NephMadness 2013 Unplugged

an eAJKD.com production

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Welcome to NephMadness 2013

It's March, and though the whole country is focused on National Kidney Awareness Month, it is also the start of the NCAA Men's Basketball Tournament. Every March people get bracket fever trying to predict the outcomes of the 67 tournament games that crown the National Champion.

In order to help the NCAA build some excitement eAJKD is running its own tournament. We are pitting the greatest achievements in nephrology against each other to determine the greatest nephrology advancement.

Today, on Selection Sunday we are releasing the brackets and seeding. We know there are bubble achievements that missed entry, I'm looking at you CRIC study (we tried to find a place for you, honestly) and how could we snub renal sympathetic nerve ablation? Please air all grievances in comments on the web.

Download the brackets as a powerpoint or PDF go through and make your picks. Then email your brackets to NephMadness@cluemail.com or take a picture with your phone and post them to twitter. Remember to tag all tweets #NephMadness

Here is how the tournament will progress for the next three weeks:

March 17: Selection Sunday! Posts are provided giving background and context for each achievement that made the tournament

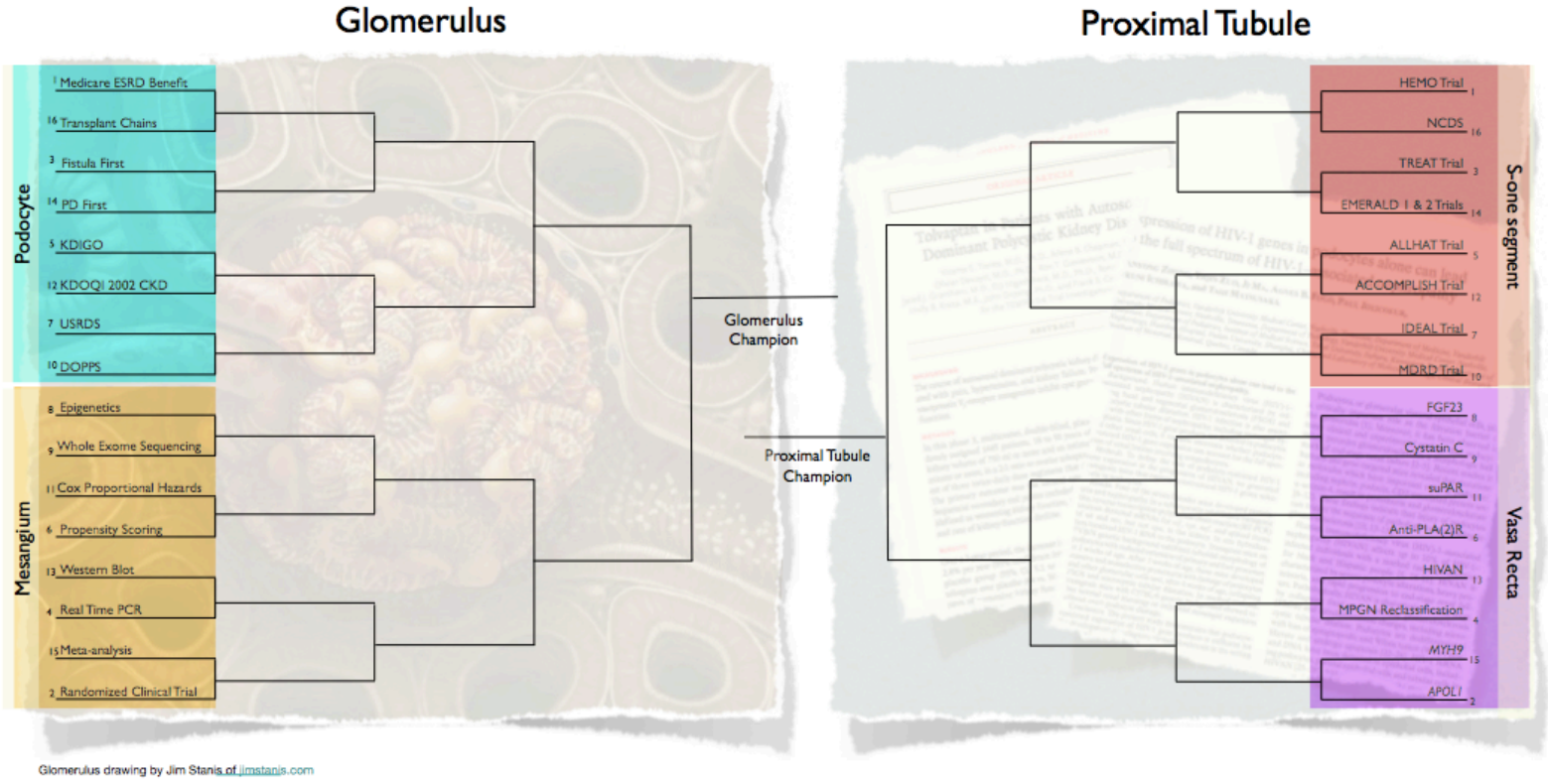
- Glomerulus Region
- Proximal Tubule Region
- Loop of Henle Region
- Collecting Tubule Region

We encourage everyone to submit their brackets, comment on the post and most of all: vote early, vote often. Have fun and may the best achievement win! Please, no wagering.

2013 Nephrology Madness

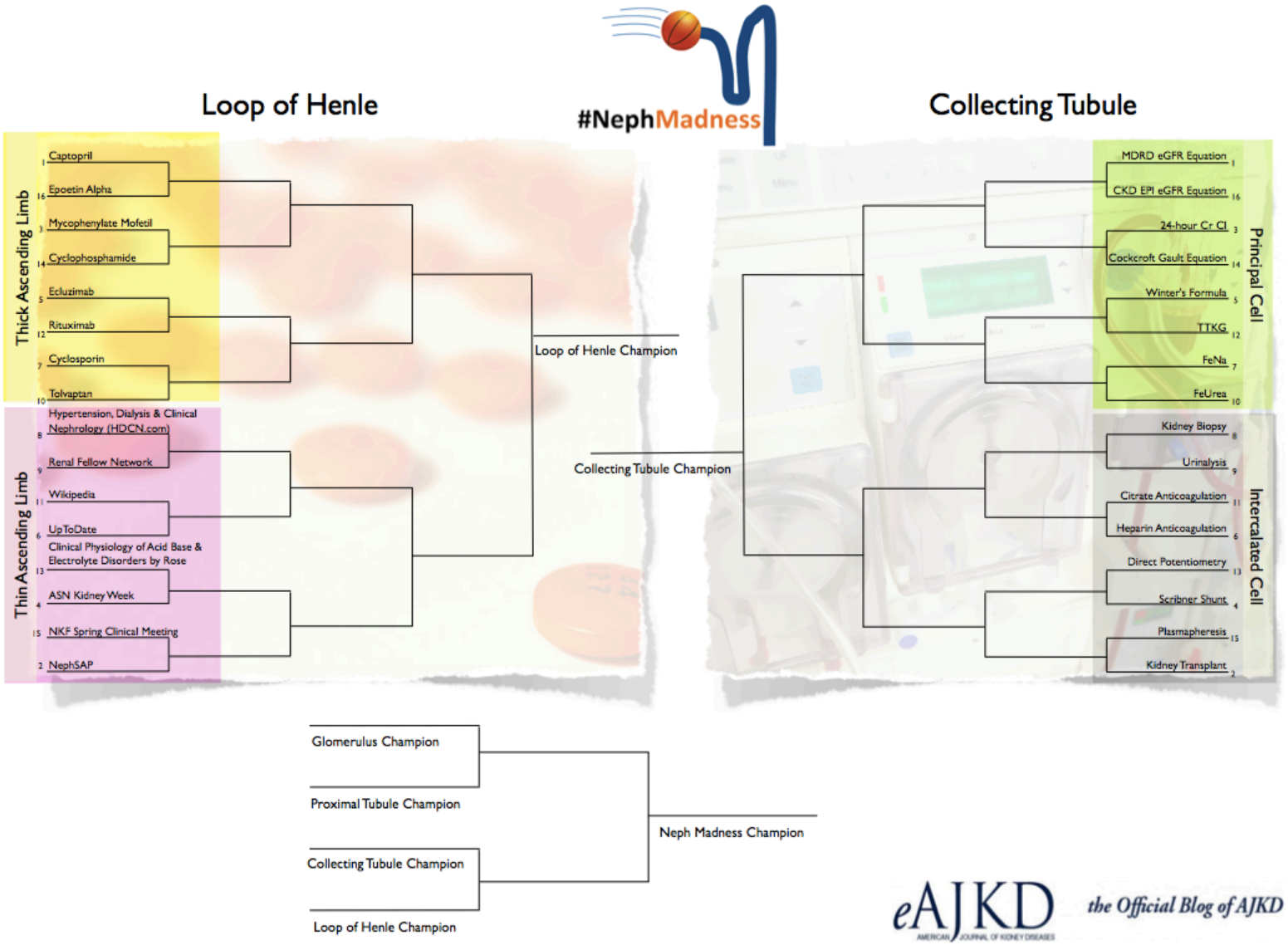
#NephMadness

March 17th- April 8, 2013



Glomerulus drawing by Jim Stanis of jimstanis.com

eAJKD the Official Blog of AJKD


Loop of Henle
#NephMadness
Collecting Tubule
Thick Ascending Limb
Captopril
Epoetin Alpha
Mycophenylate Mofetil
Cyclophosphamide
Eculizimab
Rituximab
Cyclosporin
Tolvaptan
Thin Ascending Limb
Hypertension, Dialysis & Clinical Nephrology (HDCN.com)
Renal Fellow Network
Wikipedia
UpToDate
Clinical Physiology of Acid Base & Electrolyte Disorders by Rose
ASN Kidney Week
NKF Spring Clinical Meeting
NephSAP
Loop of Henle Champion
Collecting Tubule Champion
Principal Cell
MDRD eGFR Equation
CKD EPI eGFR Equation
24-hour Cr Cl
Cockcroft Gault Equation
Winter's Formula
TTKG
FeNa
FeUrea
Intercalated Cell
Kidney Biopsy
Urinalysis
Citrate Anticoagulation
Heparin Anticoagulation
Direct Potentiometry
Scribner Shunt
Plasmapheresis
Kidney Transplant
Glomerulus Champion
Proximal Tubule Champion
Collecting Tubule Champion
Loop of Henle Champion
Neph Madness Champion
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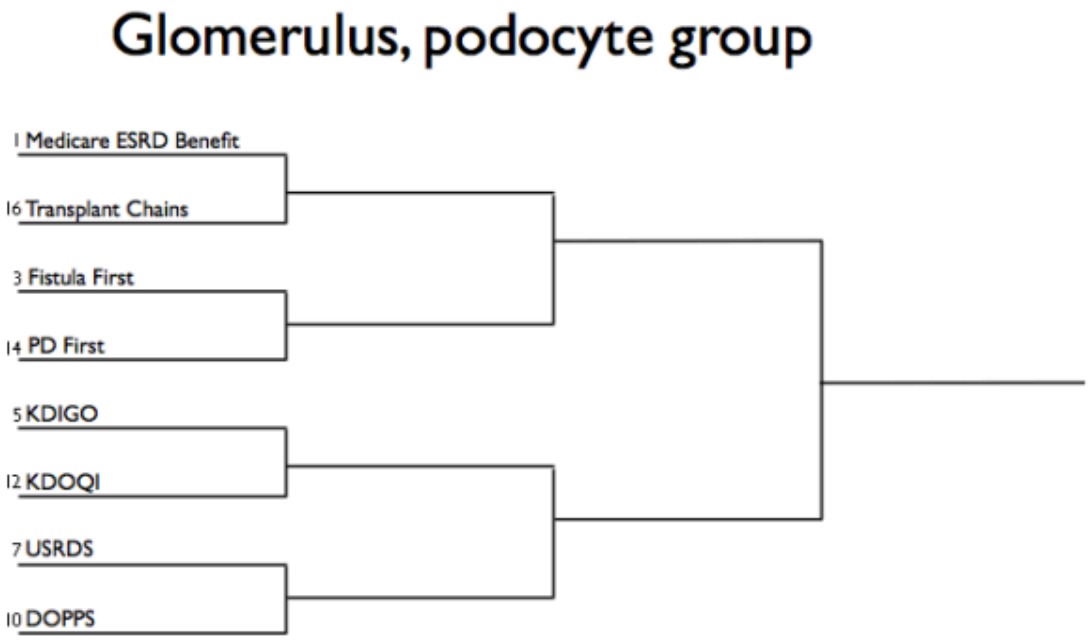
NephMadness: Glomerulus Region – Podocyte Group



(1) Medicare kidney entitlement of 1972 vs (16) Transplant Chains

A true behemoth versus a diaper dandy. Glad to see transplant chains but this could be a difficult challenge.

