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NephMadness unplugged

An edutainment project by eAJKD

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NephMadness

Introduction

NephMadness is an education project based on the belief that games are an important way to learn. The inaugural year was 2013, in that year we went from inspiration to launch in a three week sprint of over-caffeinated late nights. The moment before you release a project to the public you don't know how it will be received. Derision, delight or worst of all ignored all seem like equal outcome and you just need to take a leap of faith to push the *Publish* button. The nephrology community responded enthusiastically and we had wide participation, though the mechanics of the contest were pretty rudimentary.

Following the contest all of the educational content and the brackets were packaged into a single PDF and published online as NephMadness Unplugged. The unplugged game could be distributed to a nephrology consult service to direct teaching into corners of nephrology that aren't typically addressed on the teaching service.

NephMadness 2014 was the opportunity to systematically go through the 2013 contest and use the luxury of time and a budget to fix as many shortcomings of 2013 as possible. The field was greatly improved by sticking to themes of nephrology to populate 8 different regions. We also matched up similar competitors in the initial round match-ups to high light differences to concepts that maybe closely related, e.g. medical versus surgical care for an acute stone, KDIGO or JNC8 hypertension guidelines. We reached out to experts in various aspects of nephrology to help build our field. Our selection committee was instrumental in building out the field. The regions that made up NephMadness 2014 and the associated content experts are:

- Glenn Chertow: Renal Replacement Therapy
- Helbert Rondon: Electrolytes
- Warren Kupin: Poisons/Toxins
- Sarah Faubel: Acute Kidney Injury
- George Bakris: Hypertension
- David Goldfarb: Kidney Stones
- Stuart Shankland: Kidney Regeneration
- Jonathan Hogan: Biologics

Other notable improvements to NephMadness 2014 was the addition of online bracket registration, automatic scoring and notifications. We added prizes.

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The Field

Toxin Region

ESPN has described this region's matchups as "intoxicating" with a "lethal overdose" of talent and depth. Each team in their own right is capable of going all the way! This bracket consists of 4 international teams that represent the most lethal of all the nephrologic insults counterbalanced by 4 teams that define the best defensive strategies against renal injury. Led by Aristolochic Acid, Toxic Metals, and the much vilified and maligned DSHEA 1994 (Dietary Supplement Health and Education Act of 1994), fans will have to choose between political, oxidative, and pro-malignant offensive powerhouses versus defensive specialists utilizing adsorption, chelation, and enzyme inhibition game plans. Is the best offense a good defense or is the best defense a good offense?

Selection committee member for the Poisons & Toxins Bracket:

Warren L. Kupin, MD **Professor of Medicine** **University of Miami**	Dr. Kupin is a graduate of Medical College of Wisconsin, and completed his residency and nephrology fellowship at Henry Ford Hospital. He is a Associate Director of Transplant Nephrology at the University of Miami Miller School of Medicine and Course Director for the Nephrology Module for Sophomore Students in the regular MD track and the MD/MPH track.

MEET THE COMPETITORS FOR THE POISONS & TOXINS BRACKET

(1) Aristolochic Acid versus (8) Hemoperfusion

Cinderella stories do happen but this first round match could be a blowout. Size, speed, and worldwide distribution all favor Aristolochic Acid but analysts report that the adsorbing performance of Hemoperfusion during the regular season shows that anything is “bound” to happen in the playoffs. Is this the year of an upset?

Aristolochic Acid

A perennial powerhouse, Aristolochic Acid is a derivative of numerous flowering species, many of whom can come off the bench and take over for starters without missing a mutated DNA link. Aristolochic acid has been wreaking havoc in the urogenital tract for centuries primarily as part of Chinese herbal supplements. This carcinogen came to attention after a major outbreak of CKD and transitional cell cancer in Belgium in 1993. The cuplret was ultimately determined to be a Chinese weight-loss formula adulterated with Aristolochia . Since then Aristolochic acid has been linked as a significant cause of CKD in China and Taiwan and most recently as the etiology of Balkan Nephropathy. Aristolochia Clematis, which grows along the banks of the Danube, has been implicated as the cause of the unique transitional cell cancer risk and CKD in the Danube basin. In recognition of the success and popularity of Aristolochic Acid in causing kidney disease, the Nephrology community has honored this team with its own disease designation – Aristolochic Acid Nephropathy (AAN).

The International Agency for Research on Cancer and the World Health Organization (WHO) have labeled Aristolochic acid as a type I human carcinogen but it continues to be an undeclared ingredient in up to 20% of Chinese herbal products. Aristolochic acid is absorbed by the proximal tubule and leads to lifelong irreparable DNA damage resulting in a markedly increased risk of multifocal, asynchronous transitional cell cancers of the bladder, ureter, and renal pelvis. The true impact of Aristolochic acid on the worldwide incidence of CKD in both developed and developing countries is unknown but everyone must respect this team and its ability to mutate its way to the Final Four. This team is on a worldwide mission for domination.

Hemoperfusion

They squeaked into the tournament mainly based on their early hype. But this team may have life for one more run at the finals.

This extracorporeal treatment for intoxications was first developed in the 1940s and used clinically in the 1970s. The theory was based on the success of oral activated charcoal (carbon) for acute drug overdoses. The microporosity of both carbon and synthetic resins increases the surface area from approximately 1.7 m2 for a standard dialyzer to over 300 m2 for a hemoperfusion device. This markedly improves the clearance of certain drugs by adsorption. The combination of hemodialysis with activated charcoal resins within the dialyzer was felt to be a major scientific breakthrough. In addition to poisoning this technique was also applied to elevated ammonia levels in hepatic encephalopathy.

Hemoperfusion devices (cartridges) come in two different flavors: a charcoal cartridge for water soluble drugs and a synthetic resin cartridge to for more lipid-soluble drugs. Both of these filters targeted drugs with molecular weights up to 40,000 and are particularly useful for protein-bound drugs, which are typically poorly dialyzable.

In clinical practice these perfusion devices have been limited by thrombocytopenia (major risk), hypocalcemia, hypoglycemia, and hypothermia. Additionally, the cartridges are chemically saturable so they can only be used once and require anticoagulation with heparin.

The introduction of high-flux dialysis and hemofiltration devices has superseded the routine use of these devices. Currently there are only limited applications for hemoperfusion treatments in patients with multiorgan system failure and drug or poison intoxication.

(3) Toxic Metals versus (6) Fomepizole

This matchup highlights a marked contrast in style. The Toxic Metals have consistent success on requiting from all over the periodic table and utilize a variety of diverse mechanistic pathways. In contrast, Fomepizole has always been focused and maintained expertise in restricting itself to one specific task with deadly accuracy. This could be a toss-up !

Toxic Metals

This team was originally called heavy metals but decided that this was too confusing to rock and roll fans and a name change was required to strike fear into the kidneys of its opponents. Moreover since all the metals in this group have a diversity of molecular weights and charges, the term “heavy metals” was scientifically inaccurate and has been replaced by the more appropriate and intimidating term “toxic metals”. The systemic and nephrotoxic potential of this group and often the lack of effective prevention, detection, and treatment gives them a high ranking.

The starting five of the team are lead, cadmium, mercury, arsenic, and aluminum. However coming off the bench are the equally nephrotoxic platinum, uranium, and gold. The majority of toxic metal accumulation is a result of occupational exposure particularly in the manufacturing sector. In the U.S., the Occupational Safety and Health Administration (OSHA) protects workers from toxic metals in the workplace but in many countries of the world there is no similar legislation. Epidemics of CKD in certain parts of Sri Lanka, Thailand, Japan, and India have been linked to Lead and other toxic metal pollution from industrial waste leaching into the agricultural fields, resulting in widespread population exposure over many years.

Currently the adulteration of herbal therapy especially Aryuvedic products from India with toxic metals has led to warnings by the NKF to avoid these agents. Herbal therapy worldwide is felt to be a very significant source of inadvertent toxic metal exposure.

Most toxic metals result in proximal tubule injury and progressive tubulointerstitial fibrosis. Mercury and gold both cause secondary membranous nephropathy and nephrotic range proteinuria.

Due to an under-appreciation of their contribution to kidney disease and the lack of obvious clinical manifestations along with inaccurate or difficult to perform diagnostic tests, toxic metals have been below the radar of most nephrologists. This could be the dark horse of the tournament.

Fomepizole

Also known as 4-methypyrozole, Fomepizole is the only FDA-approved competitive inhibitor of alcohol dehydrogenase. Fomepizole is the primary pharmaceutical treatment of ethylene or diethylene glycol, methanol, or propylene glycol intoxication. The primary goal of therapy is to prevent the parent compound from being metabolized into its more toxic metabolites. There are two treatments:

The first is an alcohol drip that must be carefully titrated and monitored for excessive respiratory and CNS depression. Ethanol used for the alcohol infusion in the ER must be kept in a locked highly regulated often secretive part of the ER to avoid recreational use of this therapy by the staff. The effort to maintain control over the ethanol supply is demanding and time consuming.

The second option is Fomepizole, which requires no special invoice control. Once administered there is an immediate cessation of conversion of the alcohols to their often more toxic byproducts. This therapy can be a game changer in ethylene and methanol overdoses.

Fomepizole has a higher paid roster than the toxic metals, with an average cost being a minimum of $4000 for a treatment course. The ease of administration is balanced by the cost of this agent. Recently the use of Fomepizole may be expanded to individuals with the "Asian Flush" syndrome due to an aldehyde dehydrogenase deficiency leading to an increase in acetaldehyde and a long term higher risk of esophageal cancer.

If cost were not a factor, Fomepizole would be the exclusive treatment of these alcohol overdoses: unique, effective, and safe. A formidable opponent.

(4) Glycyrrhizic acid vs (5) Chelation Therapy

This matchup features two equally matched contenders in a battle of consonants vs vowels. Glycyrrhizic acid holds the prestige among all the competitors in the year's field for having been the only team name used in the Scripp's National Spelling Bee contest and the one with the fewest true vowels. Chelation therapy for years has been an under-achiever, never quite reaching its true potential. Will this be the year Chelation therapy binds its way to the title or will it be another easy first round inhibition victory by Glycyrrhizic acid?

Glycyrrhizic Acid

This derivative of the root of the plant Glycyrrhiza Glabra (commonly referred to as Licorice) has shown itself to be a metabolic masterpiece of selective inhibition and syndromic potential. Licorice is used worldwide for its sweet flavor and potential medicinal benefits particularly in peptic ulcer disease. It is highly prevalent as an additive to herbal candies, gums, tobacco products, traditional Chinese and Indian herbal supplements, and cooking spices.

Glycyrrhizic Acid is an inhibitor of the enzyme 11-b hydroxy steroid dehydrogenase. This leads to the condition called apparent mineralocorticoid excess (Pseudohyperaldosteronism) with hypokalemia, hypertension and metabolic alkalosis. In the U.S., all licorice that is sold has undergone a process of de-glycyrrhizination (DGL) so that none of the metabolic side effects will occur. In Europe however licorice is available as the pure form without undergoing DGL.

It is not clear how many cases of hypertension or hypokalemia worldwide could be related to ingestion of glycyrrhizic acid but it remains a very important concern and its mechanism of action is a commonly asked question on nephrology board examinations.

Chelation Therapy

This professional team should not be confused with the amateurs often seen advertising in the newspaper willing to chelate all forms of disease from cancer to autism to heart disease. Chelation therapy in this tournament represents a group of well-defined agents used for the treatment of toxic metal accumulation.

Although most of the press has focused on EDTA (ethylenediaminetetraacetic acid) which is FDA approved for the treatment of lead intoxication there is a more senior member of the team – BAL (British anti-Lewisite). This agent was the first true chelation therapy developed in WWI for the treatment of arsenic-based poison gas called Lewisite. It has subsequently been approved for lead, arsenic, and mercury poisoning. Derivatives of BAL have now joined the team and include DMSA (2,3-dimercaptosuccinic acid) and DMPS (2,3-dimercaptopropanesulfonic acid), both used for lead , arsenic, and mercury removal. In addition, not to be overlooked is deferoxamine, used for iron overload conditions, and D-penicillamine, which may be used for copper and other heavy metal overdoses.

In a clinical nephrology practice, meta-analysis demonstrates that the early use of EDTA in patients with presumptive lead nephropathy has resulted in improved renal function and can retard progression even in patients with diabetic nephropathy who have high lead burdens.

Using modern dialysis techniques, which include intensive water purification methods and the introduction of non-aluminum-based phosphate binders, the syndrome of aluminum overload in ESRD patients has become almost nonexistent. However the use of chelation therapy with deferoxamine is still considered to be the treatment of choice for this disorder should it ever be diagnosed.

Chelation therapy should only be initiated once the diagnosis of toxic metal accumulation is made. This mandates a high index of suspicion to test for Toxic Metal exposure. The Chelation therapy team motto is "It's not over, until it's bound!"

(2) Dietary Supplement Health and Education Act of 1994 (DSHEA) vs (7) Osmolar Gap

This is a dream matchup of offense vs defense. Can the legally binding and federally mandated defense of the DSHEA Act of 1994 hold off the aggressive diagnostic skills of the Osmolar gap? This is the first meeting of these two opponents in a match that could come down to the final possession.

Dietary Supplement Health and Education Act of 1994 (DSHEA)

This team represents the FDA's major defensive strategy in the management of the marketing and distribution of vitamin and herbal supplements in the U.S. Moving away from a more standard "zone' defense, DSHEA utilizes a more nontraditional, one-on-one approach. In spite of numerous Congressional efforts, DSHEA has employed the same strategy for 20 years. Only selected supplements reported by the public to the FDA due to adverse reactions are reviewed in a lengthy process to see if further actions (public warnings, removal from the market) are needed.

DSHEA is a landmark federal legislation that guides the government's role in the regulation of herbal and vitamin supplements. It guards the rights of individuals to choose what they wish to take for health benefits. The history of this act is important to truly evaluate the impact it has had on pharmaceutical safety and financial success of the supplement industry.

Prior to 1962, the FDA was not required to evaluate the efficacy and claims of any drug or supplement marketed in the U.S. The 1938 Food, Drug and Cosmetic Act only mandated that the drug companies demonstrate to the FDA that their drug was safe. However there was no regulation of advertising claims or any requirement of efficacy. The tragic thalidomide birth defects in Europe, however, forced an overhaul on the operations of the FDA. The Kefauver Harris Amendment or "Drug Efficacy Amendment" of 1962 required all manufacturers to provide proof of effectiveness of all drugs sold.

However, due to intense lobbying by the supplement industry and their persuasion of many U.S. Senators, an exemption to the Kefauver Harris Amendment was passed in 1994 called the Dietary Supplement Health and Education Act (DSHEA). This change in the law allowed all vitamin and herbal supplement manufacturers to be exempt from FDA review. No longer was the FDA required to evaluate the marketing and efficacy claims of any herbal and vitamin supplement. The manufacturers were asked to place the following disclaimer on all products that make health claims: "This statement has not been evaluated by the Food and Drug Administration . This product is not intended to diagnose, treat, cure, or prevent any disease". This is the only warning consumers are provided regarding the lack of FDA review of the supplement industry. Recent polls show that less than half of Americans know that the FDA does not review or monitor the efficacy herbal and vitamin supplements.

The market for supplements in the U.S. now exceeds 5 billion dollars a year. Numerous reports of morbidity and mortality from intentional and unintentional adulteration, improper manufacturing, unreported ingredients and microbiologic contaminants have occurred as a result of DSHEA. Multiple professional organizations including the FDA, the NKF, the

AMA have all voiced concerns that the safety of the American public cannot be guaranteed from dietary supplements due to a lack of governmental control directly related to the sweeping changes brought about by DSHEA.

Osmolar Gap

This is a quick and under-recognized team that always gets off to a fast start but has a habit of losing accuracy as the game advances into the 3rd and 4th quarter. Osmolar gap employs the same offensive strategy in the management of alcohol derivatives intoxication as the serum and the urine anion gap do for classifying acidotic states. The Osmolar Gap uses a simple, no-frills, attack meant to immediately catch their opponents off guard so treatment can be initiated before end organ damage.

The Osmolar gap measures the difference between the measured and the calculated osmolalities for the purpose of diagnosing an alcohol based intoxication. Typically used for ethylene glycol and methanol overdoses, the osmolar gap will also detect the presence of regular alcohol, diethylene glycol, propylene glycol and isopropyl alcohol. An osmolar gap of more than 10 mOsm/L is a positive result suggesting that one of these alcohols is present.

The Osmolar Gap has a limited repertoire and cannot identify the exact intoxicating agent. In addition, the metabolism of the toxic alcohols by alcohol dehydrogenase limits this formula to the first 12-24 hours of the overdose. The presence of CKD or ketoacidosis, the infusion of maltose (IVIG infusions) or mannitol and the absorption of sorbitol or glycine (TURP irrigation solutions) can hinder the sensitivity of the Osmolar Gap and create a false positive elevation.

In spite of its limitations, the Osmolar Gap has earned its seeding in the tournament as it has remained an important tool for ER physicians and housestaff in the diagnosis of a toxic alcohol ingestion.

-Written and Edited by Dr. Warren Kupin

Hypertension Region

With the last-minute addition of the highly controversial JNC8, this pressure-packed bracket now appears to be one of the most competitive in the tournament. Much anticipated dream match-ups in the first round pit thiazide vs thiazide (HCTZ vs Chlorthalidone), manometry reading vs manometry reading (Systolic vs Diastolic), and guidelines vs guidelines (KDIGO vs JNC8) in nonstop pulsating action. The bracket is headed up by two high profile failures: combination ACE/ARB and renal artery interventions, both vascular and neurogenic.

Selection committee member for the Kidney Regeneration Bracket:

George L. Bakris, MD **Professor of Medicine** **Director, ASH** **Comprehensive** **Hypertension Center** **University of Chicago**	Dr. Bakris currently serves as an Expert Consultant to the FDA Cardio-Renal Advisory Board and to CMS (Renal Medicare and Medicaid program). He has served on the JNC 6 and 7, ADA and the National Kidney Foundation (KDOQI) blood pressure and diabetes guideline committees. He is the immediate past-president of the American Society of Hypertension. He has published over 600 peer-reviewed publications in the areas of hypertension and diabetic nephropathy as well as 12 Books in the area of hypertension and diabetic kidney disease. He is the editor of American Journal of Nephrology and the hypertension, section editor of UpToDate, as well as an associate editor of Diabetes Care and Hypertension Research.

