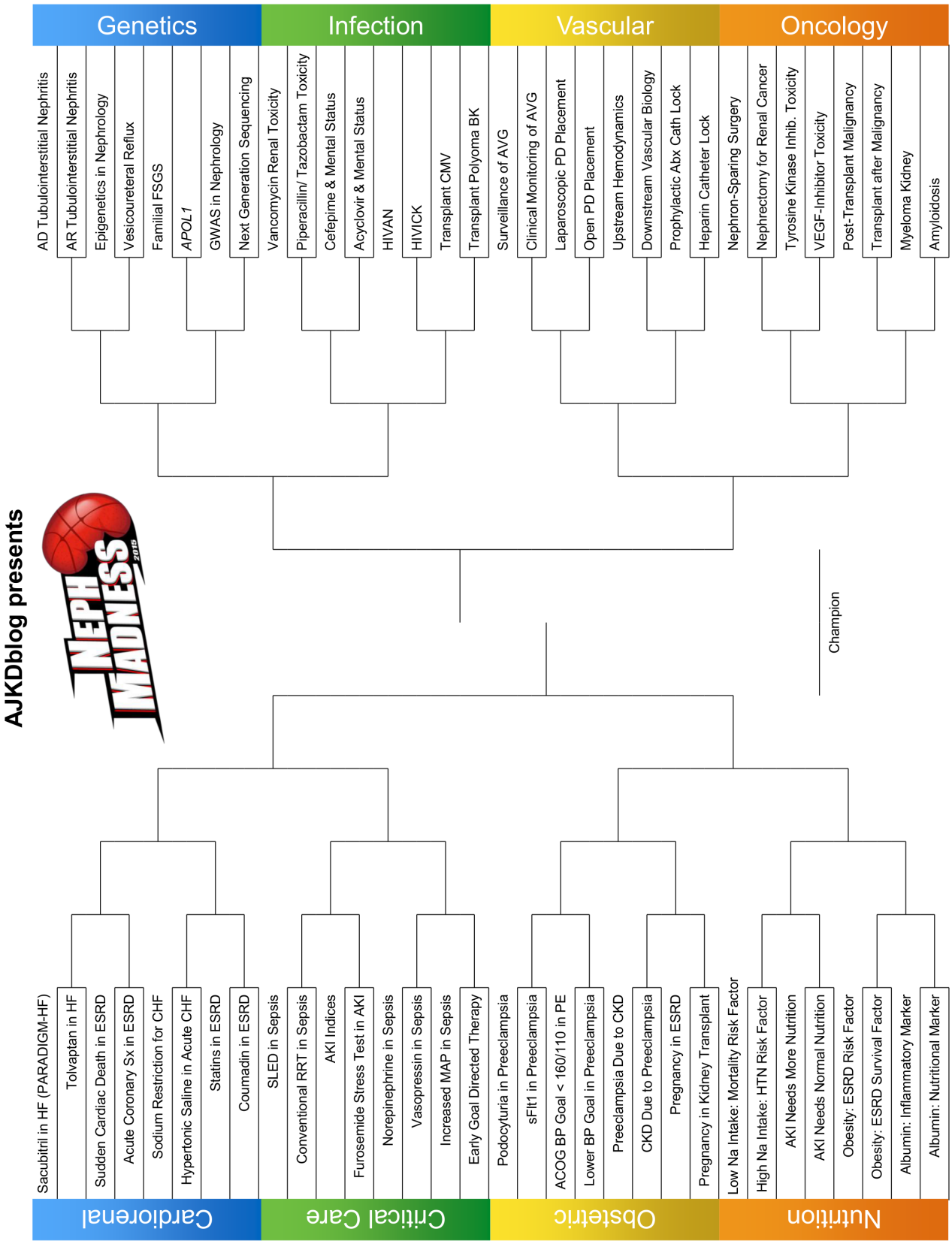
The Blue Ribbon Panel will determine the winners of each matchup by the March 22nd deadline for entering the contest. **There are prizes.** One copy of National Kidney Foundation Primer on Kidney Diseases will be awarded to the top overall score, top medical student score, top resident score, top fellow score, and top attending score. Additionally, a NephMadness travel mug & stressball will be awarded to (after excluding the scores of the grand prize winners) the 9 remaining overall top scores, the best tweeter and the best blogger. The official rules of NephMadness 2015 are available for the legally inclined. Most importantly, it is free.

Why is there a NephMadness?

The creators of NephMadness wrote an editorial in March's *AJKD*, take a look at it. Co-creator Dr. Topf wrote a post about it for MedScape, take a look at it (free registration required). We see online social media as a major game changer for medical education, but at the same time we see a significant barrier to getting started. When you are new, the social media space can be a bit bewildering. The idea was that a game may bring some purpose and focus for nephrologists trying to explore social media. This is intended to be a fun and entertaining project. Please have and engage with it. The scouting reports we created with our selection committee are intended to orient players to all the concepts that populate our field. They are fully referenced and are a great place to start your research but they are in no way comprehensive reviews or book chapters. Additionally, though they have been proofed and edited by our experts they are written by general nephrologists and research nephrologists, but out of their core area of expertise. We are sure there are mistakes.
If important and worthy studies are overlooked contact us by making a comment or tweet the mistake. If we could add a Wikipedia-like **EDIT** button we would. We want to make the content better and are delighted to fix any issues that are discovered. The purpose of NephMadness is to learn, share, teach and most importantly have fun. We hope everyone has as much fun playing NephMadness as we did creating it. Enjoy NephMadness 2015: Nephrology as a Cornerstone of Medicine.

- Joel Topf
- Matt Sparks
- Edgar Lerma
- Paul Phelan
- Warren Kupin
- Kenar Jhaveri

The Brackets



The Heart and Kidney Connection Region

This region is like the Showtime Lakers of the 80s. Cardiology always packs the house by combining crowd pleasers like acute illness, therapeutic advances, and the weight of importance (1 in 4 deaths in the US is due to heart disease). This makes the Heart and Kidney Connection region a big draw. This region begins with a pair of novel therapies for heart failure, that try to break out of the loop diuretic prison we have been in for the last few decades. After that intro there are three match-ups that are just dripping with controversy:

1. The nature of cardiac mortality in ESRD: electrical versus plumbing
2. What should we do with sodium intake in acute and chronic heart failure
3. And the eternal question. If a drug works with intact kidneys, does it need to be re-vetted for dialysis patients?

Andrew House, MD

Dr. House is a Professor in the Faculty of Medicine at the Schulich School of Medicine & Dentistry, Western University, and is currently the Chair of the Western University Division of Nephrology, in London, Ontario. He completed his training in Physiology & Pharmacology at Western before his MD and specialist training at the University of Ottawa, and Masters in Epidemiology & Biostatistics at Western. In 2007 he completed a six-month sabbatical in Vicenza, Italy, where he developed an interest in Critical Care Nephrology and Cardiorenal Syndromes. He participated in the Acute Dialysis Quality Initiative (ADQI) consensus conferences on Cardio-Renal Syndromes held in Venice in 2008 and 2012.

Sacubitril in HF (PARADIGM-HF) vs Tolvaptan in HF

This is a real show stopper. Two novel therapies going head to head in a grudge match. Sacubitril is a neprilysin inhibitor that is now coupled to a new partner (an ARB) hoping to shed a toxic past. The toxic past was a drug called omapatrilat which has combined ACE and neprilysin inhibitory effects that initially showed promise in heart failure but angioedema stole the show and proved too hazardous. The blockade of vasopressin receptors with tolvaptan continues to make appearances as a potential therapy in multiple arenas. How will tolvaptan hold up to an old renin-angiotensin system behemoth with shiny new neprilysin inhibition rims? This one will go down to the wire.

Sacubitril in HF (PARADIGM-HF)

The hype was palpable, like Kentucky in the John Calipari era. Will it be another group of one and dones or will this be a John Wooden UCLA dynasty? The PARADIGM Trial was reported at European Society of Cardiology Congress in Barcelona in 2014 and simultaneously published in the *NEJM*. This trial tested whether a neprilysin inhibitor

coupled to valsartan provided more benefit than enalapril in patients with heart failure. First things first, what is neprilysin? And why should we block it? It is ubiquitously expressed but enriched in the renal proximal tubule, heart, lung, lymphocytes, and brain. Neprilysin is a circulating and membrane-bound metalloprotease that cleave peptides. In such, inactivates several peptide hormones including natriuretic peptides, vasoactive peptides (eg, endothelin 1, bradykinins, angiotensin II), neuropeptides (eg, substance P, enkephalins), and the beta-amyloid peptide amongst others. Some of these are "good" and others "bad". So, the net effect of neprilysin inhibition is difficult to predict. The inhibition of neprilysin alone (in the form of candoxatril) was studied back in 1993 and reported in the journal *Clinical Science*. This showed no effect in blood pressure and a decrease in angiotensin II metabolism. This is why it is important to add neprilysin inhibition to either an ACEi or an ARB.

The results of the PARADIGM Trial were impressive, but not without controversy. This was a double-blind trial, with 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily). LCZ696 is a combination neprilysin inhibitor sacubitril and valsartan. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure. The trial was stopped early because of an overwhelming benefit with LCZ696.

- The primary outcome had occurred in ~22% in the LCZ696 group compared to ~27% in the enalapril group.
- Death from any cause occurred in ~17% receiving LCZ696 and ~20% receiving enalapril.
- As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21%.
- LCZ696 decreased the symptoms and physical limitations of heart failure.

In regard to side effects, the LCZ696 group had higher proportions of patients with hypotension and non serious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

These results were viewed by the cardiovascular community with great enthusiasm. However, questions remain about why enalapril was used as the comparator and not valsartan.

But what about kidney disease? Well, as mentioned previously, neprilysin is highly expressed in the proximal tubule of the nephron. Hence, there is much interest in using inhibitors of neprilysin in CKD. A rat model of diabetes showed substantial improvement in both proteinuria and kidney damage with the use of omapatrilat compared to ACEi use. What about human data? In an analysis of patients in the PARAMOUNT trial (designed to look at

heart failure with preserved ejection fraction (HFpEF) showed that treatment with LCZ696 for 36 weeks led to slightly better eGFR than valsartan. However, the LCZ696 had a small but statistically increase in urinary ACR. The UK Heart And Renal Protection III (UK HARP-III) trial will compare LCZ696 to irbesartan in a planned 360 patients with proteinuric CKD (urine ACR > 20 mg/mmol and eGFR 20-<60 mL/min/1.73 m^2). The trial will investigate the short-term safety and efficacy of LCZ696 in CKD with a primary outcome being the difference between the two arms in change in measured GFR from baseline to 6 months. This class of medications could become a potential therapy to slow the progression of CKD. We still await definitive clinical trials. Team Sacubitril has a lot of promise and will likely make some serious noise in NephMadness.

Tolvaptan in HF

The antagonists of vasopressin (vaptans) have shown great versatility, from the treatment of hyponatremia to polycystic kidney disease to heart failure, provoking the question whether Team Tolvaptan in HF can be stopped. Why should we block vasopressin in heart failure? Well, increases in vasopressin has been shown to play a role in mediating water retention in HF. Therefore, the interruption of inappropriate activation of vasopressin could be of therapeutic benefit. The vaptans (or small molecule antagonists to the V_2 receptor) now give us the ability to treat disorders with increased vasopressin levels. Short-term treatment with vaptans leads to improved fluid balance, renal function, and electrolyte composition compared to loop diuretics.

The EVEREST trial, reported in *JAMA* in 2007, was a randomized, double-blind, placebo-controlled study in patients (~4100) acutely decompensated and admitted to the hospital with either tolvaptan or placebo. This is in direct contradistinction to the PARADIGM Trial in which "stable" outpatients were studied. You have to give the authors of the EVEREST trial credit for going after an extremely difficult patient population. There have been no definitive studies that have shown benefit in acutely decompensated heart failure. Unfortunately, no difference in HF morbidity or mortality was identified. A benefit with tolvaptan was seen in day 1 dyspnea scores and body weight. There was also improved serum sodium concentrations in patients with hyponatremia. However, these effects did not translate to hard outcomes. So, where do we stand? ClinicalTrials.org lists several trials in both acute and chronic HF. Maybe vasopressin antagonism therapy needs to be given chronically and not acutely to be effective in HF.

Sudden Cardiac Death in ESRD vs Acute Coronary Syndrome in ESRD

Two very important topics that contribute heavily to mortality and morbidity in patients with ESRD. Both overlap in their pathophysiology and take from the same playbook (think 4-corners offense and Dean Smith).

Sudden Cardiac Death in ESRD

This is the scourge of nephrology and will be a difficult concept to overtake in NephMadness. An alarming statistic to think that almost 1 in every 4 deaths among hemodialysis and peritoneal dialysis is from sudden cardiac death. Even worse, the risk of sudden cardiac death (SCD) increases substantially as kidney function declines (in the absence of ESRD). We need to understand why this is occurring so we can introduce interventions to help decrease this trend. To put it a different way–the risk of sudden cardiac death in this patient population is actually *above and beyond the risk attributable to classical risk factors*.

What is the reason behind this? The pathophysiology of SCD has not been clearly established and this is why SCD represents a formidable foe. In the general population structural heart disease with reduced left ventricular ejection fraction is responsible for the majority of SCD events. However, this is not the case in CKD and ESRD. Coronary artery disease in general population consists of lipid-laden intimal atherosclerotic lesions. This pattern is not the case in CKD where diffuse multivessel arterial stiffening and calcification of the medial layers of the vessels predominates. In fact, Bleyer et al showed that ischemic cardiomyopathy with reduced ejection fraction was only present in less than 30% of patients on hemodialysis who died from SCD. Patients with CKD predominantly have HF with preserved ejection fraction (HFpEF) presumedly from left ventricular hypertrophy. MRI studies of patients on hemodialysis describe a diffuse pattern of myocardial fibrosis underlying left ventricular hypertrophy without a background of ischemic coronary artery disease. Multiple factors could be contributing to this in patients with CKD such as

- microvessel disease and capillary deficit (capillary/myocyte mismatch)
- disorders of mineral metabolism and secondary hyperparathyroidism
- repetitive myocardial injury from reduction in myocardial perfusion during dialysis
- dialysis-induced myocardial “stunning.”

These differences in pathophysiology may explain why the traditional risk factors fail at explaining the enhanced risk of SCD in dialysis patients.

What about arrhythmic triggers? This could be another factor besides just structural abnormalities leading to the increased risk of SCD in patients with ESRD. First, SCD occurs most frequently on hemodialysis days, especially on the first hemodialysis day after the long dialysis-free weekend for patients on a three times a week dialysis. This suggests that factors related to the hemodialysis procedure itself can potentially trigger a fatal arrhythmias. What are some of the factors:

- both hyperkalemia and hypokalemia (Pun et al)
- exposure to low potassium and calcium dialysate (Karnik et al)
- rapid ultrafiltration rate (Movilli et al)

Therefore, these findings suggest that shifts with varying amounts of potassium and calcium are critical risk factors for SCD in patients maintained on hemodialysis.

What can be done to prevent SCD in this vulnerable patient population? This is the ultimate question. There is no doubt that fatal ventricular arrhythmias can be prevented in patients with ischemic heart diseases and HF with reduced ejection fraction (HFrEF). But what about patients maintained on hemodialysis? Well, unfortunately all patients with advanced kidney disease were excluded from automatic internal cardiac defibrillator (AICD) trials such as MADIT-2 trial. However, a retrospective analysis of patients with reduced EF and ESRD in Michigan and Ottawa, Canada did show a mortality benefit with placement of an AICD for both primary and secondary prevention combined. A definitive randomized controlled trial looking at the primary prevention of SCD with AICD in ESRD has not been performed. A recently published matched cohort study in *NDT* utilizing data from the National Cardiovascular Data Registry's ICD Registry did not detect a difference in overall mortality in AICDs as primary prevention for SCD. What about pharmacologic therapy in preventing SCD? A study by Cice et al in *JACC* linked beta-blockers to improved survival in patients on hemodialysis with dilated cardiomyopathy. However, a secondary analysis of the HEMO study published in *AJKD* did not find a difference in SCD in patients taking beta blockers compared to those who were not. In looking at the renin-angiotensin system blockers, multiple studies have failed to show a reduction in cardiovascular mortality in patients on dialysis (albeit they do show reduction in LV mass). Altogether, we still have much to learn about SCD in ESRD. It is clear that it will take different strategies to curtail SCD. Lastly, it will also be important to start including patients with CKD and ESRD in clinical trials so we can start to achieve a degree of evidence when seeing patients with what we think are risk factors for SCD.

Acute Coronary Syndrome in ESRD

This matchup couldn't be more similar. Definitely a knock down drag out. Acute coronary syndrome, just as SCD, is just a completely different phenomenon in patients with diminished kidney function (CKD and ESRD) than in the general population. To be fair, the discrete ruptured plaque in an isolated stenotic vessel still occurs in this population but this is far less common than in the general population. The pathophysiology and thus the clinical presentation differ. Not to mention to risk of restenosis, bleeding, or the obligatory AKI event after contrast exposure in CKD. Acute coronary syndrome might need a name change to acute coronary syndrome^{CKD}.

First, let's tackle the clinical presentation of acute coronary syndrome (ACS). Patients with diminished kidney function present differently than what is typically seen. To be fair, ACS represents a spectrum of syndromes from unstable angina (UA) to non-ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI). So, how are they different?

First, patients with CKD are ***less likely*** to have:

- typical angina symptoms
- EKG changes (ST elevation or depression), Q waves, LBBB

Secondly, patients with CKD are ***more likely***

- to be admitted with alternate diagnoses
- to have HF symptoms

Making the diagnosis of ACS becomes even more confusing when you factor in alterations seen in serum troponin levels. Troponin levels have become ubiquitous in the diagnosis of ACS. Troponin issues in CKD was a recent topic of #NephJC. Case in point: the mere presence of an slightly elevated serum troponin level portends to worse cardiovascular outcome in patients with advanced CKD or ESRD. The delta change (from baseline level) in troponin is more sensitive for AMI than the absolute level.

What is different in patients with CKD? Why this different presentation and accelerated phenotype? Several theories have emerged. Patients with CKD tend to have a higher burden of multivessel disease with complicated anatomy (longer and more tapered stenoses). The diseased vessels typically have more medial calcification (instead of intimal fibroatheromatous plaque). The traditional risk factors like LDL cholesterol, tobacco use, and family history are weaker associations in CKD despite the higher burden. Postulated pathophysiological reasons are:

- chronic inflammation
- less nitric oxide availability
- chronic oxidative stress
- phosphate retention
- secondary hyperparathyroidism
- elevated FGF-23
- intravascular calcium phosphate crystallization
- uremia-related metabolic exposures

Even after the diagnosis is made the treatment of ACS in CKD remains a poorly studied area. Even worse are studies that show that patients with CKD receive suboptimal care than patients with normal kidney function (however, evidence from clinical trials are lacking to truly say these are "evidence based" as CKD is a typical exclusion criteria).

Just as with AICD trials for primary prevention of SCD, ACS treatment trials typically excluded patients with advanced kidney failure. For instance the NORDISTEMI trial (looking at percutaneous intervention (PCI) after thrombolysis) excluded patients with creatinine > 2.8 and the TACTIC-TIMI-18 Trial (looking at PCI in NSTEMI) excluded patients with a creatinine > 2.5. What are we to do? A systematic review published in 2009 reported that patients receiving an early invasive strategy for UA/NSTEMI fared better in CKD. What about coronary artery bypass grafting (CABG) in CKD/ESRD? Only observational studies looking at PCI versus CABG have been performed in patients with advanced CKD or ESRD. A meta-analysis published in *European Journal Internal Medicine* in 2013 looking at 28 retrospective studies showed that patients with CKD fared better with CABG compared to PCI. However, this sort of analysis is fraught with problems. It is conceivable that only the "healthier" patients were referred for CABG thus leading to bias in these studies.

Where do we go from here? We need to start including patients with kidney failure in clinical trials for one. We need to start advocating that patients with diminished kidney function receive the same attention as any other patient. We also need to widen our differential diagnosis when seeing patients present with fatigue, shortness of breath and consider ACS. ACS versus SCD will be a tough matchup. Both are serious contenders to go far in NephMadness. However, we still have a lot to learn about each of them.

Sodium Restriction for CHF vs Hypertonic Saline in Acute CHF

Salt, or more specifically sodium, is central to this truly Hamlet of a match up! One has to really take a deep breath and relax before tackling this heavyweight battle. “To be or not to be” he said. Or more fittingly for this bout “to give or not to give!”

Hypertonic Saline in Acute CHF

For many decades sodium restriction has been central in the management of HF over the long term. However, in recent years high concentrations of saline has been used with high-dose loop diuretics for the treatment of acute decompensated failure.

The use of hypertonic fluids has been described as far back as 1919 when Penfield and colleagues described the use of hypertonic fluids in the resuscitation of experimental animals. More recently a number of small trials in the last decade or so have highlighted the potential benefit of using a low volume of hypertonic saline with furosemide for the treatment of acute decompensated HF. Experiments have shown that hypertonic saline can increase regional blood flow to the coronary and renal circulations and can increase cardiac contractility.

A recent meta-analysis looked at 10 randomized but small studies that compared hypertonic saline solution (HSS) and furosemide to furosemide alone. The interventions in each trial varied in terms of the volume of hypertonic saline or normal saline given and the dose of IV furosemide given. The HSS concentrations varied from 1.4% saline to 7.5% saline and the IV furosemide doses ranged from 40 mg daily to 1000 mg twice daily. Furthermore, some trials varied the tonicity of the hypertonic saline depending on baseline serum sodium using a higher percentage sodium solution in people with lower baseline serum sodium.

The largest study (Paterna 2011) compared:

- Furosemide 250 mg IV with *150 ml of hypertonic saline* twice a day
  - moderate sodium restriction (~ 2.7 g/d) with
- Furosemide 250 mg IV *without* hypertonic saline
  - low sodium intake (~1.8 g/d).

The hypertonic saline group had an increase in diuresis and serum sodium levels, reduction in hospitalization time (3.5 vs 5.5 days), lower rate in readmissions (~19% vs ~34%) and lower mortality (~13% vs ~24%). This study also reported a survival benefit for the groups that received the hypertonic saline.

The aforementioned meta-analysis also concluded that hypertonic saline improves weight loss, preserved renal function, and decreased length of hospitalization, mortality, and HF rehospitalization. Of note, the Paterna 2011 study was by far the largest trial and may have driven much of the meta-analysis results. Furthermore, sodium restriction (included in the Paterna 2011 study) is a separate intervention. It is therefore hard to say a short course of hypertonic saline alone leads to improved long-term survival.

Overall, hypertonic saline for the treatment of acute decompensated HF is very promising. A large well-conducted randomized clinical trial needs to be performed to assess the long-term benefits of hypertonic saline treatment.

Sodium Restriction for CHF

The US Department of Agriculture and the Department of Health and Human Services recommend a 2300 mg daily intake of sodium for the general population (2010). Sodium restriction has been the mainstay of treatment for those with hypertension, CKD, and HF. Although there are now many pharmacological and device therapies with proven benefit in HF patients, there is inconsistent evidence supporting the use of sodium restriction in HF management. An Institute of Medicine assessment of the evidence report in *JAMA Internal Medicine* last year (2014) states there is evidence for potential harm in restricting sodium intake to less than 2.3 g/d in patients with congestive HF. Guidelines for sodium restriction are largely based on expert opinion and the available data is likely flawed by patient non-adherence to restrictive diets and inconsistent self-reporting of sodium intake.

The 2013 AHA/ACC guidelines for HF management suggest a sodium restriction of less than 3 g/d for heart failure stages C+D. This is based on opinion due to the fact that sodium consumption in the general population in the US is over 4 g/d.

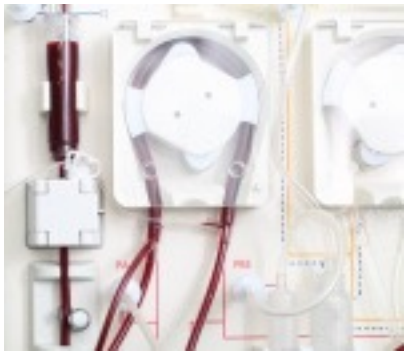
Lennie et al showed sodium intake of less than 3 g/d was associated with better outcomes in HF class 3+4. This was an observational study that also reported sodium restriction to below 3 g/d in HF class 1+2 was associated increase hospital visits and mortality. This is contrary to the observational study by Arcand et al that showed sodium intake greater than 2.3 g/d in HF class 1+2 patients was associated with more hospitalizations compared to lower intake.

There are more examples in the literature of contradictory findings with regard to sodium intake and outcomes in HF patients. Most studies include other interventions such as water restriction and various pharmacological treatments. Not all patients enrolled in older trials

received current standard to care such as ACE inhibition or beta blockade. Another flaw in this literature is predominance of white patients making it hard to generalize these findings to the total US HF population. Furthermore, there has been no large study investigating the effects of sodium restriction on patients with heart failure and preserved ejection fraction.

In summary it seems that the medical community has little to no evidence to guide the short- or long-term management of sodium balance in heart failure patients. Both the administration of HSS and sodium restriction are cheap interventions with the potential to impact the many millions of patients with heart failure in all parts of the world.

Statins in ESRD vs Coumadin in ESRD



Statins in ESRD

Both the ACC/AHA and KDIGO came out with new recommendations regarding lipid management in late 2013. The ACC/AHA guidelines made no specific recommendations regarding lipid management in ESRD patients. The KDIGO guidelines for lipid management are based on three RCTs:

4D (Die Deutsche Diabetes Dialyse Studie). 4D consisted of 1233 patients on hemodialysis that were treated for 4 weeks with *atorvastatin 20 mg or placebo* and followed for 4 years.

- LDL was reduced to a greater extent in the statin group.
- no difference in the primary endpoint of cardiac death, non-fatal MI and fatal and non-fatal stroke: the RR was 0.92 (95% CI, 0.77-1.1; p=0.37).
- Atorvastatin did have an effect on fatal stroke (RR, 2.02; 95% CI, 1.05-3.93; p=0.04).
- Overall there was no effect on the primary end points or total mortality.