Medicare kidney entitlement of 1972

In 1960 Belding Scribner working with Wayne Quinton invented a permanent and reusable vascular access device for intermittent hemodialysis, The first patient, Clyde Shields lived 11 years. Soon after that initial advancement small dialysis units began to spring up around the country but few patients were dialyzed. In 1972 the Congress was expanding the original Medicare bill to cover disabled people. As part of the testimony Shep Glazer received dialysis in front of the House Ways and Means Committee. He was attended by Georgetown nephrology fellow James Carey, In late December 1972 Section 299I passed granting medicare coverage for dialysis to all medicare eligible people in the United States (90% of the population). (See Rettig)

Transplant chains

Just over a year ago the New York Times published a story about a transplant chain that provided 30 patient with ESRD with kidney transplants. The chain began with Rick Ruzzamenti, an altruistic living donor, and ended with Donald Terry who had no friends or family members able to donate. The idea of allowing patients with a willing but incompatible donor to give their kidney to another person in the same situation was popularized in an article in the NEJM by Lainie Friedman Ross et al. in 1997. They attributed the idea to Rapaport in 1986. The first paired exchange was performed at Johns Hopkins in 2001. Hopkins also participated in the first multi-hospital complex chain involving 12 patients. In the US there are 90,000 people on the waiting list for a kidney. This system of facilitating living donors has the potential to move the needle and get lots of patients off dialysis who would otherwise just gaze at the unattainable spare kidneys of their loved ones.

(3) Fistula First vs (14) Peritoneal Dialysis First

Two initiatives to promote important topics in nephrology. Lets refresh ourselves.

Fistula First

The mortality of patients receiving dialysis in the United States is worse than many other countries. Numerous theories and explanations have been put forth to explain this gap but one fact that was always inescapable was the low rate of fistulas and high rate of AV grafts/catheters found in the US. In 2003 CMS, the ESRD Networks and other stakeholders initiated a National Vascular Access Improvement Initiative. The goal was to meet the current K/DOQI target of 50% incident patients and 40% prevalent patients using Fistulas. The program has been successful in moving patients from grafts to fistulas but the worst access of all, catheters, has not fallen, indicating additional work to be done. There is some data indicating that the increased focus on fistulas, with their finicky maturation rate, means that patients are relying on catheters for longer periods of time waiting for the fistula to mature. (See Lok Clin J Am Soc Nephrol. 2007;2:1043-53.)

Peritoneal Dialysis First

In the last 25 years peritoneal dialysis has fallen from representing about ~15% of the dialysis population to ~7%. This decrease in peritoneal dialysis use comes during a time when the modality is becoming safer, more convenient and more efficient. Consider:

Less infections. Hemodialysis patients have 102 infections per 1000 patients years, PD patients have only 66.7 per 1000. (see USRDS 2011 Atlas, Figure 3.1)

Home therapy. By allowing patients the opportunity to perform dialysis at home it gives them greater flexibility to manage their lives and continue working.

Better transplant results. After transplant there is less delayed graft function, but that benefit may be balanced with other types of early graft loss. A more recent examination of the datafound a small survival and graft benefit with PD.

More cost effective. PD is $20,000 cheaper per year.

Better satisfaction with care.

It's what nephrology professionals would choose if they needed dialysis.

A good summary of the peritoneal dialysis can be found here.

(12) K/DOQI vs (5) KDIGO

These are similar teams that should come down to the last seconds. Do I smell overtime?

K/DOQI

The kidney disease quality outcomes began in 1989 at a conference on in Dallas on excess morbidity in dialysis with a focus on dialysis dose. Following that conference a diverse group of stake holders banded together to produce clinical practice guidelines for the treatment of dialysis patients:

- Centers for Medicare and Medicaid Services [CMS]
- Association for the Advancement of Medical Instrumentation (AAMI)
- Renal Physicians Association (RPA)
- National Institutes of Health (NIH)

This crew, organized by the National Kidney Foundation, produced the Dialysis Outcomes Quality Initiative, DOQI guidelines. These guidelines published in 1997 called for:

- hematocrit of 33-36%
- spKt/V of at least 1.2
- URR of at least 65%
- Increase fistulas from 10 to 15% (compared to 50% elsewhere around the globe)
- Eliminate subclavian temporary catheters in favor of cuffed internal jugular catheters

By 2002 it was clear that DOQI was a success:

- Hematocrit rose from 30 to 34.5%
- URR rose from 63.8 to 69.9%

- Temporary catheters fell
- Permanent catheters rose
- Fistula rates increased

DOQI shows that the U.S. dialysis apparatus was able to change practices and achieve goals laid out in clinical practice guidelines. Use of these guidelines was able to decrease variability of care from dialysis unit to dialysis unit and from doctor to doctor.

As the achievements of DOQI began to be actualized, it became clear to actually move the needle on dialysis outcomes the health of patients initiating dialysis would need to improve. This was the thinking behind targetting guidelines upstream and improving the health and performance status of people with the yet to be defined chronic kidney disease. The name for these expanded guidelines was Kidney Disease Outcome Quality Initiative, K/DOQI. The scope was bigger than dialysis, it would target the full range of chronic kidney disease from screening and diagnosis to dialysis and end of life issues.

In 2000 the first K/DOQI guidelines were published. They were updates of the four DOQI guidelines, it wasn't until 2002 that the increased scope of K/DOQI was realized. In 2002 Spring Clinical meeting in Chicago The Chronic Kidney Disease: Evaluation, Classification, and Stratification guideline was released. This codified, for the first time, various levels of renal insufficiency, gave guidance on how to diagnose and screen for them and how to monitor these patients. This has ushered in a new era in nephrology.

KDIGO

Following the success of KDOQI other countries and other organizations assembled their own clinical practice guidelines. Naturally the guidelines varied in terms, targets, strength of evidence, and measuring techniques. To prevent an emerging tower of Babel and to minimize duplications of effort an international coalition was made to create an organization dedicated to:

> *"improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines."*

KDIGO just published its CKD guidelines, the first revision of the initial CKD guidelines from 2002. One of the concerns about the initial guidelines was just how many people were diagnosed with CKD stage 3. Prior to automatic GFR reporting we had rampant underestimation of renal dysfunction as the frail and aged would escape notice with normal creatinines despite poor GFRs. After the CKD guidelines we had the reverse with vast populations getting caught in the GFR net due to normal aging and without structural or progressive renal failure. In 2007 Coresh et al. used NHANES data to project that 26 million

Americans had CKD. To put this in perspective only 20 million Americans have diabetes. They projected that fully half of Americans over the age of 69 had CKD. A number of high profile editorials began to push back on the CKD definitions (see here andhere).

KDIGO attempts to make this course correction by dividing the stage 3 into Stages 3A (GFR 45-59 ml/min) and 3B (GFR 30-44 ml/min) to grow the traditional 5 stages into 6 and then further risk stratifying patients by albuminuria:

- A1: < 30 mg/d
- A2: 30-300 mg/d
- A3: >300 mg/d

By combining the GFR and albuminuria stages into a 3×6 table they created a risk map to better judge prognosis. See the entire guideline at:http://www.kdigo.org/clinical_practice_guidelines/ckd.php

(10) DOPPS vs (7) USRDS

DOPPS

It is unfortunate but a reality that nephrology is based largely on retrospective data. We have only a few, mostly negative, randomized controlled trials, so our framework of care is largely based around retrospective observations and expert opinion. A large source of those observations comes from DOPPS.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) comes out of the realization that outcomes differ from dialysis unit to dialysis unit and differences are even larger when you compare country to country. And behind those outcomes are different practices. Some of the variability may be due to different populations, comorbidities and genetic predispositions, but some of the variability is due to how dialysis is done. DOPPS' mission is to mine those differences to determine which ones are translate into improved patient outcome.

DOPPS acts as the canary in the coal mine, able to quickly test theories and provide early guidance. It is not infallible and the organizers have not been dogmatic but looked to find where mistakes were made and improve the predictions for the future.

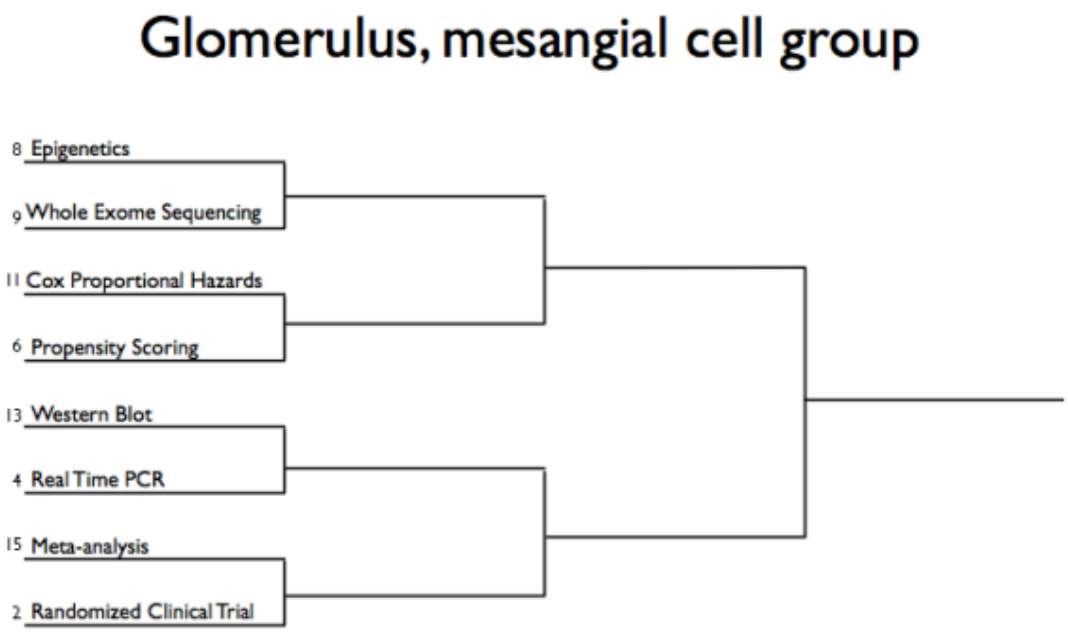
USRDS

The United States Renal Data Service is charged by congress to gather and track information on Medicare beneficiaries in the dialysis program. They also track patients not covered by medicare and provide the most complete data set on dialysis and transplant in the United States.