MEET THE COMPETITORS FOR THE HYPERTENSION BRACKET

(1) ACE-I/ARB Combination versus (8) Renal Artery Interventions

This is a bracket of two major disappointments, both teams came in with huge expectations and have fallen flat on their faces. These chumps made it to the dance on reputation and expectations alone.

ACEi/ARB Combination Therapy

ACEi/ARB are the Gonzaga Bulldogs, 16 straight years in the tournament and they never made it past the Sweet 16. Combination therapy with ACE inhibitors (ACEi) and Angiotensin-receptor blockers (ARBs) have individually been shown to decrease proteinuria and prolong renal survival in proteinuric renal disease. However, neither agent can completely block the renin-angiotensin-aldosterone system (RAAS), and studies have shown that various combinations of dual RAAS blockade using ACEi, ARBs, mineralocorticoid-receptor antagonists, and direct renin inhibitors lead to decreased blood pressure and albuminuria. This led to the hypothesis that patients with type 2 diabetes and proteinuria may benefit from combination therapy to slow CKD progression.

Three important studies (ONTARGET, ALTITUDE, and VA NEPHRON D) failed to demonstrate renal and/or cardiovascular benefits from such combination regimens, and instead showed increased adverse events, primarily hyperkalemia, acute dialysis and hypotension. In fact both ALTITUDE and VA NEPHRON D were terminated early due to lack of benefit and higher risk of adverse events with dual therapy.

- ACEi with ARB is harmful.
- ARB or ACEi with renin inhibitor is harmful.

Should we be hesitant to also use ACEi or ARB with aldosterone antagonists? Though this promises the benefits as the above combination therapies, reduced proteinuria and blood pressure does it also have the same risks? This has been examined to some degree in the RALES Trial. This landmark study demonstrated the advantage of spironolactone in the treatment of heart failure. In the 822 patients treated with spironolactone (12.5-25 mg daily) there was no increase in potassium over 6 (10 with placebo and 14 with spironolactone). Potassium on average went up by only 0.3 mmol/L and serum creatinine rose by between 0.05 and 0.1 mg/dL. For the purpose of investigating the safety of combined ACEi and aldosterone antagonists, 95% of the spironolactone cohort was concurrently treated with ACEi.

The EPHESUS trial of eplerenone for heart failure following an acute MI provides further data on this combination. In EPHESUS 86% of the aldosterone antagonists arm was on concurrent ACEi. The patients had excellent renal function with average creatinine clearance of 79 mL/min. Use of eplerenone caused an increase in hyperkalemia (180 cases vs 126 with placebo, P=0.002) and an increase in hospitalization for hyperkalemia (12 in the eplerenone group and 3 in the placebo group). The authors found this association with renal function:

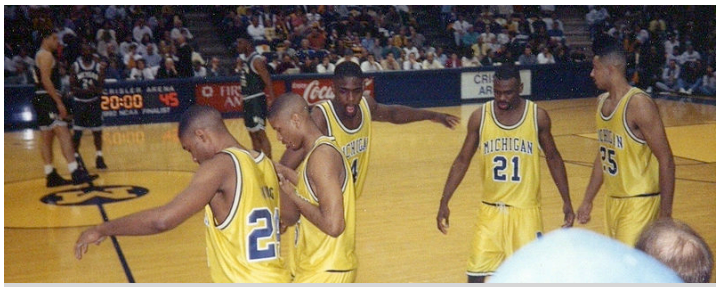
The Library of Celsus in Ephesus, Turkey by Neil Howard

> *Among patients with a baseline creatinine clearance of less than 50 mL/min, the incidence of serious hyperkalemia was 10.1 percent in the eplerenone group and 5.9 percent in the placebo group (P=0.006). In regard to eplerenone's effect on serum creatinine, it rose only 0.06 mg/dL after 12 months compared to only 0.02 in the placebo arm; P<0.001.*

There is some suggestion that the incidence of hyperkalemia with combination therapy may vary with race, e.g., with blacks with heart failure exhibiting less hyperkalemia and more hypokalemia with spironolactone.

Renal Artery Therapies

Renal artery therapies for the purpose of this entry are renal artery revascularization and renal denervation. Collectively they play the role of The University of Michigan's Fab Five. A lot of hype but in the end they never won anything. No Big 10 championships, two trips to the NCAA finals but no rings.



The Fab Five by Skoch3.

Revascularization

Revascularization of RAS is done to preserve renal function and correct renal vascular hypertension in the presence of critical renal artery stenosis. It has also been proposed as a treatment of serious conditions as flash pulmonary edema. Several studies (ASTRAL, CORAL) have shown that renal artery revascularization carried substantial risk and was not associated with any benefit with respect to renal function, blood pressure, renal or cardiovascular events, or mortality

However, a number of retrospective studies have shown a significant improvement in a few patients. For instance, a recent study supports guidelines citing flash pulmonary edema as an indication for renal artery revascularization in atherosclerotic renovascular disease, suggesting that patients presenting with a combination of rapidly declining kidney function and refractory hypertension may benefit from revascularization and may represent a subgroup worthy of further investigation in clinical trials. The challenge is to identify the subgroup of patients if any who benefit from renal artery revascularization.

Renal Denervation

In the 1950s, thoracolumbar sympathectomy (in which sympathetic nerve trunks and splanchnic nerves were destroyed), was utilized to control BP in patients with malignant hypertension. Fraught with intolerable side effects such as postural hypotension, erectile dysfunction, and syncope, this procedure was largely abandoned. In 2009, a proof of principle study utilizing a novel, catheter-based, technique for renal sympathetic denervation for treatment of resistant hypertension was published.

The rationale for this procedure is based on the premise that the sympathetic nervous system plays a major role in initiating and sustaining hypertension, as sympathetic nerves supply the the kidneys' efferent and afferent renal arterioles, juxtaglomerular apparatus, and tubules. Enhanced sympathetic activity in chronically hypertensive individuals is believed to play a role in subsequent target-organ damage. Riding on the encouraging findings of SYMPLICITY-1 and SYMPLICITY-2, in terms of BP control and safety, SYMPLICITY-3 (billed as the most rigorous of all renal denervation trials) brought much bravado only to be derailed in January 2014, when it failed to show a sustained reduction in systolic BP.

Another recently published study suggested that adjusted pharmacologic treatment may have superior BP-lowering effects as compared to renal denervation in patients with true treatment resistant hypertension (after excluding those who are noncompliant with pharmacologic treatment), thereby further questioning its value.

On the other hand, it has to be noted that in the SIMPLICITY trials, despite the failure to further reduce BP, no safety issues arose, thereby suggesting that although the catheter device may have been ineffective, there may still be some potential role in conditions characterized by hyperactivity of the sympathetic nervous system, such as heart failure, obstructive sleep apnea, arrhythmias, etc.

(3) Systolic Blood Pressure versus (6) Diastolic Blood Pressure

Since the JNC7 hypertension guidelines were published in 2003, there has been the natural tendency to consider SBP as a much more potent risk factor for coronary artery disease than DBP. For one thing, it has been known that SBP increases steadily with age, while DBP increases until around age 55 then it begins to decline. Age-related changes in blood pressure are naturally brought about by a generalized increase in arterial stiffness due to gradual replacement of elastin by collagen in the large arteries. Pulse pressure also increases with age. A wide pulse pressure is a marker of arterial stiffness that is also associated with increased adverse outcomes.

However, 2 studies have demonstrated a J-shaped association of BP with mortality in older adults, those with pre-existing CAD, and those with non-dialysis dependent CKD. So is lowering the BP (in the above groups) beneficial by dropping the SBP to a safer target or is it harmful because concomitant decreases in DBP are associated with higher mortality rates. This is a serious dilemma that is particularly common in CKD, where elevated SBP frequently pairs with a low DBP.

- Agarwal showed that different levels of SBP and DBP have disparate effects on mortality and ESRD in patients with CKD:
- A lower SBP and DBP was associated with better ESRD outcomes
- SBP of less than 110 and DBP less than 70 was associated with increased all-cause mortality
- SBP over 170 mmHg was associated with greater mortality
- The worst outcomes were seen in patients with high SBP and lower DBP

Even the JNC 7 and 8 Guidelines recognize that this is a great match up: although DBP control was more important than SBP control for reducing CV risk in patients over age 60, SBP control remains asthe most important factor.

Systolic blood pressure

The SBP supporters emphasize the predominant effect of SBP on risk of CKD progression. In a recently published study, higher SBP was independently associated with higher ESRD risk among persons with established CKD. This risk started at SBP of 140 mm Hg and it was highest among those with SBP of at least 150 mm Hg. The authors also demonstrated that (after accounting for SBP) PP was not independently associated with ESRD risk; most of the wide PP was a result of high SBP rather than low DBP. One study showed that whereas SBP and PP are closely related independent CVD risk factors that yield similar diagnostic and prognostic information, SBP is more robust when compared to DBP as a CVD risk factor.

Diastolic blood pressure

DBP has also been associated with increased mortality. In older individuals in particular, especially those with CKD, as well as those on hemodialysis, low DBP has been shown to be associated with increasing mortality, eg, future CHD.

It has been suggested that the J-shaped association of blood pressure with outcomes could be due to compromised blood flow to vital organs (especially low DBP compromising coronary perfusion) or due to confounding by the presence of stiff arteries or the high burden of comorbid conditions (for example, CHF). Kovesdy et al reported that categories of lower SBP-DBP combinations are associated with lower mortality rates only as long as the DBP component remains greater than approximately 70 mm Hg and that patients with BP in the range of 130 to 159/70 to 89 mm Hg had the lowest mortality rates.

(4) Hydrochlorothiazide versus (5) Chlorthalidone

Hydrochlorothiazide

Thiazide diuretics act by inhibiting the NaCl transporter in the distal convoluted tubules. They were the first antihypertensive agents whose use led to decreased cardiovascular morbidity and mortality in placebo-controlled clinical trials. Furthermore, they are well-tolerated. Discovered in the late 1950′s, thiazides have remained at the forefront of blood pressure management. Hydrochlorothiazide and chlorthalidone were the initial thiazides approved, in 1960, for the treatment of hypertension. For many years they were considered to be interchangeable. However, recently, controversy has been heating up.

When the VA Cooperative Studies on the Treatment of Hypertension were begun in the 1960s, hydrochlorothiazide was the diuretic of choice in both clinical medicine and large research trials. In fact, it was subsequently combined with various classes of antihypertensive agents because of its widespread utility. One study showed lesser incidence of electrolyte abnormalities, eg, hypokalemia, as compared with chlorthalidone.

In a recently published study looking at prevention of calcium containing kidney stones, hydrochlorothiazide was the most frequently prescribed thiazide diuretic, perhaps because it has been a perennial crowd favorite.

Chlorthalidone

Since 2004, several studies have raised the possibility of superiority of chlorthalidone over hydrochlorothiazide, in terms of reducing cardiovascular events, (MRFIT, SHEP, VHAS and ALLHAT among others). This effect is thought to be due to chlorthalidone having longer half-life and stronger efficacy. In one study of patients with resistant hypertension, where a more potent diuretic is particularly required, chlorthalidone was chosen for only 3% of the patients. In a meta-analysis of randomized trials, the antihypertensive efficacy of hydrochlorothiazide at a daily dose of 12.5 to 25 mg was shown to be consistently inferior as compared to other antihypertensive agents. The authors of that study went on to suggest that because outcome data on those doses were lacking, hydrochlorothiazide was an inappropriate first-line drug for the treatment of hypertension.

Another study showed that chlorthalidone reduced 24-hour BP more effectively than hydrochlorothiazide. Additionally, fet ventricular mass was significantly lower for those on chlorthalidone vs hydrochlorothiazide and the authors postulated that this may contribute to mortality benefits seen in other studies (MRFIT). The chlorthalidone fans rally behind the longer half-life and larger volume of distribution allowing the drug to achieve a more evenly distributed BP control throughout the day as compared to hydrochlorothiazide. The chlorthalidone camp points to clinical trials favoring chlorthalidone over hydrochlorothiazide. Although there is more aggregate clinical trial data demonstrating the superiority of chlorthalidone in

terms of hard clinical outcomes, the hydrochlorothiazide fans vehemently argue that these trials are not direct comparisons.

(2) JNC8 Hypertension Guidelines versus (7) KDIGO Hypertension Guidelines

JNC8 Hypertension Guidelines

The JNC8 experts attempted to simplify management of hypertension with a simple approach to treat to 150/90 in those over the age of 60 and 140/90 for all others; similarly, they also simplified the drug regimen, that is, ACEi, ARB, calcium-channel blockers (CCB), and thiazide-type diuretics are reasonable choices, just to get patients to goal BP. However, critiques abound over this somewhat 'oversimplified approach.' As compared to its predecessor (JNC7), several differences are particularly noted, namely: the JNC8 Guidelines define the target BP thresholds for initiation of pharmacological intervention, eg, decrease blood pressure to < 150/90 mm Hg in patients aged ≥ 60 or older and a DBP < 90 in those aged 30 to 59 (based on HDFP, Hypertension-Stroke Cooperative, MRC, ANBP, and VA Cooperative); they recommend a broader range of anti-hypertensive agents for initial treatment in non-blacks, including those with DM; and lastly, they recommend ACEi or ARB for all patients with CKD with or without DM regardless of race.

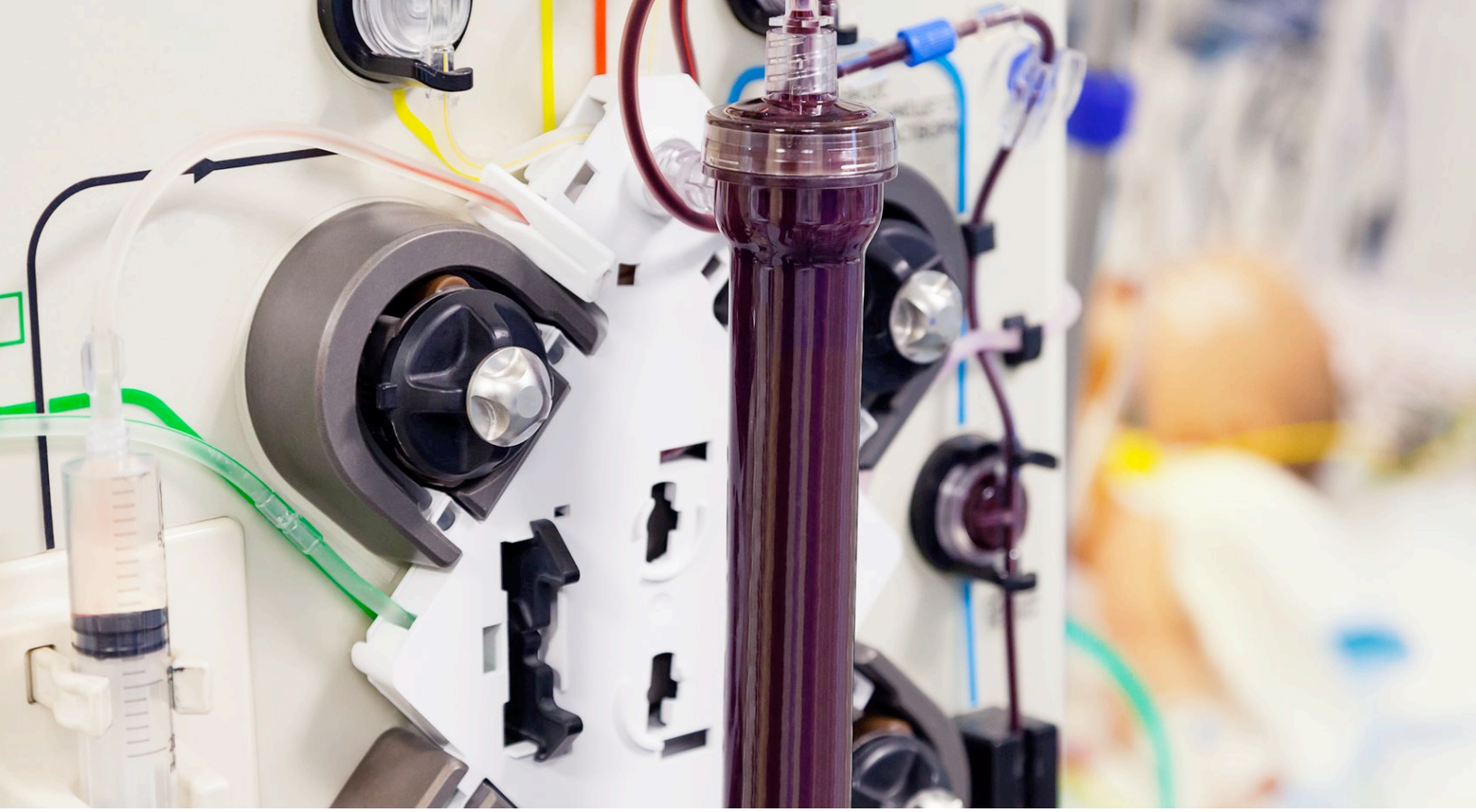
JNC8 adheres closely to the quality standards published by the the National Institute for Health Care Excellence (NICE) Guidelines published in March 2013.

KDIGO Hypertension Guidelines

The Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for management of BP in CKD has been designed to assist clinical decision making in patients with CKD who are not receiving dialysis. In stark contrast to JNC8, these guidelines recommend that no single BP target is optimal for all CKD patients and instead encourage individualization of treatment depending on age, the severity of albuminuria, and comorbidities.

They recommend that for all CKD patients without albuminuria the target SBP should be ≤140 and DBP ≤90 mm Hg diastolic. However, recognizing that microalbuminuria is a risk marker for cardiovascular events and possibly for kidney disease development, in most patients with an albumin excretion rate of ≥30 mg/24 hours, a lower target of SBP ≤130 mm Hg and DBP ≤80 imm Hg has been suggested (with very low level of evidence).