AURORA Study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Dialysis: an Assessment of Survival and Cardiovascular Events). AURORA had similarly negative results, with 2776 patients on hemodialysis randomized to *rosuvastatin 10 mg or placebo* with 3.8 years of follow up.

- There was no effect on the primary end point or any component of the primary end point or on all-cause mortality.

SHARP (Study of Heart and Renal Protection). SHARP was the largest and most recent of these studies. This was a randomized trial that assigned 9270 participants aged 40 years or older with CKD to receive *simvastatin 20 mg plus ezetimibe 10 mg daily or placebo*, and

followed them for 4.9 years. ~33% of the patients (n=3023) were receiving maintenance dialysis at randomization.

- This combination treatment did not significantly reduce the risk of primary endpoint in the dialysis subgroup in this study.

A meta-analysis of eighty trials including ~50,000 patients with CKD demonstrated the variable benefits of statin therapy in different CKD stages. Statins reduced all-cause mortality, cardiovascular mortality, and cardiovascular events in patients with CKD not on dialysis but had little or no effect on all-cause mortality (RR, 0.96; 95% CI, 0.88-1.04), cardiovascular mortality (RR, 0.94; 95% CI, 0.82-1.07), or cardiovascular events (RR, 0.95; 95% CI, 0.87-1.03) in persons receiving dialysis.

Overall, there is no evidence for the use of statins in ESRD patients and guidelines suggest not starting a statin on patients who had not already been on one prior to starting dialysis. These trials are disappointing given the huge cardiovascular comorbidity and risk that our patients carry and the large benefit of statins seen in the general population.

Coumadin in ESRD

The use of warfarin (coumadin) in patients with ESRD is unfortunately very common given the frequency of comorbid conditions such as valvular heart disease and thrombosis seen in this patient population. In many of these situations the use of warfarin is unavoidable. Controversy over the use of warfarin arises when considering its use on non-valvular atrial fibrillation (AF). Patients with ESRD are already at increased risk of bleeding and hemorrhagic stroke. Warfarin is a risk factor for vascular calcification through its actions on matrix Gla protein and vascular smooth muscle cell phenotype. Warfarin has also been shown to increase the risk of aortic valve calcification in the general population. We also know that there is greater variability of INR in patients on dialysis and warfarin compared to those on warfarin but not on dialysis. All these issues make the decision to use warfarin a difficult one. On the other hand we know that dialysis patients are at increased risk of ischemic stroke and have higher rates of atrial fibrillation than the general population.

There is little evidence to guide the use of warfarin in dialysis patients with AF and the data that does exist is contradictory.

- A Danish registry study found that the use of warfarin in dialysis patients at high risk for stroke or thromboembolism based on the CHA2DS2-VASc score was associated with significantly *lower all-cause mortality*.
- Chan et al examined the outcomes of 1671 incident dialysis patients with pre-existing AF treated with warfarin or not. In comparison with nonuse, warfarin use associated with a significantly *increased risk for new stroke*.

- Shah et al performed a retrospective cohort study of Canadian patients over 65 years of age admitted to hospital with AF. 1626 of these patients were on dialysis. 46% of these dialysis patients were prescribed warfarin. Warfarin use, compared to no warfarin use, was *not associated with a lower risk for stroke* but was associated with a *44% higher risk for bleeding* (adjusted HR, 1.44, 95% CI, 1.13-1.85) after adjusting for potential confounders.

The CHADS2 score in patients on dialysis needs to be interpreted with caution. Two components of this score, hypertension and HF, do not independently predict stroke risk in dialysis patients. This tends to misclassify low stroke risk patients as being high risk. This study by Wizemann et al also demonstrated that warfarin use among patients with pre-existing AF was associated with elevated stroke risk in patients >75 years.

Overall, the data for warfarin use for dialysis patients with AF supports a cautious approach to its use and we probably should be prescribing warfarin less frequently than we do for these patients given the risks outlined above.

Both coumadin and statins may not affect long-term outcomes in ESRD patients. You decide which one of them deserves to move to the next round.

– Post written and edited by Drs. Matthew Sparks, Andrew Malone, and Andrew House.

Critical Care Nephrology Region

The critical care region is packed with interesting story lines, SLED was a bubble team that not many people thought would make the tournament but they navigated their way through the selection process to face an experienced conventional renal replacement therapy (RRT)

Lakhmir S. Chawla, MD

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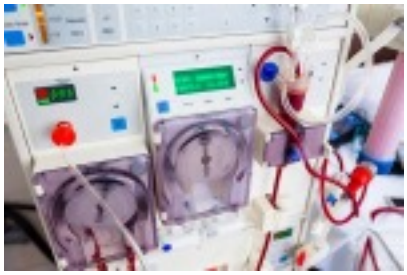
team. Will team SLED be able to outlast conventional RRT? Another new face is the furosemide stress test. They got hot at the end of the season and get to face the urinary

indices, a team that just got taken to the woodshed in their conference tournament by NephroCheck. It's hard to imagine they have anything left in the tank. It is always a compelling matchup when long time rivals like norepinephrine and vasopressin get paired up in a first round matchup. Norepinephrine has had the upper hand for a while, but maybe this is the year of vasopressin. But, the most interesting storyline is team MAP and team early goal directed therapy. Both of these teams have taken it on the chin in 2014 with devastating RCT results. We're amazed they even made it to the tournament. This matchup might be a contest of who's suffering less.

SLED in Sepsis vs Conventional RRT in Sepsis



Some debates about which team is better can be settled on the court. Want to know if Duke or UNC is better? Good news: they play each other at least twice a year. But other discussions are unanswerable. For instance, is the 2015 University of Kentucky team better than the University of Kentucky team from 2012 (NCAA champions, most wins (38) in a season ever, and 4 first round NBA picks)? This is unanswerable, and the lack of head to head competition allows armchair fans to endlessly debate the question.

Nephrology has our own version of the data-less question, though intermittent hemodialysis has been compared to CRRT in numerous trials, there is no data on an head to head match up of IHD versus SLED. Let the debates begin!

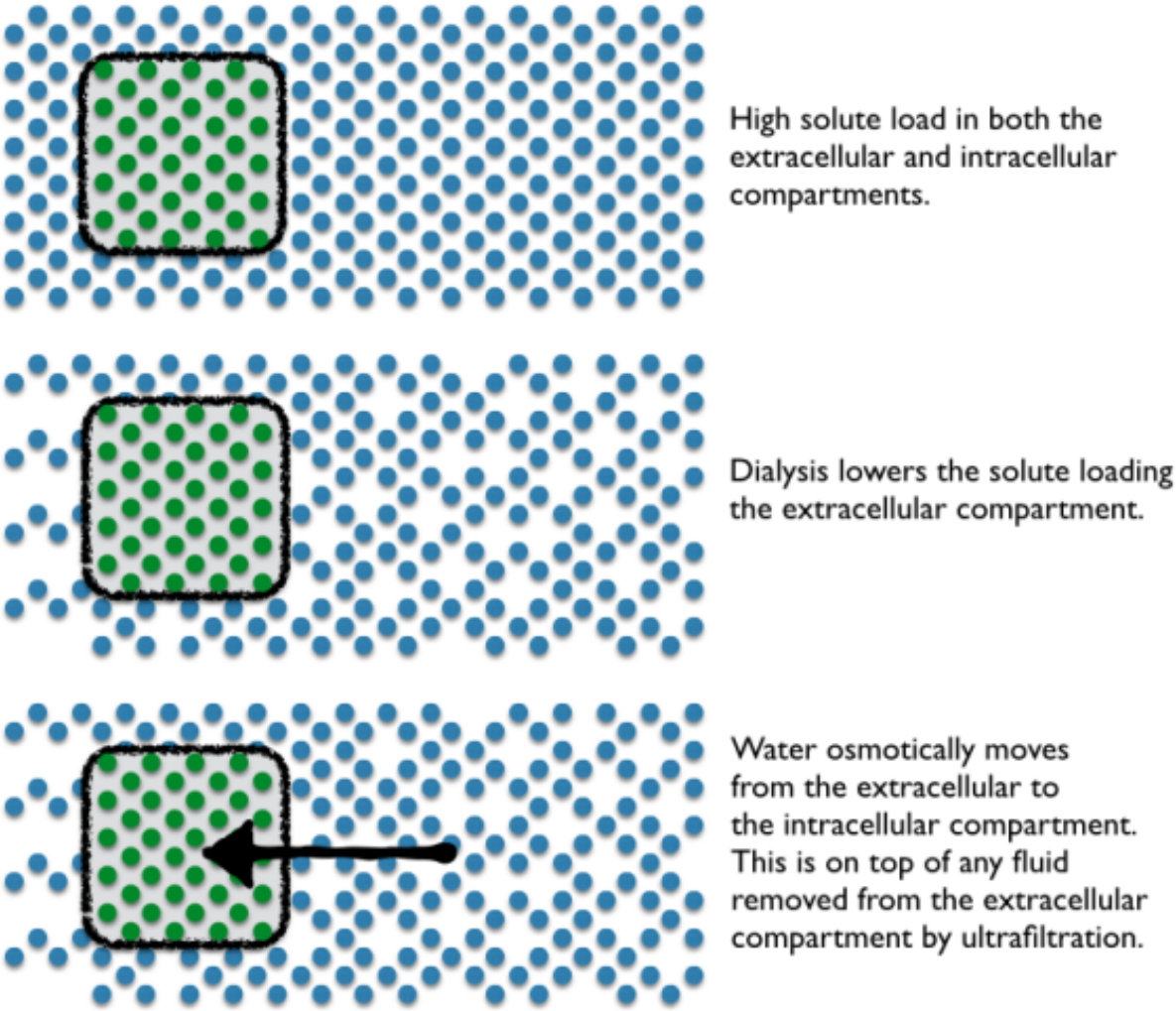
In acute kidney injury there is a moment of clarification, the moment you decide the patient needs renal replacement therapy (RRT). Not only that, you need to decide while type of RRT to use. The delicate balance between keeping a patient dry for the heart/lungs and wet for kidney evaporates with the decision to take over the essential task of fluid and solute control with a machine rather than relying on the damaged kidneys. Biomechanical engineers have developed novel machines dedicated for ICU patients, CRRT machines, but often those machines or the personnel required to use them are unavailable. In those situations nephrologists are forced to adapt conventional dialysis machines to the unique needs and limitations of septic AKI patients. In those situations one can use conventional hemodialysis techniques or a specialized technique such as sustained low efficiency dialysis (SLED).

SLED in Sepsis

Also referred to as prolonged intermittent renal replacement therapy (PIRRT)–and sometimes derided as *poor man's CRRT*–SLED is a hybrid form of dialysis that takes the

best parts of intermittent hemodialysis and continuous RRT. Some of the goals of this modality are:

1. Slower blood flow rates as compared to standard intermittent HD
2. Slow solute removal to prevent solute disequilibrium
3. Slow ultrafiltration to provide hemodynamic stability
4. Sustained treatment to maximize dialysis dose
5. Intermittency for convenient access to patients for out-of-unit procedures and scheduled down-time.



One of the other advantages of SLED is that it leverages the existing chronic HD equipment and personnel. SLED is also fairly well tolerated in hemodynamically unstable patients. For example, MD Anderson uses a standard Fresenius 2008H K dialysis machine with the

ubiquitous F16nr dialyzers. However, they program these machines completely unlike conventional HD. MD Anderson uses a blood flow of 200 mL/min and a dialysate flow of 100 mL/min. To avoid clotting they run an additional 100 mL per hour of normal saline pre-filter. Three quarters of this cohort was on vasopressors and seemed to tolerate the dialysis as evidenced by a trend toward decreasing vasopressor support over time and the ability to successfully remove fluid with the technique (average of 360 ml/h). The technique also provided good solute control with an 80% reduction in pre-treatment BUN and 73% reduction in pre-treatment creatinine by 48 hours.

Berbece and Richardson looked at cost and found daily SLED was about half the cost of CRRT ($1,431/week compared to $3,089 for CRRT with citrate and $2,607 with heparin). The same study also provided urea kinetics and found higher urea clearance with SLED (weekly Kt/V of 8.4 with SLED and 7.1 with CRRT). SLED was well tolerated with no hemodynamic instability in 86% of the treatments.

CRRT has two distinct advantages over SLED that keeps CRRT near and dear to the critical care nephrologist. Because CRRT is 'continuous', it allows for better volume control. Bouchard and colleagues have demonstrated that patients on CRRT are subject to less volume overload than intermittent HD. The other advantage is drug dosing. When SLED is deployed, the patient has two distinct periods of machine-induced clearance through the day: a period of excellent drug clearance with RRT is running, and then a clearance of zero when it is off. Because of this dichotomy, drug dosing is much more complicated and in order to get drug dosing right, many drugs need to be redosed immediately after SLED. When CRRT is running, drug dosing is much simpler–dose to the clearance that the machine is providing.

SLED has also been shown to be effective in lithium and salicylate toxicity.

Column1	IHD	SLEDD	CRRT
Name	Intermittent hemodialysis	Slow (or sustained) low efficiency daily dialysis	Continuous renal replacement therapy
Mechanism and molecules removed	Dialysis – mostly low MWt	Small + middle molecules with SLEDD/F	Small + middle molecules with CVVHDF
Use	Ambulatory CRF	Critically ill	Critically ill
	Hyperkalemia	Hyperkalemia	Non-ambulatory
Blood flow	300-400 mL/min	200-300 mL/min	50-200 mL/min
Dialysate flow	500-800 mL/h	1-2L/h	2-3 L/h
Efficiency	High	Moderate	Low
			(but increased clearance of high VD molecules over time)
Hemodynamic stability	Poor	Good	Good
	(hypotension common)		
Duration	3-4 h 3x/week	6-12 h daily	Continuous (24h/filter)
Access	Fistula or vascath (must be good!)	Fistula or vascath (must be good!)	Vascath only
Anticoagulation	Not needed	Usually not needed	Important
		(if filter clots lose 150 mL blood)	(if filter clots lose 150 mL blood)
Dialysis Dysequilibrium Syndrome (DDS)	Insufficient time for equilibration between compartments can cause cerebral edema	N/A	N/A
Drugs and toxicology	Risk of rebound if high VDBetter for low VD (e.g. toxic alcohols)	Unclear effects on drug pharmacokinetics	Slower removal
Logistics	Need tap water supply,	High start up costs, low familiarity,	High workload, clearance limited by interruptions, costly sterile dialysate bags, immobility
	need hygienic effluent removal, Technically difficult	low running costs, Hypophosphatemia	

Conventional RRT in Sepsis

Conventional intermittent HD has repeatedly been tested against the darling of critical care nephrologists, CRRT. However, despite going head to head in meta-analysis after meta-analysis, intermittent HD continues to hold its head up high. When CRRT and conventional intermittent HD were compared as initial modality for RRT, there was *no significant difference* in mortality or renal recovery.

These studies might all be suffering from selection bias, because they typically exclude conventional intermittent HD from patients too unstable to tolerate the therapy.

Additionally a recent negative study showing that SLED combined with antimicrobial therapy failed to decrease the initial high plasma IL-6 concentrations noted in patients with sepsis, ie, high initial plasma IL-6 concentrations have been shown to directly correlated with in-hospital mortality. Though no data was presented on whether intermittent HD was able to lower IL-6.

Intermittent HD is like Northern Iowa. A throwback to an older style of college basketball, a time where coaches would recruit players to play for 4 years and mature in the program, a time before one-and-done stars. Intermittent HD has loads of theoretical reasons why it should not be effective and have inferior patient outcomes, but it just keeps plugging away, defying the predictions and matching continuous therapies outcome for outcome.

AKI Indices vs Furosemide Stress Test in AKI

In the excitement that surrounds biomarkers, no major biomarker has emerged as a true functional *troponin of the kidney*. Unfortunately though, without novel drugs or therapies nephrologists are left a bit like the mythic Cassandra, able to predict the coming AKI but with unable to alter the outcome.

The discussion of functional markers is important beyond the question of diagnosis, the other critical question nephrologists and intensivists are faced with in AKI is when to initiate renal replacement therapy. As Dr. Chawla wrote:

RRT is an invasive procedure with inherent risks, and one would not want to initiate this therapy if the patient were destined to recover renal function without intervention. However, a more conservative approach of initiating RRT late in the course of the AKI can subject the patient to adverse consequences.

So there is a need for a test that can do more than determine who will develop AKI but hint at the natural history that AKI will take in any individual patient. While biomarkers may play a role in this determination, NephMadness will be going old school to look at two functional markers and how they may help determine this, the traditional AKI indices, FENa, FEUrea, urine microscopy versus a new provocative test, the furosemide stress test.

AKI Indices

What physicians are more enamored with equations than nephrologists? The kidney has inspired equations for GFR, proteinuria, sodium correction, acid-balance, and just about any

other renal metric you can put a number to. With all these equations and smart phones remembering both the equation and doing the math we are left with too many people with mathematical precision but lacking physiologic context. Even as long as 40 years ago nephrologists were stressing the importance of context in order to understand the equations and numbers that spill out of the chemistry laboratory. Kimmel et al look at how CKD confounds FENa evaluations and discusses other pitfalls in common nephrology equations. It is a good read.

The time-honored renal indices have fallen on hard times as their validity has been questioned. Recently, Pons *et al* looked at whether FENa, FEUrea, Urine/Plasma Creatinine, or Urine/ Plasma Urea could differentiate transient AKI (less than 3 days) versus persistent AKI (more than 3 days) among critically ill patients in the ICU. None of the four indices was much better than a coin toss in predicting the duration of AKI (area under the receiver-operating characteristic curve 0.50 to 0.59). A similar trial looking only at FEUrea confirmed these findings.

Interestingly, urine microscopy has been evaluated for its ability to predict AKI prognosis. Bellomo's group looked at urine microscopy in septic and non-septic AKI and found more tubular cells and granular casts with sepsis. The higher urine microscopy scores also predicted worsening AKI with a specificity of 97% as well as need for RRT and death. Perazella found similar results in his cohort of 249 patients with AKI.

The traditional calculations of renal sodium handling and concentrating ability seems to provide little prognostic information but the urinalysis, essentially a liquid biopsy of the tubules, provides diagnostic and prognostic information. Maybe it is time for us to fire up the centrifuge instead of the iPhone apps during AKI consults.

Furosemide Stress Test in AKI

The furosemide stress test (FST) is a provocative test to separate out patients with AKI who are going to progress to higher AKI stages and possibly dialysis from those who will have a less severe course. The FST relies on the intuitive concept that responding to furosemide requires a patient to have a mixture of an adequate GFR, a functional proximal tubule (to move furosemide from the blood into the proximal tubule via organic anion transporter), and a functional thick ascending limb of the loop of Henle. Chawla et al hypothesize that "the kidney's response or lack of response to a furosemide challenge, as a clinical assessment of tubular function, could identify patients with severe tubular injury before it was clinically apparent."

In the first publication, Chawla created and validated a standardized approach to using furosemide to assess the likelihood of progressing to more advanced AKI. They gave AKI patients 1 mg/kg of furosemide IV, or 1.5 mg/kg if the patient had received loop diuretics in

the previous 7 days. They replaced all urine output mL for mL with isotonic crystalloids to prevent hypovolemia. Retrospectively it was clear that patients that had progressive AKI had much poorer response to the FST right from the first hour through the 6 hours of observation but the biggest spread, the point of maximum differentiation, came at hour two. A urine output of over 200 mL in the second hour after the FST indicated a lack of progression, with an AUC of 0.87. Sensitivity was 97.1% and specificity was 84.1%. To make matter worse for FeNa, its AUC was 0.51, a hair above the threshold of being completely useless.

Koyner et al took a look at the same cohort but used frozen specimens to see if the addition of biomarkers added additional information. They found that the FST out performed NGAL, IL-18, KIM-1, IGFBP-7xTIMP-2 (the recently licensed nephrocheck), urine creatinine, and FENa. From the discussion:

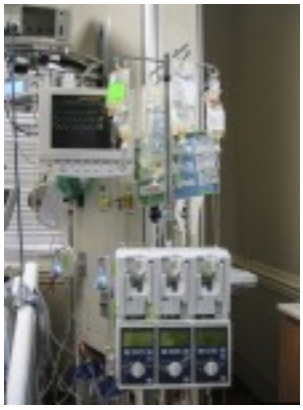
> *Specifically, FST was significantly better than our complete panel of urinary biomarkers at predicting progression to AKIN stage 3. The addition of biomarkers to FST results did not provide any additional benefit. Similarly, FST outperformed all other biomarkers in predicting the end point of receipt of RRT and inpatient death.*

The FST has also been used to determine if a patient can successfully discontinue CRRT.

We have all had an intuitive sense that the patient who doesn't respond to diuretics is the person more likely to need dialysis and likely to do poorly. The difference between that foreboding and data is the standardized approach created by Chawla. Remember 1 mg/kg should provide 200 mL of urine in 1-2 hours.

Which one will move on to the next round? The urinary tests that predict AKI or the furosemide stress test–both common approaches that we perform on a daily basis. Tough decision here!!

Norepinephrine vs Vasopressin in Sepsis



Sepsis is characterized by increased cardiac output but even greater vasodilation such that patients are often hypotensive. Initial volumes on the order of 30 mL/kg are typically recommended. Following initial resuscitation, additional volume can be given and should be continued as long as additional fluid continues to improve the hemodynamic response. When the response fades and the patients are still hypotensive, they should be given vasopressors. When deciding on the vasopressor to choose the physician is confronted with a wide variety of choices: dopamine, epinephrine, norepinephrine, vasopressin, and phenylephrine are all on the menu.

NephMadness is throwing two of these gladiators into the arena: norepinephrine and vasopressin. Which one is better for sepsis? How do they affect renal function?

Norepinephrine in Sepsis

Norepinephrine has emerged from the pack of vasopressors on the back of randomized controlled trials, meta-analysis, and international consensus guidelines. The Surviving Sepsis campaign lists norepinephrine as the first-line vasopressor with an evidence grade of 1B. From the rationale:

> *Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock.*

In head to head trials norepinephrine had lower short-term mortality (RR, 0.91) while dopamine had a higher rate of arrhythmias (RR, 2.34).

Nephrologists get skittish with this recommendation because intra-renal norepinephrine has been used in experimental models of ischemic AKI. Forgive us if we don't want to give our patients the same poison we are using in the lab to induce renal failure. Consistent with this is that decreases in renal blood flow are seen in normal volunteers given norepinephrine.

However, in a detailed study that looked at norepinephrines effects on renal perfusion, resistance, oxygen supply and oxygen uptake in post-cardiac surgery patients with AKI (KDIGO grade 1) found surprising results:

- Renal blood flow remained stable across a range MAPs from 60-90 mm Hg
- Oxygen delivery was highest at a MAP of 75 (higher than at 60 or 90)
- Renal vascular resistance rose with increasing MAP
- GFR was highest at a MAP of 75 (higher than at 60 or 90) and did not go up as blood pressure climbed to a MAP of 90
- Renal oxygen consumption was highest at the low MAP of 60
- Urine flow increased linearly with MAP

The authors concluded that using norepinephrine to increase MAP to the generally recognized target of 75 improved rather than compromised renal perfusion and oxygenation. Further increase of the MAP to 90 mm Hg did not further affect these variables.

Norepinephrine seems to stand strong in sepsis whether you look at renal perfusion and oxygenation or patient survival and adverse events.

Vasopressin in Sepsis

Vasopressin is one of the endogenous hormones secreted in response to hypotension, and known to stimulate a family of receptors, namely AVPR1a, AVPR1b, AVPR2, oxytocin receptors, as well as purinergic receptors. It causes a catecholamine-independent arterial smooth muscle contraction.

Septic patients relationship with vasopressin is complex. Patients have a relative deficiency of circulating vasopressin, particularly in advanced stages, but vasopressin receptor levels are downregulated as are oxytocin receptors in the heart. This is important because oxytocin receptors cause vasodilation. The loss of oxytocin vasodilation may explain the increased cardiac mortality with vasopressin in some mouse models of ischemia/reperfusion injury.

Early in septic shock, vasopressin spikes, but endogenous vasopressin supplies quickly exhaust themselves, leaving the patients with low levels. Supporters of vasopressin in sepsis cite the following plausible mechanisms for its major role on the resuscitative management of such patients:

- There is a deficiency of vasopressin in septic shock
- Low-dose vasopressin infusion improves blood pressure
- Low-dose vasopressin decreases norepinephrine requirements
- Low-dose vasopressin improves renal function

The rubber met the road of vasopressin versus norepinephrine in the epic Vasopressin and Septic Shock Trial (VASST). This trial randomized pressor-dependent patients with septic shock to either vasopressin or norepinephrine. Outcome was 28-day mortality. The study was double blinded and the trial used fixed dose study drug but the nurses used additional open label vasopressors to keep MAP at 65-75. The investigators predicted 60% mortality in the norepinephrine group and powered the study to detect a 10% reduction in mortality with vasopressin. However the mortality rate was only 39%, vasopressin's mortality was 35.4% (P=0.26). So the drug hit the predicted reduction in mortality of 10% but the unpredicted better outcomes of the patients resulted in an underpowered study. Adverse events were similarly balanced between the groups, though there was a trend toward a higher rate of cardiac arrest with norepinephrine (2.1% vs 0.8%, P = 0.14) balanced against a trend toward higher rate of digital ischemia with vasopressin (2.0% vs 0.5%, P=0.11).

Though the investigators suspected that vasopressin would provide more protection in more severe sepsis, they actually found a lower mortality in the patients with less severe sepsis (as defined by lower norepinephrine infusion rates at baseline). The authors cautioned that these were secondary outcomes and were not adjusted for multiple comparisons.

Interestingly, a post hoc analysis of the VASST study that looked at patients with AKI (RIFLE Criteria risk) suggested that septic patients treated with vasopressin had decreased risk of progression to more advanced stages of AKI and a trend to decreased mortality. However, the authors cautioned that perhaps the observed beneficial effects of vasopressin may have been actually secondary to a decreased exposure to norepinephrine.

At this time, vasopressin still seems to be a drug on the precipice. VASST was its chance to shine but due to the excellent care and improved sepsis survival, it was unable to meet expectations. The most recent meta-analysis continues to show what the authors of the Surviving Sepsis campaign concluded: good enough for second line; not yet ready for prime time.