As part of the data distribution, USRDS publishes an Atlas of information regarding people with kidney disease. The Atlas does not look like any other government information I have ever seen. It is graphically

rich and done with flourishes normally reserved for coffee table art books. Every year the Atlas has new design aesthetic. It is awesome.

NephMadness: Glomerulus Region – Mesangial Cell Group



(9) Whole-exome Sequencing vs (8) Epigenetics

Whole-exome sequencing

Whole-exome sequencing has changed how we study rare Mendelian disorders. Although acquiring full genome sequences is a lot cheaper than it used to be, it's not been practical to use whole genomes in genome-wide association studies, so researchers have tended to scan SNPs instead. But, since a lot of the action, mutation-wise, occurs in the coding regions of DNA (the exome), an alternative is to sequence this subset instead of the whole enchilada. Result? Sequence-level information on all genes for a (relatively) economical cost, giving way more information than even a half-million SNPs. Furthermore, smaller sample sizes can be utilized instead of larger numbers of family members using traditional linkage analysis. The speed at which whole-exome sequencing can be performed and the lower costs are two reasons that this technique is being utilized more and more. A recent paper by the Lifton group identifying muta-

tions in kelch-like 3 and cullin 3 causing hypertension and electrolyte abnormalities is the latest to show the promise of this technique for nephrology.

Epigenetics

If whole-exome sequencing is the Reader's Digest book of life, epigenetics are the notes in the margins. Epigenetics refers to the processes by which cells can alter the expression of genes beyond the actual DNA sequences of exomes. The full implication of epigenetics on gene regulation yet to be uncovered. Examples of epigenetics include DNA methylation status, chromatin structure, imprinting, gene silencing, X chromosome inactivation just to name a few. Epigenetics has the potential to answer many important unanswered questions in nephrology, especially in complex diseases with possible environmental triggers. However, the application into kidney disease is only in its infancy. I think this is a true "diaper dandy" of the group.

(11) Cox Proportional Hazards vs (6) Propensity Scoring Matching

Cox Proportional Hazards

Nephrology operates in sea of observational and retrospective data. This data needs to be adjusted and controlled in order to make sense of it. Cox proportional hazards model allows multiple variables to be analyzed simultaneously to see which affect the outcome of interest. Hazard ratios over one, indicate the outcome is more likely and HR less than one indicate it is less likely.

One of the first uses of Cox proportional hazards was in nephrology. Burton and Walls studyestimated the life expectancy of patient on hemodialysis, peritoneal dialysis and with a transplant. It was published in 1987.

A nice video review of Cox Proportional Hazards can be found here.

Propensity score matching

One of the largest problems in observational studies is bias by indication, i.e. patients who receive antibiotics are more likely to die of an infection, does this mean that antibiotics cause death by infection or rather it means people with infections are both more likely to get antibiotics and more likely to die of an infection than people without infections.

Propensity score matching is one way to adjust for this, every subject gets scored on how likely they are to receive an intervention (treatment). This is done with logistic regression, importantly the patient outcome is not considered at all here, just the variable that determine whether a patient get treated. In the

antibiotic example, variables likely associated with antibiotics would be positive blood and urine cultures, elevated white count, fevers, etcetera. Patients with equivalent propensity scores for the treatment of interest, but who received different treatments are compared. So in the above example, all patients with fever and elevated white count are included and patients with antibiotics are compared against people who were not treated.

Propensity score matching is a sophisticated way to avoid a number of biases that contaminate observational studies. An early use of propensity scores in nephrology was Mehta's article on diuretic use in acute kidney injury.

(13) Western Blot vs (4) Real-time PCR

Western Blot

The laboratory technique for determining protein abundance termed Western blotting finds its way into just about every basic science paper published. Western blotting was first described by 3 different labs back in 1979-1981. Renart et al published the first paper back in 1979, Towbin et alfollowed shortly thereafter in the same year and described the technique as it is still performed today, and Burnette et al coined the name back in 1981. The name Western is a play on the related Southern blot method (for detecting DNA) named for its creator Dr. Edwin Southern (there are Northerns, too, but no "Easterns"). The technique relies on the separation of proteins by size using gel electrophoresis, transfer onto a nitrocellulose membrane, and subsequent "blotting" with primary and secondary antibodies. Western blotting is a mainstay in the field but has several limitations. Many antibodies lack requisite specificity, furthermore, the technique is frequently not quantitative, and knowledge about protein activity level and cellular localization is lacking.

Real-time PCR

Real-time PCR has emerged as another powerful tool used in basic science and clinical medicine. It is oftentimes used in conjunction with Western blotting to measure the expression level of a gene of interest. This technique was born out of the ability to replicate DNA using polymerase chain reaction (PCR), which was originally described in the mid 1980s and which earned Kary Mullis (later infamous for his flirtations with HIV/AIDS denialism) a Nobel Prize for this discovery in 1993. For gene expression analysis, real-time PCR relies on serial amplification of DNA that has been synthesized from mRNA transcripts (so-called complementary DNA, or cDNA). The technique, which relies upon fluorescent readout of reaction products, is relatively inexpensive and quantitative. Real-time PCR is used to monitor viral replication of many viruses such as polyoma, CMV, and HIV. In functional genomics, real-time PCR shows if a gene is being

expressed in a cell/tissue of interest; however, since RNA levels don't always correspond directly to protein amounts or activity, it's an indirect measure of gene products.

(15) Meta-analysis vs (2) Randomized Clinical Trial

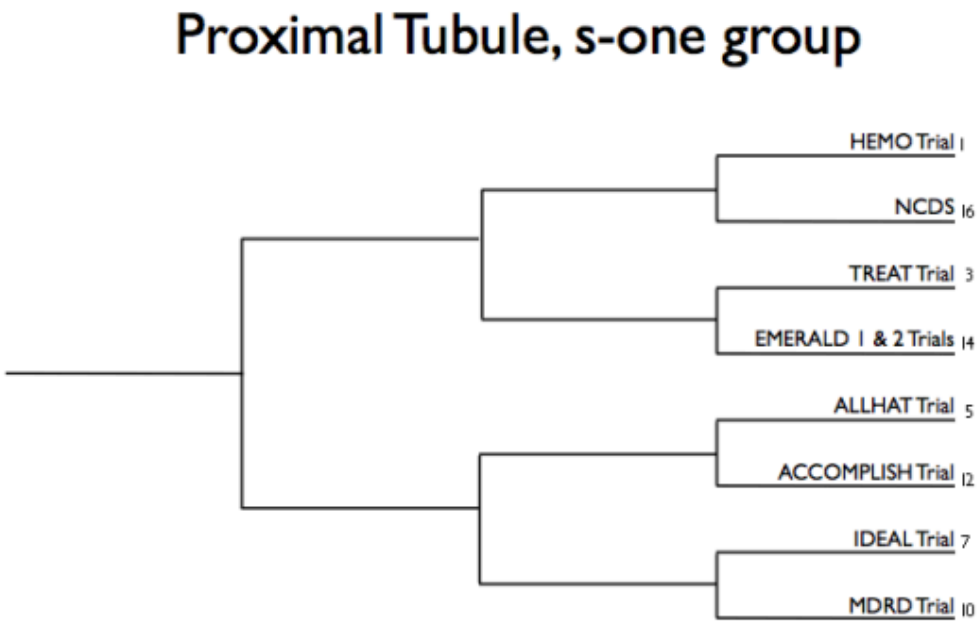
Meta-analysis

Meta-analysis is a popular technique to combine many smaller studies to try and understand trends that could be evident by using various statistical models. This differs from a classical literature review which only compiles the studies performed on a topic to date. This approach often combined with systematic reviews can help to provide very valuable information but often times is performed when there hasn't been a definitive trial performed on a certain topic. The nephrology community has utilized such methodologies over the years. A recent examplepublished in AJKD examines the use of induction and maintenance treatment of proliferative lupus nephritis.

Randomized Clinical Trial

The sine qua non for clinical trials are randomized double blinded clinical trials. This is where the rubber meets the road as far as evidence goes for evaluating treatment efficacy. Also, it has proven quite difficult in the field of nephrology to show efficacy of a particular treatment. These trials are very expensive and consume a considerable amount of up front time figuring out what the right patient population is, how to pick and measure the appropriate outcome and what the duration of the trial should be. This are critical to the success of a RCT. Recent failed examples include the BEACON trial. However, recently we have seen several positive studies including the TEMPO and FHN trials.

Nephrology Madness: Proximal Tubule Region's S-one Segment Group!



(16) NCDS vs (1) HEMO

This is like father and son. Both are seminal trials to the field.

NCDS

The National Cooperative Dialysis Study (NCDS) was the first randomized control trial in dialysis to test the importance of small and middle molecules as uremic toxins. Furthermore, this trial lead to the establishment of minimum standards for dialysis dose. The NCDS trial was published in the NEJM in 1981. Patients in the study were randomized to two different BUN concentrations averaged with respect to BUN: high or low, and to two dialysis treatment times: long or short, in a 2 x 2 factorial design. There was no difference in mortality between groups. However, more patients in the high BUN category were withdrawn from the study for medical reasons.

A subsequent paper by Gotch and Sargent introduced the measurement of Kt/V and also reanalyzed the primary data from the NCDS showing that Kt/V <0.8 was associated with a relatively high rate of patient morbidity, whereas Kt/V values between 1.0 and 1.2 were associated with a low rate of morbidity. Some

feel that there has been an over interpretation of the NCDS results putting too much emphasis on achieving a target Kt/V and ignoring dialysis treatment time which missed significance with a P value of 0.06.

HEMO

After the NCDS trial, a large number of observational data suggested that a dose of dialysis substantially higher than the one provided in the NCDS trial was associated with a lower mortality rate. In response to this, national standards for dialysis dose were developed in the US advocating a minimum spKt/V of 1.2. The Hemodialysis Study Group (HEMO) study was a large controlled trial designed to determine whether further increases in dialysis dose above current standards or the use of high-flux membranes would improve patient outcomes. The patients in the trial were randomized to a standard (Kt/V=1.25) or high dose (Kt/V=1.65) of dialysis, and a low- or high-flux dialyzer, in a 2 x 2 factorial design. The primary outcome was death from any cause. There was no difference in all-cause mortality between standard or high dose dialysis, and low or high-flux membranes.

The HEMO trial overturned 20 years of observational data and shocked the nephrology world.

(3) TREAT vs (14) EMERALD 1 and 2

TREAT

TREAT was a multicenter, randomized, double-blind controlled trial that compare darbopoetin alfa versus placebo in non-dialysis chronic kidney disease (CKD) patients with type 2 diabetes mellitus and moderate anemia targeting a hemoglobin of 13 g/dL in the intervention group. The primary endpoints were the composite outcomes of death or a cardiovascular event and of death or end-stage renal disease. The study showed that darbopoetin alfa not only did not reduce the risk of the primary outcome but was associated with an increased risk of stroke.