-Written and Edited by Drs. Edgar Lerma and George Bakris



Renal Replacement Therapy

This bracket offers teams from the past, present and hopefully the future of the management of acute and chronic renal failure. The glaring omission of transplantation from this section has resulted in a potential planned boycott of this bracket by transplant nephrologists, recipients and donors. However, as 90% of patients receive dialysis prior to transplantation and over 90% of nephrologists are not transplant physicians, the steering committee has respectfully declined to change the seeds citing the dominant win of Transplant in last year's inaugural NephMadness. Like Kentucky, champion one year and NIT the next. It's going to be a spirited and competitive contest of physiologic principles and access techniques matched against research proposals. Who will achieve maximum clearance and filter their way to the championship? Selection committee member for the Renal Replacement Therapy Bracket:

Glenn Chertow, MD, MPH **Normal S. Coplon/Satellite Healthcare Professor of Medicine** **Chief, Division of Nephrology** **Stanford University School of Medicine**	Dr. Chertow is a renowned clinical researcher in nephrology. His research interests are focused on epidemiology, health services research, and clinical trials in acute and chronic kidney disease. Dr. Chertow is involved in research sponsored by the National Institutes of Health and has written numerous papers on end-stage renal disease, acute renal failure, nutrition, mineral metabolism, and the costs and outcomes of dialysis therapy. He is Co-Editor of Brenner and Rector's The Kidney and serves on the editorial board of the Journal of the American Society of Nephrology (JASN). Dr. Chertow has designed and/or monitored several NIH- and industry-sponsored cohort studies and clinical trials in kidney disease, including CRIC, ATN, FHN, DAC, SPRINT, TREAT, ADVANCE and EVOLVE. In addition to his research and teaching activities, Dr. Chertow has an active clinical practice, focused on inpatient and outpatient nephrology care.

MEET THE COMPETITORS FOR THE RENAL REPLACEMENT THERAPY BRACKET

(1) Convective clearance versus (8) Diffusive clearance

Convective clearance

Convective clearance is back in the big dance, for the last few years we have seen convective clearance make a splash from the AKI conference in the form of CVVH, but after the recent conference realignment they now are showing up from the ESRD conference.

We all remember the epic battles that convective clearance used to wage with intermittent hemodialysis but this is an all new convective clearance wearing the online hemodialfiltration uniforms and it is ready to take on the all-time tournament leader, hemodialysis.

Convective clearance has long been known to improve middle molecule clearance, it does that by employing a highly porous filter and jacking up the ultrafiltration to around 30 liters in a single 4 hour dialysis session. In order to prevent turning the patient into a pile of salt, the technique requires replacing nearly all of that fluid.

Unlike dialysate, which flows past venous blood in the dialyzer, replacement fluid is infused directly into the veins, so not only does it need to be electrolyte balanced, it needs to be ultra-pure and sterile. Providing that ultra-pure replacement fluid, hundreds of liters a week for each patient was prohibitively expensive. The breakthrough that allows this to be used in the outpatient arena is a technique termed online purification. Online purification is the creation of sterile replacement fluid straight from the public water system in the dialysis unit. This is a major breakthrough.

However, this major breakthrough has not yet translated into breakaway results. In multiple randomized controlled trials hemodiafiltration has failed its primary end-point. Only in subgroup analysis has it been better than traditional hemodialysis. Then in 2013, the ESHOL study hit its primary end-point with a 30% risk of all-cause mortality. However, they did not do an intention-to-treat analysis and in a subsequent meta-analysis, no signal was found for improved all-cause mortality, non-fatal cardiovascular events or hospitalization, but there was a modest reduction in cardiovascular

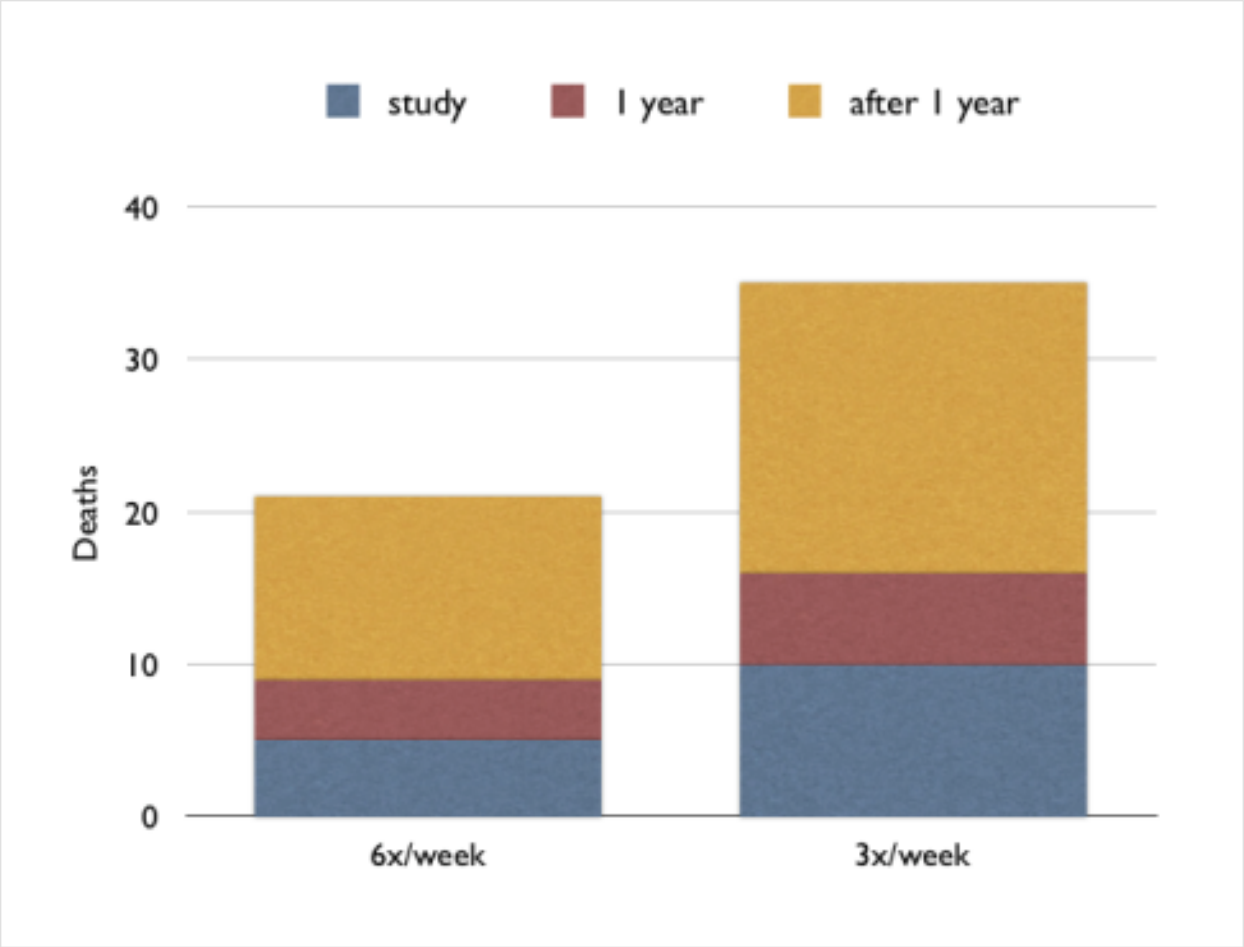
Data from FHN abstract (see abstract FR-PO342 in Kidney Week 2013 abstract supplement).

mortality.

Diffusive clearance

Diffusive clearance is a John Wooden lead UCLA. This dominant technique has been extending and saving lives since Kolff first used it on people during World War 2. It's hard to imagine a NephMadness without a diffusive clearance entry.

How do they look this year? Well despite interesting results with convective clearance and new pushes to increase peritoneal dialysis, standard diffusive clearance hemodialysis is still being used by 92% of all Americans with ESRD. But most importantly hemodialysis keeps innovating. When the Frequent Hemodialysis Network published their original study on 6-times per week versus 3-times per week study, the dialysis nephrology community practically snored. The reason was that the study was not powered to show a mortality benefit. The study couldn't answer the questions nephrologists and patients were asking about 6-days-a-week dialysis. Well, better late than never. At this year's Kidney Week the FHN crew published an abstract with follow-up data. After an average follow-up of 3.7 years, the trends to improved survival with 6-days a week dialysis is now significant with a HR of 0.54.



(6) Residual Renal Function vs (3) Buttonhole Technique

Residual Renal Function

Residual renal function is like a Tarkanian lead UNLV team, they a super successful but they can't get any respect. Win 30+ games in a season and people complain about a weak schedule. They are the Rodney Dangerfield of dialysis. This critical factor probably drives more survival outcomes than we care to admit and is specifically excluded from CMS Quality Incentive Program. Peritoneal dialysis patients do get to include residual renal function.

Here is what the Joseph Vassalotti, chief medical officer of the NKF, had to say about the lack of RRT in CMS plans:

> *Nonetheless, we are disappointed that residual renal function is not included in the calculation of hemodialysis Kt/V as some patients may have residual renal function that, in combination with dialysis, provides an adequate clearance for uremic toxins. Excluding residual renal function may lead to more aggressive (i.e. longer) dialysis prescriptions to meet the adequacy target.*

Similar concerns were raised by Andrew Howard and Klemens Meyer, President Elect and President of the ESRD Networks:

> *The requirement to exclude residual renal function from reported Kt/V presents those facilities which choose to measure residual renal function with a dilemma: either accept a QIP penalty for supposedly*

> *(but not really) inadequate dialysis, or coerce the patient to accept a medically unnecessary prolongation of treatment time. This hardly sounds like patient-centered care, and we suggest that as written, the proposed Rule fails fairly to answer the question "How did the patient do?"*

Residual renal function improves numerous patient factors including:

- lowers B2 microglobulin
- lowers potassium
- lowers aluminum levels
- raises bicarbonate level
- improves phosphate balance

But maybe Chandna and Farrington put it best when they wrote:

> *There is no logic in advocating aggressive measures to preserve RRF the day before dialysis initiation and ignoring RRF the following day. Likewise it is reasonable to question the practice of prescribing the same dose of dialysis soon after initiation—when many patients have considerable RRF—and to patients many years down the line—when RRF has long gone.*

The benefits of residual renal function should be maximized and dialysis units incentivized to do this. DOPPS has shown improved RRF by using diuretics, this needs to be verified prospectively but these types of investigations won't be done if the quality police ignore RRF.

Buttonhole Technique

Buttonhole cannulation is like a Brad Stevens-less Butler, a once high-flying mid-major, now living through some tough times. Buttonhole cannulation is a method for accessing AV fistulas for hemodialysis. The access needle is placed in the same location for every dialysis session, so that after a few weeks scar tissue forms a track. The track can then be accessed with blunt needles. It changes dialysis needle placement from a needlestick to something more similar to putting in a pair of earrings.

The buttonhole technique has a number of applications but the place where it was most appreciated was with home hemodialysis. The buttonhole technique is a way to greatly reduce the anxiety of accessing a fistula. It is not an exaggeration to say that much of the recent success of home hemodialysis was in part due to the re-emergence of the buttonhole technique.

However in January of 2014, Muir et al published data from a home dialysis cohort and did a systematic review of the literature and found an increased rate of infections with the buttonhole technique compared to the traditional sharp needle or rope ladder technique. Fifteen infections with buttonhole versus 2 with rope ladder. The systematic review of 15 studies (all published since 2007) likewise found a three-fold increase in infection risk with the buttonhole technique. Though, this was not significant in the four RCTs ($P=0.07$), it did reach significance in the observational ($P=0.0005$) and the before-and-after studies ($P<0.001$). The discussion remarked that even the higher rate of infection found with the buttonhole technique was still one fourth the rate seen with tunneled venous catheters.

Nephrology is waking up to the trade-offs that seem to be inherent in buttonhole cannulation, the signal across numerous studies points to increased infection. Whether this can be improved with better aseptic technique or use of mupirocin antibiotic creams has yet to be determined.

(4) Urgent Start Peritoneal Dialysis vs (5) Fistula First Campaign

Urgent Start Peritoneal Dialysis

Acute peritoneal dialysis (PD) is a scrappy Rick Pitino inspired team. While they may not be running a full court press defense, they are re-writing some of the oral tradition of dialysis. Patients that present to the hospital with severe renal failure in need of immediate dialysis have always been directed to hemodialysis. As described by Ghaffari in AJKD, the newest innovation in peritoneal dialysis is the realization that with special consideration patents can start peritoneal dialysis almost immediately after having a PD catheter placed. This requires careful attention to the peritoneal volume and patients need to remain prone while their bellies are full of dialysate. But they can get early clearance and may never need to be exposed to a tunneled venous catheter.

This is changing the rules of PD. Patients that in the past who show up without previous CKD care were often classified as too irresponsible to do the self-care needed for PD. However, we are finding that a lot of these patients who start dialysis via acute PD stay with the modality for years. It is an innovative way to get incident dialysis patients to consider PD.

Fistula First Campaign

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 KDOQI 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 CJASN).

(2) DreamRCT ESRD versus (7) DreamRCT AKI

A DreamRCT is a thought experiment where people imagine what is the most important question in nephrology and then design an hypothetical RCT to answer the question. This next pairing pits two DreamRCTs against each other.

DreamRCT ESRD

(Chronic Hemodialysis versus Peritoneal Dialysis RCT)

This DreamRCT is whether Peritoneal Dialysis or Hemodialysis is the better modality for ESRD. Forever nephrologists have been torn on which modality was better PD or HD. This is a civil war in the field of nephrology. Truly brother versus brother.

The tragedy of this schism is that this is an answerable question. You could run a trial that answers this question once and for all.

- Is PD better than HD?
- Is that advantage durable?
- Does it last only as long as there is residual renal function or is this a durable effect?

And don't forget the stakes. Hemodilaysis costs were $71,889 per patient per year in the U.S. compared to only $53,327 for those on peritoneal dialysis. Unfortunately, instead of a randomized controlled trial to shine the light of truth we are left with retrospective studies and USRDS statistics to wade through.

Attempts to randomize people to either modalities have been hampered by patient preference, people are hesitant to let something as big as modality choice be left to randomization. The Netherlands attempted to do this in a multi-center trial of 38 sites but after interviewing 773 people they could only entice 38 to consent to be randomized to HD or PD. The study is clearly underpowered and would be ignorable if the results were not so tantalizing. There was no difference in quality of life after one year (the primary end point) with a trend leaning toward HD. However, the 5-year survival data shows a relative risk of 3.8 for HD. Imagine, telling people that they could choose peritoneal or hemodialysis, but if they choose hemodialysis they will have nearly a four times higher risk of death in the next five years. To put this in perspective a permacath has a RR of 3.0 compared to a fistula. If this difference held up in a trial of significant size, it's hard to believe it would do anything short of rewrite the landscape for incident dialysis patients.

However, beyond that one attempt to randomize patients, we are left to wade through retrospective data. In 2012, NDT published a large comparison of HD and PD among Canadians. From the discussion:

> *…comparing PD versus HD over time and by calendar cohort period showed that for the most recent cohort of 2001–04, patients receiving PD were associated with significantly better survival during the first 2 years of dialysis and that long-term survival (3– 5 years) was similar for PD and HD patients.*

This survival advantage for PD does not necessarily apply to patients with diabetes. The Canadian trial found increased mortality hazard for women with diabetes that increased as the patients aged:

> *When overall survival was compared specifically for males and females, mortality was significantly higher for PD in both genders for patients with diabetes.*

Unfortunately, one of the best done studies, a matched cohort trial (CHOICE Trial) found mortality benefit for HD.

Trying to make sense of the retrospective and observational data is like trying to trace the origin of a single noodle in a bowl of spaghetti. We should throw-up our hands, declare equipoise and get to the business of doing a randomized controlled trial.

The long held claim that is impossible to randomize patients to PD versus HD is untenable in a world with patients being randomized to brain surgery or sham brainsurgery, CABG or catheterization, and home hemodialysis or traditional in-center dialysis.

DreamRCT Acute Kidney Injury
(Intermittent Hemodialysis versus Continuous Venovenous Hemodialysis in AKI)
Intermittent versus continuous therapies is a rivalry as deep as Syracuse versus Georgetown or Kentucky versus Louisville. These guys hate each other. The situation in acute kidney disease is also completely different from PD versus HD, because in AKI we a have head to head data from randomized controlled trials and still no clear winner.

Mehta did one of the early trials comparing the modalities and he successfully randomized 166 patients in a multicenter trial in California, but someone slipped him some loaded dice because the randomization wasn't balanced and the CRT group had higher APACHE-3 scores (P<0.045) and more liver failure (P<0.05). After that Table 1. failure, the results understandably showed increased ICU mortality (59.5% for CRT and 41.5% for IHD, P<0.02) and hospital mortality (65.5 for CRT and 47.6% for IHD, P<0.02) for continuous treatment. Using logistic regression to adjust for imbalances in group assignments, eliminated the increased danger of death with CRT.

The largest trial of IHD versus CRT was done by the French, the Tony Parker of RCTs. This multi-center trial randomized 360 patients to one of these two modalities and found no difference in 60-day mortality. 32% with intermittent and 33% with CRT.

Photo credit: Christopher Johnson

A Cochrane Systematic Review was unable to find much benefit from CRT:

- In-hospital mortality (RR 1.01; 95% CI, 0.92-1.12)
- ICU mortality (RR 1.06; 95% CI, 0.90-1.26)
- number of surviving patients not requiring RRT (RR 0.99; 95% CI, 0.92-1.07)
- hemodynamic instability (RR 0.48; 95% CI, 0.10-2.28)
- hypotension (RR 0.92; 95% CI, 0.72-1.16)
- need for escalation of pressor therapy (RR 0.53; 95% CI, 0.26-1.08)

Though patients on CRRT were likely to have significantly higher mean arterial pressure (MD 5.35; 95% CI, 1.41-9.29) at the expense of higher risk of clotting dialysis filters (RR, 8.50; 95% CI, 1.14-63.33).

These are two equally matched powerhouses.

Regeneration

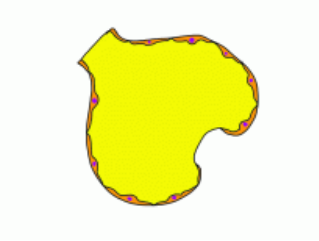
Not to be confused with the concept of “resurrection” this secular bracket holds no religious affiliation and preaches the concept of renewal through re-directional maturation and re-birth. Each candidate team has established itself scientifically as having the potential for a lead role in reparation of kidney injury. You don’t have to be a regular subscriber to Nature or have an RO-1 grant to appreciate the remarkable replicating metamorphosis skills of each member of this bracket. Which cell line will transition their way to the championship of this group?
Selection committee member for the Kidney Regeneration Bracket:

Stuart J. Shankland MD, MBA **Belding H. Scribner Endowed Chair in Medicine** **Head, Division of Nephrology, Professor of Medicine** **University of Washington, Seattle**	Dr Shankland is actively involved clinically, and prides himself on being a teacher to housestaff and students. His research interests are in glomerular disease, where his laboratory focuses on the mechanisms and potential therapeutic targets of proteinuria and glomerular scarring. His current funding includes the study of podocyte and parietal epithelial cell apoptosis, proliferation and regeneration.