Increased MAP vs Early Goal Directed Therapy in Sepsis

This is a contest between two ideas in critical care that have failed after high-profile randomized controlled trials. One, increased MAP targets, was trying to muscle out the long-time standard of care MAP of 65 mm Hg, while the other, Early Goal Directed Therapy (EGDT), has been a staple of sepsis resuscitation for over a decade.

Increased MAP in Sepsis

$$\text{mean arterial pressure} = \left(\text{Cardiac Output} \times \text{Systemic vascular resistance}\right) + \text{Central Venous Pressure}$$

$$\text{mean arterial pressure} = \tfrac{2}{3}\,\text{Diastolic Pressure} + \tfrac{1}{3}\,\text{Systolic Pressure}$$

It has been a time-honored dictum that “a higher MAP is better than a lower MAP.” This is supported by observational studies showing lower MAP in patients who develop AKI and increased need for RRT when the MAP was below 75 mm Hg. This data is bolstered by a small interventional study that demonstrated improved urine output when the MAP was increased from 65 to 75, but without further improvements at 85. Likewise, it has been shown that prolonged hypotension (MAP < 60 mm Hg) is associated with increased mortality.

Target MAP of > 65 mm Hg has been used by most studies based on the premise that lactate clearance was diminished when targeting lower MAPs. However, the upper MAP threshold has remained controversial. It has been shown that maintaining an MAP > 70 mm Hg at the expense of increased vasopressor dose and duration coincided with increased mortality.

In 2002, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine partnered to form the Surviving Sepsis Campaign (SSC). Their stated goal was to investigate physicians' views on sepsis focusing on current definitions, routes to diagnosis, and treatment options. In 2012, SSC published the International Guidelines for Management of Severe Sepsis and Septic Shock was published. In the section on hemodynamic support and adjunctive therapy, the guidelines made a grade 1C recommendation to target an MAP 65 mm Hg as an initial goal, though they advise practitioners to consider a higher goal for patients with a history of hypertension or atherosclerosis. Additionally they advise that frequent assessment of end-organ perfusion such as urine output, lactate, mental status, and skin perfusion supplement the blood pressure data.

In 2014, the multi-center, open-label trial SEPSISPAM supported these recommendations. 776 patients with septic shock were randomized to either a high-target MAP of 80-85 mm Hg or a low-target MAP of 65-70 mm Hg. 28-day and 90-day mortality was the same in both groups. The study also supports the secondary recommendation to individualize MAP targets, as there was less need for RRT among patients with a history of hypertension who were randomized to the higher blood pressure target.

Early Goal Directed Therapy

Occasionally there are advances in medicine that make a clean break before and after. In sepsis that occurred with the publication of Rivers' Early Goal-directed therapy (EGDT). Rivers' study was published just a handful of months after activated protein C made a splash with PROWESS. But while PROWESS was a phenomenally expensive treatment with significant associated risk of bleeding to provide 20% improvement in survival, EGDT promised a 35% reduction in mortality by providing a logical, intuitive, systematic, approach to improving perfusion in sepsis. Rivers' approach was hailed as a breakthrough and put in place as the standard of care worldwide.

The Rivers study was a single-center RCT with 263 patients with severe sepsis (2 of 4 SIRS criteria and either a lactate > 4 mmol/L or SBP <90 after fluid resuscitation). They randomized 263 patients to either protocol-based therapy or standard therapy. The protocol focused on three goals to improve perfusion:

1. Increase the central venous pressure to 8-12 mm Hg. The protocol used IV colloids or crystalloids to achieve that.

2. Get and regulate the MAP to between 65 and 90 mm Hg. The protocol used vasopressors and vasodilators to achieve that.
3. Get the mixed venous oxygen saturation over 70%. The protocol used transfusions and inotropic agents to achieve that.

The main concept underlying EGDT is that generalized tissue hypoxia precedes overt hypotension, and early recognition of this situation allows one to optimize oxygen delivery to tissues. By utilizing an organized approach to certain hemodynamic parameters (CVP, MAP, SCVO2), one can avert the complications that may arise from tissue underperfusion. This straightforward protocol became the mantra of sepsis care for a decade. The 2012 International Guidelines for Management of Severe Sepsis and Septic Shock gave EGDT a 1C recommendation. This adoption of protocolized care led to significant improvements in morbidity and mortality rates (10-12% decrease in mortality nationally). Adherence to EGDT has translated to a 20% decrease in hospitalization-related costs and decreases in length of hospitalization by 4-5 days.

But all good things must come to an end…

In 2014, PRoCESS (Protocolized Care of Early Septic Shock Trial) was published. This 5-year, 31-center, trial randomized 1,241 patients to one of three resuscitation strategies for early septic shock:

1. Protocol-based EGDT: 439 patients
2. Protocol-based Standard Therapy (DID NOT require a CVC, inotropic drugs, or blood transfusions): 446 patients
3. Usual Care: 456 patients

The primary outcome was in-hospital death from any cause at 60 days and no difference among the three protocols could be detected. Interestingly, the authors used an estimate of 30-45% mortality for their power calculation based on the Rivers study but the 21st century has been kind to sepsis patients and they found only 20% mortality. The authors concluded that “protocol-based resuscitation of patients in whom septic shock was diagnosed in the emergency department did not improve outcomes.” Of note, the incidence of AKI was higher in the Protocol-based Standard Therapy (6% vs 3% in the other groups).

A second study from Australia/New Zealand, also published in 2014, comes to much the same conclusions. The ARISE study was done in 51 emergency departments. They randomized 1,600 patients to EGDT or usual care. They also found no difference between therapies in the background of dramatically lower mortality from sepsis.

Did EGDT only offer advantages in a world that was not as good at treating sepsis as it is now? Was EGDT an important step in getting people familiar with the goals and tools for treating sepsis such that after a decade and a half we no longer need a protocol, we do it by nature? Or was EGDT just a small single-center study subject to bias and inflated effect size?

When all is said done, we can conclude that EGDT per se is not better than good old-fashioned bedside titration of care, but there are some real advances that we have taken from the original EGDT study that we must acknowledge.

- First, elevated lactate levels often allow us to 'reveal' shock early in the course of the disease and lactate clearance is an excellent marker for improved outcomes.
- Second, none of the new trials compared 'late' therapy to 'early' therapy, they only compared protocols on how early therapy is conducted.
- All emergency departments and ICUs now recognize that 'shock' is a medical emergency, and that prompt resuscitation is mandatory.

This situation was not always the case – many a patient sat in the ED after getting their 1 liter of saline awaiting an ICU bed prior to the publication of the original EGDT study. There is no going back, early is better and although this should have been obvious, we can thank the EGDT investigators for making this abundantly clear.

– Post written and edited by Drs. Joel Topf, Edgar Lerma, and Lakhmir Chawla.

Obstetric Nephrology Region

The most intense and emotional moments one can have as a nephrologist are centered around obstetrics.

Phyllis August, MD, MPH

Dr. August is the Ralph A. Baer, MD Professor of Research in Medicine, and a Professor of Medicine, Public Health, and Medicine in Obstetrics and Gynecology at Weill Cornell Medical College. She is Director of the NYP-Weill Cornell Hypertension Center, and the Program Director for the Nephrology Fellowship training program. Dr August is an expert in the field of hypertension and nephrology, Dr. August is committed to the prevention and treatment of high blood pressure. Her clinical practice at Weill Cornell is largely devoted to prevention and treatment of hypertension, kidney disease, and cardiovascular disease. She has served on numerous government advisory boards providing guidelines for the treatment of hypertension and hypertension in pregnancy. She is currently an Associate Editor for JASN.

Some examples include:

- Discussing fertility with young women about to start cyclophosphamide

- Deciding if it is safe for a patient with CKD from IgA nephropathy to try and have children
- Helping a patient with Gitelman syndrome through pregnancy
- Going from “I’m pregnant” to “It’s a girl!” with a patient on dialysis

These scenarios can be terrifying while simultaneously being intensely rewarding. These obstetric issues and clinical scenarios are thankfully rare but that means that few nephrologists deal with them regularly enough to be fully comfortable. That is the reason the Obstetric Nephrology region is in the tournament and the reason nephrologists need to buckle down and know their obstetrics. Any of these concepts could break out and make a run for the final four. Podocyturia in Preeclampsia vs sFlt1 in Preeclampsia

Preeclampsia represents the intersection between nephrology and obstetrics. Some have even suggested that it is the most common glomerular disease in the world. The last two decades have seen some significant advances to understanding both the treatment and pathophysiology of this disease. Nephrologists were at the center of many of these advances. Preeclampsia affects ~3-5% of all pregnancies worldwide and contributes to significant maternal and fetal morbidity and mortality. sFlt1 really jumped on the scene first in 2002 in a *JCI* paper (a nephrology fellow at the time, Dr. Maynard, was the first author!) and then in 2004 with this publication by Levine et al in the *NEJM*. sFlt1 is like the the UNLV of the mid-90s. The news of sFlt1 radiated throughout all of medicine not just nephrology and obstetrics. It was a major breakthrough. Team podocyte is starting to emerge as a serious contender as well. Let’s take a look at this intriguing matchup a little closer.

Podocyturia in Preeclampsia

Podocyturia is all the rage in almost every form of kidney disease. From diabetes, to FSGS, to lupus to glomerulonephritis. In fact, recent evidence is pointing to the presence of low level podocyturia even in normal individuals. A recent *JASN* paper discusses the possibility of using podocytes captured in the urine for genetic testing. Studies have demonstrated the presence of podocyte protein markers in the urine of women with preeclampsia. To further explore whether the presence of urinary podocyte shedding would predict the onset of preeclampsia a study published in the journal *Hypertension* in 2013 looked at 3 groups of women all of which were followed prospectively from their initial clinic visit. They matched in a 3:1 ratio normotensive controls (n=44) against patients with gestational hypertension (n=15) and the study group who eventually developed preeclampsia (n=15). What did they find at the end of the second trimester.

- 100% of patients who eventually developed preeclampsia had podocyturia
- *None* of normotensive or gestational hypertensive patients did!

This equals 100% sensitivity and 100% specificity. Unbelievable! This paper also measured angiogenic factors (sFlt1, PIGF, and Endoglin). These produced much more heterogeneous data and it was difficult to predict which patients would eventually go on to develop preeclampsia. Since 2007, there have been ~11 studies (mostly small) that have demonstrated podocyturia in patients with preeclampsia according to a review published in *Kidney International* in 2014.

So why are patients with preeclampsia losing podocytes?

Since the presence of podocyturia predates the development of high blood pressure it stands to reason that this might be a very proximal event. This also suggests that the defect leading to preeclampsia also represents more than just endothelial injury and the podocyte might be involved as well. It has been postulated that the loss of podocytes could prompt glomerular destabilization, resulting in more podocyte loss and ultimately proteinuria. However, this is a small study that needs to be reproduced in a larger population. Advances in detection could help make the detection of podocytes in the urine a viable test.

sFlt1 in Preeclampsia

The identification of sFlt1 as a "biomarker" and a potential "pathogenic" factor was a huge advance in the field. What is sFlt1? It is soluble fms-like tyrosine kinase-1. It is actually a splice variant of the better known vascular endothelial growth factor receptor 1 (VEGF-R1). sFlt-1 freely circulates and reduces the level of both VEGF and placental growth factor (PIGF). A paper in *JCI* and another in *NEJM* solidified its role in preeclampsia. These publications demonstrate increasing levels of sFlt-1 and decreasing levels of PIGF in preeclampsia.

What is really happening here?

Is it the actual sFlt1 causing preeclampsia or is it preeclampsia itself leading to increased sFlt1 levels? Evidence has pointed to the production of excess sFlt-1 by the hypoxic/ischemic placenta. The sFlt-1 acts as a sort of sink for VEGF, not allowing it to bind to VEGF-R1 on the cell surface of the vasculature, further leading to generalized systemic endothelial dysfunction, and possibly worsening placental ischemia. In a real tour de force, Karumanchi and colleagues demonstrated that the administration of sFlt1 to pregnant rats induces the classic lesion of preeclampsia:

- Hypertension
- Proteinuria

- Glomerular endotheliosis

These results argue that sFlt-1 is “the” pathogenic entity responsible for causing the renal lesion of preeclampsia. This heralded great potential to actually offer novel treatment beyond blood pressure control, magnesium, and delivery. In 2010 another breakthrough came. A pilot study published in *Circulation* attempted to remove sFlt-1 with the use of apheresis treatment; however, this was not a randomized study. The authors examined the efficacy of using a negatively charged dextran sulfate cellulose column to adsorb sFlt-1 in 5 women with preterm preeclampsia and increased sFlt-1 levels. They showed that with one apheresis treatment, levels of sFlt-1 decreased. They also treated 3 women with very preterm preeclampsia and elevated circulating sFlt-1 levels with multiple rounds of apheresis. Again, they observed decreased sFlt-1 levels, reduced proteinuria, and stabilization of blood pressure without any evident adverse events. Just to note that there was no control group in this study. However, since this report nothing more has surfaced. A quick look at ClinicalTrials.gov shows a few trials that are currently in various stages of recruiting. Team sFlt-1 will be a difficult challenge for any team in this year’s NephMadness. A real UNLV from the Jerry Tarkanian era.

ACOG Blood Pressure Goal < 160/110 in Preeclampsia vs Lower Blood Pressure Goal in Preeclampsia

ACOG Blood Pressure Goal < 160/110 in Preeclampsia

Hypertension in pregnancy can be due to multiple etiologies:

- Pre-existing chronic hypertension
- Preeclampsia
- Gestational hypertension
- Preeclampsia superimposed on chronic hypertension

The prevalence of chronic hypertension among pregnant women has increased by 50% from 1995 to 2008 (0.9% to 1.5%). Gestational hypertension has likewise increased 184% from 1987 to 2004. Regardless of the etiology, the therapeutic goals in the treatment of hypertension are to prevent maternal morbidity (stroke, cardiac complications) while maintaining placental circulation and limiting medication toxicity to both the fetus and mother.

The definition of hypertension in pregnancy is the same as in non-pregnant patients (see last year's NephMadness winner, JNC8), however the American College of Obstetrics and Gynecology (ACOG) *doesn't recommend drug intervention until the blood pressure reaches or exceeds 160/110* and then recommends physicians to target SBP between 140 and 160 and a DBP between 90 and 100. They point to a case series by Martin et al in which 28 patients with either eclampsia or preeclampsia who sustained strokes were scrutinized in terms of blood pressure control. Martin et al showed that all strokes occurred at SBP > 155 mm Hg and all but one exceeded 160 mm Hg. Diastolic blood pressures and mean arterial pressures were not nearly as reliable at predicting stroke. Thus, the argument is that treatment is warranted only if the systolic is sustained over 160 mm Hg.

Doctors urging more aggressive blood pressure control, more in line with the rest of medicine, have been stymied repeatedly by the Cochrane review which has not been able to find any benefit to treating mild to moderate hypertension during pregnancy. This review includes the most recent RCT published this past January which randomized ~1000 pregnant women to either a target diastolic BP of 100 mm Hg (less tight control) or 85 mm Hg (tight control) and could not detect a difference in pregnancy loss or high-level neonatal care. There was also no difference in serious maternal complications or preeclampsia.

For now the weight of data rests on the side of decreased medical interventions and a "let it ride" mentality when it comes to mild to moderate hypertension in pregnancy. This will be a tough battle for first round supremacy for sure.

Lower Blood Pressure Goal in Preeclampsia

Obstetricians are more tolerant of hypertension than other fields in medicine. The reason behind this is three-fold:

- The outcome of interest is delivery of a healthy baby, and after delivery most of the hypertension and all of the controversy melts away. Given the limited time exposure there are fewer maternal events to worry about.
- There is legitimate concern regarding fetal exposure to antihypertensives: renin-angiotensin-aldosterone inhibitors are known teratogens and diuretics in the third trimester can induce premature delivery.
- Lowering blood pressure could adversely affect uterine hemodynamics, leading to decreased fetal growth and poor fetal outcomes.

Let's take a look at the fetal growth story first. In the absence of well done, adequately powered clinical trials, the alarmists point to this meta-analysis from 2000 which found a decrease in fetal weight of 145 grams for every 10-mm Hg decrement in blood pressure. However the R^2 was only 0.15, meaning that other factors were much more important than

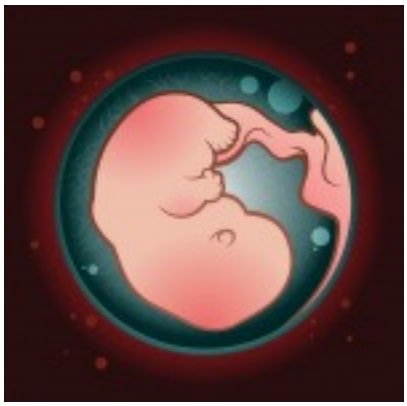
blood pressure at determining fetal weight. In the most recent RCT published in *NEJM*, there was no difference in the proportion of babies born at less than the tenth or third percentile for weight.

In regard to exposure to teratogens, there are certainly drugs that should be avoided but there is a cohort of drugs including methyldopa, labetalol, nifedipine, hydralazine and thiazides that are commonly utilized in pregnancy and have a long safety record.

And the last reason doctors are tolerant of hypertension in pregnancy is the belief that since pregnancy is a time-limited medical condition, there is little maternal morbidity from mild to moderate hypertension. This is probably false as the Martins et al case series of 28 women who had hypertensive strokes shows hypertensive morbidity is real and likely avoidable with judicious treatment of hypertension. Additionally, more aggressive use of antihypertensives in moderate maternal hypertension was shown to reduce the progression to severe hypertension while helping to avoid thrombocytopenia and elevated liver enzymes.

People are endlessly worrying about the over medicalization of natural human processes, but hypertension in pregnancy is pathologic and we have the means to treat it and should to prevent serious maternal complications.

Preeclampsia Due to CKD vs CKD Due to Preeclampsia



This is a chicken-and-egg–like paradox. We know that CKD is a risk factor for preeclampsia and we know that having preeclampsia predicts future kidney disease. The association of adverse renal and cardiovascular outcomes after preeclampsia is certain and conclusive. What remains to be determined is the etiology of this association. Does the preeclampsia cause renal and vascular damage that subsequently manifests as renal and cardiovascular disease? Or is preeclampsia merely the first symptom in a patient with underlying kidney disease that would have ultimately presented later even if the patient never became pregnant or developed preeclampsia?

Preeclampsia Due to CKD

Pregnancy in patients with CKD is surprisingly rare. The HUNT II study was an epidemiologic study performed in Nord-Trøndelag, Norway that recorded MDRD eGFRs for 66,149 people.

- In the subsequent 11 years there were 5,655 singleton pregnancies in women in HUNT II.
  - Only 6 were to women with an eGFR < 60 mL/min
  - None were to women with eGFR < 30 mL/min.

In the HUNT II study, no association was found between decreased eGFR and preeclampsia. However, very few patients had significant CKD. In contrast, women with hypertension and an eGFR < 90 had an increased odds ratio for preeclampsia:

- OR of 1.82 in women with hypertension and GFR > 90 vs normotensive women
- OR of 4.24 in women with hypertension and GFR < 90

Most other reports on preeclampsia in CKD have been case series. Cunningham reported 64% of women with severe CKD developed preeclampsia. In a case-control study women with CKD had an OR of 7.2 for preeclampsia.

While the data for increased risk of ESRD and kidney biopsy are compelling, what is surprising is that the results of the biopsies and the etiologies of ESRD are no different than found in the surrounding background population. One would think that if preeclampsia caused kidney disease it would cause one particular type of kidney disease that would be identified by providers at dialysis or at least by pathologists at biopsy. This may mean that the association of preeclampsia and future kidney disease is not due to kidney damage from preeclampsia but already existing subtle CKD increasing the risk for both the preeclampsia and subsequent kidney disease.

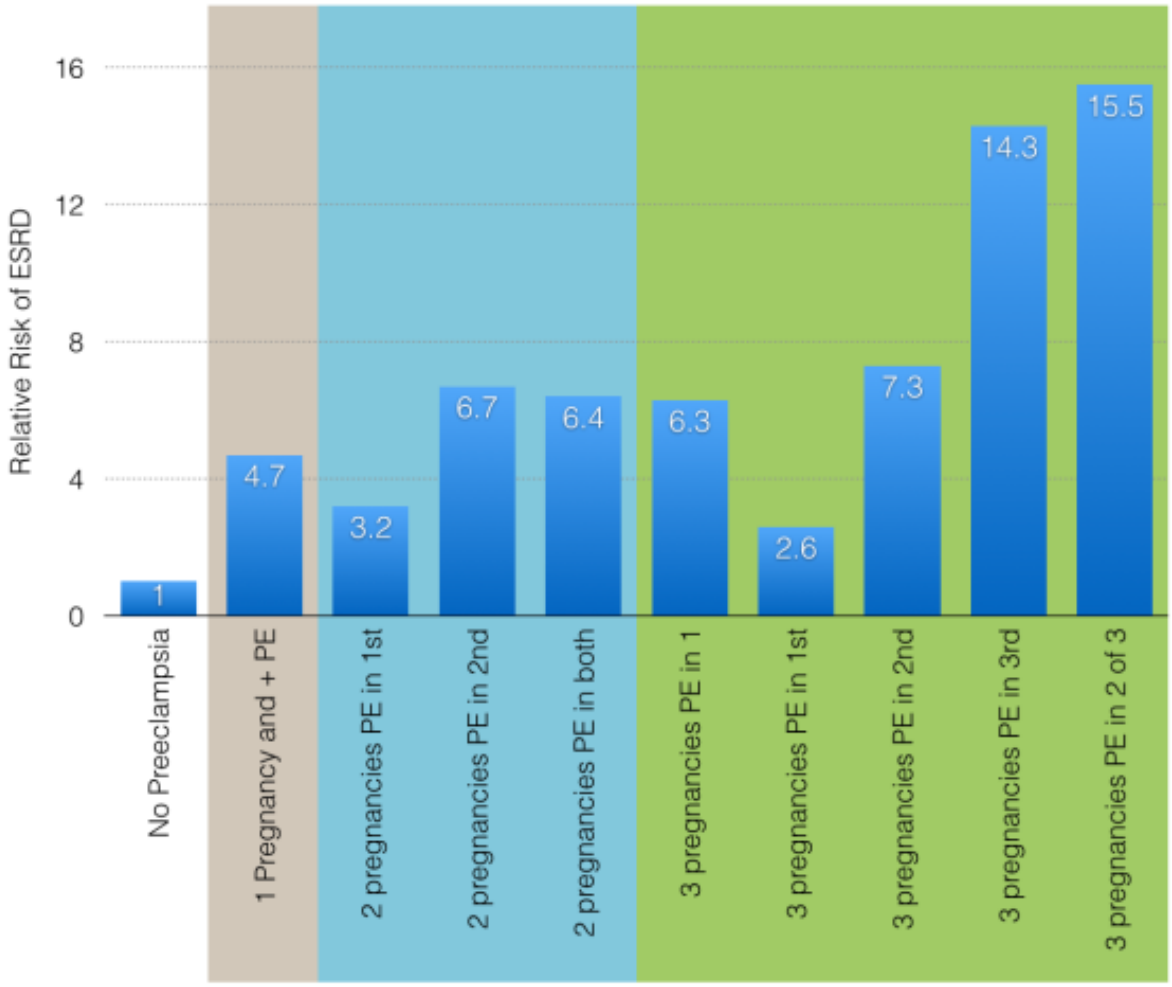
CKD Due to Preeclampsia

The more one looks at patients with preeclampsia the more it looks like the disease has significant health effects that last for years after the pregnancy. Hypertension, ischemic heart disease, cardiovascular death (8 fold higher in women with preterm preeclampsia compared to women with either term, or no preeclampsia!), albuminuria, and future kidney biopsy have all been shown to occur at increased rates after preeclampsia.

The most feared renal end point is dialysis dependence. Vikse et al did a comprehensive study of the association between preeclampsia and ESRD in Norway. Of the 570,433 women who had a baby between 1967 and 1991, 20,918 developed preeclampsia with the first pregnancy and 8,531 developed preeclampsia with a second pregnancy.

Preeclampsia during the first pregnancy was associated with a RR of ESRD of 4.7. The authors demonstrated a clear dose-dependent relationship with increased risk with more

episodes of preeclampsia. In women with multiple pregnancies, having preeclampsia in a later pregnancy was worse than having preeclampsia in an earlier pregnancy.



Data from Vikse et al.

To strengthen the findings, the authors examined the data after excluding patients with pre-pregnancy hypertension, diabetes or renal or rheumatic disease. Even with these patients censored the risk of ESRD remained, thus strengthening the assertion that the preeclampsia caused the kidney disease rather than the other way around.

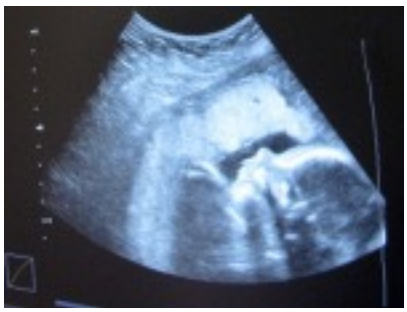
The association of pregnancy complications and ESRD is not limited to preeclampsia, having a low birth weight baby or premature delivery has also been associated with increased cardiovascular disease and ESRD.

Could preeclampsia and ESRD have a common cause that puts patients at risk for both diseases? Obesity, hypertension, insulin resistance, and endothelial function are all risk

factors for both outcomes. Antiangiogenic factors are another possibility leading to preeclampsia and for CKD.

Despite the accumulating evidence of harm that follows preeclampsia it is important to keep in mind that the vast majority (more than 99%) of women with preeclampsia never develop dialysis-dependent renal failure.

Pregnancy in ESRD vs Pregnancy in Kidney Transplant



Pregnancy in ESRD

Pregnancy in dialysis-dependent kidney failure leads to significant maternal and fetal morbidity and mortality. As a result, most experts advise women who want children to wait until a successful transplant, but when the biologic clock is ticking and the PRA is high and the wait for a transplant can be years. As such, pregnancy while on dialysis may actually be the best option. And sometimes it just happens.