Although a negative study, darbopoetin is still in use and TREAT increased awareness that targeting Hb levels >13 g/dL in non-dialysis chronic kidney disease patients with type 2 diabetes is detrimental.

EMERALD 1 and 2

Peginesatide was a very promising drug. It is a synthetic peptide that activates the EPO receptor. Peginesatide is a PEGylated molecule and hence it has a long half-life allowing once a month administration. Because its amino acid sequence is unrelated to erythropoietin, it also does not cross react with erythropoietin antibodies or AMGEN patents.

The EMERALD 1 and 2 trials showed that peginesatide was safe and effective in maintaining the hemoglobin concentration among hemodialysis patients. However, the PEARL-1 and PEARL-2 trials in non-

dialysis CKD patients showed that peginesatide (in comparison to darbopoetin) increased cardiovascular events, and was associated with a higher incidence of sudden death and AKI. To make matters worse, several cases of serious hypersensitivity reactions associated with peginesatide use have been recently reported to the FDA and the manufacturer has withdrawn the drug from the market.

(5) ALLHAT vs (12) ACCOMPLISH

ALLHAT

ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) is the biggest prospective blood pressure study ever performed and was sponsored by the NIH. Thus, freeing it from drug company bias that contaminate many other blood pressure trials. When the study was conceived it was designed to pit newer and more expensive anti-hypertensives:

- **Doxazosin**, an alpha blocker
- **Amlodipine**, a dihydropyridine calcium channel blocker
- **Lisinopril**, an ACE inhibitor
- against the old familiar **chlorthalidone**, a thiazide type diuretic.

Beta blockers were not a randomized arm of the trial but were kept in reserve as a second-line agent for all arms of the trial.
The Doxazosin arm was stopped early because of excess heart failure (RR, 2.04; 95% CI, 1.79-2.32) and stroke (RR, 1.19; 95% CI, 1.01-1.40).
After 4.9 years there was no difference in the primary outcome (combined fatal CHD or nonfatal myocardial infarction) among the three remaining arms (amlodipine v chlorthalidone P=0.65, lisinopril v chlorthalidone P=0.81) though the chlorthalidone group had slightly lower systolic but higher diastolic blood pressures compared to amlodipine and better better systolic and diastolic blood pressures than lisinopril. On secondary end-points, chlorthalidone was superior to:

- Amlodipine for
  - heart failure RR 1.38; 95% CI 1.25-1.52
- Lisinopril for
  - combined CVD RR 1.10; 95% CI 1.05-1.16
  - stroke RR 1.15; 95% CI 1.02-1.30
  - heart failure 1.19; 95% CI 1.07-1.31

Although it was a negative trial, ALLHAT was lauded as showing an older generic drug beating (on secondary end-points) newer branded competition and was the basis of much of JNC 7.

ACCOMPLISH

ACCOMPLISH (Avoiding Cardovascular events through COmbination therapy in Patient LIving with Systolic Hypertension) may have the most awkward, forced acronym for a title ever, but nonetheless is a critical study in the way we treat hypertension today. In the wake of the HOPE trial everyone with a whiff of cardiovascular risk was put on an ACEi. However that was rarely enough to get patients to their goal blood pressure. With JNC7 and ALLHAT in hand the logical next drug would be chlorthalidone. ACCOMPLISH put this under the blade of a RCT, benazepril plus hydrochlorothiazide versus benazepril plus amlodipine.

ACCOMPLISH used hydrochlorothiazide instead of chlorthalidone as the diuretic of choice. One of the missteps after ALLHAT may have been the general conflating of chlorthalidone and hydrochlorothiazide, though they are both thiazide type diuretics, they are different molecules and there is reason to believe that chlorthalidone may be superior to hydrochlorothiazide. Some may scream that ACCOMPLISH used a straw man diuretic, but I prefer to think of it as using the typically prescribed version (eighth most prescribed drug, wedged between Lipitor and Xanax), rather than the odd duck, chlorthalidone.

The ACEi-CCB group had a small blood pressure advantage, SBP was 0.9 mmHg lower and DBP was 1.1 mmHg lower, but that small advantage cannot explain a 20% relative risk reduction and a NNT of 45.

(10) MDRD Trial vs (7) IDEAL Trial

MDRD Trial

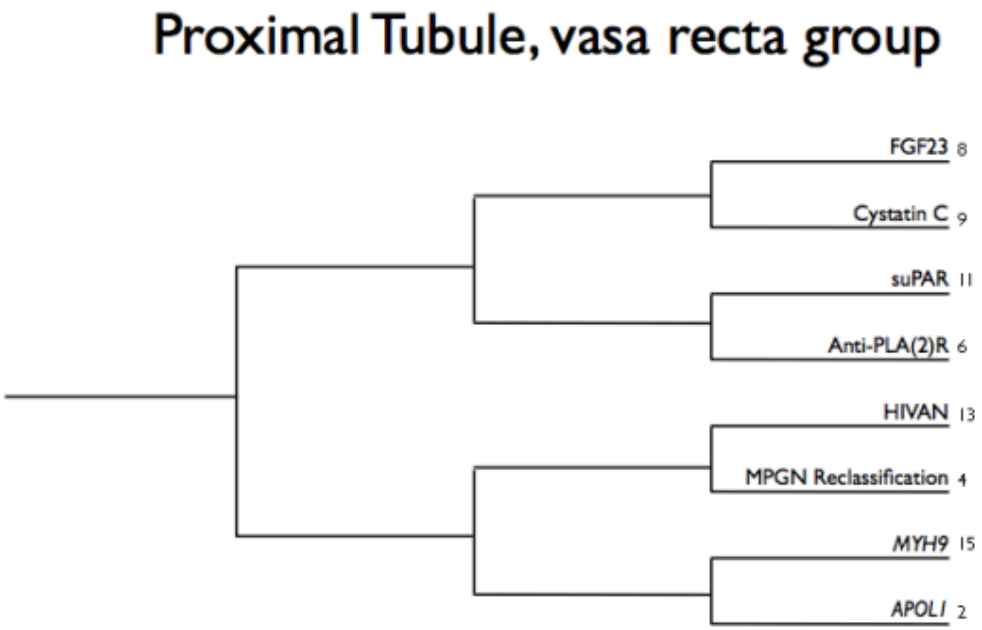
The MDRD trial (Modification of Diet in Renal Disease) was a seminal trial in the nephrology community. This trial has given rise to 2 different teams in the NephMadness tournament. The actual trial and the MDRD eGFR equation (not sure if this is fair). The results of the trial were published in the NEJM in 1994. This was a large [included 2 groups, 1- 1,585 patients with GFR 25-55 (mean creat 1.9) and 2- 255 patients with GFR 13-24 (mean creat 3.4)] multicentered clinical trial testing the hypothesis that restricting dietary protein and strict blood pressure control (MAP 107 vs 92 mm Hg) would delay the progression of kidney disease. The 2 groups were chosen (low and very low GFR) secondary to concerns that patients in the second low GFR group might not be able to consume the usual protein diet. The results of this study were not conclusive for the use of low protein diet to slow the progression of CKD. However, they did report

- slightly slower decline in GFR in the moderate GFR group using low-protein diet 4 months after the intervention (decline of 3.9 usual vs. 2.8mL/min/yr low protein diet).
- this benefit was not seen in the more severe CKD group.
- There was no delay in the time to the occurrence of end-stage renal disease or death.
- In both studies, patients in the low BP group who had more pronounced proteinuria at baseline had a significantly slower rate of decline of GFR.

IDEAL Trial

The decision to start a patient on dialysis is a frequent clinical issue faced by Nephrologists. TheIDEAL (Initiating Dialysis Early and Late) trial published in the NEJM in 2010 shed some light onto this topic. Researchers from Australia and New Zealand randomized 828 patients to either starting dialysis early (eGFR of 10-14 regardless of uremic symptoms) or late (eGFR of 5-7 or uremic symptoms were present). No differences were seen in the primary or secondary outcomes after an average of 3.5 years of follow-up. Although, this trial doesn't definitively answer this question, it does allow for more comfort when following a patient with with advanced CKD. The majority of patients in the late group were initiated on RRT secondary to symptoms of uremia. Waiting for symptoms to occur did not adversely affect the outcome in the late initiation group. Providing excellent pre-ESRD care to all patients with CKD is paramount. Getting timely access and providing medical therapy for complications of hypertension, fluid overload, electrolyte/acid-base derangements while listening closely to the patients symptoms of uremia, seems to trump the eGFR.

Nephrology Madness: Proximal Tubule Region's Vasa Recta Group



(8) FGF23 vs (9) Cystatin C

These two teams have been knocking on the door of nephrology lab orders for a few years now. Lets look at each more closely.

Cystatin C

Two markers have arose in the last decade that have changed the thinking in nephrology. In search for the troponin for acute kidney injury, cystatin C is a front runner at the current time. While urinary markers have been studied, a serum marker is usually easier to measure and very useful in the anuric patient. While many of you know that cystatin C is a potential biomarker for kidney disease, many might not be aware of its role as a predictor of worsening cardiovascular disease and apparently it plays a role in disorders involving amyloid in the brain such as Alzheimer's disease. Based on large studies, the reference interval is usually 0.57- 1.12mg/dL.

FGF23

FGF23 is a fibroblast growth factor protein that is responsible for phosphate metabolism. While it's role in CKD and ESRD is evolving. FGF-23 is a phosphatonin, a hormone that increases renal phosphate excretion. Increased activity of this protein leads to increased renal phosphate wasting and diseases such as autosomal dominant hypophosphatemic rickets and some tumors can over produce this hormone leading to tumor induced osteomalacia. Loss of this protein leads to familial tumoral calcinosis.

(11) suPAR vs (6) anti-PLA2R

The hype in this matchup is palpable. Might as well be a dunk contest.

suPAR

In 2011, the identification of circulating urokinase receptor (suPAR- serum soluble urokinase receptor) as a cause of focal segmental glomerulosclerosis (FSGS) was reported in Nature Medicine. This received considerable attention in the scientific community. They initially reported that high levels of suPAR was detected in 2/3rds of patients with FSGS. The group who initially described the association also recently published a letter in AJKD describing mother to child transmission of suPAR causing proteinuria. There has been some controversy surrounding this story as some have argued that suPAR is non-specific for idiopathic FSGS. This discovery has led to much speculation and definitive large clinical studies to better understand how suPAR levels can be used to guide therapy are yet to be completed.

anti-PLA$_2$R

The description of the M-type phospholipase A2 receptor anti-PLA$_2$R as the long sought after antigen causing membranous nephropathy was a huge story in 2009 when this was published in the NEJM. Since this time we are beginning to understand more and more about how the detection of antibodies against this receptor can help in the treatment of patients with membranous nephropathy (MN). In the future, the detection of anti PLA$_2$R antibodies may help in parsing out if a patient has primary MN who require aggressive therapy or has secondary disease. Levels of circulating anti-PLA$_2$R antibody may also aid in monitoring disease activity and in assessing response to therapy. A recent review in ACKD can be found here. We are still awaiting properly performed clinical trials to guide us on how identification of this antibody will be useful in clinical medicine. However, there is a lot of potential to benefit patients and guide therapy. This is an exciting discovery for sure.

(13) HIVAN vs (4) MPGN reclassification

The nephropathologists will have a front row seat for this matchup.