MEET THE COMPETITORS FOR THE KIDNEY REGENERATION BRACKET

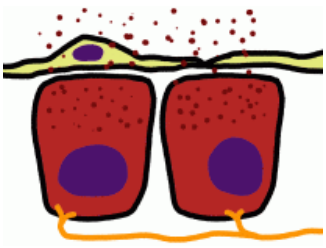
(1) Parietal epithelial cells versus (8) Renin lineage cells

Parietal epithelial cells



The parietal epithelial cell (PEC) is a unique cell type of the glomerulus. PECs live in a monolayer adherent to Bowman's capsule lining the urinary space of the glomerulus. These peculiar cells are finally starting to make a wave in world of kidney regeneration. An upstart from the formidable glomerular conference which includes the old-school mesangial cell and the international powerhouse "team podocyte". PECs arise from the same ancestral cell as the better-known and media-hogging "team podocyte". This is where the story gets interesting. Although PECs and podocytes arise from a common ancestor, important differences exist. Podocytes are terminally differentiated and therefore have a limited capacity to proliferate, whereas PECs proliferate even during physiological conditions, making PECs agile and evasive. Several groups studying these cells have demonstrated that PECs can proliferate, and then migrate and differentiate into podocytes in certain conditions. Moreover, evidence is beginning to accrue showing that PECs participate in a variety of glomerular diseases such as FSGS and RPGN. However, the viewpoint that PECs can give rise to podocytes is not universally held, and several investigators studying mice have challenged this idea. Finally, evidence in human disease suggests that an excess of proliferation by a subpopulation of PECs may lead to collapsing FSGS, characterized by pseudo-crescents. As new research emerges about the role of PECs in physiology and disease, it will become more clear how this unique cell type participates and interacts with other glomerular cells. The PEC is a team to watch during NephMadness 2014. They have potential to be a surprise team, but many questions about the true nature, and the (regenerative) potential of the PEC persists.

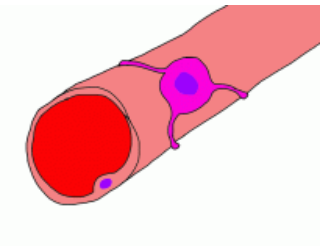
Renin lineage cells



Renin-lineage cells play an important role in the normal development of the kidney. For instance, renin-lineage cells are integral to proper development of the renal vasculature and furthermore, renin is expressed throughout the renal vasculature during embryogenesis. However, renin-producing cells regress in adulthood and are only found in specialized cells of the juxtaglomerular apparatus in the kidney. Interestingly, during states of physiological stress such has low blood pressure or salt deprivation, juxtaglomerular recruitment ensues whereby renin-producing cells begin to line the arterial tree leading to the glomerulus. This highlights the amazing capacity of this cell-type to quickly expand and retract either by proliferation, differentiation of other cell types such as smooth muscle or recruitment and differentiation of a stem cell progenitor. Nevertheless, the stage is set for the renin-lineage cell to serve as a potential progenitor to other cells of the kidney during injury. Pippin et al used the technique of cell identity fate mapping (by permanently labeling cells in vivo with GFP or tomato (red) using Cre/LoxP technology) to track the ultimate fate of renin lineage cells during experimentally induced glomerulonephritis in 3 different mouse models. This demonstrated that a small subset of adult PECs and podocytes are indeed of renin lineage after glomerular injury and may serve as progenitors for these cell populations with a limited capacity for regeneration. However, many questions remain to be answered about this process. The results are intriguing and open new lines of investigation on potential strategies to enhance podocyte repopulation after injury. This is important as podocyte loss has emerged as a critical pathophysiological determinant of many glomerular diseases including diabetes mellitus and FSGS. This is the newest member of the bracket and a true diaper dandy but the renin-lineage team could make a deep run with their quickness, athleticism, and ability to differentiate between offense and defense as needed.

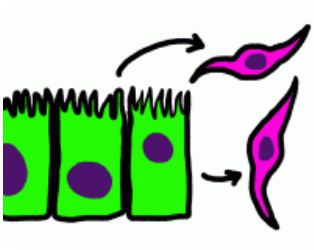
(3) Renal pericytes versus (6) Epithelial to mesenchymal transition

Renal pericytes



The study of pericytes has also emerged as a new player in the kidney regeneration/ fibrosis paradigm. Pericytes, once the forgotten cell type of the microvascular, are now surfacing as an important mediator of fibrosis in the damaged kidney. This is truly the cinderella of NephMadness and a team to watch out for. T0 review our anatomy, four cell types make up the microvasculature; the smooth muscle cell, endothelial cell, perivascular fibroblast cell and pericyte cell. Pericytes are cells with long tentacle-like processes adjacent to and in close proximity to endothelial cells. Pericytes are located at the interstitial side of microvascular embedded in the capillary basement membrane. Indeed, specialized pericytes such as the podocyte and mesangial cell have over the past 20 years garnered much attention by the nephrology community. The pericyte, in the past, was characterized as playing a fundamental role in the regulation of blood vessel development and stability. While vessel integrity is big role of the pericyte, a novel function in mediating fibrosis has emerged in recent years. Lin et al demonstrated that pericytes can transform into the collagen-producing myofibroblast. This group utilized a reporter mouse that marks any cell type producing collagen1 with green fluorescent protein (GFP). They found that the majority of myofibroblasts that accumulate in the parenchyma of the obstructed mouse kidney (a model of chronic kidney disease) are of pericyte origin. Finally, this group used the technique of cell identity fate mapping (by permanently labeling cells in vivo with GFP using Cre/LoxP technology) to track the ultimate fate of several cell types in order to establish the origin of myofibroblasts. Again this group showed that myofibroblasts were of pericyte origin. Investigators have also pointed to pericytes in other organs as mediators of fibrosis. For example the liver stellate cell (hepatic sinusoidal pericyte) has been shown to be the progenitor of myofibroblasts in the liver in mouse models of alcoholic and toxic liver injury. However, the pericyte-centric myofibroblast viewpoint is controversial as the established viewpoint of epithelial to mesenchymal transition (EMT) continues to garner support and a considerable amount of evidence exists. The pericyte vs. EMT should be an interesting battle.

Epithelial to mesenchymal transition (EMT)

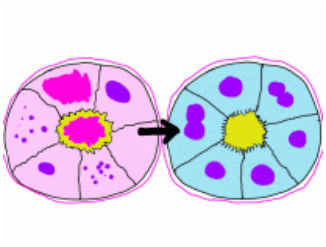


The process of epithelial to mesenchymal transition (EMT) was first described as an early embryonic event whereby primitive epithelia migrate as mesenchymal cells to form early structures. It is clear that EMT is an important mechanism for complex mammalian organ development. In the 1980s Greenburg and Hay showed that a variety of adult epithelial cells including kidney cells had the capacity to display a fibroblast phenotype upon exposure to collagen gels in vitro. A robust body of literature exists (briefly reviewed in this JASN article) in regards to the contribution of EMT to fibrosis. The theory is that cells (in this case renal tubule epithelial cells) when exposed to a toxic stressor or inflammatory mediator undergo a transition to a more primitive phenotype potentially to avoid imminent death. The fundamental principle governing EMT is that cells, which are normally polarized and interact with its native basement membrane via its basolateral surface, undergoes multiple biochemical changes enabling the cell to assume a mesenchymal cell phenotype which includes the capacity for migration, degradation of its native basement membrane and the potential to assume a collagen producing or fibrotic phenotype. For example, Neilson and colleagues have demonstrated through epithelial cell marker immunostaining coupled with fibroblast marker staining and EMT transcriptional program activation evidence for EMT in the kidney. Furthermore, Neilson and others have demonstrated by lineage tracing that the bulk of fibroblasts that accumulate in the kidney after ureteral obstruction in the mouse (an experimental model of CKD) are of renal tubular cell origin. An abundant literature exists describing the existence of EMT in the kidney as a mechanism for fibrosis. Understanding the principles

governing this important process that is common to every form of kidney disease will be an important step to halting the progression of kidney disease. EMT is the reigning favorite in the regeneration bracket with the most experienced body of literature. They will be a team to watch closely.

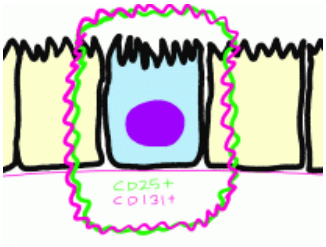
(5) Self-duplication of tubules versus (4) Tubule regeneration from resident stem cells

Self-duplication of tubules



How renal tubules repair after an acute insult can be quite impressive — from no kidney function for several weeks to normal kidney function within a month. How are the individual cells of the nephron replaced? One viewpoint is that fully differentiated tubular epithelial cells can self-duplicate by a process of dedifferentiation, migration, proliferation and redifferentiation to replace tubule cell death in response to injury. To garner evidence into whether or not this mechanism is important Kusaba et al performed a lineage-tracing study. They labeled terminally differentiated proximal tubular epithelial cells in vivo using Cre/LoxP technology and subjected these mice to ischemia reperfusion injury (a mouse model of AKI). They showed that a majority of cellular proliferation of the injured tubules was from reduplication of terminally differentiated tubular cells and not from expansion of a progenitor cell population. These are intriguing results, but many questions arise. First, do human tubule cells have the same capacity for self-renewal like the mouse kidney? Second, a better understanding of the molecular mechanisms governing self-renewal are needed before broader translational efforts to exploit these processes can take place. Lastly, it will be important to distinguish the properties of self-renewal from those of oncogenic transformation as this could be an unforeseen side-effect of exploiting this pathway. Self-duplication will be a formidable foe in the regeneration bracket. They have strength in numbers and have always traveled well.

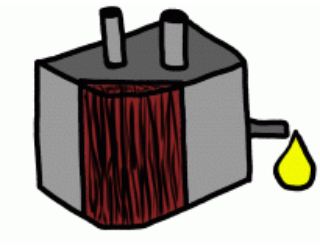
Tubule regeneration from resident stem cells



Insults to the kidney can take a variety of forms. From toxic drug exposure, to ischemic events. Kidney recovery from such an event can be profound or in some cases devastating. What factors are related to repair of the injured kidney? One dogma holds that stem cells with true pluripotent capacity exist in the adult kidney ready for deployment if an injurious situation arises. Evidence for this comes from Maeshima et al who reported in 2003 the identification of renal progenitor-like tubular cells in the proximal tubule, thick ascending limb and collecting duct using a combination of cell surface markers coupled with BrdU labeling to detect “slow cycling cells.” This same group reported that the so-called slow cycling cells have the ability to to create tubule-like structures in vitro and integrate into the nephron structure in vivo. Several other investigators have also attempted to pinpoint the renal tubular stem cells. Recently, Angelotti et al reported that a CD133+, CD24+, VCAM-1-, podocalyxin- cell population existed in proximity to the renal proximal tubule and distal convoluted tubule that are capable of tubule differentiation. These are just a few of the studies attempting to identify a resident renal stem cell population capable of tubular regeneration. However, these studies are not without controversy as a majority rely upon immunostaining with antibodies and lineage-tracing studies have not yet been performed as have been done many of the other teams in the regeneration bracket. Nonetheless, the potential existence of renal resident stem cells to regenerate injured tubule segments is quite intriguing. They could be a huge hurdle for the first and second rounds of NephMadness. Surviving past the second round will be the true test.

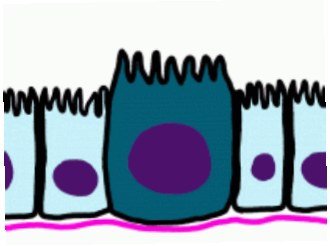
(2) Bioartificial kidney versus (7) Hypertrophy

Bioartificial kidney



The holy grail in the kidney world is the creation of a completely vascularized bioartificial kidney. This would have a huge impact in offering a potential therapy to patients with kidney failure awaiting a suitable donor. In the US alone ~100,000 individuals are on the transplant list and ~400,000 are on some form of dialysis. How far are we from the creation of a bioartificial kidney? Let's look at the literature. The idea for of an artificial kidney has been around since Willem Kolff in the early 1940s demonstrated, by using a rotating-drum dialyzer, that the removal of uremic toxins from patients with kidney failure is life-saving. Since this time numerous improvements have been made in renal replacement therapy. From the Scribner shunt, to peritoneal dialysis, to advances in kidney transplantation to name a few. However, the ultimate creation of a completely vascularized artificial kidney has been elusive. A few examples utilizing animal models have emerged over the last few years. A report in Nature Medicine sent a few shock waves in 2013. The main problem with a bioengineered kidney is the complex 3-dimensional nature of the kidney. Song et al used a technique whereby rat kidneys are decellularized with detergent perfusion to create whole-organ "scaffolds" with intact and perfusable vascular, glomerular and tubular compartments. They next repopulated the scaffold via the renal artery with rat endothelial/epithelial cells plus they added human umbilical venous endothelial cells (HUVECs). Finally they infused at neonatal kidney cells through the ureter. The system was perfused in vitro for a few weeks then implanted into a rat. The results were astonishing. They demonstrated as early as day 4 of the scaffold culture, histological evidence of epithelial, endothelial, vascular and glomerular repopulation were seen. This was verified by a combination of immunostaining, histology and electron microscopy. Morphometric analysis showed that ~70% of glomeruli were repopulated. Finally, this group demonstrated both in vitro and in vivo that the bioengineered kidneys were able to make urine. However, it is unclear whether or not the bioengineered kidney would be able to sustain the life of the rat if it was the sole provider of kidney excretory and endocrine function for an extended period of time. Other groups, such as that of the Kidney Week 2013 plenary speaker Anthony Atala, are already making progress decellularizing pig kidneys as a potential scaffold for a human bioengineered kidney. Another, exciting advancement in the creation of the bioartificial kidney was recently reported in Cell Stem Cell by Taguchi et al. This group derived metanephric mesenchyme from pluripotent stem cells and were able to reconstitute glomerular, proximal and distal tubule structures in vitro. Furthermore, these reconstituted nephrons were implanted beneath the renal capsule of mice and new vascularization commenced. Tom Oates discusses this further on RFN. This is a formidable foe and an odds-on favorite to win the kidney regeneration bracket. However, this part of the NephMadness bracket is filled with a variety of teams that could give the bioartificial kidney a run for its money.

Hypertrophy



Hypertrophy comes in as the perennial underdog. They always seem to make the big dance but never go very far. A true Gonzaga of the tournament. Other topics in the regeneration literature seems to always predominate the media. It might be because the processes that govern cellular hypertrophy are not clear. Let's look a little closer at the phenomenon of hypertrophy that many cell types are capable of using in states of physiological stress. Hypertrophy is the process whereby an individual cell gets big, due to an increase in its protein content, without an increase in its DNA content. When a cell engages the cell cycle, it ordinarily starts to produce increase protein content in anticipation of it dividing into two daughter cells. Therefore, when they arrest at the G1/S interphase prior to DNA synthesis, cells are larger than normal (hypertrophy) because the ratio of protein to DNA is increased. This occurs in part due to an increase in cell-cycle

inhibitors such as cyclin kinase inhibitors. Is bigger always better? How will they fare in the fast-paced regeneration bracket? Let's look at this more closely. Mesangial cell hypertrophy commonly occurs following a reduction in kidney mass following such as uninephrectomy. This type of hypertrophy is compensatory and physiologic. In contrast, mesangial cell hypertrophy which occurs in diabetes is considered pathologic. Another example is that of podocyte depletion, which occurs in a variety of glomerular diseases. Podocyte depletion leads to areas of bare or denuded glomerular basement membrane. This ultimately causes segmental glomerular scarring. Wiggins et al showed that because podocytes cannot proliferate to replace those cells who are lost, their neighbor podocyte will undergo hypertrophy to cover the bare area of glomerular basement membrane. This is called compensatory hypertrophy. However, with time, these large cells produce an excess of deleterious factors such as cytokines, and augment rather than reduce disease. This hypertrophy is also maladaptive and pathologic. It may well be that this "hypertrophic" team will do well early in the tournament as it does in disease states, but how will they fare later in NephMadness? We will have to wait and see.

-Cartoon Illustrations by John K. Roberts, MD, MS
-Written and Edited by Drs. Matt Sparks and Stuart Shankland

Acute Kidney Injury

These competitors will surely challenge each fan's loyalty to nephrology tradition for both seasoned professionals and those in their rookie years. Extra security has been brought in to ensure that game-time emotions are appropriately diuresed and kept under pH control especially for the international matchup of KDIGO vs KDOQI AKI guidelines, the potentially acidic battle between Saline and Balanced Solutions, and the playoff round of old (Traditional urinary indices) vs new techniques (Urinary biomarkers) for diagnosing AKI. Not to be overlooked among all this controversy is the king of AKI, CIN (Contrast-Induced Nephropathy) that may very well prove to be too overwhelmingly nephrotoxic to be seriously challenged by any of the other teams.
Selection committee member for the Acute Kidney Injury Bracket:

Sarah Faubel, MD
Associate Professor of Medicine
University of Colorado Denver
Staff Physician at the Denver VA Medical Center

Dr. Faubel's primary area of research is the distant organ effects of AKI in rodent models, particularly proinflammatory cytokine production and lung injury. Studies are focused on the generation and resolution of inflammation after AKI, with the view that dysregulated inflammation after AKI is a key driving force behind the deleterious systemic effects associated with AKI. Complications from the distant organ injury of AKI are now recognized as a potential mechanism for the increased mortality observed in patients with AKI.

MEET THE COMPETITORS FOR THE ACUTE KIDNEY INJURY BRACKET

(1) Contrast Nephropathy vs (8) Remote Ischemic Preconditioning (RIPC)

When told that their first round opponent was Remote Ischemic Preconditioning (RIPC), Contrast-Induced AKI skeptically queried "who?" and started to make comments about who they would have to play in the second round. On paper, this looks like a complete blowout but there is a reason RIPC was chosen as a sleeper for the tournament. Employing a completely unique defensive strategy, RIPC has stunned opponents with their anti-oxidant and anti-inflammatory potential. Not impressed, Contrast Induced AKI predicted that their opponent will definitely need to R.I.P. after they experience the full nephrotoxic power of iodinated contrast. Could the overconfidence of Contrast-Induced AKI set them up for a first round upset?