The first hurdle with pregnancy in dialysis is fertility. Menstrual irregularities typically begin with a GFR of 15 mL/min and amenorrhea occurs at a GFR of 5 mL/min. Even when menstruation is maintained, ovulation can be absent due to loss of the LH surge. In a registry of female dialysis patients of childbearing age from the 90s the fertility rate was 2.4% for HD and 1.1% for PD over 4 years (0.5% per year for the entire registry). There is data that shows that fertility improves with a higher doses of dialysis. Also, registries and case series include women who get pregnant before starting dialysis and then required dialysis later in the pregnancy.

The earliest outcomes reported for pregnancies while on dialysis tended to be poor with only ~23% resulting in a live baby, with a mean gestational age of 32 weeks. But in 1998 Okundaye at al reported a trend toward better fetal survival in women who received more than 20 hours of dialysis a week. Three series have been published with all of the pregnancies occurring after 2000, and they have reported live delivery rates from 86% to 100% and dialysis hours from 20-48 hours per week (Eroğlu et al, Haase et al, Barua et al). In the two series that reported 100% live births, both employed intensive dialysis, either hemodiafiltration for 28 hours a week or nocturnal hemodialysis 48 hours a week. More impressive is that, in neither of those series did the women have significant residual renal function.

Anemia is a difficult problem in pregnancy given reports of increased EPO and iron requirements in pregnancy. Additionally estimating dry weight can be a challenge. Usually

there is little weight gain in the first trimester followed by up to a pound per week during the second and third trimester. Physicians should target weight gain of 25 to 35 pounds. Frequent reevaluation of dry weight is needed and extra care should be taken to avoid hypotension.

Another issue that can complicate pregnancy is fetal polyhydramnios (or excessive amniotic fluid). Polyhydramnios is postulated to be the result of fetal solute diuresis secondary to a high urea concentration. This was corrected by increased dialysis time and has not been reported in contemporary series with intensive hemodialysis.

Pregnancy in dialysis is rare, but increasingly possible with good outcomes. The most generalizable lesson from pregnancy and dialysis is that a formerly hopeless situation has been completely transformed by a radical rethinking of what the appropriate dose of dialysis should be. Might pregnancy be a lantern shining a the way to think about dialysis dose in general?

Pregnancy in Kidney Transplant

Fertility usually returns to ESRD patients within ~3-4 months after a kidney transplant. However, menopause typically occurs 4-5 years earlier in patients with ESRD than in the general population, so this should be considered if there is a delay in the return of fertility. Pregnancy is fairly common after kidney transplantation. Despite a number of registries to track pregnancy after kidney transplant a minority of pregnancies are actually tracked. This means there is, almost certainly, a significant reporting bias in these registries that needs to be kept in mind when looking at the data.

Guidelines suggest delaying pregnancy until after the peritransplantation period as this is the time patients are exposed to the most fetotoxic and teratogenic anti-rejection medications. Previously, guidelines have suggested delaying pregnancy at least 2 years. However, given the increasing age of transplant patients these guidelines are being replaced with more realistic guidelines. Look for a stable creatinine less than 1.5 mg/dL with less than 500 mg/24 hours of proteinuria and of course no fetotoxic infections (CMV, etc) or fetotoxic/teratogenic medications prior to pregnancy.

Current recommendations advise against mycophenolate mofetil (MMF) and rapamycin for 6 weeks before pregnancy. Though some recommend using higher doses of calcineurin inhibitors, most recommend doctors maintain pre-transplant drug levels. Frequent monitoring may be required due to changes in eGFR and plasma volume with pregnancy. Transplant rejection can be difficult to detect clinically but kidney biopsy is generally considered safe during pregnancy, as is methylprednisolone to treat rejection. The gravid liver may be more prone to azathioprine toxicity, so regular assessment of liver enzymes is

recommended. Tacrolimus pharmacokinetics can be altered during pregnancy and dose adjustments could be required.

Drug	FDA Category
CALCINEURIN INHIBITORS	
Cyclosporine	C
Tacrolimus	C
ANTIPROLIFERATIVE AGENTS	
mycophenolate mofetil	D
azathioprine	D
rapamycin	C
leflunomide	X
CORTICOSTEROIDS	
prednisone	B
ANTI-REJECTION MEDICTIONS	
methylprednisolone	C
muromonab-CD3	C
anti-thymocyte globulins	C

The National Transplant Pregnancy Registry reports that about a third of post-transplant pregnancies are complicated by preeclampsia, possibly related to calcineurin inhibitor effects. Most registries report a high risk of preterm birth and low birth weight, on the order of 50-60%, and usually it is due to maternal or fetal compromise, rather than spontaneous labor.

Patients with functional kidney transplants have been conceiving and delivering babies for ~50 years. They represent a high-risk population and care must be taken for the fetus, mother, and graft but good outcomes are still likely and it is probably the best road through ESRD to motherhood.

– Post written and edited by Drs. Joel Topf, Matthew Sparks, and Phyllis August.

Nephrology and Nutrition Region

At ASN Kidney Week anytime you go to a lecture that has to do with nutrition, it is standing room only. Nephrologists and everyone who takes care of kidney patients are intensely interested in what we put in our bodies. This is going to be a region to watch.

Team sodium is one of the most vilified and misunderstood teams in tournament history. How will they be remembered? High sodium intake driving increases in blood pressure or low sodium intake associated with increased mortality? As this matchup has important ramifications for global health, either could go deep in this year's tournament. The nutritional requirements of AKI is another grudge match between long time rivals.

Allon N. Friedman, MD

Dr. Friedman is an Associate Professor of Medicine and Medical Director of the Hemodialysis unit at Indiana University School of Medicine. Dr. Friedman completed his nephrology fellowship at Tufts Medical Center in Boston, MA, and is formally trained in medicine, nephrology, and clinical nutrition. He has received funding from the NIH and other non-profit institutions to perform clinical research on the overlapping topics of nutrition and kidney disease. He is actively involved in the American Society of Nephrology and the American Association of Kidney Patients on a national level.

Rounding out this region are two factors potentially modifying dialysis outcomes: low albumin and low BMI. In the former we look at the nature of low albumin inflammation versus malnutrition and in the later we dissect the epidemiologic data showing potential survival benefits of morbid obesity in patients on dialysis.

Wait, what? How can something called morbid be a survival factor?

Low Sodium Intake is a Risk Factor for Mortality vs High Sodium Intake is a Risk Factor for Hypertension

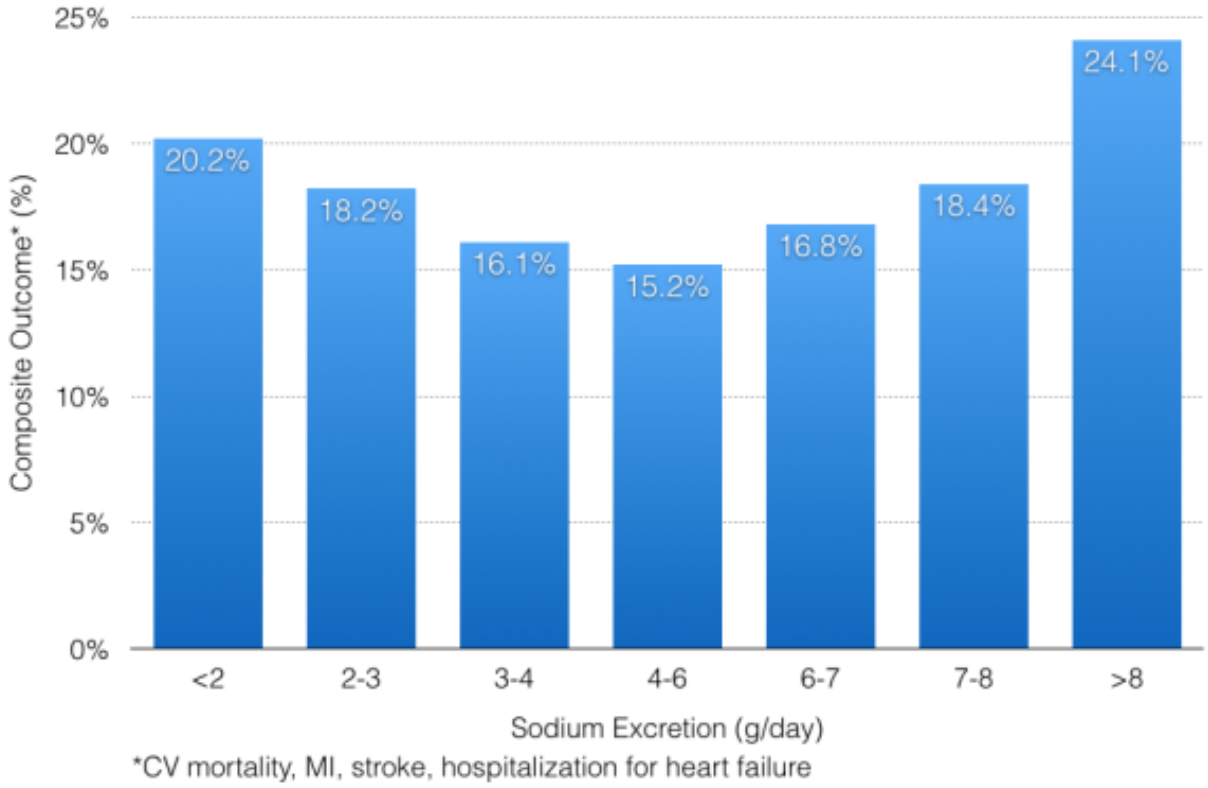
Sodium is the Wilt Chamberlain of nephrology boogiemen. Nothing in nephrology will ever earn both Rookie of the Year and MVP in its debut season, and the renal world will never see another player average 50 points a game for a season like Wilt the Stilt did in 1962. But when it comes to legacy, controversy, and importance, sodium is the Wilt Chamberlain of nephrology.

Sodium has been identified as a global health burden. Restricting sodium intake in order to reduce blood pressure and cardiovascular disease is a goal of just about every professional society or government health organization that walks the earth. The World Health Organization, US Department of Agriculture, NICE public health guidelines, American Heart Association, KDIGO, the CDC, and the Institute of Medicine have all recommended lower sodium intake. Despite all of those recommendations, US sodium intake has remained stubbornly elevated with no sign of dropping over the last 50 years.Given the ubiquity of the recommendations one could reasonably expect the science to be settled on the ill effects of dietary sodium, but emerging data over the last few years has kept the conclusions mired in controversy.

Low Sodium Intake is a Risk Factor for Mortality

Cross-sectional and epidemiologic data has repeatedly shown low-sodium diets to be associated with worse outcomes This was made clear when O'Donnell et al looked at sodium intake and adverse outcomes in the ONTARGET and TRANSCEND trials. Both of these trials looked at high-risk patients over the age of 55 with either established CV disease or high risk diabetes. Average 24-hour sodium excretion was 4.8 grams (208 mmol) or roughly double the recommended sodium intake for individuals. Expectedly morbidity and mortality rose as sodium excretion went up, but surprisingly, morbidity and mortality also rose as sodium

excretion went down from the average. The mortality was lowest at precisely the average sodium intake.



Data from O'Donnell et al.

The Belgians did a comprehensive evaluation of Flemish sodium habits and followed them for 8 years. Unlike just about any other study on sodium excretion, the Flemish Study on Genes, Environment, and Health Outcomes (1985-2004) and the European Project on Genes in Hypertension used honest-to-goodness 24-hour urine collections for all 3,681 participants. CV mortality was increased in the *lowest* tertile of sodium intake. During the follow-up, over 500 previously normotensive people developed benign hypertension. The incidence of hypertension was not influenced by baseline sodium excretion. Though interestingly, the cross-sectional analysis showed exactly what the large epidemiologic studies have shown, that increased sodium excretion was associated with increased blood pressure.

This curious association of increased CV mortality with low sodium excretion has also been found in the analysis of the NHANES 1, 2, and 3. Low sodium diets increase renin, aldosterone, and the sympathetic nervous system activity, possibly driving the increased adverse outcomes.

High Sodium Intake is a Risk Factor for Hypertension

He et al performed a Cochrane Systematic Review to determine the effect a reduction in dietary sodium (or more often urinary excretion of sodium) has on blood pressure and consistently found that even modest reductions of sodium for a month reduce blood pressure. In 22 trials of 1,990 people with hypertension, a reduction of salt excretion of 75 mmol (4.4 g) reduced blood pressure 5.39/2.82 mm Hg. A larger, 100 mmol (6 g) reduction in salt excretion lowered systolic blood pressure 10.8 mm Hg. The meta-analysis examined 2,240 normotensive individuals from 12 trials. A reduction in salt excretion excretion of 75 mmol (4.4 g) reduced blood pressure 2.4/1.0. A larger, 100 mmol (6 g) reduction in salt excretion lowered systolic blood pressure 4.4 mm Hg.

Translating these reductions in blood pressure to lives saved gives dramatic results. In the 2010 report of the Dietary Advisory Committee on the Dietary Guidelines for Americans, the authors estimated that a reduction in sodium intake of 400 mg/d would:

- Reduce heart attacks by 20,000 to 32,000 per year
- Reduce strokes by 13,000 to 20,000 per year
- Save between 17,000 and 28,000 lives *every year*

From a financial perspective this represents a savings of between $12 and $20 billion dollars annually.

Various experimental studies have been done to prove the relationship of sodium intake to blood pressure, and ultimately to lives saved, but few were quite as devious as Hsing-Yi Chang's study of Taiwanese nursing homes. Chang's group secretly randomized 5 nursing home kitchens to either normal sodium chloride or a mixture of sodium and potassium chloride. Sodium intake in the control group was 5.2 g/d and 3.8 g/d in the intervention group. In total, 768 veterans were served by the kitchens with low salt and 1,213 were served by control kitchens. After an average follow-up of 31 months there was significantly lower cardiovascular death in the intervention group (1,310 deathsvs 2,140 deaths per 100,000 person-years). This represents a reduction of CV death of about 60% compared to the control group. The authors also noted less health care expenditures in the group fed in the low-salt kitchens. Of course, the improvements in outcomes could as much be due to the increased potassium intake as the decreased sodium intake.

The world's government, medical, and professional organizations urge low-sodium diets because despite the holes, on balance low-sodium diets deliver reduced risk of hypertension, stroke, and cardiac disease.

AKI Needs More Nutrition vs AKI Needs Normal Nutrition

The AKI conference is one of the most important conferences in the Renal League. With 2 million people dying with AKI every year and AKI being the most common reason for inpatient nephrology consultation this is the conference to watch. Despite all the attention given to AKI, something as fundamental as how to feed patients with AKI is still controversial.

The two rivals in this conference are The Big Eaters (AKI needs increased nutritional support) and the Normal Nerds (keep nutrition needs steady despite the catabolic AKI). Another nutritional team, CKD, has almost no lessons for the AKI teams here. No one is advising protein restriction in AKI, even if it could curb uremia. Negative nitrogen balance is associated with mortality in observational trials of AKI.

Supporting the use of **increased nutrition in AKI** is a series of observational trials and underpowered interventional trials. There is no conclusive evidence on either side of the debate and the crowd must go with whatever observational data strikes their fancy.

Metabolic rate does not directly increase with AKI, however common co-morbidities like sepsis stimulate catabolism, resulting in increased energy requirements. If these patients are not provided any adequate protein nutrition (dextrose IVF only), a common situation in early in sepsis, they go into profound negative nitrogen balance. Energy and protein requirements rise as the body upregulates protein synthesis in order to synthesize acute phase proteins. Additionally, metabolic acidosis is catabolic, increasing energy demands. Use of renal replacement therapy can further increase calorie and protein demands.

method	protein loss
Conventional RRT	6-12 grams of amino acids and 2-3 grams of protein per HD session link
CRRT	1.2-7.5 grams protein per 24 hours 6-15 grams amino acids per day link

All of this supports the notion that protein and energy intake should be increased in AKI because negative nitrogen balance and malnutrition is associated with poor outcomes. Additionally, increasing protein intake does increase the nitrogen balance. Interestingly, increased protein supplementation has not been shown to improve outcomes in modestly sized studies.

The cheerleaders for normal nutrition point to the fact that the same study that showed improved nitrogen balance with high doses of protein also showed increased need for dialysis due to increased uremia. Likewise metabolic studies have showed that increased protein intake is catabolic in and of itself and will increase PCR. Lastly, energy consumption and supply in septic and critically ill patients is difficult to estimate because wildly differing metabolic rates from day to day. Additionally procedures, intolerance and other considerations means that prescribed nutrition is rarely delivered as anticipated.

Beyond protein requirements, increased calories have also been tested. In a RCT of 30 versus 40 cal/kg/d, the investigators found no difference in nitrogen balance but the increased calorie load was associated with more hyperglycemia, greater insulin requirements, and increased triglycerides. Certainly not a compelling case for more nutrition. Go Normal Nerds!

Obesity: ESRD Risk Factor vs Obesity: ESRD Survival Factor

At no point in his career did Shaquille O'Neal's points per game (career 24.6, highest season average 28.1 in '97-'98) exceed his BMI (35), but what a career he had, spanning 18 years. So could these two factors be linked, could increased BMI drive a long career, and could the same go for dialysis patients?

Obesity: ESRD Risk Factor

One large weakness in the reverse epidemiology theory is how can it just disappear after transplant. But study after study finds that obesity is no longer protective but harmful for kidney transplant recipients.

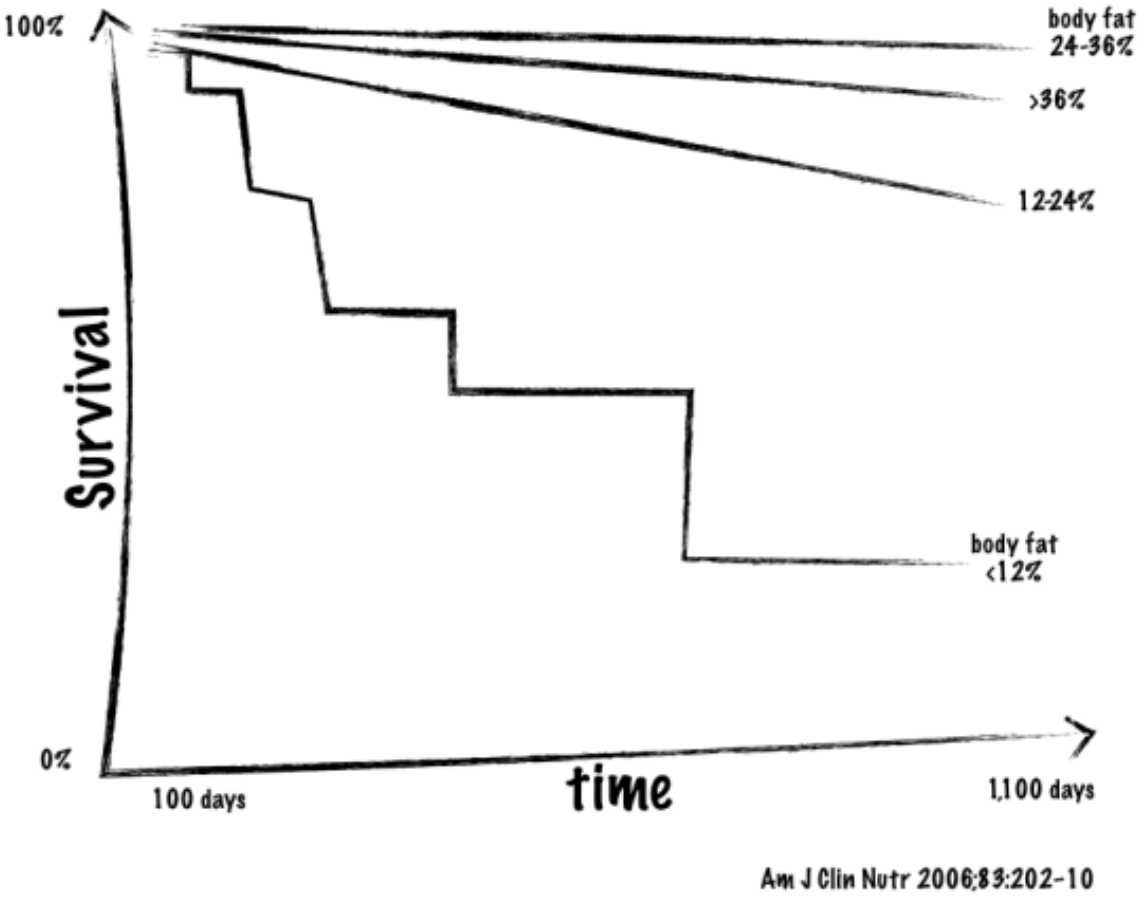
Meier-Kriesche et al looked at patient and graft survival after transplant based on the BMI at transplant, examining 52,000 transplants from 1988 to 1997. The authors found a U-shaped curve, similar to the one found for the normal population, with increased risk of death/graft loss at a BMI below 20 and ever-increasing risk as BMIs rise over 26. Similar results were seen in a surgical study that looked at both delayed graft function and non-death censored graft survival. For both outcomes, increasing BMI were harmful.

Additionally, while much of the increased BMI is due to fat, when attempts were made to look into what drove survival, patients with increased muscle mass driving the increased BMI did better than patients with fat driving the increased muscle mass. In fact the high BMI group with low muscle mass actually did worse than the normal BMI and high muscle mass (14% higher all-cause and 19% cardiovascular death). A second group looked at the

same question but instead of using 24-hour urine creatinine clearance at the onset of dialysis (a potentially suspect methodology) they used dual X-ray absorptiometry to look at body composition. Not surprisingly BMI was positively correlated with both lean mass index (LMI) and fat mass index (FMI). After 54 months of follow-up they found the familiar finding of lowest mortality in the highest BMIs but they then had data which separated out *fat* and *lean* body mass:

> *Patients in the highest FMI tertile had the lowest risk for all-cause mortality, although it was not statistically significant (P = 0.134). The patients in the highest FMI tertile showed a significantly reduced risk for non-CVD mortality (P = 0.004).*
>
> *Similar analyses were performed for LMI, although no significant univariate association was found between the LMI tertiles and the risk of death from all-cause, CVD, or non-CVD events.*

So this data doesn't seem to be consistent with the CrCl data. Another team used near infrared (NIR) interactance technology to determine the percentage body fat. They also used the Short Form 36 quality of Life Scoring System to expand the research beyond survival. And they tried to correlate the data with inflammatory markers. Interestingly, CRP and TNF-alpha concentrations were significantly higher in the lowest body fat percentage group than in the other 3 groups. (P=0.06). Quality of life scores worsened as percentage body fat went up. However the benefits of obesity still shined through with increased fat percentage being associated with better survival.

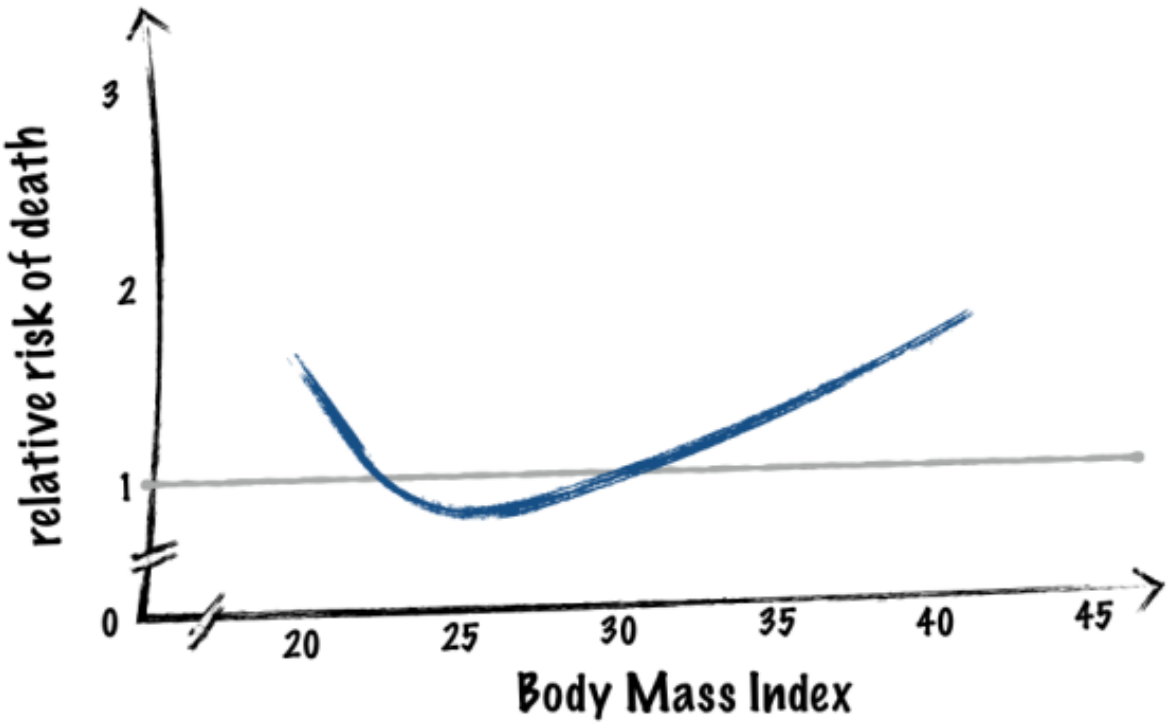


And once again when investigators looked at weight loss they found the same concerning findings uncovered in other trials, loss of at least 1% body composition fat resulted in a 30-month mortality HR of 1.98.

Though the bulk of data seems to be be in line with obesity, the weight-loss data should be stratified for intentional versus unintentional weight loss. In total this theory is being driven by epidemiologic data and association does not indicate causation. It is time for a trial of intentional weight loss so we can get some real answers.

Obesity: ESRD Survival Factor

Everyone feels like they know health when they see it. And everyone knows that obesity is not good for you. It is common sense that if you are obese you need to lose weight. Strangely, these seemingly immutable laws break down in the topsy-turvy world of dialysis. Obesity, which is a potent risk factor for death in normal populations, becomes a survival factor in dialysis.