HIVAN

HIV-associated nephropathy (HIVAN) refers to the collapsing variant of FSGS. HIVAN was first described in 1984. Mounting evidences showed that that the HIV virus directly causes kidney damage. This was an important event for the field of nephrology. Currently, due to the treatment of HIV, HIVAN is seen less in US but still has a strong prevalence in other parts of the world. This discovery also led to an important form of FSGS discovery or an entity entirely unto its own—collapsing glomerulopathy. This is important as the prognosis of this entity, especially if its primary, is very poor.

MPGN reclassification

MPGN has always been written in textbooks as Type 1, 2 and 3. This classification has been based on electron microscopic findings. Recently, scientists and pathologists have reclassified MPGN based on immunofluorescence (IF) and that has led to a different form of thinking for MPGN. If there is immunoglobulin and C3, there is likely a viral, or paraprotein injury or idiopathic. If there is strong C3 only, then it is more likely to be this new entity called C3 nephropathy (and dense deposit disease would be included here).

(15) MYH9 vs (2) APOL1

We have been waiting for this matchup. They used to be in the same conference until *APOL1*decided to be an independent.

MYH9

One of the mysteries of American nephrology is why there are so many African Americans on dialysis. The facts:

US Population is 13% African American yet they account for 32% of the prevalent dialysis population and 48% of the patients on dialysis due to hypertension. The disparities are seen beyond dialysis to early stages of albuminuria as discussed in this interview with Deidra Crews on eAJKD.

There is likely a social, acquired component but there is also likely a genetic component and in 2008 a candidate gene came up, *MYH9*. I read the paper and couldn't understand the technique but I've never seen such a small P value.

$$P = 4 \times 10^{-23}$$

The P value was as small as Avogadro's number is big (6.02×10^{23}). As far as I was concerned, it was the reason for the increase in African Americans with kidney disease. You can hear all the excitement about *MYH9* in this Kidney International Podcast.

APOL1

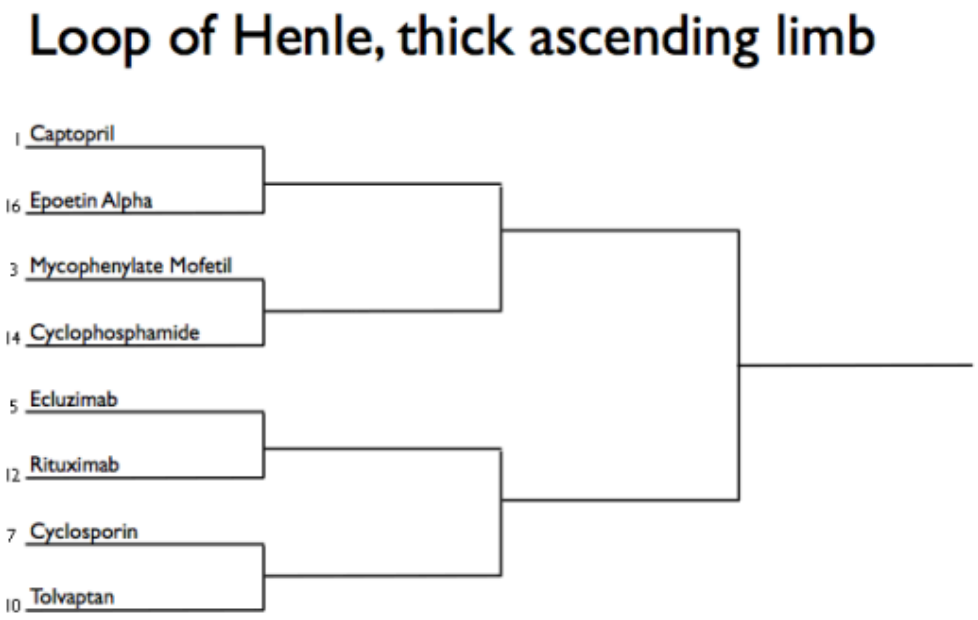
Well even a P value as small as Avogadro's number is large indicates uncertainty and that uncertainty was exploited by *APOL1*. Additional genetic testing indicated that *MYH9* was tightly associated with the phenotype FSGS and HIVAN but just to the centromere side of *MYH9* was*APOL1*. *APOL1* had a tighter association with FSGS, hypertensive associated ESRD and HIV associated nephropathy than *MYH9*. And the most convincing part:

After controlling for *APOL1*, *MYH9* ceased to be significantly associated with FSGS

After controlling for *MYH9*, *APOL1* remained associated with FSGS

APOL1 is found in 30% of African Americans. *APOL1* is so prevalent because of a balanced polymorphism. Having two alleles increased susceptibility to kidney disease but having at least a single allele provided immunity to Trypanosoma brucei rhodesiense and Trypanosoma gambiense,African Sleeping Sickness. The mutation which created *APOL1* occurred in Africa 10,000 years ago, the ancestors of Europeans and Asians left Africa 60,000 years before that. Almost no Caucasians or Asians have the mutation.

For more on parasites and the kidney see this interview with Rashad Barsoum.



Nephrology Madness: Loop of Henle Region's Thick Ascending Limb

(1) Captopril vs (16) Epoetin Alfa

A battle of the elites. Captopril is representing all of the anti-angiotensin II drugs. Its always nice to be the go to drug with proven mortality benefits. However, epo is a formidable foe but its enthusiasm in recent years is waning and they barely made the tournament.

Captopril

If captopril was a basketball team they would be the Vipers. Angiotensin converting enzyme inhibitors (ACEi) had been theorized and many drug developers were looking for candidate molecules. John Vane, the Englishman who won the Nobel prize for discovering the mechanism of aspirin and defining prostaglandin physiology, learned about the venom of the Bothrops jararaca viper that induced death via a massive drop in blood pressure. He secured snake venom and his team discovered that the mechanism was inhibition of angiotensin converting enzyme. They later isolated a 9 peptide derivative of the venom that was actually used in human trials for hypertension and heart failure. The peptide had to be given parenterally since it was not stable orally (See Gavras et al). Vane took this discovery to the pharmaceutical company Squibb, where scientists, David Cushman and Miguel Ondetti, began searching for an orally stable ACE inhibitor. Ultimately they modified a carboxypeptidase inhibitor to resemble the functioning ACEi and created captopril. This is one of the early examples of structure-based drug design (See Patlak).

Epoetin Alfa

In June of 1989 the transfusion rate for dialysis patients was 15.8% every three months. By March of 1990 that had fallen to 6.6% and by December 2000 that had fallen below 1%. This night and day change in the transfusion rate in patients receiving hemodialysis is a tribute to the use of epoetin alfa and the scientists and clinicians at Amgen who brought it to market. Today, it is nearly impossible to recondition your mind to think about what it meant to dialysis patients to be receiving recurrent blood transfusions every few months. The country was in the middle of the AIDS epidemic and though an antibody test existed, PCR for viral load was not available, meaning no transfusion was completely safe. A drug that could reduce transfusion requirements was not just a convenience it was a life line. The other benefit to the fall in transfusions was the decrease in antigen exposure to patients on the wait list for kidney transplantation. Through the '90s and '00s the proportion of unsensitized patients on the kidney transplant wait list roughly doubled from 25 to 50%. This decreased sensitization is a direct result of the decreased transfusion de-

pendence in patients on hemodialysis. Though our relationship with the miracle of epoetin alfa has been tarnished of late it is difficult to imagine nephrology without it.

(3) Mycophenolate Mofetil vs (14) Cyclophosphamide

"The battle everyone wants to see is MMF against cytoxan."
–early discussion among the selection committee.

Mycophenolate Mofetil

Mycophenolate Mofetil (MMF) began life in transplant and earned its stripes in a randomized controlled trial against azathioprim, where it showed decreased acute rejection. However, this may have been an illusion, as recent studies have not been able to replicate these successes.

The jump to glomerular nephritis is where MMF is changing nephrology. First in lupus where MMF was shown to be equivalent to cyclophosphamide for induction and maintenance therapy. MMF has consistently showed non-inferiority to cyclophosphamide in lupus. A meta-analysis published in the AJKD also supported MMF vs. cytoxan with less ovarian failure and alopecia, major sources of morbidity.

MMF is finding some success with membranous, ANCA vasculitis and MPGN.

Cyclophosphamide

Cyclophosphamide is the Hannibal Lecter of drugs, a drug with a side effect profile almost perfectly created to make it not just dangerous but cruel. Like all alkylating agents, cyclophosphamide causes bone suppression, increases the risk of hematologic malignancies, alopecia, ovarian failure, and teratogenicity, but cytoxan has a couple of unique properties that propel it above and beyond the typical bad actor.

Cyclophosphamide causes bladder cancer. And it can cause bladder cancer decades after the drug has been stopped (see Radis et al.) The poor patient may have stopped the drug 15 years ago, the prescribing doctor may have retired and moved to Boca when the cancer breaks through (seeMonach et al). To make matters worse, the conventional GU cancer screen, urinalysis for hematuria is not so helpful in cyclophosphamide whose patients usually have glomerular hematuria at baseline.

Additionally cyclophosphamide causes hemorrhagic cystitis. The standard advice for this is to encourage drinking inorder for patients to maintain a brisk urine flow so that the cyclophosphamide is not in contact with the urinary epithelium for long. This would be great advice if cyclophosphamide didn't have ADH-like activity. Increased water intake can turn around and predispose the patient to life threatening acute hy-

ponatremia. This has even been seen in low dose cyclophosphamide IV and PO. (see Salido et al and Kato et al) Would you like some fava beans and chiante with that lupus therapy?

(12) Rituximab vs (5) Eculizumab

Now this is an interesting battle. The basic question is what's better – stopping antibody production with rituximab or blocking the effector pathway with eculizumab? Let's look at the data and make some wagers. [editors note: please no wagering]

Rituximab

Rituximab is a monoclonal antibody directed against CD20 which is found on B cells. It was born in the field of oncology and gained fame in the treatment of various B cell lymphomas. It made its way into nephrology as an answer to diseases attributable to antibody mediated injury. In transplantation rituximab has been used to treat antibody mediated rejection. It has also been used in combination with intravenous immunoglobulin to improve transplant rates in patients with anti-HLA antibodies (desensitization of the highly sensitized patient). In addition it has also made its way into the arena of glomerulonephritis. Rituximab has been used to treat membranous nephropathy, lupus nephritis, recurrent FSGS post transplantation and pauciimmune glomerulonephritis. But does it really work? Most of the mentioned trials are not placebo controlled and involve a very limited number of patients. In addition rituximab may target B cells but not long lived plasma cells which produce antibodies and are CD20 negative. Finally it clearly increases the risk of serious infections. Though rituximabs gained much fame in the nephrology community not everyone is a fan!

Eculizumab

Eculizumab is a monoclonal antibody that inhibits C5. Without C5 you prevent the formation of the MAC complex and stop the most potent pathway of complement mediated cell injury. Not only does this stop the effecter pathway of antibody mediated injury, but it also prevents injury from the disorders of complement dysregulation. Case in point – this drug has revolutionized the treatment of paroxysmal nocturnal hemoglobinuria (PNH). In fact it is the only drug that is FDA approved to treat it. In nephrology it has revolutionized the treatment of atypical HUS where it is also FDA approved. It is even being studied in kidney transplantation to prevent and treat antibody mediated rejection. Again, antibodies cant do much damage if you block complement. However, we need to remember that eculizumab is still a rooky in nephrology. The diseases it is approved for are quit rare and it is not clear when, if ever, the drug can be stopped. Perhaps equally important is that this drug does not come cheap. One year treatment for atypical HUS in an adult costs about $500,000 – now that's an expensive contract!