Contrast Nephropathy

The #1 seed is well deserved by this team composed of an array of ionic and nonionic iodinated benzene ring derivatives. Relentlessly coming at you in waves of high, low, and iso osmolar boluses, the defenseless proximal tubule is no challenge for Contrast-Induced AKI. ATN magazine ranks Contrast-Induced AKI as the leading cause of hospital-acquired ATN for over 20 consecutive years. This team is offensively driven unleashing both intense renal cortical and medullary vasoconstriction as well as direct cellular injury.

Contrast-Induced AKI leaves a long lasting impact on its opponents who are rarely able to completely recover and perform back at their full capacity accompanied by an accelerated development of CKD in their future. Both short and long term mortality is markedly increased after Contrast-Induced AKI is present.

As a sign of its popularity, over 500 peer reviewed articles are written yearly about Contrast-Induced AKI. Molecular size, speed of toxic injury, and widespread exposure all make Contrast-Induced AKI a formidable and almost unbeatable team.

Remote Ischemic Preconditioning (RIPC)

RIPC was the last team to get into the tournament and was initially overlooked by every expert. Always playing with a hypoxic chip on their shoulders, RIPC knows there is a lot pressure on them to show they deserve to be in this bracket. RIPC utilizes a strategy never before seen in this tournament and first originated this unique game plan in 2006. The background for this approach is rooted in the classic chess gambit practice of sacrificing a pawn for later victory. RIPC is based on causing temporary remote ischemia of one organ to protect another.

Their technique is elegant yet simple: starting 2 hours before a potentially nephrotoxic event, intermittent upper arm ischemia is produced by 4 cycles of 5-min inflation of a blood pressure cuff to 200 mm Hg followed by 5 minutes of deflation. This novel procedure reduces oxidative stress by activating a variety of biochemical events including the phosphatidylinositol 3-kinase/Akt (PI3K-Akt) pathway. There may also be an anti-inflammatory component to the action of RIP but this is still not fully defined.

RIPC has been on a roll recently demonstrating significant renal protection against a variety of insults after coronary bypass surgery or abdominal aneurysm repair. Interestingly RIPC already played an early "friendly" scrimmage against Contrast-Induced AKI and shocked their opponents by pulling a stunning upset win by significantly reducing kidney injury.

RIPC knows it's a heavy underdog, but like David and Goliath, sometimes victory can be achieved against a superior opponent by using a simple unexpected weapon such as a plain slingshot or in the case of RIPC a standard blood pressure cuff.

RIPC truly believes it will inflate its way to victory.

(3) U/A and Indices vs (6) AKI Biomarkers

This bracket is a classic first-round matchup of teams with completely opposite ideologies. On one side we have Urinary Indices: Traditional Way that rely on the same game plan over and over again that has worked so well in the past no matter who the opponent is, as opposed to Urinary Indices: Modern Way who have developed a whole new game strategy based on more modern scientific techniques. Past vs Present! Is it finally time for Urinary Indices to enter the 21st century and retire the Traditional Way once and for all? Do years of Tradition prove to be too powerful to push aside just because they are considered to be old fashioned? It's a toss-up!

U/A and Indices: Traditional Way

This team is well known to medical students, junior staff and senior staff of all specialties. The starting five consist of FENA, FEUREA, Urine Lytes, Granular casts and Urinalysis with Urine Osmolality and Specific Gravity coming off the bench for added diagnostic and scoring accuracy. In spite of the low salary for each player, the quick turnaround of the games and the widespread ease of ordering, critics have long argued that this team is getting on in years with no new players having been added for decades. More importantly, recent reviews have further questioned the "accepted" accuracy of these indices in predicting the severity and outcome of AKI.

Once considered to be the star player FENa has had a challenging time when faced against a team that uses diuretics, CKD, or heme pigment toxins. In addition, FEUrea has similarly slowed down over the years having a very difficult time in sensitivity (61%) and specificity (59%) in ICU patients.

These weaknesses have exposed this team and questioned the ability of Urinary Indices: Traditional Way to stay on top of the rankings in the workup of AKI. Nevertheless, Urinary Indices: Traditional Way continues to be a fan favorite and when they approach the bedside to their anthem "Tradition" from Fiddler on the Roof, even the most stoic critic will find themselves joining in and measuring along.

AKI Biomarkers: Modern Way

Embracing the recent breakthroughs in molecular and immune monitoring for tissue injury, this team is poised to go to the next level. Certainly not household names yet, this group of enzymes and cytokines have joined together to prove a worthy successor to the title of AKI champion. The current team consists of NGAL (Neutrophil Gelatinase Associated Lipocalcin), KIM-1 (kidney Injury Molecule 1), IL-18 (Interleukin 18), NAG (N-acetyl-β-D-glucosaminidase), and Cystatin C. More new players are being recruited regularly.

The team is primarily from the proximal tubule and have been shown to be particularly sensitive in the diagnosis of incipient AKI after radiocontrast exposure, surgery, sepsis, or kidney transplantation. In addition, these biomarkers have been shown to predict short and long term outcomes after AKI more accurately than the Traditional Way. The lack of widespread availability and defined normal parameters of this team has hindered their recognition and application by nephrologists. In addition, current KDIGO Guidelines have yet approved Urinary Indices: Modern Way as an accepted alternative or adjunct for the diagnosis of AKI over the Traditional Indices.

This is a team of limitless potential that may need more time to work together as a unit and a few more key players before it can compete at the highest level.

(4) Fluid Resuscitation: Normal Saline versus (5) Fluid Resuscitation: Balanced Solutions

These 2 teams are so closely matched that they differ only by a slight difference in pH, a few milliosmoles of tonicity, and a few milliequivalents of chloride. Each solution remains under the radar as a serious threat to win the AKI bracket but never underestimate the simple elegance and long lasting economic and survival benefit of successful fluid resuscitation

in reducing the risk of AKI. Strong vocal advocates abound for each team and they remain undeterred in their loyalty. This game is going to go down to the last ml.

Fluid Resuscitation: Normal Saline

This team manages to hold its own even with just 2 players: Na and Cl. Somehow in spite of their small numbers they manage to fill the entire intravascular volume and put up a valiant fight to prevent hemodynamic and contrast-induced AKI. Promotional material handed out by the team point to the many peer-reviewed publications confirming successful pre-emptive deployment of Normal Saline in the prevention of AKI. Importantly the Saline vs Albumin Fluid Evaluation (SAFE) study confirmed the benefit and cost-effectiveness of Normal Saline compared to albumin in preventing AKI. In addition, compared to colloids such as hydroxyethyl starch (HES), Normal saline has again prevailed as a safe and effective option for fluid resuscitation. Finally, the KDIGO AKI guidelines recommend Normal Saline as the first option for volume expansion basically labeling it as the MVP (most valuable player) of fluid replacement.

In spite of this string of victories and awards, critics continue to call Normal Saline an "unbalanced solution" that causes excessive hyperchloremia and metabolic acidosis. They point to research studies that show direct injury from hyperchloremia to the vascular endothelium that when coupled with the iatrogenic lowering of the pH leads to disruption of the renal microvasculature and worsening AKI. Finally, Fluid Resuscitation: Normal Saline has been accused of being overly aggressive and not knowing when enough is enough. Overzealous team effort has led to excessive volume expansion and increased mortality.

Fluid Resuscitation: Normal Saline shrugs off these comments and has only one thing to say to its critics: Bring it on!

Fluid Resuscitation: Balanced Solutions

Respect! All this team is looking for is R-E-S-P-E-C-T. This is a well "balanced" squad that isotonically achieves volume normalization without altering systemic pH or the electrolyte concentration. Each member of the team was chosen specifically to maintain the Na, Cl, HCO3 and potassium concentration with the added benefit of calcium and magnesium control as a bonus option.

This team has labored in the shadow of Fluid Resuscitation: Normal Saline for years and has yet to breakthrough into the mainstream. In order to change the prescribing patterns of physicians, Balanced Solutions knows that they will need concrete evidence and a blockbuster study to support their cause. So far things are looking promising at the bench research level. Compared to their arch nemesis Normal Saline, Balanced Solutions resulted in improved renal blood flow and a reduced risk of AKI. Clinically, even better news is on the horizon as Balanced Solutions own an early victory in comparison with Normal Saline in critically ill patients for the prevention of AKI.

(2) KDIGO: AKI Definition vs (7) KDOQI: AKI Definition

Front and center is an international battle of definitions and recommendations between KDIGO:AKI and KDOQI:AKI. Nationalism has always played an important role in the Olympics and this competitive spirit has now extended itself to the field of AKI. Representing the international community in one corner is the widely popular KDIGO:AKI, carrying the hopes and dreams of thousands of nephrologists and primary care physicians to finally unify AKI like the Euro has unified Europe. Standing in the way of KDIGO and world domination is a team from the United States, KDOQI:AKI, representing the American way of dealing with AKI. No amount of diplomacy can prevent this battle from occurring. There will be only one winner.

KDIGO: AKI Definition

This is a powerhouse team that commands immediate respect. No other team is so well known just by its initials and boasts an international reputation – Kidney Disease Improving Global Outcomes: Acute Kidney Injury – KDIGO:AKI. Initially conceived in 2011, it took a whole year for a workgroup of 18 experts and an entire evidence review team from Tufts Medical Center to assemble the final 138 page product. No controlled trial or meta-analysis was ignored in the collation of 783 references spread out over 5 chapters, 23 tables and 17 figures. A new working classification of AKI, recommended evaluation strategies and clinical maneuvers for prevention of AKI have been detailed and supported by evidence-based analysis. This awe-inspiring compilation of 87 recommendations immediately intimidates every opponent whether at home or on the road.

KDIGO:AKI appears to have emerged as the AKI definition champion after overwhelming RIFLE and AKIN in the playoffs. Many of the players of both RIFLE and AKIN made their way to join KDIGO:AKI knowing that together they may be able to win it all!

KDOQI: AKI Definition

No stranger to international competition, the National Kidney Foundation has assembled an all-American team to challenge for the definition and evaluation of AKI title called the Kidney Disease Outcomes Quality Initiative (KDOQI). The gauntlet was thrown down against KDIGO:AKI at the opening press conference with KDOQI:AKI announcing "we question whether these staging criteria of AKI (by KDIGO) are currently appropriate to guide clinical management of adult patients." As if that wasn't enough to stir emotions, KDIGO went on to say "we believe that current data are inadequate to support the reliance on oliguria as a surrogate endpoint in clinical trials or in performance metrics."

KDOQI:AKI places emphasis on the cause and duration of AKI as a major predictor of long-term outcome and does not believe patients should be individually treated based on the stage of AKI as per KDIGO.

KDOQI:AKI states that its sole mission is look out for U.S. citizens and that implementation of KDIGO:AKI will result in a "dramatic increase in unnecessary nephrology consultations" and inappropriate labels of AKI in hospitalized patients.

In total, KDOQI:AKI provides its 76 recommendations in a lean 23 pages with 164 references. With chants of "USA, USA, USA" in the background, KDOQI:AKI could be the surprise dark horse of the tournament.

-Written and Edited by Dr. Warren Kupin

Electrolytes

This is a highly charged bracket of teams all trying to balance, bind, or buffer their way to the title. For those fans that miss the science lessons in “Breaking Bad” there are representative teams from all parts of the periodic table in addition to organic and inorganic synthetically derivative molecules and mathematical formulas. Arch rivals in the treatment of acute hyponatremia, Hypertonic Saline and Vaptans square off in a first-round osmotic demyelinating showdown of epic tonicity! As if that wasn’t enough osmoles for one round, there is the battle of the Gaps, a duel of K+ sequestrants and topped off by a bicarbonate battle that will go likely down to the last proton. Let’s get ready to rumble!
Selection committee member for the Electrolytes Bracket:

Helbert Rondon, MD **Assistant Professor of Medicine,** **Renal-Electrolyte Division** **University of Pittsburgh School of Medicine** **eAJKD Contributor**	Dr. Rondon is the associate program director for the nephrology training program at the University of Pittsburgh School of Medicine. He is developing and employing innovative teaching strategies to aid in nephrology fellow education. Specifically his group is developing virtual patient simulation coupled with a space education curriculum to teach electrolyte disorders. His group is also in the process of implementing a kidney biopsy simulation training module to increase procedural skills. Dr. Rondon is exploring the role of eNaC in sodium retention during nephrotic syndrome.

MEET THE COMPETITORS FOR THE ELECTROLYTE BRACKET

(1) Hypertonic Saline versus (8) Vaptans

Hypertonic Saline

Hypertonic saline is usually administered as 3% NaCl (513 mEq/L of Na & Cl or 1026 mOsm/L) whereas 'normal' saline is obviously 0.9% NaCl (154 mEq/L of Na & Cl or 308 mOsm/L). Hypertonic saline as 1.8% & 5% is also available, but its teammate 3% gets the hype so I will concentrate on this. Hypertonic saline is useful in SIADH, a condition with a relatively fixed urine osmolality with urine volume varying depending on solute load. This is because response to Na handling by aldosterone is normal but water handling (ADH effect) is abnormal. This leads to a situation where the serum sodium will only rise if the electrolyte content of the administered fluid exceeds the urine electrolyte concentration.

Let us say a patient with SIADH has a urine Na of 150mEq/L and urine K of 70mEq/L (urine cations = 220mEq/L).

- The patient is slowly given 500 mL of 3% NaCl (257 mEq of Na).
- As the urine osmolality is 'fixed', these 257 mEq will be excreted in 1.17 L of urine (257/V = 220 → V = 257/220 → V = 1.17 L, i.e., net free water loss of 1.17 L – 0.5 L = 0.67 L or 670 mL.
- This is what accounts for the Na rise, despite all the Na being excreted.
- This also explains why hypertonic saline's teammate, isotonic saline, will never beat an opponent like SIADH.
- If 500 mL of 0.9% NaCl (77 mEq of Na) were given instead, the sodium would again be excreted but in 350 mL of urine (77/V = 220 → V = 77/220 → V = 0.35 L, i.e. leading to a net retention of 0.5 L – 0.35 L = 0.15 L or 150 mL of free water, exacerbating hyponatremia!

Hypertonic saline is particularly indicated in cases of moderate to severely symptomatic hyponatremia (eg, seizures), usually acute but also severe chronic (Na < 120 mEq/L), as it is the only method to rapidly increase the serum sodium. Only small increases in sodium (2 – 6 mEq/L) are usually necessary to abort seizures. It is suggested that in marathon runners who become unwell with probable hyponatremia, a bolus of 100 mL of 3% NaCl should be administered in the field (predicted to rise serum sodium by 2 mEq/L) and this could be repeated up to 2 more times 10 min apart if symptoms continue.

Potential drawbacks of hypertonic saline again relate to the risk of over-rapid correction of sodium with potential for osmotic demyelination. For acute hyponatremia, the goal should be to stop life-threatening symptoms with a suggested rise in serum Na of 6 mEq/L in the first 6 hours and postpone any further correction for next day (Rule of Sixes). It should be noted, however, that in cases of acute hyponatremia (present for < 48 hours), the risk for demyelination appears to be less, as full brain adaptation has not yet occurred. Hypertonic saline is a veteran team that plays an aggressive game and frequently intimidates opponents. Their early match-up with team Vaptan is possibly the pick of the first round. We can't call it!

Vaptans

The hyponatremia matchup is a perennial contest often full of controversy. Just to set the stage, hyponatremia is one of the most commonly encountered diagnoses made in medicine. Obviously, a lot of interest will be brewing for this one. The vaptan team, led by the big man tolvaptan, is no longer the new kid on the block and has accumulated experience over the past number of years. Hypertonic saline, the dinosaur of the conference, continues to stay relevant and will not be intimidated by the tricky opposition.

Vasopressin (ADH) has multiple receptors which mediate its vasoconstrictive (V1a), ACTH release (V1b) and antidiuretic effects at the distal nephron (V2). ADH antagonists that are licensed in the US include the intravenous preparation conivaptan, an inhibitor of V1a and V2 receptors, and tolvaptan, an oral selective V2 antagonist. Vaptans are licensed for short-term in-hospital treatment of hyponatremia and will work when excess ADH is implicated, ie, SIADH (inappropriate) and heart failure or cirrhosis (appropriate ADH release). Inhibition of V2 will cause a water diuresis although subsequent thirst stimulation may limit the rise in serum sodium. Efficacy of tolvaptan was demonstrated by 2 combined trials (SALT 1 & 2) including 448 patients with a combination of SIADH, cirrhosis and heart failure and mean serum sodium 129mE/L. Compared to the placebo group, the tolvaptan group had a 4-5 mEq/L higher sodium level at day 4 & 30.

New team members have so far been redshirted, with lixivaptan failing to get an outpatient license granted despite proving efficacy, mozavaptan only granted license in the Japanese league and satavaptan not yet approved either. Preseason controversy regarding tolvaptan centered on its failure to achieve FDA approval for use in ADPKD despite results from the TEMPO 3:4 trial which demonstrated a slower increase in kidney volume and better GFR compared to placebo. There are some concerns for fans of Team Vaptan. TEMPO 3:4 reported abnormal liver enzymes more commonly in the tolvaptan group, although it must be noted that doses used were much higher than the hyponatremia dose. Also, liver enzymes settled with cessation of the drug. Another concern is that over rapid correction of sodium may occur, potentially leading to osmotic demyelination syndrome, so close monitoring of sodium correction is necessary. In the SALT trials, 1.8% of patients corrected by > 12mEq/L/day (now suggested ≤ 10 mEq/L and ≤ 8 mEq/L for patients at high risk). If this is a concern, some clinicians (including this one) have started at a lower than licensed dose, 7.5 mg daily. Despite being a young squad, the big-money Team Vaptan have the swagger of conference veterans and will be confident of a successful run to the latter stages of this year's NephMadness tournament.

(3) Serum Anion Gap versus (6) Urine Anion Gap

Anion Gap (AG): the difference between the measured cations (positively charged ions) and the measured anions (negatively charged ions) can be very helpful in acid/base disorders. This matchup sees the heavyweight serum AG go up against its lesser-known rival, the urine AG.