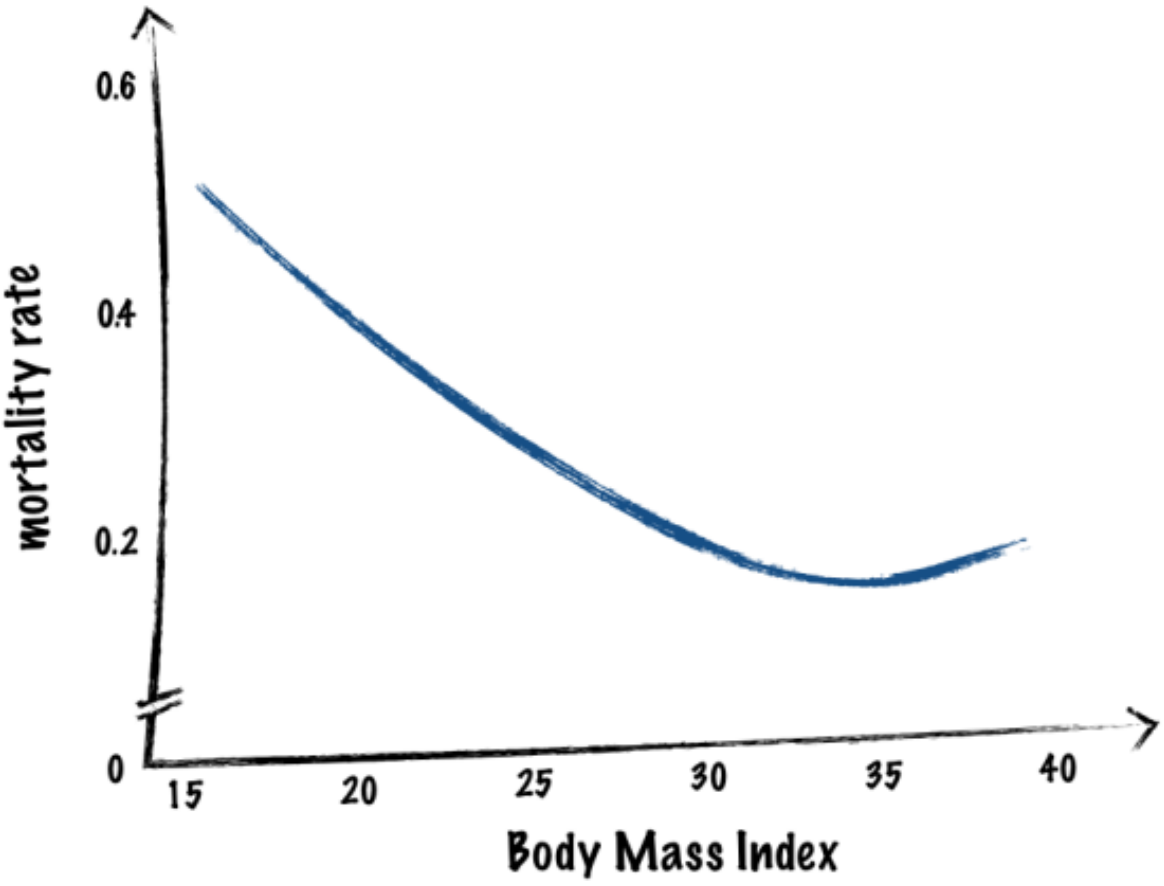


N Engl J Med. 2006 Aug 24;355(8):763-78.

How can a condition called “morbidly obesity” be a survival factor? From Kalantar-Zadeh’s analysis of weight and survival, “Both all-cause and cardiovascular mortality showed almost strictly decreasing rates across increasing BMI categories, ie, morbidly obese MHD patients had the greatest survival rates.” Reading that article you can almost feel the authors’ frustration at their inability to find an association of mortality with obesity, “Obesity, including morbid obesity, was associated with improved survival and decreased cardiovascular mortality, even after ***exhaustive adjustment for time-varying laboratory markers***. These associations were independent of changes in BMI over time.”

Kalantar-Zadeh then looked at patients with low and high protein intake, obesity was still protective, right up to and including the morbidly obese. Probably most troubling was the data on patients who changed weight. Half the cohort maintained a stable weight, the other half of the cohort gained or lost more than 1% of their baseline weight. Gaining weight had a higher mortality than a stable weight but losing weight was the most dangerous of all. Consider that, the next time the transplant team recommends your patient lose weight to become transplant eligible. The obesity paradox persists regardless of dialysis vintage or patient age.

As perplexing as that is, it is not unique to ESRD, obesity has been described as a survival factor in congestive heart failure.



Arch Intern Med Vol 165, Jan 10, 2005

COPD also has increased survival with increased BMI, as has rheumatoid arthritis. But the story truly takes a turn for the weird if you believe the results of Kovesdy et al, who looked at pre-dialysis CKD and found a survival advantage for obesity. And the advantage got larger the greater the BMI, with the best survival being reserved for patients with BMI over 36.7. The pattern was stronger in non-diabetic patients than diabetic patients, but the pattern was still there, even in diabetics. However other researchers have found obesity to be a potent risk factor for developing ESRD. Alan Go's team used Kaiser Permanente data to demonstrate a strong BMI dependent risk of increased ESRD. One possible limitation of that data is, if obesity is actually a survival factor, one would expect more ESRD with obesity because fewer patients would be dying of other illnesses leaving them alive and at continued risk of ESRD. Thinner patients with higher risk of death would be less likely to survive to dialysis.

Albumin: Inflammatory Marker vs Albumin: Nutritional Marker

Albumin is the Kentucky of our tournament. While every other biochemical marker of uremia has come under the control of the medical team–either through drugs, dialysis, or surgery–albumin remains elusive. Every year Kentucky sends 2, 3, or 6 players to the NBA. You might think this would deplete their ranks, but Coach Calipari keeps cupboard full with year after year of epic recruiting and the team remains great.

Albumin is the most stubborn biochemical marker in dialysis patients. Nearly every other marker of uremia and metabolic control has been improving with advances in dialysis:

- Dialysis dose has increased (URR from 63% to 73% from 1994 to 2004)
- Hemoglobin has increased (up 2 g/dL from 1994 to 2004)
- Creatinine has decreased (down 1.5 mg/dL from 1994 to 2004)
- Bicarbonate has increased (up 2.5 mmol/L from 1994 to 2004)
- Phosphorus has decreased (0.8 mg/dL from 1994 to 2004) and, importantly, has also narrowed its standard deviation

All of those characteristics have improved and may be driving steady improvement in dialysis survival. But one bad actor hasn't budged in decades: albumin. And in case you think things might have gotten better since 2004, take a gander at the USRDS which shows average albumin stuck at 3.2 for incident patients, with a fixed 20% of prevalent patients with an albumin below 3.2.

What makes it especially frustrating is that of all those metabolic markers, albumin is the one factor most associated with mortality. In Fresenius' examination of their own data, low albumin was a more powerful predictor of mortality and hospitalization than access type, diabetes status, or age. And it wasn't even close.

You would think that with it being such an important factor in dialysis mortality and morbidity, hypoalbuminemia would be public enemy number one at dialysis units. But instead we are left with some basic questions about the very nature of albumin. Is hypoalbuminemia an indicator of poor nutrition or an indicator of inflammation?

Albumin: Inflammatory Marker

The problem with albumin as a nutritional marker is the numerous and obvious places it falls down. There is no better model of malnutrition than starvation, yet in experimental conditions, starvation does not reliably result in hypoalbuminemia until very late. The degree of protein calorie malnutrition we see in dialysis patients is, quite simply, insufficient to cause the ubiquitous hypoalbuminemia seen in dialysis patients. Additionally, dialysis patients often experience rapid changes in albumin that are independent of changes in diet and have prolonged decreases in albumin that correlate better with increased inflammation. Inflammation simultaneously decreases albumin synthesis and increases albumin catabolism.

For example in multiple regression analysis, CRP replaces albumin as a predictor of all-cause and of CV mortality.

CKD (dialysis-dependent or not) is not alone in being a chronic disease associated with hypoalbuminemia. Other chronic diseases associated with wasting such as cancer and HIV also have prominent hypoalbuminemia. All of these conditions are unable to reduce resting energy expenditure (REE). The inability to reduce REE is likely part of the inflammatory response and drives the nutritional wasting that is a hallmark of these conditions.

A prospective study measured albumin and CRP while assessing nutrition through the subjective global assessment (SGA) and normalized protein nitrogen appearance rate (nPNA). When the authors related mortality to albumin they found the usual association of increased mortality with decreased albumin (HR of 1.47 for each 1-g/dL decrease in albumin). Strangely, adjusting for SGA had no effect on the risk and adjusting for nPNA had a tiny effect (HR, 1.45). However when the authors adjusted for inflammation, the risk was no longer significant (HR, 1.30; 95% CI, 0.95-1.78), indicating inflammation was a better proxy for hypoalbuminemia than malnutrition.

Part of the problem with the albumin and nutrition theory is that interventions that restore nutrition have a minimal impact on albumin. In an RCT that targeted 10 individual limitations on nutrition for dialysis patients that included etiologies as diverse as depression, shopping, and dentition, it was only possible to increase the albumin 0.21 g/dL (from a baseline albumin of 3.4), while the control group increased 0.06, a delta of only 0.15 g/dL.

In the most recent reviews of oral and parenteral nutritional supplements (Bossola et al, Dukkipatti et al, Sigrist et al, Kalantar-Zadeh et al) even when these techniques were able to improve albumin they have never been shown to improve survival. Some of this has been due to short treatments and underpowered trials but if these interventions are unable to improve survival, targeting low albumin is just a meaningless surrogate endpoint.

Albumin: Nutritional Marker

Conventional wisdom has long held that albumin reflects nutritional status. This is reflected in the numerous recommendations for dialysis patients to eat high-quality protein in response to a low albumin. See Davita's patient facing site or the numerous patient education posters that decorate dialysis units, "*Adequate protein nutrition is measured by serum albumin. If the albumin level is less than 3.6, the risks of dying or needing hospitalization increase several fold.*" Accepting the link between albumin and nutrition begins to explain other observations, such as the omnipresent hypoalbuminemia and the low protein and calorie intake of dialysis patients, typically 30% below guidelines.

Supporting this are dietary interventions that improve albumin. Enteral supplements given during dialysis have a variable history of increasing albumin, sometimes the supplement works, and sometimes it doesn't. A meta-analysis shows a small positive effect on albumin but nearly all the studies are small and short–a situation that invites publication bias. Likewise more exotic therapies such as intradialytic parenteral nutrition have been shown to improve albumin. Now granted, the improvement in albumin is modest, often as low as 0.2 g/dL. But the retrospective data show that seemingly modest changes in albumin can have dramatic effects on mortality; from Kalantar-Zadeh:

> *The sensitivity of measuring serum levels of albumin to predict outcomes in patients with CKD is high, with a granularity of as little as 2 g/L (0.2 g/dL) or less. In other words, a patient on dialysis with a baseline serum albumin concentration of 2 g/L (0.2 g/dL) above or below that of another patient with similar demographic features and comorbidities has a substantially decreased or increased risk of death, respectively.*

In summary, albumin has long been the most accessible indicator of nutrition, its value can be influenced by changes in nutrition, and so it must be a nutritional marker.

– Post written and edited by Drs. Joel Topf and Allon Friedman.

Genetic Nephrology Region

Genetics is a disparate collection of franchise players and rising stars. Just like in college basketball one dominant player can lift an entire team. Look at forward Frank Kaminsky from Wisconsin. While most people think he defines the prototypic "soft-shooting big man with quickness around the hoop". Here at NephMadness headquarters we think that is a pretty apt description of epigenetics in nephrology, which squares off against the genetics of vesicoureteral reflux.

Conall O'Seaghdha, MB MRCPI

Dr. O'Seaghdha earned his medical degree from University College Dublin, Ireland and his nephrology fellowship training in Ireland and subsequently in Sydney, Australia. He also completed the Harvard fellowship in nephrology. During his fellowship, he worked as a clinical researcher for three years in the Framingham Heart Study where his interests were in the epidemiology of CKD in the general population, novel biomarkers of CKD, and the genetic epidemiology of kidney disease. He was also editor of the nephrology blog Renal Fellow Network during this time. After his fellowship he was an attending physician and Transplant Nephrologist in Massachusetts General Hospital and Instructor in Medicine in Harvard Medical School. He returned to Ireland in 2013 to take up his current position as Consultant Nephrologist and Transplant Physician in Beaumont Hospital, Dublin and Honorary Senior Lecturer in Medicine in the Royal College of Surgeons and in Trinity College Dublin. He is also the National Specialty Director for Nephrology higher training in Ireland.

AD Tubulointerstitial Nephritis, medullary cystic disease, UMOD Nephropathy wow it has as many names as Ron Artest/Metta World Peace/Panda Friend. It faces off against arch enemy AR Tubulointerstitial Nephritis. The next matchup is the congenital form of a disease too familiar to basketball fans in its sporadic form, focal segmental glomerulosclerosis. Sean Elliott and Alonzo Mourning both had FSGS while in the NBA. APOL1 makes its second appearance in NephMadness after a strong showing in 2013 where it advanced to the elite 8 before falling to eventual tournament winner Kidney Transplant. APOL1 is going up against familial FSGS, a topic gaining strength with an explosion of basic science data. This one will be contested from tip-off to the final buzzer. Jahlil Okafor is a dominant force for Duke but like Magic Johnson and King James, he is known as much for his ability to score as his ability to find the open man and make his teammates better. This is similar to how genome wide sequencing and next-generation sequencing are merely the tools that will unlock todays secrets to discover tomorrow's cures. #NephForward indeed.

AD Tubulointerstitial Nephritis vs AR Tubulointerstitial Nephritis

This match-up of local rivals should be a humdinger! We have learned a lot more about the line-ups of both teams through recent genetic advances, although AD Tubulointerstitial Nephritis may be the pre-match favorite due to its star performer UMOD Nephropathy. Overall, however this appears to be an evenly matched contest and a highlight of the NephMadness first round.

AD Tubulointerstitial Nephritis

There have been a variety of names for these conditions, including medullary cystic kidney disease (MCKD), despite medullary cysts being far from universal, and familial juvenile hyperuricemic nephropathy. Modern genetic techniques have helped us hugely in characterizing these disorders and providing a molecular diagnosis in the face of nonspecific clinical data. Therefore, in the current era they are termed autosomal dominant (AD) tubulointerstitial nephritis.

AD tubulointerstitial nephritis comprises a group of familial disorders characterized by

- Bland urinary sediment
- Minimal hematuria
- Minimal proteinuria

- Progressive CKD

Histology is

- Generally nonspecific
- Tubulointerstitial pattern of injury
- Variable amount of tubular atrophy and interstitial fibrosis depending on the point in the natural history of the condition that the biopsy is performed.

1. UMOD Nephropathy

UMOD codes for uromodulin (also known as Tamm–Horsfall protein), which is expressed exclusively in the thick ascending limb of the loop of Henle and is the most common protein in normal urine.

Missense mutations in *UMOD* cause tubulointerstitial nephropathy with hyperuricemia, previously named MCKD type 2 or juvenile hyperuricemic nephropathy type 1. Common variants in *UMOD* have also been demonstrated in large genome-wide association studies (GWAS) to confer independent risk for both hypertension and kidney disease illustrating the shared risk for both phenotypes within this locus (see the GWAS in Nephrology team description for more).

The *UMOD* story got a lot more interesting when Trudu et al published an intriguing set of experiments establishing a link between uromodulin, hypertension, and kidney disease via activation of the renal sodium cotransporter NKCC2. *UMOD* risk variants identified in the above-mentioned GWAS are located in the promoter region of the gene leading to a theory that they altered *UMOD* expression. This was confirmed using human nephrectomy specimens and a large population cohort with urinary uromodulin levels. To model the effect in vivo, the authors used a transgenic mouse which over-expressed *UMOD* leading to salt-sensitive hypertension and interstitial nephritis. Moreover, they demonstrated that phosphorylated NKCC2 levels rose in tandem with *UMOD* gene dosage. In contrast to wild-type mice, the transgenic *UMOD* mice had marked improvement in blood pressure with furosemide (an inhibitor of NKCC2). Hypertensive humans with the variant showed a similar response to furosemide. We have known about the existence of uromodulin for some time but we are only beginning to understand it.

2. MUC1 Nephropathy

This disease, previously referred to as MCKD type 1, is due to a mutation in the variable-number tandem repeat region of the *MUC1* (Mucin 1) gene. The locus at chromosome 1q21 was identified by linkage mapping in 1998 but the gene has only recently been discovered due to difficulty with sequencing this highly repetitive region and was previously missed

using next-generation sequencing. Mucin 1 lies on the tubular cell apical surface and has a role in signal transduction pathways. The frameshift mutation results in the formation of a truncated protein which cannot fold properly, promoting aggregation, and subsequent deposition in tubular cells. These mutations could also occur sporadically in which case the lack of a family history would make the diagnosis even more difficult. It is certain that there are individuals and families with MUC1 nephropathy who are labelled as having hypertensive (or other) nephropathy with bland urinalysis and tubulo-interstitial fibrosis on biopsy.

3. Other Mutations

Mutations in the gene coding for renin (*REN*) also cause AD tubulo-interstitial kidney disease. Low renin expression has been demonstrated in renal biopsies of affected family members. It is thought that the toxic effects of the mutant protein reduce the viability of renin-expressing cells in and the juxtaglomerular apparatus, leading to nephron dropout and progressive tubulo-interstitial injury.

HNF1B encodes a transcription factor, hepatocyte nuclear factor 1β, involved in the early development of the kidney, liver, pancreas, and genital tract. Mutations in *HNF1B* may be sporadic or dominantly inherited and cause diabetes mellitus, pancreatic atrophy, abnormal liver function, early-onset gout, and mental retardation. Renal involvement may be evident early as cystic dysplastic kidneys, solitary kidney, or later as a tubulo-interstitial pattern of injury. The prevalence of spontaneous whole-gene *HNF1B* deletions may be as high as 50% in affected cases, explaining a lack of family history in many kindred. Some mutations may be incompatible with life and overall, *HNF1B* mutations appear to be the most frequent monogenic cause of developmental kidney disease. An excellent review of the spectrum of *HNF1B* nephropathy has recently been published.

With a big-name player like UMOD Nephropathy and rising stars such a MUC1 & HNF1B Nephropathy, AD Interstitial Nephritis may possess the right blend to go deep in this year's tourney.

AR Tubulointerstitial Nephritis

Familial tubulo-interstitial nephritis may also be inherited as an autosomal recessive (AR) trait. It is usually termed nephronophthisis, a rare disorder but one of the most common causes of ESRD in pediatric populations. The incidence is estimated at 1–20 cases per 1,000,000 live births. It presents earlier than AD interstitial nephritis, occurring in the first 3 decades of life. It may also have extra-renal manifestations, the commonest being retinitis pigmentosa. There are many syndromal forms of nephronophthisis/AR tubulo-interstitial nephritis with Bardert-Biedl syndrome being perhaps the most well known and others being Jeune syndrome, Joubert syndrome, and Senior–Løken syndrome. Bardert-Biedl syndrome

is characterized by retinal degeneration, obesity, learning difficulty, and a variety of other features such as polydactyly, hypogonadism, and hypercholesterolemia which show variable penetrance.

Histologically, nephronophthisis appears similar to AD interstitial nephritis with tubular atrophy, interstitial fibrosis and even corticomedullary cysts present. Genetic testing is the only way to distinguish nephronophthisis from AD interstitial nephritis, apart from mode of inheritance. Similar to AD tubulo-interstitial nephritis, there has been much progress recently in the molecular characterization of this phenotype.

The use of positional cloning and next-generation sequencing has facilitated the discovery of many nephronophthisis genes (*NPHP*). Their protein products, termed nephrocystins, localize to primary cilia placing nephronophthisis in the realm of other renal ciliopathies such as AD & AR polycystic kidney disease. Primary cilia are microtubule-like sensory organelles present on many cell types, including the apical surface of renal tubular cells. Currently 17 NPHP genes have been discovered, which together explain <50% of total cases (NPHP1 itself causes approximately 30% of cases). NPHP1-9 genes were discovered using a combination of genome-wide linkage and direct sequencing approaches in large pedigrees. More recent discoveries have been aided by next-generation sequencing. However, simultaneous analysis of all known mutations using massively parallel sequencing only led to a molecular diagnosis in 25% of cases, highlighted what remains to be discovered. Employing a candidate gene approach has proved useful (for *NPHP16/ANKS6*) by first identifying cilia gene products using proteomics and working back to the genes of interest. With >1000 known cilia proteins, this may enable the identification of many more nephronophthisis genes.

Nephronophthisis may also display polygenic inheritance, where mutations may be found in 2 or more susceptibility genes. Several families have been described that harbor mutations in several *NPHP* genes, which are known to interact. Furthermore, families with a nephronophthisis phenotype have been described having a single mutation in an isolated *NPHP* gene, suggesting they may have mutations in other, yet undiscovered *NPNP* genes as the condition is AR. These polygenic phenomena may also explain some of the incompletely penetrant extra-renal manifestations in certain individuals and families. For example, modifier effects of co-existing *ANH1* and *NPHP6* mutations have been suggested to cause extra-renal manifestations in Joubert syndrome due to *NPHP1* mutations.

While not as celebrated as its bitter rival, AR Tubulointerstitial Nephritis has made big progress of late thanks to modern genetic advances. It will fancy its chances against its conference rival in this big first round matchup.

NPHP Gene	Name	Location	Gene product
NPHP1	NPHP1	2q13	Nephrocystin 1
NPHP2	INVS	9q31.1	Inversin
NPHP3	NPHP3	3q22.1	Nephrocystin 3
NPHP4	NPHP4	1p36.31	Nephrocystin 4
NPHP5	IQCB1	3q13.33	IQ motif-containing protein B1
NPHP6	CEP290	12q21.32	Centrosomal protein of 290 kDa
NPHP7	GLIS2	16p13.3	Zinc finger protein GLIS2
NPHP8	RPGRIP1L	16q12.2	Retinitis pigmentosa GTPase regulator-interacting protein 1-like
NPHP9	NEK8	17q11.2	Serine/threonine-protein kinase Nek9
NPHP10	SDCCAG8	1q43	Serologically defined colon cancer antigen 8
NPHP11	TMEM67	8q22.1	Meckelin
NPHP12	TTC21B	2q24.3	Tetratricopeptide repeat protein 21B
NPHP13	WDR19	4p14	WD repeat-containing protein 19
NPHP14	ZNF423	16q12.1	Zinc finger protein 423
NPHP15	CEP164	11q23.2	Centrosomal protein of 164 kDa
NPHP16	ANKS6	9q22.33	Ankyrin repeat and SAM domain-containing protein 6
NPHP17	IFT172	2p23.3	Intraflagellar transport protein 172

Table 1: NPHP Genes so far identified

Epigenetics in Nephrology vs Vesicoureteral Reflux

This unlikely match-up sees 2 teams that have never met in the big dance face off in the first round. Both have had quiet pre-seasons but have certainly earned their right to this year's tournament with a number of standout performances. We continue to learn more on the genetics of Vesicoureteral Reflux

and Epigenetics in Nephrology is an exciting team for the future that has commentators buzzing.

Epigenetics in Nephrology

Epigenetics refers to alterations of gene expression at the level of gene transcription and translation without changes to gene sequence. These processes are modifiable by the cellular environment, potentially inheritable, and include DNA methylation, histone (major proteins in the chromatin) modifications, and regulatory changes induced by microRNAs (miRNAs). DNA methylation involves the addition of a methyl group to a cytosine base within CpG sites within promoter sequencing which influences gene expression, generally causing gene silencing. These mechanisms may, at least partly, explain how environmental factors interact with the genome to influence complex traits like kidney disease. The epigenome may also be thought of as a genetic-environmental footprint, explaining why in utero and early-life environmental conditions may lead to persistent lifetime and subsequent generation phenotypes (see Dutch Famine of 1944-45). Technologies to perform large-scale epigenetic analysis are evolving and have lagged behind traditional genomic techniques. However, the International Human Epigenome Consortium is creating a reference map of the human epigenome which will facilitate in-depth epigenome wide studies. The influences of miRNAs may be particularly exciting given their ability to be manipulated, either antagonized or over-expressed, it is methylation where much of the evidence currently exists.

With GWAS failing to explain much of the variability in blood pressure, epigenetics may uncover some of the missing heritability. A genome-wide animal study of salt-sensitive hypertension in rats has implicated hypermethylation of the renin promoter. A human epigenome-wide methylation study in young males with hypertension reported hypermethylation of the *SULF1* gene which was confirmed in the validation sample for individuals ≤30 years old.

Transplantation is also an area where epigenetics play a large role. T regulatory cells (Tregs), so important in immune recognition and restricting self-reactive T cells, are regulated by their transcriptional factor FOXP3. The expression of FOXP3 is governed by methylation/ demethylation of Tregs. This system may be crucial in achieving the holy grail of transplant medicine, operational tolerance.

The realm of epigenetic gene silencing in renal fibrosis is a standout topic in nephrology genetics research with huge translational potential. Fibrosis, a pathological wound repair process that persists even when the initial injury has been removed, is a final common pathway of many disease processes. There is accumulating evidence that the underlying molecular mechanism of fibrosis includes epigenetic processes, particularly gene hypermethylation. Bechtel *et al* demonstrated that hypermethylation of *RASAL1* (an inhibitor of the Ras oncoprotein pathway) results in less inhibition of the Ras pathway and

led to sustained fibroblast activation and subsequent renal fibrosis. The potential of using de-methylating agents to allow RASAL1 to inhibit the Ras pathway and thus lead to less fibrosis appears very attractive. As mentioned above, gene silencing of *RASAL1* via methylation results in increased intrinsic Ras-GTPase activity in affected fibroblasts leading to fibrosis. Tampe et al showed successful inhibition of experimental renal fibrosis via reversal of aberrant *RASAL1* hypermethylation. They achieved this using bone morphogenic protein 7, known to have anti-fibrotic activity.

This toss-up is difficult to call. With 2 relatively unknown teams facing off for the first time it's anyone's guess who will progress to the Round of 32. Is 2015 a year too early for the rookies of Team Epigenetics? We'll have to wait and see.