(7) Cyclosporine vs (10) Tolvaptan

This will be an interesting battle. Cyclosporin is a true veteran. Been there done that. Its side effect profile is well know and it is generic. Tolvaptan is just beginning to receive accolades and is expensive, new and unclear toxicity. Lets take a closer look.

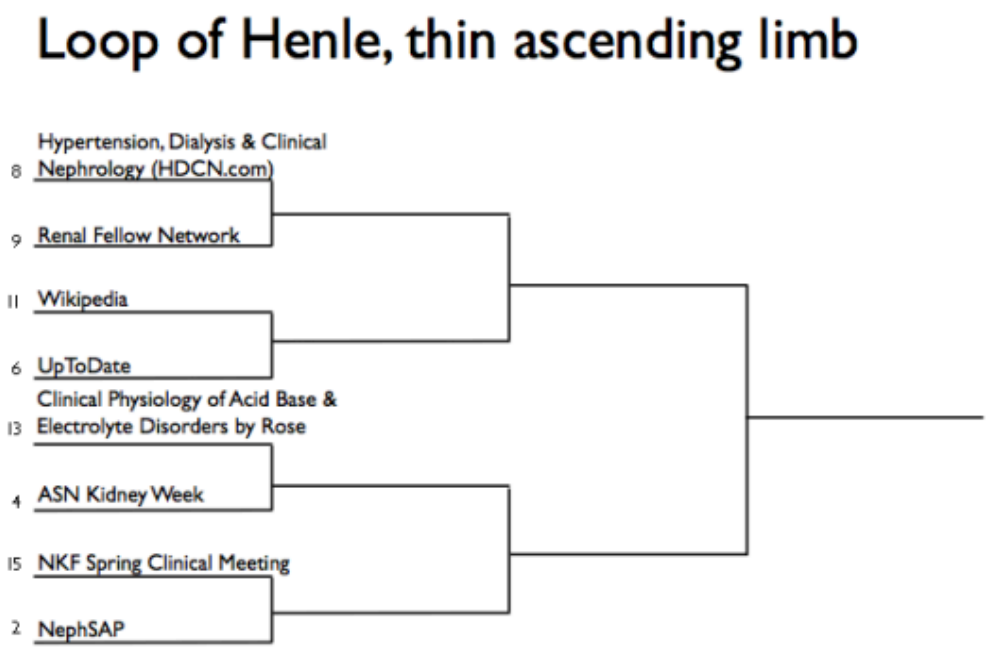
Cyclosporine

Cyclosporine has been a mainstay drug in transplant nephrology for many years. Only recently has tacrolimus (FK506, Prograf) supplanted its use. The drug was first isolated from the fungus Tolypociadium inflatum contained in a soil sample obtained in 1969 from Hardangervidda, Norway. However, the immunosuppressive effects were unknown until 1972 when employees from Sandoz in Switzerland discovered its effects. The first description of its use in solid organ transplants was in a cadaveric kidney transplant discussed in a paper in the Lancet from 1978. This paper described 7 patients receiving cyclosprin A after kidney transplant. The characteristic nephrotoxcitiy was evident even at this time. The primary mode of action of this drug is to lower the activity of T cells by inhibiting calcineurin which in turn decreased IL-2 production. The drug was a mainstay for many years after the seminal 279 patient trial was paper published in the NEJM in 1994.

Tolvaptan

Tolvaptan is the new kid on the block in the nephrology world. The drug is a competitive vasopressin receptor 2 antagonist. The vaptan class of non-peptide vasopressin antagonists were developed in the mid 1990s. These molecules competitively block the binding of vasopressin to V2 receptors on renal collecting duct cells. The first large scale clinical trials to use the vaptan class of drugs were Study of Ascending Levels of Tolvaptan in Hyponatremia or SALT 1 and 2 trials. These were published in the NEJM in 2006. However, concerns about costs and potential liver toxicity remain for this indication. More recently Tolvaptan made a splash at Kidney Week 2012 when the results of TEMPO 3:4 clinical trial were released showing decreased cyst growth and slower progression of loss of GFR in autosomal dominant polycystic kidney disease (see Torres et al).

Nephrology Madness: Loop of Henle Region's Thin Ascending Limb Group!



(8) HDCN.com vs (9) Renal Fellow Network

HDCN.com

HDCN stands for hypertension, dialysis and clinical nephrology. This is a website that hosts many updated nephrology lectures from national, international conferences and the latest articles with links and summaries. It is constantly updated and has been used by many around the world. The content is peer reviewed material with minimal editorial commenting and opinion-based information. Flash slides and audio streaming allow for listening to lectures using multimedia. The website lacks glamor, feels outdated and is not easy to navigate. It requires a subscription to get most of the information that the website hosts. The RPA and ASN endorse this website.

Renal Fellow Network

Renal Fellow Network (RFN) is the most popular nephrology blog. It was started in 2008 by Nathan Hellman a nephrology fellow at Harvard. Since then, the website has blossomed to be the-go-to site for many fellows in training. It is a blog and the writing is coloquial with opinion based snippets of current updated

research in nephrology. In addition, the website offers good board review material, links to conferences and fellow specific grants. Renal Fellow Network was important to nephrology because it ushered nephrology into the online world. Many of the nephrology bloggers currently active online were inspired by RFN and this led to the creation of many teaching sites including eAJKD. It is a well designed website, has many commenting features and endorsements from NKF and ASN. RFN is also unique in that it is run by fellows from around the US and world. This allows for material to be presented by the learner as it is happening. The site promotes networking and exchange of ideas across fellowship programs and countries.

(11) Wikipedia vs (6) UpToDate

Wikipedia

I find that more and more when I need to remember something in nephrology I just type the question into Google. I don't bother with a specific search engine. I don't seek out Renal Fellow Network or Wikipedia or UpToDate, I just drop the question on to Google. The reason I'm doing this more and more is that it works. It is easier for me to use google to find a reference for a specific paper than to find the paper on my own hard drive. I started to notice how many times these random google search would drop me in Wikipedia. It was a lot. Then I sat down at lunch and plowed through 12 nephrology terms. Here are the terms and the sources that came up on my iPad without scrolling:

Wikipedia stands alone with a first or second in every term but one. Wikipedia is the Michael Phelps of online nephrology answers.

	Wikipedia	NIH	PubMed	UpToDate	MedScape	WebMD	Neph Journal
Aminoglycoside toxicity	2		1	3	4		
CPM	2	1			5		
Diabetic nephropathy	2	1			5	4	
Epoetin alpha	1	2					
FGF-23	1	4					
FSGS	1						
Kt/V	1	4		5			
Pauci-immune	1		3				5
Primary Hyperaldo	1	3				4	
Thin Basement	1		4				2
Urinary eos	5		2	1			

UpToDate

UpToDate is a juggernaut which rewrote the rules of medical publishing. It was the first successful electronic textbook. When textbooks were just thinking about gluing a CD-ROM to the back page as a multimedia extra, Rose had thrown out the whole book and just used the CD-ROM. This allowed him to ship the textbook before it was done. I remember ordering UpToDate in the mid-90s and internal medicine was not even complete. It was almost finished but some specialties were completely absent. However, every 3 months I would get a new CD with updates to the current files, newly written sections and cards and an update to the abstracts of Medline. In the days before PubMed, UpToDate shipped with a copy of index medicus.

The other freedom of the CD-ROM, was it allowed an all new editorial style. Instead of doling out strict word limits in order for the textbook to hit the length determined by the marketing department. Rose was able to go into as much detail as he wanted.

Completely disruptive. He outflanked all of the internal medicine textbooks and they still haven't caught up.

(13) Clinical Physiology of Acid-Base and Electrolyte and Disorders vs (4) ASN Kidney Week

Clinical Physiology of Acid-Base and Electrolyte and Disorders by Burton D. Rose

I was finishing my first month of my first rotation as a third year med student when I asked my resident what I should read to help me understand fluids and electrolytes and he told me to getBurton Rose's book. This may have been the worst advice ever: 893 pages (excluding the index) of electrolytes. I bought the book and it went on my shelf. The book remained unopened for 2 years. During my internship year I finally started reading it. His straightforward, mechanistic explanations of the physiology made everything logical. The yellow book (4th edition cover) taught me most of what I know about physiology. I don't think my experience is unique. I have a feeling that lots of nephrologists out there and probably some endocrinologists and critical care doctors understand the body because of the clear, visual prose that is Rose's gift.

ASN Kidney Week

Every year the nephrology community arranges coverage, books flights and finishes posters in order to come together at ASN's Kidney Week. It is a week probably not much different than what the cardiologists and hematologists do. We listen to experts, we show off our work, reunite with colleagues and collaborators. Meet old heros and future partners. Kidney Week is an opportunity to show off the specialty to shiny medical students and exhausted residents delighted to be away from the wards for a week (even if it is Philadelphia in November). Beyond the acres of symposia, we meet with editorial teams, build fellowship curricula and organizational policies. We meet as principal investigators in ongoing longitudinal studies. We get a chance to go beyond the screen and phone and break bread with our extended renal family. National meetings have a way of inspiring and renewing us. ASN's Kidney Week has woven itself into the very definition of the renal community and nephrologists who don't go need to reconsider.

San Diego Convention Center, 2012 Renal Week. Picture by Joel Topf, used with permission

(15) NKF Spring Clinical Meetings vs (2) NephSAP

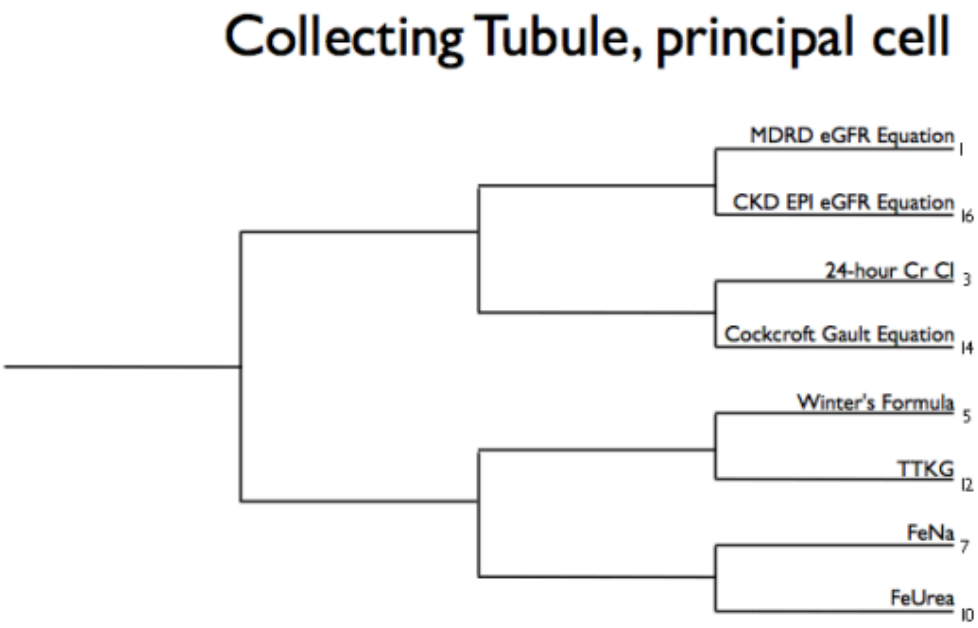
NKF Spring Clinical Meetings

The NKF sponsors the Spring Clinical Meetings each year. The spirit of the meeting is multidisciplinary and patient centered. The meeting is also friendly to fellows as case reports are always highlighted. It is where the annual national nephrology Fellows' research competition is held each year. This is a great event pitting fellows across the country against each other. This year's meeting is April 2-6 at the Walt Disney World Swan and Dolphin Hotel in Orlando, FL. The theme is always patient centered and typically draws nurses, dietitians, physician assistants, nurse practitioners, social workers, technicians and nephrologists. The meeting is small in size and scale and is a great place to touch up on bread and butter skills. The sessions are practical and informative.