Serum Anion Gap

$$\text{Serum Anion Gap (SAG) (in mEq/L)} = Na - (Cl + HCO3).$$

The SAG is arguably the most used biochemical calculation in nephrology. It provides the user with a reflection of unmeasured anions, and hence unmeasured organic acids. The normal AG is mainly due to negatively charged proteins (albumin) and unmeasured acids. SAG is traditionally used in cases of metabolic acidosis, which can be divided into high gap (additional unmeasured organic acids) or normal/low gap (often due to bicarbonate loss). While the entire conference is aware of the strengths of the SAG in cases of high gap (see MUDPILES or the most updated mnemonic GOLD MARK) even in the context of a normal pH (SAG > 20 mEq/L is highly predictive of an underlying AG metabolic acidosis), the hidden strength of this team is its non-gap utility. Non gap acidoses may be due to HCl precursors gain (TPN, Cl-rich IV fluids), decreased NH4+ excretion (RTA I & IV, Fanconi syndrome, renal insufficiency), or bicarbonate/bicarbonate precursors loss, either from the gut (diarrhea, GI fistula or ostomy) or from the kidney (RTA II, post-hypocapnia, treatment of DKA). Causes of low AG, without acidosis, may also confuse opponents and is often due to hypoalbuminemia, where the expected normal values for the SAG should be adjusted downward (2.5 meq/L for every 1 g/dL reduction in the serum albumin below 4g/dL). Other causes include elevated cations (lithium, severe hyperkalemia, rarely hypercalcemia and hypermagnesemia, IgG paraproteins). Note that for this to occur, the increase in the unmeasured cation must be accompanied by a measured anion, eg, with Cl or HCO3. We must also watch out for lab error which may underestimate Na in severe hypernatremia (Na+ > 170 mEq/L) and hyperviscosity, or overestimate chloride in severe hyperlipidemia or

bromide intoxication (ie, pyridostigmine bromide used in myasthenia gravis). SAG enters this contest with a heavy reputation amongst fans but a somewhat stagnant line-up, with few recent recruits. It is a team full of big men who could be caught out by more mobile opponents.

Urine Anion Gap

$$\text{Urine Anion Gap (UAG) (in mEq/L)} = Na + K - Cl$$

In healthy people, the UAG is positive (between 20 and 90) as more Na & K is absorbed from the GI tract than chloride. In metabolic acidosis, urinary acidification should occur via NH4+ excretion, in combination with chloride leading to a high urine chloride.

$$NH_3 + H^+ \leftrightarrow NH_4^+ + Cl^- \leftrightarrow NH_4Cl$$

Therefore, UAG is used as a surrogate for NH4+ and will be negative if urine acidification is normal in the context of a systemic acidosis. This is the case in diarrhea associated acidosis or Type 2 RTA in steady state (not undergoing active treatment with NaHCO3) where distal acidification remains normal. Conversely, a positive UAG in the face of systemic acidosis suggests inappropriately low NH4+ production and therefore impaired urinary acidification. This occurs classically in cases of

- type I RTA but also in type 2 RTA not on steady state (undergoing active treatment with NaHCO3 in which spilling of HCO3 in urine is accompanied by increase in urine Na+)
- Fanconi syndrome (proximal tubular dysfunction impairs ability to form NH3 from glutamine)
- type 4 RTA (hyperkalemia inhibits NH3 production in proximal tubule).

A weakness of the UAG is its utility as most cases of metabolic acidosis can be figured out with history, serum K and urine pH assessment. Another drawback is that non-chloride anions are not accounted for. These anions include ketoacids, bicarbonate or hippuric acid (toluene/glue sniffing). They may be excreted with Na+ or K+ (contributing to a positive UAG as Na+ or K+ are measured but anion are not) or with NH4+ (unchanged UAG as both anion and cation are unmeasured). In these cases, the urine osmolal gap (UAG rival, did not make it to the tourney this year) may be useful to estimate NH4+ excretion as all NH4+ salts are accounted for by the urine osmolal gap. Despite this, the UAG does remain a useful tool in a physician's armamentarium in assessment of non gap metabolic acidosis. The urine AG will relish this contest against its more famous neighbor, despite the obvious weakness in their line-up. UAG has had a quiet but productive early season, has kept under the radar and will be well up for this potentially giant-killing contest against their more celebrated rivals.

(4) Kayexalate versus (5) ZS-9 (novel potassium binder)

Hyperkalemia — this is a battle of old versus new. The old guard kayexalate — hardly studied but widely used — and the new guard ZS-9, now rigorously studied but never used.

Kayexalate

Kayexalate is the trade name for the drug sodium polystyrene sulfonate (SPS). This is a popular drug given around the world for hyperkalemia. It is an ion-exchange resin designed to exchange sodium for potassium in the colon. However, some degree of calcium is also exchanged. SPS was first reported in Lancet in 1953 and approved by the US FDA in 1958 as a treatment for hyperkalemia. This was 4 years before the FDA required drug manufacturers, as directed by

the Kefauver-Harris Drug Amendments, to prove the effectiveness and safety of drugs submitted for indication and approval. This amendment, was a reaction to the thalidomide tragedy in which thousands of children were born with birth defects after taking thalidomide for pregnancy-associated nausea.

So, lets take a look at the data in regards to SPS. The theory is that the resins reactive sulfonic group, which is preloaded with sodium, exchange the bound cation with a cation in the colon (in this case potassium). The original reports from the 1953 Lancet paper demonstrated a hypokalemic effect of the resin in 4 patients with renal failure and 1 healthy volunteer. Sherr et al reported in the NEJM in 1961 the largest clinical data in regards to kayexalate. This uncontrolled study showed serum potassium lowering in a majority of the 30 patients treated with kayexalate having hyperkalemia and acute or chronic kidney failure. Based on this and several other case series the FDA continued to label the product at "effective".

However, it was recognized that severe constipation was a significant side effect of kayexalate. This lead to the desire to speed the delivery of kayexalate to the colon by the addition of osmotic laxative sorbitol. On the basis of a preliminary study published in the NEJM with 10 patients with oliguria and hyperkalemia the combination of kayexalate and sorbitol was effective at lowering potassium. By 1981, a convenient prepackaged kayexalate and sorbitol suspension gained wide popularity in the US. However, a study published in 1998 which included 6 patients with ESRD with normal or mildly elevated serum K+ found that the serum K+ rose slightly (0.4 mEq/L) on placebo and did not change during the course of 12 hours in response to a single dose of 30 g of SPS in water, 30 g of SPS in 60 g of sorbitol, or 60 g of sorbitol alone. Also, the FDA had started to receive reports of the combination of sorbitol and kayexalate causing severe bowel injuries such as bowel infarction and ischemia. In 2005, the concomitant use of sorbitol was removed from the FDA-approved labeling. However, the largest maker of the combination agent continued to package this albeit as a lower sorbitol concentration of 33%. In 2009, the FDA issued a Warning of intestinal necrosis with the combination of kayexalate with sorbitol. The popularity of kayexalate has waned in recent years, but its continued use despite a paucity of data regarding efficacy and numerous side effects (others are magnesium and calcium binding).

ZS-9 (Novel Potassium Binder)

ZS-9 was unveiled at ASN Kidney Week 2013 in Atlanta during the late-breaking clinical trials session. This was a surprise indeed for many in attendance, as we are in desperate need for better pharmacologic therapy for hyperkalemia. The study is still not published so we have limited information to share about the drug. ZS-9 is a novel investigational treatment for hyperkalemia. ZS-9 is an inorganic cation exchanger (zirconium silicate) with a high selectivity for potassium. According to the company (ZS Pharma), the drug can bind 9 times as much potassium as sodium polystyrene sulfonate. ZS-9 reported preliminary results of a phase III trial and results of a phase II safety and tolerability study. The phase II study looked at 3 doses of ZS-9 (0.3 g, 3 g, and 10 g) and placebo in 90 patients with mild-to-moderate CKD and hyperkalemia. Both the 3 g and 10 g doses lowered serum potassium as compared to placebo. No hypokalemia, hypocalcemia or hypomagnesemia was noted. Mild constipation was seen in the 3 g dose and vomiting with the 10 g dose. They reported that no discontinuation or serious adverse event occurred. The acute portion phase III randomized placebo controlled trial enrolled 753 patients with hyperkalemia; some with CKD and others with normal kidney function. The phase III trial tested 4 doses of ZS-9 (1.25g, 2.5g, 5g and 10g) or placebo. The primary endpoint was change in serum potassium level over 48 hours. This was met at the 2.5g (-0.46 mEq/L), 5g (-0.54 mEq/L), and 10g (-0.73 mEq/L) doses. Adverse events were minimal and similar to placebo. The chronic portion of the phase III clinical trial were released by the company in January 2014. This tested the same 4 doses of ZS-9 and placebo as the acute portion but for 12-days. Both the 5 g and 10 g doses lowered serum potassium and had similar side effects as placebo. The company intends to present their results at a national meeting in 2014. This is not the only new potassium binder in

development. The company Relypsa is developing a potassium binding polymer RLY5016. This has shown some success in hyperkalemia in conjunction with heart failure.

ZS-9 comes to NephMadness with a lot of hype. However, the drug is untested in the real world and we still await a full peer-reviewed publication. Should be an interesting matchup in an area of medicine with a true need for innovation.

These issues make it difficult to pull for kayexalate during the NephMadness tournament. However, kayexalate has been widely used for years. The matchup between ZS-9 and kayexalate should be a good one.

(7) Bicarbonate in CKD versus (2) Bicarbonate in Acute Metabolic Acidosis

Acidosis RX — this portion of the electrolytes bracket pits two almost identical but actually completely different foes. Bicarb for anion gap acidosis is the perennial favorite, but if you dig deeper you see a real identity crisis. Bicarb for acidosis in CKD is gaining popularity and is a favorite to go deep in the tourney. Should be an interesting battle.

Bicarbonate in CKD

Metabolic acidosis is seen in 30-50% of patients with an eGFR of less than 30 ml/min/1.73 m2. In recent years treatment of metabolic acidosis with sodium bicarbonate has gained more attention. Chronic metabolic acidosis is associated with bone disease, muscle protein catabolism, and some studies have linked metabolic acidosis to progressive glomerular filtration (GFR) loss. As such, the KDOQI guidelines have recommended to keep serum bicarbonate level > 22 mEq/L. What are reasons to be vigilant about treated metabolic acidosis in CKD? It has been shown that muscle wasting is a direct consequence of metabolic acidosis from CKD by impairing insulin signaling, leading to muscle protein breakdown. This leads to a negative nitrogen balance with decreased albumin synthesis. Evidence exists showing that correction of acidosis in CKD ameliorates this catabolic factor. Chronic metabolic acidosis stimulates large production of NH4+ with the aims of excrete the acid load and experimental evidence suggest that NH4+ can activate the alternative pathway of complement causing inflammation and ultimately fibrosis. We have few treatments in our armamentarium to slow the progression of CKD so if simply correcting metabolic acidosis can achieve this important goal, then why not. In an important study de Brito-Ashurst et al randomly assigned 134 patients with CKD (CrCl 15-30ml/min) and serum bicarbonate of 16-20 mEq/L to either sodium bicarbonate (goal >23 mEq/L bicarb) or usual care. The bicarb group had a slower decline of kidney function and number of patient advancing to ESRD over the 2 year study. Two other studies have shown similar results with alkali treatment.

Its clear that treating metabolic acidosis in CKD has grown in popularity and data is coming in to back up this treatment strategy. Most exciting is the data showing a slower loss of kidney function with successful correction of acidosis. Some physicians have expressed concerns regarding the sodium load that accompanies the use of bicarbonate but this concern is unjustified since evidence suggest that the kidneys handle NaCl in a different way then how NaHCO3 is handled and therefore the use of NaHCO3 does not lead to as much hypertension or ECF volume overload as NaCl. This makes bicarb in CKD a threat to go the distance in NephMadness. However, the studies are quite small and more data is needed before we can call them a contender of the whole tournament.

Bicarbonate in Acute Metabolic Acidosis

The use of bicarbonate in the setting of high anion gap acidosis is fraught with issues.

Lets begin with lactic acidosis. First, you have to realize that lactate is a metabolizable organic anion that when oxidized will generate bicarbonate. Remember Lactated Ringers solution? Well, same deal here. If the insult, such as tissue ischemia, is corrected then the generated lactate will be oxidized to form bicarbonate. So, if the underlying pathologic process is abated then the acidosis will generally resolve. Two randomized trials have been performed that fail to show a

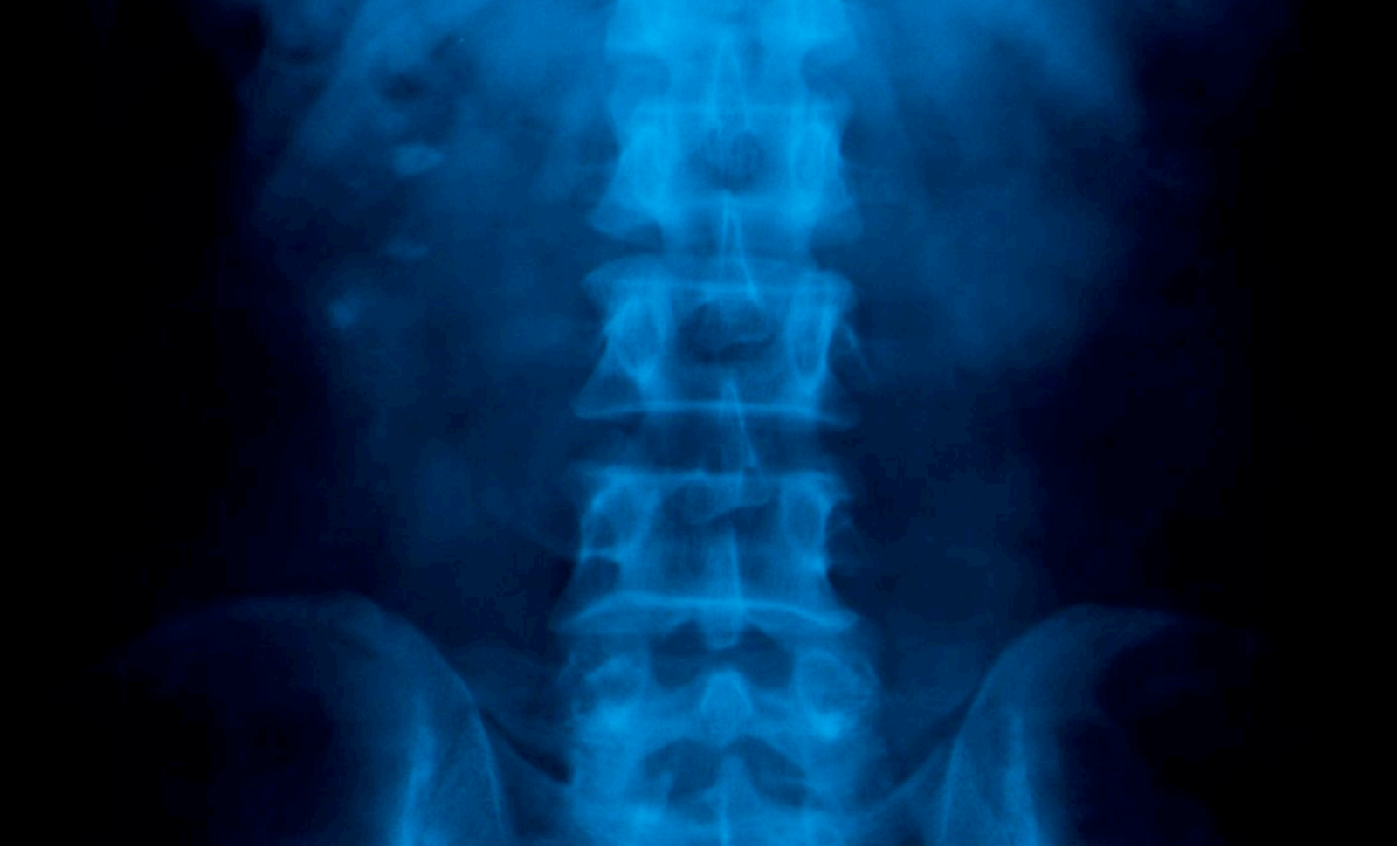
benefit of using bicarbonate in patients with lactic acidosis and a serum pH of >7.1. However, most would recommend (without much evidence) giving sodium bicarbonate when the serum pH drops below 7.1. The concern is that rapid infusion of sodium bicarbonate may increase the pCO2, accelerate the production of lactate, lower the ionized calcium, expand the extracellular space and raise the sodium concentration. For these reasons it is important to ensure that the patient is adequately ventilated before giving IV sodium bicarbonate in patients with severe lactic acidosis.

What about sodium bicarbonate for diabetic ketoacidosis? Several concerns should be noted before giving bicarb in this situation. First, giving an alkali can lead to a rise in pCO2 just as discussed prior. This can result in a paradoxical fall in cerebral pH as CO2 can cross the blood brain barrier leading to neurological deterioration. Second, the addition of an alkali such as bicarbonate may actually slow the rate of recovery of the underlying ketosis possible by augmenting hepatic ketogenesis. Lastly, overzealous alkali administration can lead to post treatment metabolic alkalosis, since the metabolism of ketoacid anions with insulin will result in the generation of bicarbonate and spontaneous correction of the metabolic acidosis. However, some have recommended to give bicarbonate when the arterial pH dips below 7.0 or if severe life-threatening hyperkalemia is present. It must be recognized that there is no significant evidence that supports the use of sodium bicarbonate in the treatment of hyperkalemia. Bicarbonate administration failed to decrease serum K after 1 h and bicarbonate infusion over 4-6h was found to mildly decrease serum potassium in a study. The mechanism of reduction of serum K+ is likely due to increasing distal Na+ delivery and not due to the classic mechanism of H+/K+ exchange. Actually the traditional use of an ampule of hypertonic sodium bicarbonate in the setting of acute hyperkalemia can exacerbate hyperkalemia by causing hypertonicity and driving potassium out of cells by a solvent drag mechanism.

What about a situation where sodium bicarbonate/or another alkali is appropriate in anion gap acidosis? The administration of sodium bicarbonate in the setting of metabolic acidosis in suspected methanol or ethylene glycol intoxication can help in limiting the end-organ accumulation of toxic acids such as formic acid. Then it works by converting the toxic acids to the anion state (formate), which is unable to diffuse across the cell membrane and can be easily excreted in the urine.

This will be an interesting matchup as bicarb in anion gap acidosis is limited its use only in extreme situations (severely acidotic or after toxic ingestion). Whereas, bicarb in CKD can be used at milder forms of acidemia.