Vesicoureteral Reflux

Vesicoureteral reflux (VUR) is another condition where modern genetic advances have revolutionized our understanding of pathogenesis and heritability. It is the most common type of congenital anomaly of the kidney and the urinary tract (CAKUT) with an estimated prevalence of 1–2%, but may well be even higher. It is characterized by retrograde flow of urine from the bladder back to the ureter and the kidney. VUR will often resolve with few significant sequelae but may be complicated by recurrent UTIs, scarring, and progressive renal disease. It remains unclear if the scars are a consequence of urine reflux/infections or if they represent co-existent developmental or dysplastic abnormalities. VUR may co-exist with other genitourinary abnormalities (ie, CAKUT) or as a part of syndromes with extra-renal developmental defects. Family studies have long supported the heritability of VUR. There is a 30–50% incidence in first-degree relatives, full concordance among monozygotic and 50% among dizygotic twins. The mode of inheritance is often AD but AR and X-linked pedigrees have been described. However, specific genetic causes of VUR remained elusive until recent technological advances.

Results of genome-wide linkage analysis in several families across various populations suggested linkage at multiple different loci. This is likely due to genetic heterogeneity of VUR in the families studied. GWAS data also demonstrate this heterogeneity with multiple SNPs across the genome giving significant or borderline significant association with VUR.

Whole-exome sequencing has brought the most productivity in discovering single-gene causes of VUR. Most of the genes reported have not been in families with syndromic VUR/CAKUT and required large kindreds with many affected individuals. An example of this is a 97-member pedigree with 16 affected individuals over 5 generations. Sequential genome–wide linkage and whole-exome sequencing was performed on the family. The causative mutation was discovered in *TNXB*, a gene associated with the joint hypermobility variant of Ehlers-Danlos syndrome. Other genes implicated using next-generation sequencing have included *ROBO2*, which may have multiple associated congenital abnormalities and *HNF1B*

which may have liver, pancreas, and genital phenotypes (see Team AD Tubulointerstitial Nephritis above). *RET* may cause Hirshprung disease and multiple endocrine neoplasia type 2 as well as VUR and CAKUT. *BMP4* mutations may cause defects in the eye, brain, and digits as well as CAKUT. *PAX2* mutations cause renal coloboma syndrome and variants in this gene have also been described causing an FSGS phenotype (see Team Familial FSGS). These genes do not appear to play a major role in isolated, non-syndromic VUR. This underlines the complexity of genotype-phenotype interaction. It is likely that modifier genes with second "hits" or epigenetic alterations determine some of the varying phenotypes associated with certain gene variants and mutations.

The big clinical story regarding VUR in the past year was the RIVUR study published in *NEJM* (and covered on #NephJC). It demonstrated that prophylactic co-trimoxazole reduced the incidence of UTIs in children with VUR and a symptomatic UTI. However, this did not translate into less renal scarring at 2 years, which again questions the etiology of the "scars."

Therefore, modern genetic techniques have helped us understand that VUR is a complex phenotype. It may be an isolated, non-syndromic finding or inherited as part of a myriad of non-renal developmental abnormalities. Some VUR can be considered a complex trait, influenced by multiple genes each having small effect sizes, as demonstrated using genome-wide linkage and association. It can also be inherited as a single-gene disorder in multiple different risk genes, as demonstrated using next-generation sequencing. This genetic complexity should not be surprising given multi-component nature of the lower urinary tract and its intricate development. A major challenge of clinical relevance that remains is to distinguish children who will have a benign course from those who will develop severe, complicated reflux nephropathy.

Familial FSGS vs APOL1

These 2 powerhouses know each other well. There is no love lost between the two with *APOL1* being a franchise breakaway in recent years and has gone on to make a name for itself in the Genetics conference. *APOL1* continues to captivate audiences although there is still a lot we don't know about this exciting team. Familial FSGS is a conference stalwart dating back to the old "Podocyte Conference" with its breakthrough player *Nephrin* but has continued to attract new talent as discussed below.

Familial FSGS

FSGS is the third-leading cause of ESRD in the US with an increasing incidence in recent years. It describes a pattern of injury with many etiologies and proteinuria as the

predominant clinical feature. It is caused by podocyte injury manifested by foot process effacement histologically. Several single-gene mutations have been identified that cause FSGS which has helped us understand the pathogenesis of glomerular disease. The genes have mostly been in podocyte-protein genes, a notable exception being *LAMB2* which localizes to the glomerular basement membrane and causes Pierson syndrome (diffuse mesangial sclerosis, microcoria, and neurological anomalies).

Inheritance may be AD or AR, with AD conditions having a less severe and later onset phenotype and often exhibiting incomplete penetrance. FSGS due to single-gene mutations does not recur post-kidney transplantation. The first described gene was *NPHS1* which codes for nephrin, an integral slit diaphragm protein, a mutation in which causes congenital nephrotic syndrome (so called "Finnish type"). This landmark study demonstrated the importance of the podocyte in congenital nephrotic syndrome/FSGS with multiple subsequent genes being described causing congenital nephrotic syndrome/FSGS (see Table below). The proteins of interest are often integral slit diaphragm proteins (nephrin, podocin, CD2AP), foot process cytoskeleton components (ACTN4, INF2), or involved in regulation/ expression of these proteins (WT1, perhaps PLCE1). Transient receptor potential cation channel type 6 (*TRPC6*) is a calcium channel located in the body of the foot process as well as the slit diaphragm. Mutations in *TRPC6* are gain-of-function causing increased intracellular calcium influx. *TRPC6* knockout mice are protected from albuminuria following angiotensin II infusion but how the gene causes podocyte injury remains unknown.

The advent of next-generation sequencing (see below section) has enabled the recent identification of additional single-gene causes of FSGS including *ANLN*, which codes for the F-actin binding protein Anillin. Potentially of more interest, next-generation sequencing has also expanded the phenotypic spectrum of known genes to include familial FSGS. These include *PAX2*, mutations in which were previously described to cause congenital abnormalities of the kidney and urinary tract and mutations in *COL4A3* & *COL4A4* which have recently been reported to be disease segregating in 10% of a large cohort of familial FSGS families, without an Alport phenotype. The Wilms Tumor 1 gene (*WT1*) encodes a zinc finger binding protein critical for kidney and genitourinary development. It is also involved in expression of essential slit diaphragm proteins such as nephrin, podocin, and podocalyxin. Renal phenotypes associated with *WT1* mutations include Wilms tumor and several syndromic forms of FSGS associated with genitourinary anomalies and mental retardation. These include WAGR syndrome (with aniridia, genitourinary malformations, and mental retardation), Denys–Drash syndrome (with diffuse mesangial sclerosis, male pseudohermaphroditism), and Frasier syndrome (male pseudohermaphroditism, FSGS and

Gene	Phenotype
Autosomal Recessive	
NPHS1 (Nephrin)	FSGS; Congenital Nephrotic Syndrome
NPHS2 (Podocin)	FSGS; Congenital Nephrotic Syndrome
NPHS3 (PLCE1)	FSGS
LAMB2	FSGS; Pierson Syndrome
MYH9	FSGS; Sensorineural Deafness; Macrothrombocytopenia; Epstein, Fechtner & Sebastian Syndromes
MYOE1	FSGS
PAX2	FSGS; Papillorenal Syndrome
Autosomal Dominant	
ACTN4	FSGS
ANLN	FSGS
ARHGAP24	FSGS
CD2AP	FSGS
TRPC6	FSGS
INF2	FSGS; Charcot–Marie–tooth Disease
LMX1B	FSGS; Nail-Patella Syndrome
WT-1	FSGS; Denys–Drash, WAGR & Frasier Syndrome

Table 2: List of major genes implicated in familial FSGS

gonadoblastoma). A recent study employed next-generation sequencing to identify *WT1* mutations causing non-syndromic FSGS. Functional studies implicated *WT1* in the transcriptional regulation of nephrin as well as synaptopodin expression, another crucial podocyte protein.

Genetic testing for familial FSGS has moved a step closer with the advent of next-generation sequencing although precisely when and how it may be useful remains a challenge. In transplantation, it may be helpful to assess risk of recurrence or to screen potential living related donors. In adolescents or young adults presenting with FSGS, having a molecular diagnosis may help tailor treatment as the presumption is that immunosuppression will not work in familial FSGS. However, it is not as simple as this, and certain agents, particularly cyclosporin (blocking calcineurin-mediated dephosphorylation of synaptopodin) and rituximab may have beneficial podocyte-specific effects, possibly regardless of etiology of the podocytopathy.

This team has strong comparisons and connections to Duke in the NCAA. FSGS is a perennial competitor with a rich tradition and will expect to go far in the tourney. APOL1 represents a huge early potential banana skin.

APOL1

Apolipoprotein 1 (*APOL1*) related nephropathy is surely one of the biggest nephrology genetics stories in recent times. The APOL1 risk alleles, G1 and G2, are mutually exclusive (never occur on the same chromosome copy) and 2 copies are necessary to confer kidney disease risk (genotype may be G1/G1, G2/G2, or the compound heterozygous state of G1/G2). The alleles are common in individuals of West African ancestry and almost unheard of in those of European ancestry. Variation in these alleles is now known to be responsible for the vast majority excess risk of non-diabetic kidney disease including FSGS, HIV-associated nephropathy, severe lupus nephritis, and unspecified CKD (often previously labelled as hypertensive nephropathy in African Americans). The alleles are common, with about half of African Americans having either one or two risk alleles, and 10%–15% possessing both. The effect size is large, with a 7-10 fold increased risk of FSGS or unspecified ESRD, and an even higher risk for HIVAN. Despite this, they should be considered risk alleles rather than a single-gene disorder. The presence of the alleles is not enough to have the phenotype and additional "hits" are necessary, which may be genetic, environmental, or both. The origin of the *APOL1* variants is a fascinating story, with initial genome-wide approaches suggesting *MYH9* as the gene of interest in African American patients with FSGS. This was a reasonable theory given the fact that MYH9 is expressed in the podocyte and mutations in the gene cause syndromic FSGS (see Team Familial FSGS). However the excess risk was found to be due to variants in the nearby *APOL1* gene. These alleles have risen to high frequency in individuals of African descent via a beneficial effect in resistance to *Trypanosoma brucei rhodesiense*. A succinct review of *APOL1* (and other genetic nephropathies) is worth exploring.

A recent study reported in *NEJM* examined *APOL1* variants in 2 large CKD cohorts, namely AASK and CRIC. AASK enrolled all African American patients with CKD attributed to

hypertension that did not have diabetes. The CRIC study included black and white patients with CKD, approximately half of whom had diabetes. Interestingly this finding was also evident in the patients with diabetic kidney disease. Diabetic nephropathy has not been previously identified as phenotype influenced by *APOL1* variation.

Little is known about the kidney-specific biology of *APOL1*. Only the genomes of humans and a few primate species carry the *APOL1* gene making study in animal models difficult. Recent work has explored the role of innate viral immunity in over-expression of *APOL1*, particularly of the variant *APOL1* which more injurious to cells than wild type. In the study, several patients (10/11 African American) were noted to develop a collapsing FSGS pattern of injury after treatment with interferon. Interferons and Toll-like receptor agonists hugely increased *APOL1* expression. Note that HIV is a potent inducer of interferons, with HIV nephropathy being a particularly risk with possession *APOL1* risk alleles. Lupus nephritis, another high interferon state, has been recently recognized as lying within the sphere of *APOL1* nephropathies. Keeping with the viral pathway theme, another study demonstrated that in African Americans with both *APOL1* risk variants, JC viruria was associated with a lower prevalence of kidney disease. How would JC virus protect from development of *APOL1*-associated nephropathy? Is it a clue to an environmental "second hit" whereby the JC virus may inhibit infection with other more nephrotoxic viruses? These questions and more will need to be answered in the coming years.

The effect of transplanting kidneys from *APOL1* nephropathy risk donors demonstrated that deceased donor allografts possessing both *APOL1* risk variants failed more rapidly than those with one or no risk alleles. This concept was well, but tragically, illustrated in a recent case report of a young Afro-Caribbean monozygotic twin transplant pair. The recipient had unspecified FSGS, the donor was normal at screening. There was clinical and histological evidence of FSGS at 30 months post-transplant and allograft failure occurred early. The donor subsequently developed proteinuria and renal dysfunction, undoubtedly aggravated by his reduced nephron mass. The twins were later genotyped confirming the presence of both *APOL1* risk variants.

This leads on to the utility of testing for *APOL1* variants. Certainly a case could be made in transplantation, illustrated by the case report described above. Also if the risk of allograft failure with possession of the *APOL1* risk alleles in the donor could be validated, it would suggest genotyping donors of African origin could be beneficial. In the general CKD population, it is less clear. Certainly the alleles confer significant risk but that risk is not absolute so not all G1 & G2 carriers will develop kidney disease. Also, as there is no specific treatment for *APOL1*-related nephropathies, the utility for general testing in the African American CKD population is not evident.

Team APOL1 will be a tourney regular for years to come and may grow in coming seasons to be a big dance favorite. It's a team full of potential but remains somewhat of an unknown quantity.

GWAS in Nephrology vs Next-Generation Sequencing

These conference rivals each have a loyal following who will relish this first-round contest. GWAS promised much when it exploded onto the scene some years back and many predicted several national championships which have failed to materialize. There is similar enthusiasm for Next-Generation Sequencing at present, a team who has huge aspirations and expects silverware this season.

GWAS in Nephrology

The human genome consists of approximately 3 billion nucleotides of DNA sequence. Areas of variance at an individual nucleotide, termed SNPs, occur across the genome at intervals of about one per 300 base pairs of DNA. SNPs in close physical proximity are more likely to be inherited together as part of a group (haplotype). This phenomenon, referred to as linkage disequilibrium, allows for one SNP to serve as a proxy for the presence of other SNPs in that haplotype. This is the concept of a "tag SNP" and obviates the need for individual genotyping of every variant. This is the principle behind GWAS. We have witnessed an explosion of GWAS for complex traits including renal function (eGFR), CKD, and hypertension. GWAS are usually designed to detect relatively common SNPs (minor allele frequency > a pre-determined level, for example 5%).

GWAS in Nephrology have not proven to be as clinically useful as initially hoped. Like GWAS in other complex diseases, many variants with tiny effect sizes have been uncovered but these variants only explain a small proportion of total heritability of the disorders. Large consortiums have been created to try to provide the necessary power to detect more variants but overall, the effect sizes remain small. Examples of these GWAS meta-analyses include the CHARGE consortium (n=29,163), the Global BPgen Consortium (n=34,433) and ICBP-GWAS (n=69,395 with validation in a further 133,661 individuals) for hypertension. ICBP-GWAS reported 29 SNPs independently associated with blood pressure but together they explained only 0.9% of the BP variation in the cohort. This reflects the genetic complexity nature of the trait. Large renal function GWAS collaborations have also been formed and have demonstrated similar findings of numerous SNPs with tiny effect sizes. These finding may one day lead to useful risk scores for CKD or hypertension but demonstrate the limited clinical relevance of individual or a small group of SNPs.

Despite these limitations, genome-wide approaches have proven useful in our field. The discovery of the *APOL1* variants came from initial identification of variants in the nearby gene *MYH9* gene on chromosome 22 (see Team *APOL1*). We have also learned much about *UMOD* nephropathy and the function of Tamm-Horsfall protein (Uromodulin) from a renal function GWAS in which *UMOD* variants popped up as being genome-wide significant for eGFR (see Team AD Tubulointerstitial Nephritis). It was mentioned above that this locus appears to confer shared risk for both hypertension and kidney disease (and also cardiovascular events). Another example of shared risk loci comes from the ICBP-GWAS study where a variant in the phospholipase C epsilon gene (*PLCE1*) was associated with blood pressure variance. A coding missense mutation in *PLCE1* has been described causing steroid-resistant FSGS.

Variants in *SHROOM3* have been consistently associated with CKD/eGFR in a large GWAS but any potential mechanism remained unclear. Due to this finding, a group from Mount Sinai performed a set of experiments in a transplant cohort which was hugely insightful. They genotyped transplant donors for the *SHROOM*3 variant which correlated with increased SHROOM3 protein expression and allograft fibrosis on protocol biopsies. It also associated with eGFR in the recipient. They identified the risk allele to be located in a sequence for the transcription factor TCF7–L2 which enhanced SHROOM3 expression that in turn regulated TGF-B induced renal fibrosis. In a mouse model, *SHROOM3* knockdown strongly abrogated interstitial fibrosis. This exciting research with real translational potential was made possible by SNP associations in GWAS cohorts of the general population and firmly demonstrates the power of this approach.

Another demonstration of the power of GWAS comes from a study in >20,000 individuals of European and Asian ancestry which shed light on the complex genetic architecture of IgA nephropathy. Several genome-wide significant variants were identified which were predominantly located in pathways of immunity and inflammation including variants with overlapping susceptibility to autoimmune disorders such as inflammatory bowel disease. The study demonstrated that disease onset was related to the number of risk loci present, although they still only explained a small proportion of the variance in disease onset. A striking observation was the association of the genetic risk score with pathogen diversity, particularly helminth diversity. Helminths are common in the soil in Asia and may explain the increased incidence of IgA nephropathy in some geographical areas and the known association of mucosal infections as a trigger for IgA nephropathy.

Many SNPs from GWAS will have very small p values but will not reach genome-wide significance when corrected for multiple testing. This may be due to overly stringent criteria for genome-wide significance or underpowered studies. One method of using these variants in a clinical useful way is to perform pathway analysis not limited to only genome-wide

significant or replicated variants. A recent paper in *JASN* employed pathway analysis on GWAS data examining the development of new-onset diabetes mellitus after transplant (NODAT) post renal transplantation. This study implicated β-cell dysfunction in the pathophysiology of NODAT, contrary to traditional thinking that the etiology was merely insulin resistance. Another example is from the Wellcome Trust Case Control Consortium where no genome-wide significant associations were observed for hypertension in the original study. However, pathway analysis revealed interconnected networks in dopamine signalling including genes coding for the AMPA, NMDA, and GABA-A receptors. This suggests that the regulation of vascular smooth muscle tone is important. There is inherent bias in pathway analysis, however, as it is reliant on accuracy and depth of input from the pathway databases but it does provide an additional use of GWAS data including non-genome-wide significant SNPs.

GWAS have revolutionized the search for genetic influences on complex diseases but it is far from a panacea. As a technique, GWAS are not designed to fully uncover the interplay of multiple genetic and environmental factors which cause CKD and hypertension. Genetic variant discovered by GWAS mostly have tiny independent effect sizes and none are likely to be obligatory for the phenotype to occur.

Team GWAS is a hot and cold side who can beat anyone on their day but also may succumb to unheralded opposition. This unpredictability makes them a fascinating team to follow. Their recent success will give them confidence. Will this be enough against the next-generation sequencing new kids?

Next-Generation Sequencing

Next-Generation Sequencing, including whole-exome sequencing (WES), and whole-genome sequencing (WGS), promises in-depth coverage of the exome/genome with improved coverage of rare variants and copy number variants (CNVs; large insertions and deletions). WES involves sequencing all exons, the coding proportion of the genes, which make up about 1% of the genome and where presumably most disease-causing variants lie. Deep sequencing projects, such as 1000 Genomes, demonstrate that rare variants, which are usually not covered in GWAS, constitute the majority of polymorphic sites in human populations.

An early example of the use of WES is the identification of a potassium channel mutation in the development of primary hyperaldosteronism, one of the more frequent causes of secondary hypertension. WES has facilitated gene discovery for several kidney diseases including FSGS and VUR (see Team VUR & Familial FSGS). It has also helped identify novel phenotypes for known genes in the case of *COL4A* mutations, which cause hereditary nephritis, presenting as familial FSGS. In nephronophthisis, an AR ciliopathy which causes tubulointerstitial nephritis, Next-Generation Sequencing has expanded the breadth of

known causative genes. There are now 17 NPHP genes described, but despite this, many remain undiscovered.

The idea of WES is to remove much of the redundancy of the genome and maximise efficacy and cost-effectiveness. However, the sphere of epigenetics has taught us that non-coding portions of the genome can be vitally important, potentially heritable and influence expression of the genes and therefore phenotypes. Moreover, WES is not a perfect method for new gene discovery in familial disease and exonic regions may still prove difficult to sequence with the potential to miss causative variants. This is highlighted by the problems in sequencing *MUC1* as a cause of AD interstitial nephritis due to multiple repetitive regions in and around the gene. Successful sequencing relies on multiple reads of the regions of interest, with depths of <10X showing inconsistent call rates.

The major challenge with Next-Generation Sequencing lies in identifying the specific disease-causing variants from all the benign variants we carry. WES in one individual will typically reveal approximately 20,000 variants and even when sequencing >1 individual in a family, multiple potentially pathogenic variants will be shared between family members. Filtering methods and *in silico* techniques may predict if a variant is likely to be damaging but have the potential also to inadvertently disregard pathogenic mutations. The issue is compounded in African American families which have known increased genetic diversity. African American families may have many more variants uncovered by WES, compared to non-African ancestry families. Therefore, even bigger pedigrees are needed to identify disease causing mutations.

Aside from research settings, the utility of WES in clinical practice for precise molecular diagnosis is unknown. The spectrum of childhood nephrotic syndrome is an area where it may be useful as several genes forming a large proportion of cases have been identified. Data on likely responsiveness to certain treatments is a potential indication for testing. Other indications include transplantation, both for assessment of potential recurrence and for disease in living related donors. The use of exon sequencing of 27 genes known to cause steroid resistant nephrotic syndrome (SRNS) that manifested before 25 years of age has been reported. A single-gene cause was detected in 29.5% (526 of 1783) of families, with younger presentations more likely to have a monogenic cause identified. A UK cohort of 36 patients (all <16 years at onset) with SRNS detected a pathogenic variant in 70% of familial causes and 15% of sporadic cases.

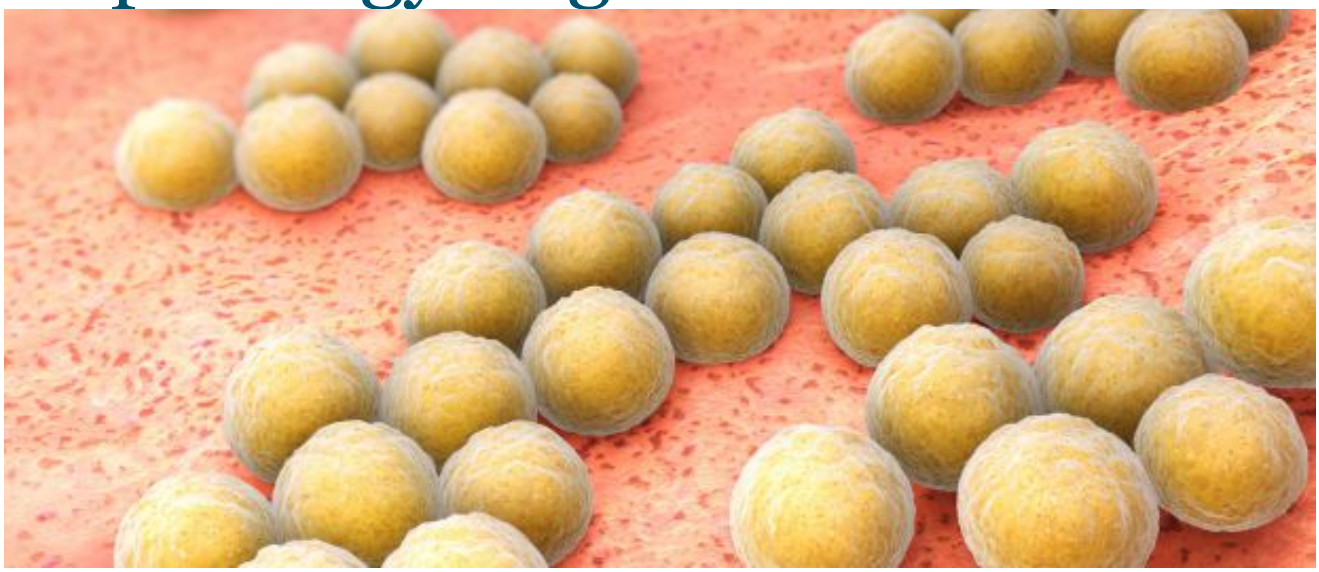
WGS is becoming more affordable and it is likely that very soon it may replace WES in the investigation of genetic diseases. So will WGS solve these issue that we shave with WES? As sequencing is not confined to the exome, gene regulatory regions, enhancers, and promoters will be covered. It will certainly add more complexity by sequencing the entire genome and will uncover millions of variants in each individual sequenced. Sophisticated filtering and

bioinformatic methods will need to be employed to identify likely pathogenic variants. Current issues with WGS include a lower detection rates for CNVs versus single-nucleotide variants and incomplete concordance between different sequencing technologies. WGS will potentially provide information about countless medical conditions, many of undetermined significance. The huge volumes of data generated by such technologies will potentially greatly aid genetic interrogation of kidney diseases but will provide logistical and ethical challenges which must be overcome.

With a strong preseason behind it, Next-Generation Sequencing expects to win this contest with some to spare. GWAS has gone under the radar so far this season but has earned some notable recent victories and has a lot to prove to its doubters. This one will go down to the wire.

– Post written and edited by Drs. Paul Phelan and Conall O'Seaghdha.

Infectious Disease and Nephrology Region



This virulent bracket has it all: insidious latent viruses, CNS toxic antibiotics, nephrotoxic antibiotics and nephrotoxic viruses. Infectious Disease specialists have now adopted nephrology as their favorite cousin! With what other medical specialty can ID consultants be constantly challenged by spur of the moment changes in drug pharmacokinetics and pharmacodynamics due to alterations in GFR leading to the potential for numerous adverse drug reactions!! Yes, this bracket is not for the frail or weak of heart (kidney)! The winner of this bracket is going to be an odds on favorite to infect their way to the Final Four and even the Championship – it's only a virion or MIC away!

Samir K. Gupta, MD

Dr. Gupta is an Associate Professor of Medicine in the Division of Infectious Diseases and Vice-Chair for Research in the Department of Medicine at the Indiana University School of Medicine. Dr. Gupta conducts research on HIV-related renal epidemiology and was the lead author of the inaugural Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients.

Vancomycin Renal Toxicity vs Piperacillin/ Tazobactam Toxicity

This matchup pits the crafty veteran team of Vancomycin Renal Toxicity against an up-and-coming qualifier in the tournament: Piperacillin/Tazobactam Toxicity. You can never overlook a hungry Piperacillin/Tazobactam rookie team that has only recently been gaining momentum and recognition in the nephrotoxic league. However, what more can be said about Vancomycin Renal Toxicity that hasn't already been fleshed out over the years. Pinpoint accuracy and relentless offense against the proximal tubule makes Vancomycin Renal Toxicity the odds-on favorite but reputation only goes so far – the game is played on the field and anything can happen when the filtering begins.