NephSAP

NephSAP is a popular publication produced by the ASN. The first installment was July 2002 and was on the topic glomerular, vascular, tubulointerstitial and genetic diseases authored by Drs. Appel and Glassock. The great value of NephSAP is that it encapsulates the latest research and information about a particular topic. The series is authored by top physicians/scientists in their respective field. This publication is truly a gem in the field of nephrology and is used by fellows and practicing nephrologists to stay abreast of the ever growing field.

Nephrology Madness: Collecting Tubule Region's Principal Cell Group



(1) MDRD Equation vs (16) CKD-EPI Equation

Creatinine based estimations of glomerular filtration rates are valuable tools clinicians use to monitor kidney function, because regular inulin clearance evaluation would be absurd.

MDRD Equation

The MDRD equation was recommended by the 2002 CKD K/DOQI guidelines. It is the most widely used creatinine-based eGFR equation. It was developed in 1999 by using the cohort from the firstMDRD study, 1,628 subjects with chronic kidney disease. In 2006, the MDRD equation was subtly changed for use with IDMS traceable (i.e., "standardized") creatinine assays. Clinically, it is easy to use by providers who have access to the patient's age, serum creatinine, gender and ethnicity. The MDRD equation provides a more accurate estimation of GFR than either the Cockcroft Gault formula or 24-hour creatinine clearance.

CKD-EPI Equation

The new kid on the block. Developed in 2009 using 12,150 diverse participant and (in 2011 and 2012 studies) using a standardized creatinine assay, CKD-EPI is the most accurate eGFRcr formula in patients with normal or near-normal GFRs. In fact, data suggests that CKD-EPI may be more accurate in risk stratification for all-cause mortality and cardiovascular events. Age, serum creatinine, gender and ethnicity are needed to compute eGFR, which is simple with any smartphone or computer. KDIGO was so impressed with CKD-EPI's performance that it is recommended in the 2013 guidelines.

(3) 24-hour CrCl vs (14) Cockcroft Gault Equation

24-hour Creatinine Clearance

$$\text{Creatinine Clearance} = \frac{\text{Creatinine}_{urine} \times \text{Volume}_{urine}}{1{,}440 \times \text{Creatinine}_{serum}}$$

The 24 hour creatinine clearance is another approach use to estimating GFR. The CrCl technique is particularly valuable in patients who have unusual amounts of muscle mass, this includes the body builder, the patient with dwarfism, the patient with multiple amputations. Measurement of the daily creatinine excretion controls for variations in creatinine production (or creatine and creatinine intake, for that matter). Like all creatinine based formulas, the 24-hour creatinine clearance depends on a stable serum creatinine. The most common source of error with a 24-hour collection is an inadequate collection, this could be missed voids, poor precision in the timing, additional family members contributing to the collection etc. One unavoidable source of error is tubular secretion of creatinine which increases urinary creatinine without filtration. Normally about 5-10% of creatinine is excreted this way but the proportion rises with decreased renal function. Thus, 24-creatinine clearance overestimates GFR in general and even more as CKD progresses.

Cockcroft Gault Equation

$$\text{eCrCl} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{72 \times \text{Creatinine}_{serum\ (mg/dL)}} \times 0.85 \text{ if female}$$

The Cockcroft Gault equation was initially described in 1976. This description was based upon 249 patients and was a popular tool to convert creatinine to eGFR. I remember having to memorize this equation during my medical school training. It is quite impressive that this formula was used for so many years. It wasn't until the MDRD equation in 1999 that Cockcroft Gault fell out of favor. The adoption of eGFR calculation with the Cockcroft Gault equation was a huge advance in nephrology and allowed for doctors to recognize patients that , though they may have normal creatinines have significant renal insufficiency. The main disadvantage of this formula was that it was derived from an entirely male population of hospitalized veterans and was designed to estimate creatinine clearance and not GFR. This formula does not work well at extremes of age or BMIs.

(5) Winter's Formula vs (12) TTKG

Winter's Formula

$$pCO_2 = 1.5 \times HCO_3 + 8 \pm 2$$

The goal of the equation is to estimate whether a given pCO2 reflects appropriate respiratory compensation for a primary metabolic acidosis, or whether one is dealing with a mixed acid-base disorder. The concept and formula are remarkably important in clinical practice and easy to apply. Unlike formulas to estimate renal compensation for primary respiatory acid-base disorders, there is no need to alter the formula to account for the acuity or chronicity of disease. Dr. Robert Winter's formula has been used since the mid-1960s and is still going strong.

Transtubular Potassium Gradient

$$TTKG = \frac{K_{urine} \times Osm_{serum}}{Osm_{urine} \times K_{serum}}$$

The TTKG attempts to assess the distal nephron's ability to maintain potassium homeostasis. A "normal" value when evaluating hyperkalemia is considered 8-9%, with values <7 suggestive, and <5 highly suggestive of hypoaldosteronism. The equation only applies when urine is not hypotonic and distal sodium delivery is adequate to allow for maximum kaliuresis. However, twenty-five years after the initial studies were published, the original authors present a hypothesis that may further limit the clinical utility of the TTKG: An important assumption of the TTKG model is that no significant osmols are reabsorbed in the medullary collecting tubules. Recent observations show significant urea recycling with reabsorbtion in the inner medulla, making this assumption invalid.

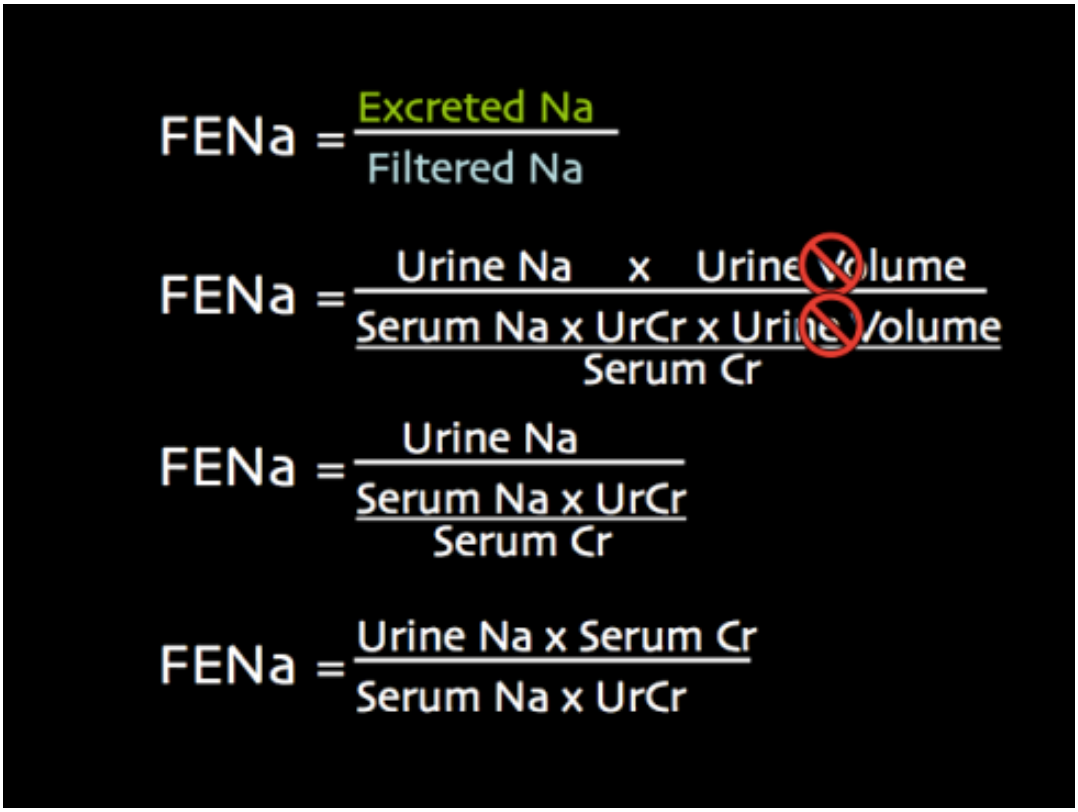
(7) FENA vs (10) FEUrea

FENa

One of the fundamental questions facing clinicians when they are evaluating a patient with decreased renal function is whether this is ischemic damage or hemodynamic changes from decreased perfusion. Or in the worlds of Rajiv Poduval is it a case of:

No BP? No Pee pee.

One strategy to differentiate these two similar conditions is to use the kidneys' sodium handling behavior to determine if this is hemodynamic or ischemic damage. One way to do this is a random urine sodium. This measure is confounded by ADH which can increase the urine sodium concentration by reabsorbing water in the medullary collecting duct.



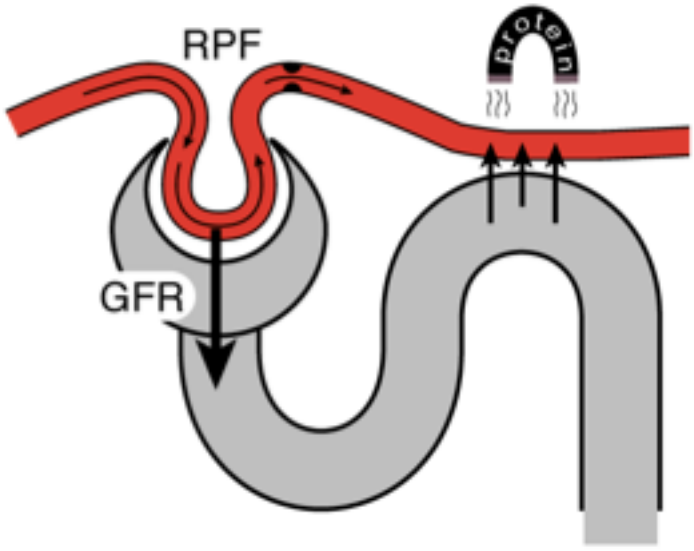
This pitfall can be avoided by directly measuring sodium handling. The fractional excretion of sodium is literally the amount of sodium excreted divided by the amount of sodium filtered at the glomerulus. Through clever algebra the calculation can be done with a single spot urine and a blood sample.
The fractional excretion of sodium does an excellent job at reflecting renal sodium handling but unfortunately, renal sodium handling does a less good job at predicting hemodynamic renal disease. There are numerous situations in which a sodium avid kidney is not dysfunctional due to decreased effective circulating volume and likewise situations where increased sodium loss occurs despite volume depletion.
See the landmark FENa study here.