-Written and Edited by Matt Sparks, Paul Phelan and Helbert Rondon



Kidney Stones

Trying to choose the winner of this bracket is like finding yourself between a rock and a hard place! So many strong teams that precipitate intense emotions from the fans. This bracket sports the sensational matchup in the first round of two stone legends: Pak vs Coe, the Bird vs Magic rivals of nephrolithiasis. In addition, the controversial role of internists vs surgeons in treating stone disease will crystallize in an exciting first round game. Fans will find that it is going to be a painful, colicky passage through each round eliminating quality opponents until the champion is either passed spontaneously, dissolved or basketed.

Selection committee member for the Kidney Stones Bracket:

David S. Goldfarb, MD
Professor, Chief of Nephrology at NY Harbor VA Medical Center
Clinical Chief of Nephrology, Department of Medicine and Neuroscience and Physiology, New York University Langone Medical Center

Dr. Goldfarb is the 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. He has a long-standing interest in kidney stone pathophysiology. His group established a registry of patients with cystinuria. The goal of this registry is to follow patients with cystinuria and learn more about the course of this disorder. He also is involved in new drug development for the treatment of cystinuria. The consortium also studies Dent disease, primary hyperoxaluria and APRT deficiency (a cause of dihydroxyadenine stones). Dr. Goldfarb is the associate editor of the Clinical Journal of the American Society of Nephrology (CJASN) and the founding editor of CJASN‘s eJournal Club.

MEET THE COMPETITORS FOR THE KIDNEY STONES BRACKET

(8) Medical Care versus (1) Surgical Care of Acute Stones

Medical Care of Acute Stones

Medical therapy for acute kidney stones is Tommy Amaker's Harvard basketball team, a group of scrappy players that just may be giant slayers. Patients with acute nephrolithiasis often are referred to the ER or urology. Some would argue that the nephrologist really has no role in the management of acute stones but should just stay on the sidelines until the acute process has run its course and then focus on preventing the next stone. Medical expulsive therapy run 180 degrees from that view. MET allows nephrologists to stay in the game with an acute stone and provide evidence-based and compassionate care to patients during an acute stone episode.

This may or may not be Preminger's research team
Photo by Adam Glanzman (CC2.0)

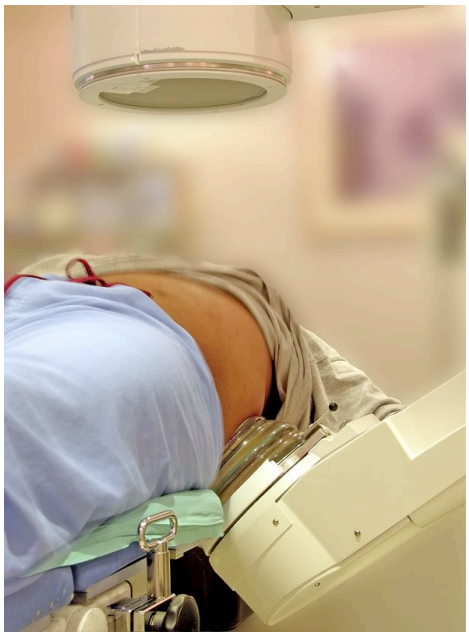
One of the foundations for medical therapy has been inducing a brisk diuresis with IVF fluids. However in 2006 Preminger's crew at Duke randomized patients with acute nephrolithiasis to maintenance fluids or 2 liters of normal saline. The result? No difference in pain, need for surgical removal, or AKI. Their results were confirmed by a subsequent Cochrane review.

One of the primary concerns of MET is pain control. Opioids and NSAIDs both can be used. In a single center RCT, the combination of ketorolac and morphine was better than either drug alone. NSAIDs may have an additional benefit by reducing ureteral edema than can impede stone expulsion.

Additional agents include alpha blockers (tamulosin, doxazosin) and calcium channel blockers (typically nifedipine) which are both effective at increasing the success and reducing the time until the stone is cleared. In a meta-analysis of 9 studies (693 patients) use of these drugs had a number-needed-to-treat of only 4 to get an additional stone expulsive. In addition, steroids may have a role, either alone, or more commonly in conjunction with one of the above agents. The steroids, may have act just like to NSAIDs to reduce the edema and ease stone passage.

Surgical Care for Acute Stones

Surgical care rides in to the Tournament with a Number 1 seed because when it comes to stones they can handle all comers. While medical expulsive therapy (MET) has the potential to reduce costs and avoid instrumentation it has many cases where it is contraindicated. No MET with hydronephrosis. Any hint of pyelonephritis? No MET for you. No MET with stones greater than 10 mm. ARF? Skip the MET. Pain unable to be controlled with elephantine-dose of morphine? Call the surgeons. Stone not moving weeks after diagnosis let introduce you to my little friend...



All of those contraindications to medical therapy melt away when the surgeon comes to play.

Two procedures are generally used for acute stone management: extracorporeal shock wave lithotripsy (SWL) and endoscopic retrieval with ureteroscopy. A meta analysis of 1200 patients showed superior stone free rate with the scope and a second meta analysis looking at cost effectiveness concurred that ureteroscopy was more effective and tended to be cheaper than SWL. What is shocking was just how expensive these therapies. The price from the three American studies:

	Shock wave therapy	Ureteroscope
Wolf et al J Endourol. 1995;9:243.	$11,138/patient	$9,173/patient
Lotan et al J Urol. 2002;167:1621.	$6,039–$6,421/patient	$3,711–$4,455/patient
Parker et al Urology. 2004;64:1102.	$20,762/patient	$12,495/patient

Data from Matlaga et al.

One of the factors that drove the price of SWL up was the relatively high rate of retreatment due to failure, 21% in SWL versus 3% with a ureteroscope. In addition to price, ureteroscopy is better in obese patients where SWL is less effective and in patients with bleeding risk due to the risk of liver or spleen bleeding with SWL.

(6) Xanthine oxidase inhibitors versus (3) The CT Scan

Xanthine oxidase inhibitors

The xanthine oxidase inhibitors (XOI) have had an up-and-down season. They have had some big wins and then they stumble against some unranked basement dweller, think UNC (beat Duke, Louisville, Kentucky, lost to Belmont, Miami and Wake Forest). It'll be interesting if they can pull it all together in the tournament and make a run.

XOIs won the big dance in 1986 when Bruce Ettinger showed that if patients with a history of calcium stones and hyperuricosuria received 300 mg of allopurinol daily, they had less stone recurrence than with placebo.

One of the concerns with allopurinol is interstitial nephritis and some have reported increased risk with concurrent use of thiazide diuretics. Given the common role of thiazides in stone disease, this may hold back use of allopurinol. Additionally many patients get under dosed. The maximum dose of allopurinol is 800 mg daily; however, many patients with CKD never get over the starting dose of 100 mg daily.

Another setback to xanthine oxidase inhibitors was Curhan's epidemiologic work that showed that, contrary to expectations, increased urinary uric acid decreased stone risk rather than increase it. This result opens the door to the possibility that the reduction in stone recurrence seen with allopurinol in Ettinger's study was due not to allopuriniol's xanthine oxidase inhibition but some other pleiotropic effect.

That becomes more important now that there is a second xanthine oxidase inhibitor, febuxostat. Febuxostat is metabolized in the liver so it may be safer in renal failure. In a 2013 study, febuxostat was more effective at lowering urine uric acid than placebo or allopurinol (though allopurinol was hobbled at only 300 mg daily versus febuxostat, which was turned to eleven, at 80 mg per day). The study was only 6 months long and was unable to show a change in stone recurrence or existing stone size. Longer follow up is needed to show that drops in urine uric acid translates to stone recurrence.

CT Scans

The CT Scan is rolling into the tournament like Syracuse. After a near perfect year they are stumbling, and stumbling hard at the finish. CT scans are the gold standard for assessing patients with renal colic. It is a near-perfect test with exemplary sensitivity, specificity, and accuracy. This has resulted in an explosion of CT scans with 68 million CT scans a year done in the US (for a country of 320 million people that is 1 in 5 Americans getting a CT scan every year!). The hunt for kidney stones employ two of the most used CT scans, both an abdominal and a pelvic scan. Some feel that we are seeing a bump in national cancer rates from our love of radiology.

Ferrandino et al looked at radiation exposure in patients with an acute stone presentation at two academic centers. Patients received on average 4 radiologic examinations in the year following diagnosis:

- 1.2 kidney, ureter bladder x-ray (KUB)
- 1.7 abdominopelvic CT scans
- 1 intravenous pyelogram

This resulted in a mean of 29.7 mSv of radiation exposure. Survivors of Hiroshima and Nagasaki received an average of 40 mSv. The International Commission on Radiation Protection has set recommendations indicating that occupational exposure should not exceed 20 mSv per year during a 5-year period or 50 mSv in any single year. In Ferrandino's cohort,

20% of the patients exceeded the 50 mSv threshold. Fahmy et al got similar results. It is possible we are doing more harm than good with CT imaging of kidney stones.

We need to empower our patients to opt out of routine imaging of kidney stones. An important part of the care of recurrent stone formers is teaching them to refuse a CT scan when everyone knows the diagnosis. Combining ultrasound with a KUB, while not as sensitive or specific as a CT scan, does do a pretty good job of picking up clinically significant stones.

The most important advance is the development of low dose CT scan options for the diagnosis and characterization of kidney stones. Because calcium stones are high contrast targets, decreased radiation can be used without intolerable loss of quality. Ciaschini was able to reduce radiation by 50-75%, Poletti was able to use a low dose CT scanner with great success, but in patients with a BMI over 30 sensitivity, fell to 50% for the detection of ureteral stones.

Radiology is allowing us to reliably and quickly diagnose kidney stones; however, this comes at a price that may be too high for our patients. Thoughtful consideration can dramatically lower radiation exposure.

(5) Dr. Charlie Pak versus (4) Dr. Fred Coe

Charlie Pak and Fred Coe are the Bob Knight and Dean Smith of kidney stones. Not only did they dominate the field and do the pioneering work establishing the fundamental discoveries of the field, but they also trained the next generation of stone scientists that are currently leading the field.

Bob Knight with, then player, Mike Krzyzewski. Photo credit: Wikipedia.

To this day the centers where Pak and Coe worked are world leaders in the field. In a plot twist, that would most likely happen in a comic book origin story, they were classmates at the University of Chicago Medical School, class of '61, and then were residents together at U of C.

Dr. Coe remained at University of Chicago but Pak went elsewhere to established the Clinical Research Center and a new Division in Mineral Metabolism at University of Texas Southwestern Medical Center at Dallas.

They even jointly won the Belding Scribner Award from the ASN in 2000.

> *The Belding H. Scriber Award is presented annually to one or more individuals who have made outstanding contributions that have a direct impact on the care of patients with renal disorders or have substantially changed the clinical practice of nephrology. Established in 1995, this award honors the physician who developed the arteriovenous shunt that first made long term hemodialysis for chronic renal failure possible.*

Intellectually they have staked out differing areas of excellence, Dr. Coe has focused on the the importance of the earliest stones to be anchored to the kidney. The location for these tiny early stones is Randall's Plaques. The theory is that these tiny crystals form in the interstitium adjacent to the thin limb of the loop of Henle, they grow and eventually erode into the renal papilla. There, they are in contact with supersaturated urine which can deposit calcium oxalate (or other other

types of stones?). The plaques can be seen on cystoscopy and their presence predicts stone formers. Stone formation correlates with the degree of plaque coverage.

Dr. Pak has performed much of the groundbreaking work on the classification of kidney stones and using that classification in defining the specific diagnosis and using that to provide specific therapy.

His work on the treatment of kidney stones established potassium citrate as the cornerstone of calcium stone treatment.

He established the categorization of hypercalciuria:

- increased intestinal absorption
- increased bone resorption
- increased renal losses

However this classification of hypercalciuria is not in clinical use because:

1. treatment based on classification was never shown to lead to better outcomes
2. patients on low calcium intake continued to have negative calcium balance
3. patients with hyperabsorption had low BMD
4. thiazides appear to work regardless of the classification.

His classification may have applicability to research but it has not found a validated clinical role.

Following his success with potassium citrate, he was asked by the FDA to lead the team that established Thiola for cystine stones.

He also did pioneering work on the use of the 24-hour urine to categorize and track the treatment of kidney stones.

(2) Oxalobacter vs (7) Bariatric Surgery and the Risk of Stones

Oxalobacter

Oxalobacter is Kentucky. It is a fresh new face in the world of stones and has the potential to rewrite our understanding of the field, but so far the results have been inconsistent leaving you with the feeling that this is more hype than revolution.

Oxalobacter formigenes are anaerobic gut bacteria that metabolize oxalate, the critical urinary metabolite in calcium oxalate stones. If you are colonized with these bacteria, you absorb less oxalate than someone with a similar diet who is not colonized with oxalobacter. People colonized with oxalobacter can plow through cans of spinach like Popeye on a bender and their urinary oxalate doesn't budge. Siener et al found a tight dose response, such that patients with stone recurrence are much less likely to be colonized with Oxalobacter and the relationship becomes tighter and tighter as the number of stone episodes rises. Unfortunately, attempts to seed stone formers with oxalobacter have not shown consistent benefit.

Regardless, if oxalobacter probiotics become the new Uro-citK, the appreciation of oxalobacter's role in nephrolithiasis opens up microbiome as an important player in the physiology of kidney stones. That is a game changer.

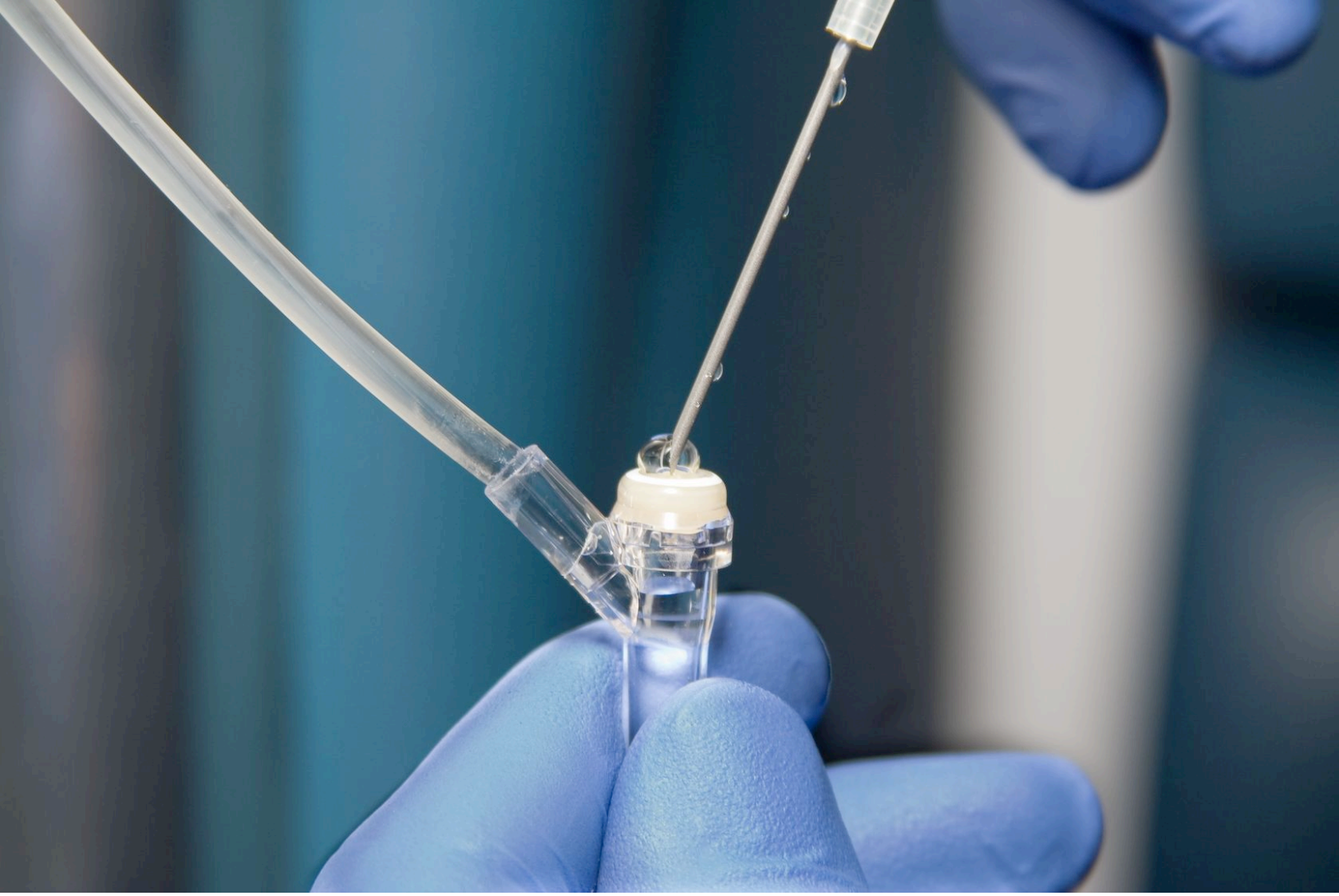
Bariatric surgery

Bariatric surgery has been riding high since it destroyed Medical Therapy in 2012's unforgetable EndoMadness Finals. Both Roux-en-Y and gastric sleeve were way more effective at reducing glycated hemoglobin below 6% (42% Roux-en-Y, 37% gastric sleeve, 12% medical therapy). But the bariatric surgery team may be a bit out of place in NephMadness. Bariatric surgery finds itself in the stone region because it doubles the risk of kidney stones.

This is due to multiple factors such as decreased water intake, hypocitraturia and increased oxalate absorption. Interestingly, some believe that decreased oxalobacter colonization may be the cause of the increased oxalate in the urine. Not all weight loss surgeries are created equal and the Roux-en-Y is the primary culprit here. In one series of non stone formers who underwent Roux-en-Y, urinary oxalate went up by 50% while protective urinary citrate fell by more than half (358 mg v 767 mg/24 hours). Interestingly urinary calcium also fell after Roux-en-Y, negating some of the stone forming effects of the citrate and oxalate. In a study comparing Roux-en-Y to gastric banding, both procedures resulted in low urine volumes, but the gastric band did not have the decrease in citrate or increase in oxalate. Unfortunately, Roux-en-Y remains the most popular procedure, though it is falling in popularity at the expense of sleeve gastrectomy.