Vancomycin Renal Toxicity

Who would have thought that vancomycin would earn a reputation as among the elite of nephrotoxic antibiotics when it was first introduced in 1958. This team has been the savior for the treatment of MRSA and has enjoyed a solid reputation for efficiency and effectiveness among housestaff and practicing physicians. However this stellar reputation was not always the case and many physicians still remember the early days of "Mississippi Mud", the nickname given to vancomycin due to its cloudy appearance in the intravenous solution. Vancomycin had a sordid reputation for nephrotoxicity and ototoxicity that restricted its early acceptance and use. It rivaled the Detroit Piston "Bad Boys" team of the 80s – lethally effective, often victorious, but tended to play rough and commit many personal fouls.

Improved purity of vancomycin preparations significantly reduced the risk of nephrotoxicity and it appeared that vancomycin had undergone an extreme makeover, with widespread popularity even among nephrologists. However, in spite of the newer formulations, the emergence of reduced vancomycin sensitivities and the targeting of higher trough levels by ASHP/IDSA/SIDP recommendations (15-20 mg/L) has now revealed a resurgence of drug-induced nephrotoxicity.

Targeting the mitochondria of the proximal tubule, vancomycin puts on a relentless full court press 24 hours a day resulting in oxidative injury and ATN. Working in concert with other risk factors such as preexisting renal disease, hypotension, critical care unit patients, obesity, and African American race, vancomycin nephrotoxicity is a serious cause of AKI that leads to prolongation of the hospital admission and increased patient morbidity and mortality.

The only defense that has worked so far to prevent nephrotoxicity has been intensive pharmacy intervention for therapeutic drug dosing and monitoring.

Vancomycin nephrotoxicity is a strong contender as a veteran team that should not be underestimated.

Piperacillin/Tazobactam Toxicity

This backcourt combination combines speed with excellent defensive skills. Formulated to neutralize the production of beta lactamase, the piperacillin/tazobactam combination has enjoyed an excellent reputation as a "go to" antibiotic for a variety of Gram-negative infections. Piperacillin/tazobactam has played around in the minor leagues of nephrotoxicity for many years but recently appears to be making a move to join the major leagues of antibiotic-associated nephrotoxicity.

Piperacillin/tazobactam has been associated with 3 forms of renal injury:

1. increased risk of nephrotoxicity when co-administered with vancomycin
2. an independent cause of direct ATN
3. through the development of acute interstitial nephritis

Particular concerns about the renal toxicity of Piperacillin/tazobactam have been raised when administered in the elderly and in ICU patients where drug dosing can be extremely complex due to unpredictable volume shifts and changes in GFR.

In order to separate and distinguish themselves from the rest of the nephrotoxic antibiotics, Piperacillin/tazobactam in the ICU setting was associated with a higher rate and severity of AKI with a marked delay in recovery compared to the nephrotoxicity of other beta lactam antibiotics. This recently described slam dunk over other drugs in its class boosted Piperacillin/tazobactam as a worthy entry into the tournament.

Piperacillin/Tazobactam Toxicity is an emerging team with a clinical impact that is just now being increasingly recognized and appreciated.

Cefepime & Mental Status Changes vs Acyclovir & Mental Status Changes

This matchup pits 2 extremely well-balanced teams that wreak havoc on the differential diagnosis of acute mental status changes in critically ill patients. Sherlock Holmes said it best– "Eliminate all other factors, and the one which remains must be the truth": each of these teams possess the ability to cause

life-threatening neurotoxicity in the presence of acute or chronic kidney disease and force physicians to carefully and sequentially consider all possible alternative causes other than the actual antibiotics themselves. How deliriously devious, how encephalopathically elegant! You have to admire the simplicity of their game plan–pretend to be helpful and then a game-winning bank shot off the cerebrum. Only one neurotoxic agent can move on to the next round. Which one dominates the brain more effectively?

Cefepime & Mental Status Changes

Cefepime is a 4th generation bactericidal beta lactam cephalosporin whose pharmacokinetics make it an ideal team to induce CNS neurotoxicity. Confusion, hallucinations, agitation, coma, myoclonus, and seizures represent the hallmark of cefepime neurotoxicity and result from competitive antagonism of g-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain. In addition, NCSE (non convulsive status epilepticus) is a characteristic finding in cefepime neurotoxicity and its presence should raise a suspicion of cefepime-induced CNS injury. This disorder may prove to be fatal unless immediate drug discontinuation is initiated. This syndrome has been consistently underappreciated and overlooked as a cause of mental status changes in septic patients and this makes cefepime neurotoxicity a dangerous opponent.

Cefepime neurotoxicity however has an Achilles heel in that it is almost completely dependent on the presence of an acute or chronic decline in GFR. Freedom from protein binding and the lack of modification or degradation by the hepatic P450 system forces the unchanged parent compound cefepime to rely exclusively on renal clearance for systemic elimination. In the presence of a reduction in GFR, cefepime blood levels rapidly increase and with a 10% CNS/blood concentration gradient, exposure of the brain to these high serum levels leads to marked CNS irritability. Rarely has neurotoxicity been reported in the presence of normal renal function, limiting this team's efforts to produce a consistent winning record as the vast majority of patients tolerate it without incident.

Prevention of cefepime neurotoxicity is focused on proper pharmacokinetic dosing using estimated GFR calculations. The pediatric population may be at significant risk due to the variability of these mathematical GFR estimates to accurately determine the GFR in this unique population. Finally, for critically ill ICU patients or comatose patients on cefepime the development of neurotoxicity may be difficult to assess and detailed EEG monitoring may be necessary or complete avoidance of cefepime in these conditions should be considered. As a last resort, hemodialysis can be an effective rescue therapy to remove cefepime in critically ill patients experiencing acute neurotoxicity.

Small and undersized but agile, cefepime neurotoxicity can sneak in a victory here and there but remains beatable by careful defensive drug dosing strategies.

Acyclovir & Mental Status Changes

Deception is often the key to victory and this is what makes acyclovir neurotoxicity a formidable opponent. Imagine the following scenario: first there is a herpetic infection localized or disseminated – this is followed by initiation of high-dose acyclovir therapy – suddenly the patient develops acute mental status changes – is it herpetic encephalitis requiring the infusion of higher acyclovir doses or is it acyclovir neurotoxicity and acyclovir must be immediately stopped? What a conundrum! Guess wrong and…

Acyclovir is a nucleoside analog that is primarily excreted unchanged (85%) in the urine based on GFR. Most scouting reports of this team fail to recognize the importance of the other 15% of acyclovir that undergoes metabolism by alcohol dehydrogenase to a bioactive product 9-carboxymethoxymethylguanine (CMMG) that is excreted by the kidney strictly through glomerular filtration. Surreptitiously, in patients with altered renal function or who are on dialysis, a greater percentage of acyclovir gets retained and is gradually converted to CMMG which then crosses the blood brain barrier leading to neurotoxicity.

The typical "run and gun" presentation of Acyclovir Neurotoxicity includes:

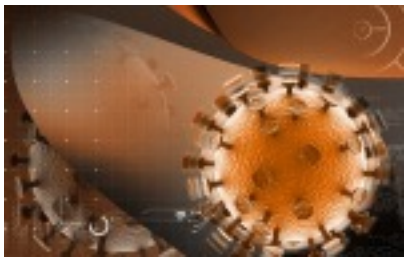
- tremor/myoclonus (58%)
- confusion (50%)
- agitation (38%)
- hallucinations (25%)
- extrapyramidal symptoms (21%)
- sedation (17%)

In comparison to cefepime neurotoxicity, which does not appear for 7-10 days after initiation of therapy, acyclovir neurotoxicity can lead to acute delirium within 24-48 hours of therapy particularly in patients with advanced renal failure.

The best defensive strategy to counter acute acyclovir neurotoxicity appears to be immediate cessation of drug administration and hemodialysis, which can remove approximately 45% of the drug and its CMMG metabolite in each session. Prevention is focused on proper drug dosing in the setting of any patient with a reduced GFR. However acyclovir neurotoxicity has still occurred even with proper drug dosing in patients on dialysis due to ongoing CMMG accumulation.

Acyclovir neurotoxicity has been in the headlines for over 20 years and shows no sign of slowing down. Its novel mechanism of toxicity and rapid onset distinguish it as a strong team in the ID region.

HIVAN vs HIVICK



The battle of the acronyms!!! HIVAN (HIV-associated nephropathy) and HIVICK (HIV immune complex disease of the kidney) used to be perennial powerhouses garnering worldwide attention. Now they may be past their primes as HAART therapy has been relegating both of these teams back to the minor leagues. However, with 35% of the world HIV population still untreated by HAART, both of these HIV-induced renal diseases still occasionally try to recapture their glory days of relentless glomerular injury and progressive fibrosis. Can either of them make one final run through the tournament or should they both default and retire so people will still remember them in their youthful glory years?

HIVAN

With a longer championship winning streak than UCLA and the Boston Celtics, HIVAN dominated the kidney from 1984 through 2005. HIVAN was always considered synonymous with HIV renal involvement but now accounts for less than 40% of the cases of renal disease found in HIV infected patients.

The offensive strategy of HIV was simple and direct – attack the podocyte, attack the podocyte, and then attack the podocyte again. With no trick plays or complicated secondary use of immune complexes, HIV directly infected the podocyte forcing the transcription of its own 9-gene viral DNA and altering the entire phenotype of the visceral epithelial cell. The subsequent gene products lead to a dysregulation of the cell cycle and the development of the classic collapsing FSGS glomerular lesion that has become synonymous with the term HIVAN. As if to leave a calling card proclaiming who was responsible for this lesion, HIVAN patients expressed characteristic reticulo-tubular inclusion bodies, which have also been called interferon footprints within the renal tubules.

HIVAN does not have only a one dimensional podocyte-centric game – additional viral infection of the tubular cells results in microcystic dilation and a concomitant acute interstitial nephritis which further intensifies the renal dysfunction. However one important weakness of HIVAN lies in the fact that it almost always requires a genetic predisposition of the host in the form of Apolipoprotein L1 variants, particularly with homozygous expression of these mutations. This significantly limits the HIV population that will be susceptible to developing HIVAN.

This simple direct viral infection strategy puzzled ID experts for years as to how HIV was able to enter the podocytes and tubular cells in the absence of the required CD4 receptor. The answer appears to be through the use of passenger T cells that transfer the HIV virus

through cell-cell contact from both the blood and urine compartments. HIVAN requires active HIV infection and until HAART became an effective regimen for eliminating viremia there was no consistent therapy for preventing or treating HIVAN.

For decades throughout the world, the presentation of an HIV patient with nephrotic syndrome, minimal hypertension, larger size kidneys on ultrasound, black race, and active HIV was virtually assured to be HIVAN with typical collapsing FSGS. However, as Bob Dylan sang, "the times they are a-changin" and in recent years HIVAN has been upstaged by both HIVICK, its opponent in the first round, as well as by classical FSGS. Moreover, HAART-related renal disease has also been dominating the discussions recently as it has significantly eliminated both HIVAN and HIVICK through sustained viral control and has even caused regression of these lesions after they have developed.

It looks like the twilight is setting on this remarkable team as a consequence of HAART. You have to give credit to HIVAN for such a consistent career and no matter what happens in this tournament, HIVAN is likely a certainty to be voted into the viral-mediated renal disease Hall of Fame.

HIVICK

Clearly the underdog and flying under the radar of most physicians in the differential diagnosis of renal dysfunction in an HIV patient, HIVICK in its own right has become a more common renal lesion than HIVAN in HAART-naïve HIV patients. This team utilizes a completely different offensive strategy that eliminates the need to directly infect the kidney one cell at a time as is the case in HIVAN.

HIVICK is an immune complex attack on the kidney that leads to a variety of histopathologic glomerular lesions: membranous, diffuse/membrano proliferative, IgA nephropathy. The unique aspect of these immune complexes is their composition involving specific HIV antigens as the source target of the antibody response. Therefore the development of HIVICK is completely dependent on the presence of active HIV viremia.

HIVICK boasts that its immune complexes produce more permanent injury than HIVAN whose podocyte dysregulation can actually regress after HAART. Unless diagnosed early when reversal is still feasible, after initiating HAART and resolution of viremia, the resorption of the HIVICK lesions leaves glomerular "holes" that never completely heal over.

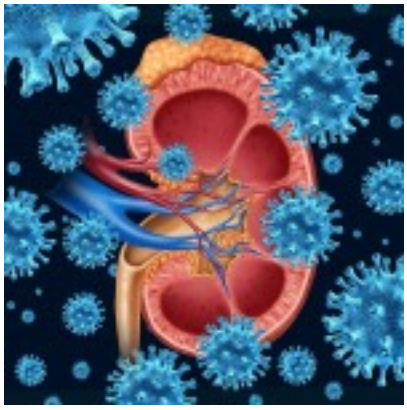
In addition, HIVICK has a much broader population base in which to produce nephrotoxic immune complexes. The Apolipoprotein L1 genetic variants do not appear to be as important as they are for increasing the risk of HIVICK as opposed to their major influence for HIVAN. Most HIVICK cases actually occur in heterozygotes or in patients with both wild-type genes.

Interestingly, HIVICK has recently bypassed HIVAN in frequency in HAART-naïve HIV patients for reasons that are not entirely clear. But similar to HIVAN, HIVICK is still decreasing overall in frequency with the widespread use of HAART.

Overall, scouting reports state that HIVICK is not as unique in its pathogenesis as HIVAN since the immune complex approach is also used by other viruses like HCV and HBV. HIVAN also remains the only renal lesion definitively caused by viral genomic infection of the podocyte.

Regardless, HIVICK is still a serious team that must be at the top of the differential diagnosis of glomerular disease in a HAART-naïve HIV patient.

Transplant CMV vs Transplant Polyoma BK



For decades, CMV and the herpes group family ruled post-transplant infections the way the Godfather and the Corleone family ruled the lower east side of New York. It was a tradition and requirement that all transplant centers pay homage and respect to CMV otherwise there would be a terrible price to be paid by the allograft and the patient. But now there is a rival family in town – The Polyomas – specifically, BK infection, that is threatening to upstage and usurp the authority of CMV in transplant patients through its own unique pathologic behavior. This is going to be a "Clash of the Titans" in the first round and in this tournament when the dust settles there is room for only one main virus to move on.

Transplant CMV

CMV has been called the Michael Jordan of the Post Transplant Infection League because it has been awarded the MVV trophy (Most Valuable Virus) for more than 25 consecutive years. This team is versatile and challenging because it can play an up tempo game almost from start to finish or it can slow down the pace and then just when the opponent has been lulled into a sense of complacency, surge at the end and put on a systemic offensive display that is lethally effective to the both allograft and patient outcomes. With 75% of the US population already harboring CMV from adolescence, the most common clinical manifestation post transplant has been re-activation from dormant latency. The use of T cell-depleting induction therapy, purine inhibition, and corticosteroid therapy have all been implicated in resulting in excessive immunosuppression and a resurgence of hibernating CMV often weeks to months after the transplant.

Alternatively, CMV can be directly acquired from the donor tissue if the recipient is CMV naïve. This primary CMV infection can be clinically far more severe than the cases of CMV reactivation, with a greater propensity to cause multiorgan involvement (liver, pulmonary, GI). In both cases CMV can directly infect the allograft and can be recognized by classic intracytoplasmic inclusions within the renal tubular cells and even may result in glomerular disease such as collapsing FSGS.

As if this massive systemic attack wasn't enough, transplant CMV makes sure there is no chance for allograft recovery by increasing the risk of rejection through upregulation of interferon production, leading to an induction of allograft HLA antigen expression. Game over!

CMV has had no true rivals for years and easily should be a guaranteed Final Four candidate except for the recent development of the ganciclovir defense. Indeed, CMV finally appears to have met its match. The prophylactic use of ganciclovir and its superior derivative valgancyclovir by all allograft recipients has virtually eliminated CMV infections in the early post transplant period from a peak incidence of 20-60% down to its current level of <5% **.** In addition, coming off the bench of every transplant center if needed is IVIG, which can pull out a last-minute victory against CMV if valgancyclovir is not enough. Other than the occasional case where CMV has erupted due to inappropriate valganciclovir dosing, CMV resistance has not been a major clinical issue and most transplant centers have called their CMV prevention strategies now employed "Mission Accomplished!"

Transplant CMV appears ready for retirement and the time may be ripe for a new MVV in the post transplant infection league. But never count out a champion ready for one last run at the title.

Transplant Polyoma BK

There is a new family moving into the transplant neighborhood called the Polyomas, BK and JC. With JC concentrating more on the CNS league, specializing in PML (polymorphonuclear leukoencephalopathy), BK has concentrated exclusively on winning the nephrotoxicity title. Similar to CMV, the majority of transplant recipients and donors have already been exposed to BK in adolescence and it remains in hibernation within the uroepithelium until a critical state of immune-incompetence is established after transplantation. While CMV may be in the twilight of its career and now occurs in <5% of solid organ recipients, BK is a team on the rise and complicates 7-10% of renal transplant patients.

Although one dimensional in its game plan approach of direct uroepithelial cell infection, who can criticize a team that has mastered the perfect three point shot at the weakest link of the allograft: the tubules. Over and over again scattered throughout the proximal and distal tubules, BK reactivates in the allograft, but this time instead of merely causing rejection as

CMV does, BK leads to interstitial nephritis, allograft dysfunction and then directly to increased apoptotic cell death!! Further infection of the uroepithelium continues the damage by leading to ureteral strictures and obstructive uropathy. Finally, BK has become the second most common cause of hemorrhagic cystitis after adenovirus in transplant patients. The triple BK threat: tubules, ureter, and bladder!

As if to taunt its opponents, BK sheds virally infected transitional cells into the urine as "decoy cells" and forms intranuclear inclusions that can be easily detected by biopsy using the SV40 stain. You have to be impressed by a virus whose stain is named after a primate (SV = simian virus). Detected by blood PCR, BK is not difficult to find yet even though the opponents know what is coming, stopping BK nephropathy has proven to be exceptionally difficult.

A variety of offensive and defensive strategies have been employed over the years with variable levels of success including a reduction of immunosuppression, addition of ciprofloxacin, IVIG infusions, discontinuation of mycophenolate and switching to pyrimidine inhibition with Leflunamide.

Transplant BK is the team no one wants to have on their schedule. It leads to an insidious progressive decline of allograft function the prevention of which has stymied most transplant centers. No one has yet been able to clearly dominate this team and with newer and more potent immunosuppressive agents being constantly employed, transplant BK unfortunately has a promising future ahead. Do not underestimate this new family.

– Post written and edited by Drs. Warren Kupin and Samir Gupta.

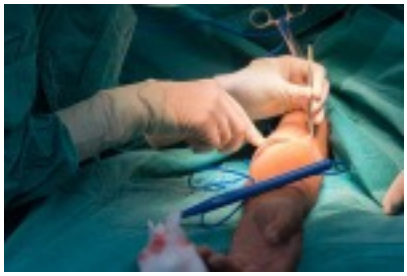
Nephrology and Vascular Surgery Region

Every year the surgeons crash the party and find a way to get a region all to themselves. Last year the urologists sat atop the Kidney Stone region and this year it is the vascular surgeons turn. The region has a diverse group of teams from various conferences. The PD Conference sent its two top teams, open and laparoscopic PD catheter placement (Acute PD, last year's cinderella was derailed by the PD Fluid shortage and was relegated to the NIT).

Timmy Lee, MD, MSPH

Dr. Lee received his medical degree from the Louisiana State University Health Sciences Center in Shreveport and his residency and nephrology fellowship the University of Alabama at Birmingham. Dr. Lee's research focuses on two main areas in hemodialysis vascular access. The first focuses on understanding the pathophysiology and mechanisms of dialysis access stenosis using clinical and experimental models. The second research area focuses on research to improve the processes of care to improve hemodialysis access placement and outcomes. Currently, Dr. Lee is an Associate Professor of Medicine, Director of Associate Director of Interventional Nephrology, and Associate Director of the Nephrology Fellowship Program at the University of Alabama at Birmingham, and Director of Dialysis at the Birmingham Veterans Affairs Medical Center.

Surveillance of AVG vs Clinical Monitoring of AVG



This is the ultimate matchup of high tech versus low tech, offence versus defense. Can surveillance of a patient's access with ultrasound provide long-term access patency over simple clinical monitoring? This could be a true game changer. The median time from graft creation to permanent failure is ~2 years. The vast majority of these failures are from irreversible thrombosis. Stenosis is a major risk factor for thrombosis. Our goal is to perform either surveillance (high tech) or clinical monitoring (low tech) of AVGs with an aim to identify those with a greater than 50% stenosis. Once discovered, the patient is sent to angiography for potential intervention with the hopes of preventing AVG thrombosis. Let's take a look at both of these in greater detail.

Surveillance of AVG

Surveillance is the ultimate in defense. We're talking the Tony Bennett, University of Virginia style defense. Monthly screening is required with the hope of finding a stenosis and intervening before eventual thrombosis develops. The ultimate test for identifying a stenosis is angiography. However, this is invasive and expensive. Therefore, non-invasive strategies such as ultrasound and Transonic technology in the dialysis unit have been employed to help screen for potential stenosis. The basic premise is that when a stenosis is present you will notice an *increase in intragraft pressure* and a *decrease in access blood flow*.

3 main forms of graft surveillance:

1. Static dialysis venous pressure: This is measured by hooking up a manometer to the arterial dialysis needle prior to beginning dialysis. The intragraft pressure is then normalized to the systemic blood pressure. This is termed static venous pressure ratio (SVPR). As stenosis worsens this value would be expected to increase.

2. Intra access flow monitoring: This technique uses the Fick principle. After reversing the arterial and venous lines, ice-cold saline is quickly injected via the arterial port. The greater the access blood flow, the quicker the rise in blood temp following injection. A computer algorithm can then compute the area under the curve and thus the flow. This was the preferred monthly method for surveillance by KDOQI 2006 guidelines.

3. Duplex ultrasound: This method is typically performed by radiology and is most costly. It involves measuring peak systolic velocity at anastomoses and sites with

visual stenosis. The ratio of peak systolic velocity at the stenotic site and the peak systolic velocity immediate upstream of greater than 2 has a 80% positive predictive rate for angiographically demonstrated stenosis.

These surveillance forms are all great at finding stenosis. However, that is not the real question at hand. Do they predict graft thrombosis? Allon *et al* looked at 4 studies that showed the positive predictive value ranging between 0.25 and 0.43 and even worse a false-positive rate ranging between 0.08 and 0.24. All being told, many will have a positive test and never go on to thrombose and others will have a negative test that will eventually thrombose. Paulson *et al* went on to show in a meta-analysis that flow monitoring was unable to identify the subset of patients with stenosis that went on to thrombose.

Clinical Monitoring of AVG

Clinical monitoring refers to physical examination or review of laboratory studies. This is standard of care and actually is not that bad. What does this include.

- Inspection, physical exam (absence of thrill, distal edema)
- Auscultation
- Difficult cannulation, aspiration of clots
- Prolonged bleeding after cannulation
- Decrease in Kt/V

A combination of these clinical parameters has a 69-93% positive predictive value for angiographically confirmed stenosis. Clinical monitoring is free. This is compared to an expensive ultrasound machine that needs constant maintenance. Moreover, additional staff and training are required for running a surveillance program. However, the success of this approach is directly related to the proficiency and consistency of the dialysis staff performing the monitoring. Furthermore, clinical trial results using clinical monitoring vary considerably across trials and may be difficult to translate to the real world where variations will only increase further.

Let's take a look at the head to head match-up

A 2015 meta-analysis reported in Seminars in Dialysis examined 7 randomized controlled trials. These were all relatively small studies ranging from ~50 to 140 patients. The data are pretty slim and really don't show a benefit. Furthermore, they show more invasive studies that don't lead to hard outcomes. This meta-analysis concluded that AV access surveillance using access blood flow monitoring to lower the risk of thrombosis is of uncertain benefit and varies substantially between AVG and AVF. As such, no consensus was possible

concerning the utility of access blood flow monitoring to predict stenosis and ultimately thrombosis in vascular access. Vascular access issues account for a huge (estimated at ~50%) amount of the total dialysis cost and are directly related to morbidity, so it is important that a proper clinical trial be performed. However, we are still routinely performing surveillance without much clinical evidence. Which team will take NephMadness — the defensively minded surveillance or the offensively minded clinical monitoring?

Laparoscopic PD Placement vs Open PD Placement

A real game changer in the field of surgery was the dramatic uptake in the use and refinement of laparoscopy. The use of laparoscopy leads to reductions in pain, bleeding, and sometimes even morbidity compared with open surgery. There is also improvement in recovery time and infection. However, the use of laparoscopy for the placement of PD catheters has lagged behind. Why is this? Well, the key to successful long-term PD (a lifeline for patients) is the presence of a well-functioning dialysis catheter. Open surgical placement offers the potential for optimal use. As such, the open technique is still the most commonly performed. However, the use of the laparoscopic technique for PD catheter insertion is seeing a huge upsurge.

Laparoscopic PD Placement

The first successful description of PD was in 1959 by Richard Ruben. Since this time refinements have been made to improve the longevity of this modality. Just as the AV access is the achilles heel in hemodialysis, the PD catheter is the achilles heel in PD. As such, placement of the Tenckhoff catheter is an important consideration in how long and well the catheter functions. The use of the laparoscope to place the PD catheter represented a potential way to improve the long term function of the catheter with direct visualization. The technique involves insuflating the abdomen with air with direct visualization while placing the Tenckhoff catheter in the abdomen. Other advantages are the ability to perform simultaneous surgeries such as lysis of adhesions or even hernia repair or appendectomy.

Open PD Placement

The most commonly used method for placement of a PD catheter is the open technique. This technique has been around the longest as well. This technique is the quickest and relatively cheap. While general anesthesia is needed, there is no need for a fancy laparascope. While the procedure itself might be quick, the recovery is longer than with the laparoscopic

technique. Lastly, the learning curve is less steep with the open approach with no need to learn to drive and operate a laparoscope and trocar system.