FEUrea

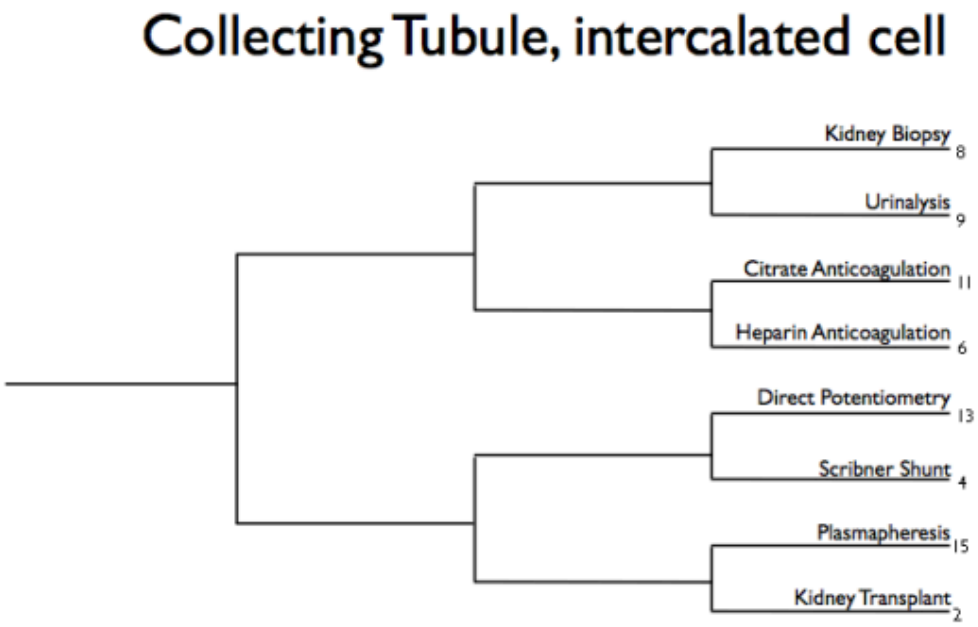
$$\text{Fractional Excretion urea} = \frac{Urea_{urine} \times Creatinine_{serum}}{Urea_{seum} \times Creatinine_{urine}}$$

One of the most common causes of a falsely elevated fractional excretion of sodium is diuretics. Diuretics directly increase sodium excretion, increasing the FENa without regard to natural renal sodium handling. The fractional excretion of urea circumvents this by measuring renal handling of urea, a molecule not af-

fected by diuretics. With decreasing renal blood flow the kidney autoregulates to maintain a stable GFR. One of the results for this autoregulation is an increase in the fraction of renal plasma flow that is filtered through the glomerulus, the filtration fraction. The increased filtration fraction means that the serum albumin, which is not filtered, is dissolved in less plasma so is found at a greater concentration and thus exerts increased osmotic pressure drawing water, sodium and urea from the proximal tubule back to the blood. This lowers the excretion of urea. This decreased clearance of urea with decreased effective circulating volume decreases the fractional excretion of urea and its unaffected by diuretics. This is also the mechanism for the increased BUN:Cr ratio seen with volume depletion,



Nephrology Madness: Collecting Tubule Region's Intercalated Cell Group



(8) Kidney Biopsy vs (9) Urinalysis

This is an interesting matchup that pits the most invasive procedure in diagnostic nephrology, the kidney biopsy against the nimble but vague urinalysis. Both are cornerstones in nephrology. This will be a tough battle. Lets take a look at the matchup.

Kidney Biopsy

The kidney biopsy and its pathological description is completely intertwined and entrenched in the field of nephrology. However, it is relatively new compared to the urinalysis. This was because it wasn't until the advent of the needle biopsy was it possible to sample kidney tissue in a living patient. The procedure was first reported in 1951 by Iverson and Brun in the *American Journal of Medicine*. Before this, most forms of kidney diseases were termed Bright's disease. This was named after Dr. Robert Bright of the 1870's and was based on the terminal appearance of end-stage fibrotic kidneys on pathological examination during autopsy. The entire field of renal pathology was born out of the technique of examining pathology specimens through out the natural history of the wide spectrum of kidney disease. There is, however, risks

involved with kidney biopsy. Namely, that is bleeding. A recent meta-analysis and review of the literature was published in the *American Journal of Kidney Diseases* examining this issue.

- The rate of macroscopic hematuria was 3.5%
- Transfusion was 0.9%

The kidney biopsy itself is a mainstay of nephrology and is integral to the diagnosis and treatment of many conditions. The interpretation of kidney pathology is also important. This is one of the attractive parts of nephrology. The monthly kidney pathology conferences where nephrology fellows sharpen their skills is a right of passage. It is a unique to nephrology and as such has a prominent spot in nephrology training programs.

Urinalysis

The microscopic examination of urine is performed on every consult for acute kidney injury. It is a liquid biopsy of the kidney and a window into the body. The remnants of kidney damage can be discovered from the microscopic and biochemical examination of the urine. The urinalysis hall of fame has inducted muddy brown casts in ATN, red blood cell casts in acute GN and calcium oxalate stones in ethylene glycol toxicity. The urinalysis can be paramount for the diagnosis of many of these conditions. Hippocrates is credited as the first examiner of urine. However, the analysis of urine goes back ~6000 years. A nice review of the history of urinalysis can be found here. some highlights below-

- Sanskrit medical works from 100 BC describe 20 different types of urine.
- Hindu cultures were aware that some people's urine tasted sweet, and that black ants were attracted to this sweet urine, a characteristic of diabetes mellitus.
- The word diabetes, which stems from the Greek word *siphon*, was coined by Areteus the Cappadocian in the second century.
- Areteus described diabetes as, 'A melting down of flesh and limbs into urine.'
- The urinalysis is cheap, non-invasive and helpful to making the diagnoses in a wide range of conditions. The "poor man's" biopsy is here to stay.

(6) Heparin Anticoagulation vs (11) Citrate Anticoagulation

Heparin Anticoagulation

Heparin is a front runner in terms of anticoagulation during hemodialysis. Heparin is a naturally occurring anticoagulant produced by basophils. Heparin is not absorbed secondary to its negative change and

large size and must be given parenterally. Dialyzer clotting is a common factor underlying poor performance especially with dialyzer reuse. This results is loss of the dialyzer and more importantly time lost during dialysis. This use of heparin is paramount to prevents thrombosis in the circuit.

- Benefits: Widely used, easily understood by most physicians and nursing staff, easy to monitor using PTT.
- Disadvantages: Risk of bleeding increasing in the uremic state, heparin induced thrombocytopenia.

Citrate Anticoagulation

The new kid on the block is citrate anticoagulation for both outpatient and continuous forms of dialysis. The fall in the free plasma calcium concentration induced by binding to citrate is responsible for the anticoagulant activity of this regimen by preventing the progression of the coagulation cascade. The citrate-calcium complex is removed across the dialyzer and a calcium free dialysate can also be used to further reduce the free calcium level in the blood.

- Benefits: No excess risk of bleeding, studies show equal comparison to heparin, no chances of heparin induced thrombocytopenia. No heparin, no HIT.
- Disadvantages: hypocalcemia, hypernatremia and metabolic alkalosis, harder to monitor and no set parameters.

(4) Scribner Shunt vs (13) Direct Potentiometry

Scribner Shunt

Before Belding Scribner and his team developed the arteriovenous shunt in 1960, end-stage kidney disease was always fatal. Read that sentence again and think about the number of lives Scribner touched, changed and saved.

Dr. Willem Kolff created the first successful dialysis machine in Nazi occupied Holland. Though his first 16 patients died, he kept hooking victims to his contraption of sausage casings, orange juice cans and a washing machine. In 1945 after dialyzing a woman for 16 hours she woke up.

In the 50's Kolff teamed with Peter Brigham to make a second generation machine, the stainless steel Kolff-Brigham kidney. This primitive form of dialysis required sacrificing an artery and vein for every treatment. A patient could receive five to seven treatments before he would literally run out of places to connect the machine. This limited the use of dialysis to episodes of reversible kidney failure. Chronic kidney failure was still a death sentence.

Belding Scribner invented a U-shaped tube that could be permanently installed between an artery and vein of the arm. During dialysis the shunt was removed and the artery and vein were attached to the di-

alysis machine, this could be repeated over and over again. The key to the success of the shunt was the use of a new material that was not predisposed to blood clotting: Teflon.
So the next time you're frying an egg on a Teflon pan think of Belding Scribner pounding out creative ideas that changed the world.

Direct Potentiometry

In the hospital, it seems that every patient, every day, has her electrolytes checked. It is hard to imagine what nephrology would be like if this was not the case. Electrolytes can be measured by ion-specific electrodes or flame photometry. The use of ion-specific electrodes is called potentiometry and is how all electrolytes are measured in the hospital, however there are two types of potentiometry: direct and indirect. Direct potentiometry is the more sophisticated technique that is behind much of the miniaturization in modern chemistry machines. All blood gas machines use direct potentiation. Indirect potentiometry is utilized by wet chemistry analyzers and involves sample dilution prior to the analysis. This dilution opens the door to a type of pseudohyponatremia with a normal osmolality that occurs when the blood has increased insoluble particles such as hypercholesterolemia, hypertriglyceridemia, hypergammaglobulinemia (multiple myeloma, Waldenstrom's)

(2) Kidney Transplantation vs (15) Plasmapheresis

Interesting matchup—I wonder who is the underdog here? Is it kidney transplantation, the best treatment for end-stage kidney disease, or plasmapheresis, the only way to quickly get rid of pathologic antibodies? Let's look at the evidence. This matchup places kidney transplantation, the best treatment for end stage kidney disease, against plasmapheresis, the only way to quickly get rid of pathologic antibodies. Let's look at the evidence.

Kidney Transplantation

Kidney transplantation has revolutionized the treatment of ESRD and led to numerous advances in immunology. The first successful kidney transplant was in December 23, 1954 by Dr. Joseph Murray who performed a living donor transplant from one identical twin to another. Transplantation led to an understanding of the immune system and the HLA system. Numerous drugs have been given birth in the field of transplantation including the first monoclonal antibody approved for clinical use – OKT3. Ok, so OKT3 is not used anymore but look at other wonder drugs like cyclosporine andmycophenolate mofetil! Transplantation is much better than dialysis when it comes to patient mortality and quality of life. With over

90,000 people on the transplant waitlist people are dying everyday to obtain a transplant. Just ask anyone with ESRD just how important kidney transplantation is. When this treatment stepped into nephrology it instantly became a game changer!

Plasmapheresis

Plasmapheresis removes antibodies and other proteins in the blood. It came about in the 1950'sand has been used for numerous conditions. In nephrology this includes pauciimmune GN, where it has been found to be as efficacious as high dose methylprednisone, and anti GBM disease. When a disease affects both the kidney and lung – plasmapheresis is the MVP! It can also be used to treatcatastrophic antiphospholipid syndrome but does not seem to help against severe lupus nephritis. Although it is paired against kidney transplant it actually works with a kidney transplant when threatened by antibody mediated rejection. In addition plasmapheresis helps facilitate transplantation in the face of a positive crossmatch. Finally it is also the treatment of choice forthrombotic thrombocytopenic purpura. In most situations the power of plasma exchange is not necessary but lets face it – when you have a really bad renal disease you definitely want