Let's compare and contrast

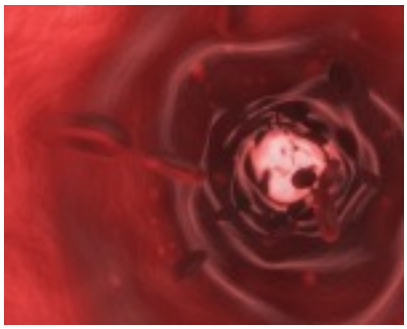
The laparoscopic technique takes significantly longer to perform than open surgery (~14 vs ~22 minutes). However, a study of 50 patients randomized between open versus laparoscopic PD catheter insertion showed no difference in the early complication rate.

A recent meta-analysis published in *PLOS one* compared the two techniques. This study included 3 randomized controlled trials and 8 cohort studies. They found:

- No difference
  - In the risk of developing an exit-site/tunnel infection.
  - In PD fluid leakage
  - In revision of poorly functional catheter
- Laparoscopic approach had
  - better 1-year survival of catheter
  - less catheter migration
  - numerically but not a statistically significant less obstruction
  - borderline improved 2-year survival of catheter
- NNT of 8 for preventing one migration using laparoscopy over open approach
- NNT of 6 for one more catheter reaching 1-year using laparoscopy over open approach

This meta-analysis concluded that laparoscopic approach is superior to the open approach. They also suggest that the laparoscopic approach would result in more postoperative comfort and less cost. However, not all of the studies included in this meta-analysis measured all of the outcomes so it is difficult to make definitive conclusions. Furthermore, these were small studies that typically only spanned 1 or 2 centers. A definitive trial will likely never be performed. Typically the choice between open and laparoscopic is made by surgeon experience and preference. It will be a tough match, but it appears like the laparoscope has the advantage.

Upstream Hemodynamics vs Downstream Vascular Biology



The biological process governing the formation of working access is complex. The process involves the arterialization of a vein in a coordinated manner that allows for patent entry and exit of blood flowing at a high rate. However, it is not so easy. A large randomized clinical trial performed in the US with 877 patients showed that ~60% of AVFs fail to mature enough to even begin dialysis is the first place. This is astounding. It is no surprise that there are concerted effort to understand the reasons for this abysmal result. This is a story of the reductionists and the engineers. Who will take NephMadness gold?

Upstream Hemodynamics

Team Upstream Hemodynamics have been around the block for a while but only recently has it experienced a huge upsurge in popularity. The principle of upstream is quite simple and takes its lead from other forms of vascular injury like atherosclerosis and coronary artery disease. The fundamental concepts to know are the difference between *laminar flow* and *disturbed flow*. To distill this down to the basics you have to understand that *endothelial cells love smooth laminar flow* wall shear stress.

- Laminar flow: endothelial cells “turn on” an atheroprotective, antithrombotic, antioxidant phenotype.
- Disturbed flow: low and reciprocating wall shear stress leading to an atherogenic, thrombogenic, proinflammatory phenotype.

In atherosclerosis lesions occur at sites where flow is not laminar such as the carotid and coronary bifurcations and the branching points of the renal and femoral arteries. This is the same for arteriovenous fistula (AVF). Neointimal overgrowth (hyperplasia) in the AVF typically occurs at areas where disturbed flow is present.

What factors influence hemodynamics

1. The surgically created anastomosis- creates complex conditions
2. The nonuniform actual anastomosis- leads to areas of disturbed flow
3. Antegrade or retrograde flow in distal artery in end-to-side anastomosis
4. Configuration of the anastomosis

How can knowledge of these factors improve vascular access? First, you can improve the vascular surgery of AVF creation to minimize these untoward hemodynamic events. More 3D real-time imaging of AVF to document areas of disturbed flow to then improve surgical technique in future AVF creations. More careful planning of the surgical technique to ensure proper anatomy for a best-case scenario.

Downstream Vascular Biology

The creation of arteriovenous access represents a critical transition point in a patient's life with kidney disease. However, the biology of access formation during the intense inflammation observed during CKD and uremia could disrupt successful access maturation. What is known about this process?

First, we need to look at the histopathology of vascular access dysfunction. If you look at a non matured AVF under the microscope you see a picture of an overly aggressive venous neointimal hyperplasia. This appears to be an overgrowth of myofibroblasts, fibroblasts, and contractile smooth muscle cells within the typically delicate intimal layer of the vessel. This leads to a scenario in which the vein tilts towards a more contractile phenotype. The stenotic arteriovenous graft appears much the same with aggressive neointimal overgrowth, more matrix deposition and neovascularization of the adventitia.

What about the repair process that occurs after balloon angioplasty? This is the primary intervention used to treat stenosis. Well, often times this actually accelerated the neointimal overgrowth that led to the stenosis in the first place. This is especially true in the patient with uremia and chronic inflammation.

Deleterious issues related to the substrate in which the fistula or graft is created likely plays a role as well. A report suggested that ~90% of veins sampled at the time of access formation in patients with CKD already had neointimal overgrowth. This may be a set-up for failure from the very beginning. Many also have pathologic calcification of the vessel as well.

What are some of the pathways affecting access maturation?

- Heme oxygenase 1 (HO-1): This enzyme, which catalyzes the degradation of heme, is upregulated during vascular injury. This upregulation induces protection from inflammation, oxidant stress, and vascular proliferation. Studies in patients with AVFs show that excessive length polymorphisms (GT repeats) in the HO-1 promoter (leading to less HO-1) are more common in patients with AVF maturation failure. These findings were also seen in a mouse model of AVF (more AVF failure in HO-1 knockout mice).

- Oxidative stress: The use of tempol (a superoxide anion scavenger) in another mouse model of AVF showed improved blood flow and less neointimal overgrowth.
- Monocyte chemoattractant protein 1 (MCP-1): This is a potent chemokine (for monocytes and macrophages) that has been identified to play a key role in atherosclerosis. Juncos et al demonstrated that MCP-1 knockout mice had increased AVF patency at 6 weeks after creation.
- Endothelial dysfunction: A clinical study assessed endothelial function in patients with CKD about to undergo AVF creation. This group used the brachial artery flow-mediated vasodilation (FMD) approach and demonstrated that enhanced FMD lead to enhanced remodeling and diameter of the AVF. Likewise a rat model in which L-NAME was used to inhibit nitric oxide (and thus endothelial function) led to significantly more neointimal overgrowth.

The problem with the downstream vascular biology team is that they are still in the development stage (think McDonald's All Americans). Full of promise but nothing to really hold their hat on. What is in the pipeline? Endothelial cell-loaded gel foam wraps, recombinant elastase therapy, drug-eluting stents, drug-coated balloons, far-infrared therapy, and even completely synthetic tissue cultured grafts are all in the offing. Overall, the prospects look great but we need to see some results on the court. Downstream Vascular Biology could be a Cinderella in this year's NephMadness.

Prophylactic Antibiotics Catheter Lock vs Heparin Catheter Lock

Defense reigns supreme in this matchup. Tough zone prevention defense guarantees you won't see a high-scoring game. Team Antibiotics has proven success but remains controversial in their ability to be seen more than a mid-major. They are akin to Gonzaga (the perennial Cinderella pick)–everyone pulls for Gonzaga in the NCAA tournament but during the year they are all but forgotten. Team Heparin is everyone's favorite lock-down defensive powerhouse, like Arizona this year. Too bad they are on the West coast or maybe the rest of us could actually watch them play.

There is a concerted effort to have as many patients as possible using either a fistula or graft for hemodialysis access. However, this is not always possible. Thus, a considerable number of patients are dependent on catheters for access. Therefore, it is imperative that these catheters stay both clot and infection free. A potential answer to this

problem is to fill (or lock) the catheter with either antibiotics or heparin to prevent these untoward events.

Prophylactic Antibiotics Catheter Lock

The rate of catheter related bloodstream infection is reported anywhere between 2.5 to 6.6 per 1000 catheter days reported. The rate of infection has remained quite steady of the last decade and is estimated to be ~40,000 per year. These lead to considerable morbidity and mortality. There have been several randomized trials showing that antimicrobial locks of dialysis catheters reduced blood stream infections. A meta-analysis published in the *Annals of Internal Medicine* concluded that the use of antibiotic locks resulted in less bacteremia and catheter removal. But, there was quite a bit variability in the studies included in this meta-analysis. However, the practice has not been widely utilized. In fact, the CDC and the Infectious Disease Society of America have not recommended the routine use for fear of developing antimicrobial resistance. A recent prospective, multicenter, observational cohort study by Moore *et al* was published in *CJASN*. This study compared gentamicin/citrate lock versus heparin in patients on hemodialysis with a catheter. The results were actually quite striking:

- ~73% reduction in catheter-related bloodstream infections
- Reduction in mortality! this is impressive
- No increase in gentamicin-resistant organisms
- Another study looking at cotrimoxazole + heparin versus heparin alone dialysis catheter lock found similar results.
- Less infection with cotrimoxazole
- However, no change in catheter removal or thrombosis

What happens if prophylactic antibiotic catheter locks becomes widespread in their use? Also, these trials only covered 6 months to a few years. What happens to bacterial resistance after 5 or even 10 years? This could lead to widespread resistance. However, it is hard not to see the benefits for patients as they would have much less infection and potentially even a mortality benefit. However, if widespread resistance occurs then this could lead to even worse infections that are now drug resistant. This will be a tricky issue and will need to help from our ID experts.

Heparin Catheter Lock

Locking catheters with heparin is a common strategy to prevent clotting. However, the practice has risks associated as well. First, is the concern of heparinizing the patient systemically and causing bleeding. The other major concern is the development of heparin-

induced thrombocytopenia (HIT). This is a feared complication as it portents a dismal prognosis. Heparin has its competition. There is team citrate and team tPA. These have both been gaining steam. A recent systematic review and meta-analysis published in *AJKD* compared the use of heparin and citrate. 13 randomized trials (~1700 patients) met the inclusion criteria for this review. However, only 3 trials compared heparin to citrate alone. The other trials had a combination of citrate with various antibiotics.

Below is a summary of the 3 citrate versus heparin trials.

- No difference in infections
- More bleeding with heparin versus citrate locks
- No difference in exit-site infection
- No difference in catheter removal for poor flow
- No difference in thrombolytic treatment

Those who are hematologic fans will chose heparin and those who are ID fans will chose antibiotics. Which one would you rather have–a clotted access or an infected access? Tough choice!

– Post written and edited by Drs. Matthew Sparks and Timmy Lee.

Onconephrology Region

Onconephrology is wide subject ranging from renal cancers, to side effects from chemo- and radiotherapy to renal paraneoplastic processes like amyloidosis. This region likewise tries to sample this diversity by taking teams from all over the field to populate the region. In the top position there are two surgical approaches to renal cancer: radical nephrectomy versus a more sophisticated nephron-sparing strategy. Next is a face off of two modern chemotherapies and their attendant nephrotoxicities. A very interesting coin flip of a contest. What is the possibility and wisdom of kidney transplant after malignancy? Or the risk and reality of malignancy after kidney transplant? Rounding out the bracket we have a pair of paraneoplastic syndromes, cast nephropathy from myeloma tipping off against amyloidosis.

Mitchell Rosner, MD

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Nephron-Sparing Surgery vs Nephrectomy for Renal Cancer

A little or a lot? Offense or defense? Nephrology versus urology? This matchup is not only the treatment of renal cancer, but also about saving valuable residual kidney function.

Nephron-Sparing Surgery

Now, what about the surgery to save the kidney? Partial nephrectomy (also termed nephron-sparing surgery) is the gold standard for the treatment of patients with small renal masses (SRMs; ≤4 cm). Surgically treated localized renal cell tumors < 4 cm carry an excellent prognosis with a >90% 10-year recurrence-free survival rate. Do we go with complete nephrectomy in such cases or advocate nephron sparing surgery?

The goal of a partial nephrectomy is to spare residual normal nephrons, thus preserving renal function, particularly in patients who at the time of diagnosis have some form of CKD. CKD is prevalent in this population and sparing renal function may improve long-term global outcomes.

Nephrectomy for Renal Cancer

For large tumors, the urologists have laid down the rules–the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend radical nephrectomy. This is the surgical removal of the entire kidney and Gerota's fascia plus or minus the removal of the ipsilateral adrenal gland. Radical nephrectomy is indicated in patients with

- A kidney tumor measuring greater than 10 cm in its largest diameter
- Multiple kidney tumors in the same kidney (but not a genetic systemic disorder such as Von Hippel Lindau disease)

This seemingly radical approach to treatment is based on evidence that patients in this category are at high risk of recurrence following surgery. But partial nephrectomy might have somewhat similar renal function and cancer outcomes in many studies.

Let's take a look at the data

- One randomized trial comparing radical nephrectomy vs partial nephrectomy for low stage renal cancers showed a 10 year superiority that was statistically significant for radical nephrectomy compared to partial nephrectomy.

- Another study that looked at analysis of Medicare beneficiaries with T1a tumors reported significantly improved overall survival with partial nephrectomy when compared to radical nephrectomy. However, this study was retrospective.
- With respect to renal functional outcomes, the European Organization for Research and Treatment of Cancer (EORTC) conducted a randomized trial compared nephron-sparing surgery versus radical nephrectomy. There was a significant reduction in the incidence of moderate and severe renal dysfunction in the partial nephrectomy arm compared to the radical nephrectomy arm.

While partial nephrectomy has not been shown to improve the overall survival outcome, preservation of renal function might be important in the CKD population.

You decide: will partial or radical nephrectomy move on to the next round?

Tyrosine Kinase Inhibitor Toxicity vs VEGF-Inhibitor Toxicity

Specific antiangiogenic medications target the vascular endothelial growth factor (VEGF) molecule. A classic example of such an agent is bevacizumab, a recombinant humanized monoclonal antibody that binds and sequesters the VEGF molecule. The tyrosine kinase inhibitors (TKI) such as sunitinib, sorafenib, axitinib, and pazopanib not only inhibit VEGF, but also have inhibitory activity against other receptor tyrosine kinases, such as the platelet-derived growth factor receptor or cKit. Both these agents are used in the treatment of renal cell cancers.

Tyrosine Kinase Inhibitor Toxicity

While the pure VEGF inhibitors are more toxic to endothelial function, the tyrosine kinase inhibitors are not quite as discreet. It's a full court press. Since the tyrosine kinase inhibitors have an anti-VEGF effect, similar renal thrombotic microangiopathy-like findings can be seen with them as well. A preeclampsia-like syndrome has been described in patients on sunitinib therapy.

Sunitinib and sorafenib are both being utilized for the treatment of renal cell and bladder malignancies.

- They have have the striking similarity in terms of their kidney effects as anti-VEGF agents.

- Other biopsy findings such as acute and chronic interstitial nephritis have been reported with these agents as well.
- Both sunitinib and sorafenib can cause a see-saw effect of chronic interstitial and endothelial damage leading to CKD.

The multitargeted tyrosine kinase inhibitors used in treatment of CML and GIST tumors, such as imatinib, have a different form of renal effects. While the mechanism is not clear, recent studies have demonstrated increased kidney dysfunction in a large series of patients with CML receiving imatinib (the blockbuster drug that ushered in the tyrosine kinase inhibitor revolution). In addition, newer tyrosine kinase inhibitors such as dasatinib and nilotinib have been linked to CKD.

Imatinib, sunitinib and sorafenib can also induce hypophosphatemia. They do this by

- Inhibiting platelet-derived growth factor receptors expressed on osteoclasts.
- Decreasing bone resorption and calcium and phosphate egress from the bone.
- PTH levels tend to increase and phosphaturia develops.

Tyrosine kinase inhibitors represent a growing class of antineoplastic agents. They are the fastest-forty of the teams, with quick onset and unrelenting in their tenaciousness, like Arkansas in the Nolan Richardson era. They could be a true contender to make it far in the Onconephrology bracket. However, they face a difficult challenge against a formidable team: VEGF-Inhibitor toxicity.

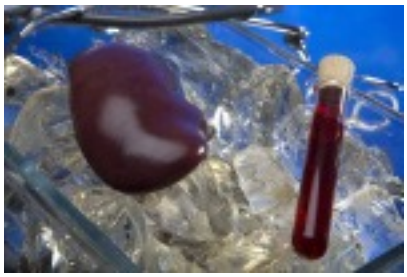
VEGF-Inhibitor Toxicity

Why do the VEGF inhibitors matter to nephrologists? Well, the renal toxicity seen with these agents are very fascinating. Kidney biopsy findings due to VEGF inhibitors helped to define the pathophysiology of pre eclampsia. These agents can lead to a preeclampsia-like syndrome in some patients. The renal involvement in preeclampsia is characterized by hypertension and proteinuria. The kidney biopsy shows glomerular capillary endotheliosis and thrombotic microangiopathy (TMA). The pathophysiology of these phenomena is explained by excess placental soluble fms-like tyrosine kinase 1 (sFlt-1), which binds circulating VEGF and placenta growth factor (PlGF) and stops them from interacting with endothelial cell surface receptors.

Similarly, anti-VEGF agents like bevacizumab can induce a preeclampsia-like state. Bevacizumab has been used for the treatment of several malignancies such as renal cell, ovarian, and breast cancer. The most common side effect is hypertension, which has been reported in up to 67% of patients. The hypertension is dose dependent. In addition, this chemotherapy can worsen the pre existing hypertension. ACEi and CCB can be used to treat

the hypertension. The mechanism of the hypertension seems to be related to nitric oxide production, direct vasospasm and endothelial injury. Proteinuria is fairly common as well and is related to TMA. Both the hypertension and proteinuria are dose related. The development of hypertension is also linked to a positive anti-tumor response. Importantly, the kidney injury from this bevacizumab can be irreversible.

Post-Transplant Malignancy vs Transplant After Malignancy



At first, these two teams sound almost identical, but they represent two fundamental concepts of transplant care. How ***long do you have to wait*** to receive a kidney transplant after having a malignancy that is successfully treated? And how do you deal with malignancy that develops ***after*** receiving a kidney transplant? This is especially a concern given the fact that patients with kidney transplants are on medications that promote rather than suppress malignancy.

Post-Transplant Malignancy

The decision to take a patient with a functional kidney transplant off or even modify the antirejection medication regimen after the development of malignancy is a difficult one. The most common malignancies after kidney transplantation are skin cancers. Other solid tumors are common as well compared to the general population. Hematologic cancers are usually post transplant lymphoproliferative disorders (PTLD). Although studies have shown that certain cancers are more likely to occur in patients with CKD or with end stage kidney disease, the overall incidence of cancer clearly increases further after kidney transplantation. After kidney transplantation most cancers have an elevated standardized incidence ratio (SIR). The SIR is calculated by dividing the observed cases of malignancy by the expected cases of malignancy. Kidney cancer is seen at a much higher rate in kidney transplant recipients, and this is secondary to the elevated risk of malignancy associated with acquired cystic kidney disease above and beyond what is seen in the ESRD population. The four most common cancers seen in transplant patients are cancer of the lung, liver, kidney, and non-Hodgkin lymphoma. Although cancers such as Kaposi sarcoma have a much higher rate post-transplant, they are still rare compared to other more common tumors. It is thought that the impaired defense against viruses, impaired immune surveillance against tumor cells, and upregulation of TGF-beta may be mechanisms involved in reasons of increased cancer risk post kidney transplantation.

Transplant after Malignancy

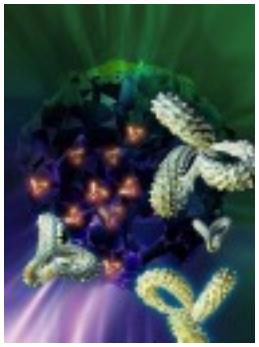
What happens if you have a malignancy which is successfully treated and you need kidney transplant. How long do you wait? Unfortunately, the data is pretty slim on how to address this question and decisions are often made on a local level by individual transplant centers who evaluate the specific patient issues. Consequently, this question makes a conscientious transplant nephrologist extremely nervous. In a study reported in 1997, patients who had cancer before transplantation were

- Found to have a cancer recurrence ~22%.
- Rate of recurrence varied, based on the time period they were treated before transplantation, with those treated within 24 months prior to transplantation having the highest recurrence rate.
- Recurrence rate also depends on the type of tumor.
  - High rates of recurrence are seen with myeloma, breast cancers, sarcomas, nonmelanoma skin cancers, and renal cell cancers.
  - Lymphomas have a lower recurrence rate.

The history of cancer prior to transplantation is also a predictor of increased mortality after transplantation. One study revealed a 30% increase in mortality in patients with pretransplant cancer mainly in solid organ transplants. A very valuable consultation tool is available for nephrologists to use via Israel Penn registry to help predict recurrence and time needed to wait for transplant. This is a really excellent tool.

While there is a risk, a transplant after malignancy that is in remission helps the patient. Malignancy after transplant seems to be a bad omen. From a patient's perspective, we have a potential winner here.

Myeloma Kidney vs Amyloidosis



This is a tough battle. It's the battle of the blues: Duke versus UNC. Tubules versus the glomerulus. While myeloma kidney is a tubular disorder, all forms of amyloidosis are mostly a glomerular and vascular disorder. However, both have one thing in common–***cancer-derived paraproteinemia***.

Myeloma Kidney

Let's start with the tubules. Myeloma kidney is also known as light chain cast nephropathy and is the most common cause of kidney impairment in patients with multiple myeloma. Although it is commonly referred to as myeloma kidney or myeloma cast nephropathy this entity can also occur in patients with Waldenstrom

macroglobulinemia and less commonly in CLL. The free light chain burden is the most important causative factor. Recent data highlights the pathophysiology of the free light chains (FLC) in the kidney. Recent studies have highlighted that they come in contact with the Tamm Horsfall protein (THP) in the loop of Henle. Experimental evidence with cast nephropathy suggests that intraluminal casts formation is the proximate cause of AKI and the most likely first step in the progressive decline of the renal function. When IV infusion of monoclonal FLC was given in rats, elevated proximal tubular pressures were noted and decrease in single nephron GFR with formation of intraluminal protein casts.

How do you treat cast nephropathy?

- Chemotherapy is the most effective (especially bortezemib)
- Increase fluid intake
- Avoiding nephrotoxic agents when the FLC burden is high is extremely important

Renal risk from myeloma is very dependent on the burden of circulating monoclonal FLC rather than the amount of M protein spike. The advent of FLC assays have really helped the diagnosis and management of renal dysfunction seen in patients with paraproteinemias. In an elegant paper in JCI, Ying *et al* investigate inhibiting the interaction of FLCs with THP. There is an area on the FLCs called the complementarity determining region 3 (CDR3) that is very important to allow interaction with the THP. The investigators show that when you competitively inhibit that peptide region, the FLCs did not bind to THP *in vitro*. Then in a rodent model of cast nephropathy, this inhibitor of CDR3 prevented cast formation and prevented manifestations of the kidney injury *in vivo*. This is an interesting study as it doesn't treat the underlying disease (multiple myeloma) but attempts to treat in an animal model a consequence of the disease. Cast nephropathy which leads to intratubular obstruction can quickly lead to dialysis in many cases. This is a study that shows by using the CDR3 inhibitor, we prevent this light chain and THP combo and prevent the precipitation in the tubules. In most cases, treating the underlying cancer will help the kidney but having an alternative method will be amazing! This is the latest in cast nephropathy research.

What about the use of plasmapheresis (PLEX)? There have been 3 randomized trials and the results are mixed. Two of the trials including the largest one were negative; however, serum FLC was not used as a marker of response in any of the trials and kidney biopsy was not used to confirm the diagnosis in the largest study (biggest limitation). A Mayo clinic report in *NEJM* found high rate of renal recovery (86%) when PLEX was combined with a bortezomib-based therapy but others have found nearly as high rates of recovery with bortezomib-based therapy alone. Finally, the high-cutoff (HCO) dialyzers with molecular cutoffs as high as 45 kDa have been used to remove FLC. Extended hemodialysis with the HCO 1100 dialyzer permits continuous and safe removal of FLC in large amounts (1.7 kg of

FLC was removed from one patient over a period of 6 weeks). Randomized trials are currently being conducted with HCO dialyzers in cast nephropathy.

Amyloidosis

What's new in amyloidosis? Tools are starting to emerge that help to identify the type of amyloidosis. Everyone is aware of the alphabet soup that one needs to recognize in the various forms of amyloidosis. Accurate typing of amyloid is necessary since treatments for different types of amyloid are themselves very different.

Amyloidosis of the kidney is typically classified as being either one of two types: AL or AA. These types are differentiated by their immunofluorescence and immunohistochemistry studies.

- AL (amyloid light chain) amyloidosis or AH (amyloid heavy chain) amyloidosis are plasma cell diseases and made up of either light chain or heavy chain chain predominance
- AA amyloidosis is usually secondary to chronic illness such as rheumatoid arthritis, familial mediterranean fever, infections, and sometimes malignancies like renal cell and Hodgkin lymphoma.

A novel technique has come into light in helping to diagnose amyloidosis. It is the LMD/MS technique or laser microdissection combined with mass spectrometry. Researchers from the Mayo Clinic have used this technique to diagnosis even rare cases that might not have been picked up on regular staining via AA or AL and perhaps even medullary amyloidosis. They have demonstrated that LMD/MS is can sensitively diagnose and type amyloidoisis, especially in problematic cases. In the method, ~10-µm-thick sections of formalin-fixed paraffin-embedded tissues are Congo Red stained, and glomeruli with Congo Red deposits are subjected to LMD. The microdissected material collected is analyzed by liquid chromatography electrospray tandem mass spectroscopy. The output includes the total number of mass spectra that can be matched to protein using proteomic software. A higher number of mass spectra denotes greater abundance and will generally provide more extensive amino acid sequence coverage. A classic case was published in *NEJM* many years ago on how diagnosis of the type of amyloidosis was crucial. Thus specific proteins were identified and diagnosis was made. So, now using this technique, one can be as specific as the protein involved in amyloidosis. This new technique still needs to be widely accepted by the pathology community.

With the enlightening new research happening in both cast nephropathy and amyloidosis, you decide if you prefer the tubule to move ahead or the glomerulus!

– Post written and edited by Drs. Kenar Jhaveri, Matthew Sparks, and Mitch Rosner.