One of the most concerning aspects of this problem is the shadow of the jejunoileal bypass procedure. This procedure also has a high rate of kidney stones, upwards of 30%, but more concerning was the high rate that patients developed CKD following the bypass. Some cases of oxalate nephropathy resulting in ESRD have been reported after Roux-en-Y for weight loss.

- Written and Edited by Joel Topf and David Goldfarb



Biologics

This state of the art section would not have existed 5 years ago. Replete with FDA approved and FDA not approved, humanized, synthetic or chimeric, monoclonal, polyclonal or fusion antibodies or receptors this group represents an immunologic cornucopia and a semantic and enuciating challenge. Spanning subcutaneous and intravenous routes, these agents run the gamut from the most expensive drug in the world, Eculizumab (more than the price of a 2014 fully loaded Lamborghini Aventador), to a still-in-research-phase but recently patented soluble CR1 receptor. The future of medicine is here in this bracket and one of these teams may very well bind their way to the final four.

Selection committee member for the Biologic Therapies Bracket:

Jonathan Hogan, MD **Assistant Professor of Medicine** **Associate Program Director of the Fellowship Training Program** **Division of Nephrology, Columbia University Medical Center**	Dr. Hogan received his medical school and residency education at the University of Pennsylvania. He completed a fellowship in nephrology at Columbia University Medical Center, followed a Fellowship in Glomerular Diseases under the mentorship of Dr. Gerald Appel at the Glomerular Disease Center at Columbia University. His clinical interests are in the understanding and treatment of glomerular diseases in native and transplanted kidneys. He has written multiple peer-reviewed review articles and book chapters in this field, and is involved in multiple clinical studies in the treatment of glomerular disease.

MEET THE COMPETITORS FOR THE BIOLOGICS BRACKET

(1) Rituximab versus (8) Bortezemib

Rituximab

B cell depletion with the chimeric anti-CD20 monoclonal antibody rituximab is continuing to attract attention in kidney diseases such as systemic lupus erythematosus, vasculitis, and primary glomerulonephritis. Rituximab is probably the most versatile team in NephMadness 2014. Rituximab has been studied and used in multiple disciplines successfully. However, many of its uses are off label and very few instances exists in which rituximab is a first-line agent. However, some uncontrolled data have even demonstrated high response rates in treatment-refractory states. However, it is important to understand that rituximab is associated with toxicity and unique infections, and most importantly the optimal dosing of rituximab in renal disease requires careful attention. The nephrology world has seen the use of this agent beyond glomerular disease, such as antibody mediated rejection (AMR) in kidney transplantation and for desensitization procedure for transplant patients for removal of prior HLA antibodies. The three glomerular diseases that have been studied the most with rituximab are ANCA-associated vasculitis (AAV), idiopathic membranous nephropathy (iMN), and lupus nephritis. Let's dig a little deeper into the literature.

While many single-center trials first demonstrated that rituximab may have a role in the treatment of AAV, the RAVE and RITUXIVAS trials are the two RCTs that really deserve significant mention. RAVE demonstrated that in patients with severe ANCA-associated vasculitis, rituximab therapy was not inferior to daily oral cyclophosphamide treatment (with both groups receiving steroids) for induction of remission, and may be superior in relapsing disease. The recently published RAVE follow-up demonstrated that a single course of rituximab was as effective as continuous conventional immunosuppressive therapy with oral cyclophosphamide followed by azathioprine for maintaining remissions over the course of 18 months. RITUXIVAS showed that rituximab-based regimen was not superior to standard intravenous cyclophosphamide for severe AAV with renal involvement. Although remission rates were high in both groups, the rituximab-based regimen was not associated with reductions in early severe adverse events. These studies have helped to at least give some traction for the use of anti-B cell therapy in ANCA vasculitis.

Now lets take a look at lupus nephritis. Rituximab has been shown (in uncontrolled case series) to be effective in refractory lupus nephritis. However, in the landmark 2012 LUNAR trial, while rituximab add-on therapy led to more responders and greater reductions in anti-dsDNA and C3/C4 levels compared to placebo, it did not improve clinical outcomes after 1-year of treatment. Similar to the AAV story, the matchup against classic lupus nephritis treatment was a draw to say the least.

With regard to IMN, rituximab is an exciting potential therapy. The mechanism of action of rituximab could be more specific than conventional cytotoxic therapy. This is because rituximab could potentially remove the deleterious B cells that produce the implicated anti-PLA2R antibody. However, it may be more advantageous to target the antibody-producing powerhouse plasma cells. A recent review published in CJASN evaluated all studies using rituximab in iMN (n=21). All of these studies were uncontrolled case reports or case series, and more than half of the published cases (50 of 85 cases) came from a single center where rituximab was used as primary immunosuppressive therapy for iMN. The results of ongoing RCTs will help to determine the role of rituximab in treating iMN.

Rituximab has a lot of name recognition and hype but so far hasn't established a real track record in RCTs in nephrology with the exception of ANCA-vasculitis. For these reasons rituximab will have to overachieve to make it far in this year's NephMadness tournament.

Bortezomib

Bortezomib is an anti-myeloma agent that has recently entered the nephrology world via its use in kidney transplantation. Bortezomib is a proteosome inhibitor and has anti-plasma cell (antibody-producing cell) activity. In severe cases of antibody-mediated rejection that are potentially mediated by plasma cells, this agent has shown promise with good remission rates. What about other glomerular diseases? A recent case report demonstrated success of treatment with bortezomib in idiopathic membranous GN. Proteosome proteolysis is crucial for the degradation of the inhibitory protein (IkB) of nuclear factor kB (NF-kB), and hence, an interesting field of research has been developed with drugs having anti-proteasome activity, particularly in diseases with hyper-expression of NF-kB. Proteosome inhibitors are being adopted in pilot studies in antibody-mediated rejection and in AL amyloidosis. Other possible applications of bortezomib are in lupus, IgA nephropathy, idiopathic nephrotic syndrome and renal fibrosis. A basic science model of lupus nephritis showed attenuated kidney disease using bortezomib and there is an ongoing clinical trial in the use of this agent in proliferative lupus nephritis. Furthermore, a study is underway utilizing bortezomib in IgA nephropathy.

Bortezomib is a true star in the myeloma world. How will all of this success translate into the kidney realm? This will be a true test for bortezomib. If they can break through and provide a needed therapy for many kidney disease this will be a huge welcome to nephrologists and patients alike. Like many in this bracket, this is an upstart with talent and potential.

(3) Belimumab versus (6) Belatacept

Belimumab

Belimumab is a human monoclonal antibody that inhibits the B cell activating factor (BAFF). Belimumab has been approved for the use in systemic lupus. These drugs prevent B cell proliferation and hinder development into mature plasma cells with a resulting drop in antibody production. This mechanism of action is very well-suited to lupus whose pathophysiology is thought to involve autoantibody formation. The approval of belimumab was based on a 52-week study known as BLISS-52 trial published in Lancet in 2011. BLISS-52 enrolled 865 patients in 13 countries outside North America and randomized active lupus patients to 10mg/kg belimumab, 1 mg/kg belimumab, or placebo in addition to their standard lupus medications. Belimumab was administered IV 2 weeks apart for the first 2 doses, and then every 4 weeks. The study met primary endpoint and the response rates were 57.6%, 51.7% and 43.6% for belimumab 10 mg/kg, 1 mg/kg, and placebo, respectively. In addition to improvement in various clinical measurements of disease activity, patients were also able to reduce steroid dosages. Notably, the drug was well-tolerated and the safety profile, including the infection rate, was comparable to the placebo arm. What about patients with kidney disease and lupus? A post hoc analysis of the BLISS-52 trial showed that many indices of kidney involvement and serologic activity favored the belimumab. However, the differences seen between groups in a majority of kidney outcomes were not statistically significant. Among the 267 patients with CKD at baseline, those receiving mycophenolate mofetil or with serologic activity at baseline had greater improvement of kidney indices with belimumab. This suggests that there might be some kidney benefit with this agent but we have to keep in mind that severe lupus nephritis patients were excluded from the trial.

Belimumab has only made progress in lupus thus far. But again this is a biologic that has tremendous potential. I'm looking forward to the first round matchup with the belatacept.

Belatacept

Belatacept is a costimulatory blockade related antibody (CTLA-4 inhibitor). The BENEFIT trial published in the American Journal of Transplantation in 2010 put belatacept on the map. This trials aim was reducing the kidney damage commonly ascribed to calcineurin inhibitor toxicity in kidney transplant patients. Besides acute rejection rates early on, long-term kidney survival was significantly improved in the belatacept group than than calcineurin inhibitor group. The

BENEFIT-EXT trial that followed showed that extended criteria kidney transplant recipients treated with belatacept achieved similar patient/graft survival, better kidney function, had an increased incidence of post transplant lymphoproliferative disorder, and exhibited improvement in the cardiovascular/metabolic risk profile versus cyclosporine-treated patients. At 3 years, immunosuppression with belatacept resulted in similar patient survival, graft survival and acute rejection, with better renal function compared with cyclosporine.

Belatacept has emerged as a true player in the kidney transplant arena. Calcineurin inhibitors are staples that help prevent rejection but unfortunately ravage the kidney. The use of this drug could really extend the life of the transplanted kidney. However, administration issues and cost make belatacept a difficult sell to the masses. Belatacept has great potential to go far in NephMadness 2014. The large clinical trials have been performed and now we as a nephrology community need to see where this drug fits into the transplant repertoire of drugs.

(5) Eculizumab vs. (4) Soluble CR1

Eculizumab

Eculizumab is a recombinant humanized monoclonal antibody against C5 in the terminal complement cascade. It is FDA-approved for use in two disorders of the alternative complement system, paroxysmal nocturnal hemoglobuinuria (PNH) and atypical hemolytic uremic syndrome (aHUS). Similarly, in glomerular disease, interest in eculizumab lies in the treatment of the C3 glomerulopathies (C3 GN and dense deposit disease), a recently discovered group of disorders of the alternative complement pathway that result in C3 deposition on immunofluorescence and often times to a MPGN pattern on light microscopy. The largest published experience of eculizumab use in the C3 glomeruopathies was a case series of 6 patients (3 with C3 GN, 3 with DDD), three of whom had improvement in clinical parameters (serum creatinine or proteinuria), and in many cases, the soluble membrane attack complex (sMAC) level improved with therapy. The identification of patient-specific defects in the alternative complement pathway may help to determine which patients may benefit from this therapy.

Soluble CR1

Complement receptor-1 (CR1) inhibits both C3 and C5 convertases of the classical and alternative complement cascade. It has been shown that recombinant soluble CR1 (sCR1) effectively blocks complement activation in vitro and in vivo. Therefore, it has been postulated that sCR1 may be a useful treatment in patients with a dysregulated complement activation such as in dense deposit disease. sCR1 acts by targeting C3 convertase and thus would affect the alternative complement cascade more proximally than eculizumab and possibly preventing the deposition of C3 in glomeruli and halt disease progression. A recent paper in the JCI showed that aCR1 was capable of restoring complement function in 2 patients with mutations in the complement factor H-related (CFHR) gene cluster. sCR1 was found to stop activation of the alternative complement pathway in one patient with dense deposit disease and ESRD. A basic science study utilizing soluble CR1 during cardiopulmonary bypass showed some promise in reducing complement activation and subsequent organ damage. Its utility in affecting clinical disease will depend on further study. Soluble CR1 is truly a diaper dandy of the group. This is almost completely untested but we are in desperate need of novel therapy that target the complement cascade.

(7) ACTHar gel vs. (2) Abatacept

Abatacept

Just like belatacept in kidney transplantation, abatacept is an inhibitor of co-stimulatory molecule CD80 (a.k.a. B7-1) in T-cell signaling. It has been approved for use in RA for patients that fail TNF alpha inhibition. In a NEJM case series recently, the authors described six cases and how this agent helped improve proteinuria. Taking a step further, they found

that post-transplant, not all proteinuric FSGS stained for B7-1 in the kidney biopsy. They only treated the B7-1 positive FSGS strain with this agent to show response. A table in the NEJM paper shows the 5 patient characteristics. Four patients were post-transplant FSGS and had failed rituximab. Two of the four responded to just one dose of 10 mg/kg of abatacept and the two remaining needed 2 doses of 10 mg/kg. This is remarkable that just few doses put the disease in remission. They had 36-48 follow up data on all of them and still in remission. The patient 5 was a nontransplanted primary FSGS case which was B7 positive and also responded to this agent but required monthly dosages for a year. Given transplant patients are on other agents that target the immune system, one dose might be sufficient compared to native FSGS. In addition, there is some interest in the role of this agent in lupus nephritis and diabetic nephropathy.

ACTHar gel

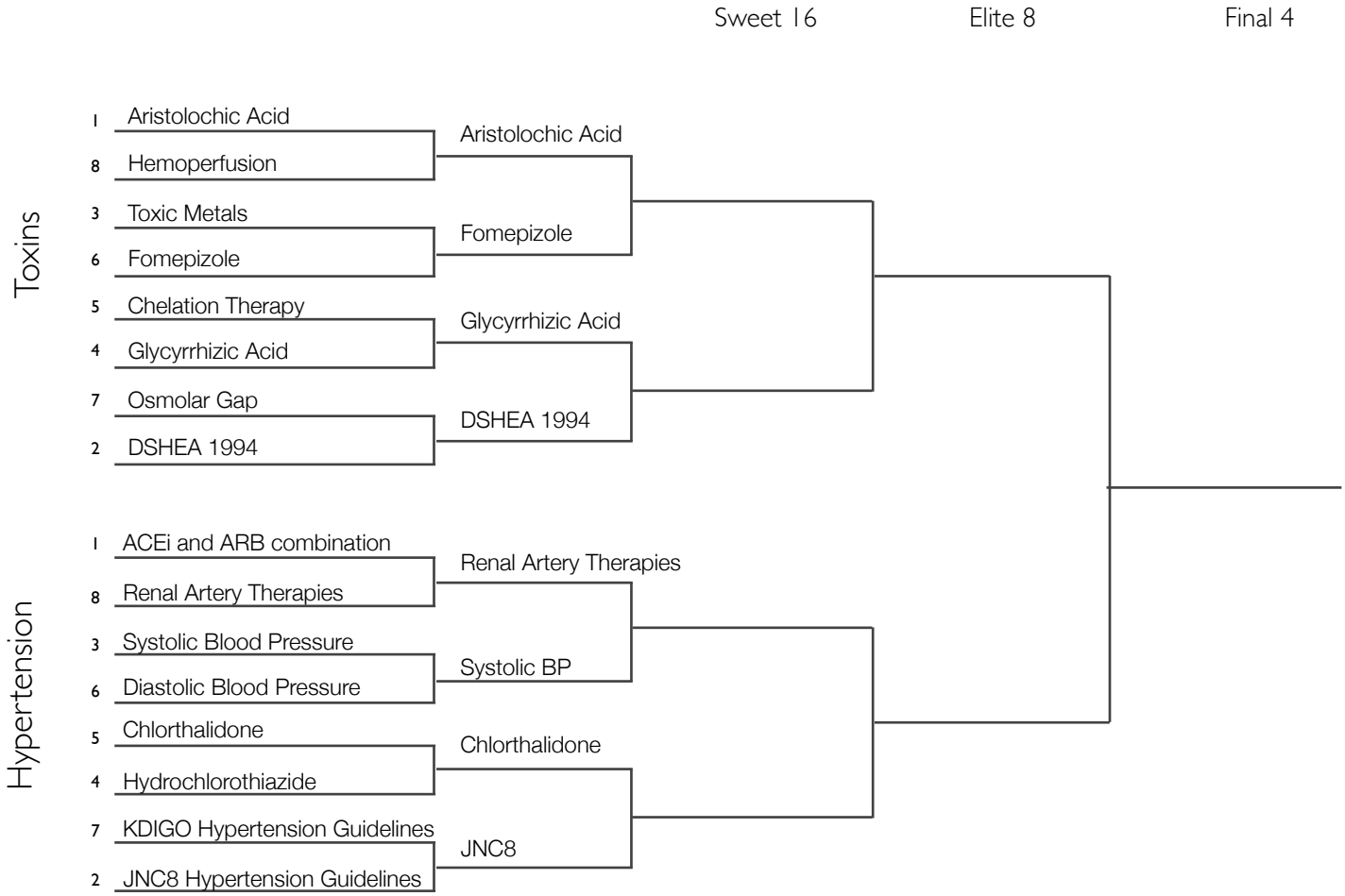
ACTHar gel is a 39-amino acid peptide form of the naturally occuring adrenocorticotropic hormone (ACTH). ACTHar gel works by stimulating the adrenal cortex to secrete cortisol, corticosterone and aldosterone. ACTHar gel was popularized in the 1960s for the treatment of a variety of conditions (in fact, 19 FDA-approved indications exist!). ACTHar gel was initially approved by the FDA in 1950 and, similar to other corticosteroids, is indicated for numerous autoimmune, allergic and inflammatory conditions in adults. Believe it or not, ACTHar gel is the only FDA approved "treatment" for nephrotic syndrome. Here is the exact indication from the FDA:

"Inducing a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus."

Currently, it has re-emerged since 2009 as a potential treatment for refractory proteinuric diseases. In a small prospective trial that included patients with idiopathic membranous nephropathy and minimal change disease, ACTHar gel showed promise in inducing remission of proteinuria in refractory disease. Prior to that, the landmark paper by Bomback et al showed that in 21 patients with nephrotic syndrome of various etiologies, that ACTHar gel was capable of achieving remission. However, this was an uncontrolled study. Pontecelli performed a vigorous RCT with synthetic ACTH in membranous nephropathy in 2006 pitting ACTHar gel against his own Pontecelli regimen and found ACTHar gel to be non inferior. What about its use in FSGS? The largest experience is a recent case series of mostly steroid-resistant and steroid-dependent patients. This suds showed that 29% of patients experienced a remission with ACTHar gel therapy. However, given its significant cost ($28,000 a vial) and high frequency of steroid-like side effects, more data is needed to determine the role that syntheic ACTH will play in the treatment of FSGS or other glomerular diseases. A search query in clinical trials suggest ongoing or completed trials in use of this agent in lupus nephritis, diabetic nephropathy and resistant nephrotic syndrome. ACTHar gel is an interesting opponent. They have FDA approval for a condition that is hard to earn. This is mainly because this indication was earned before rigorous randomized trials and safety data were required for such approval. That being said. ACTHar gel is gaining popularity in a world where case reports and series still predominate the landscape. ACTHar gel will be a team to watch in NephMadness as clinical trials are only now being performed.

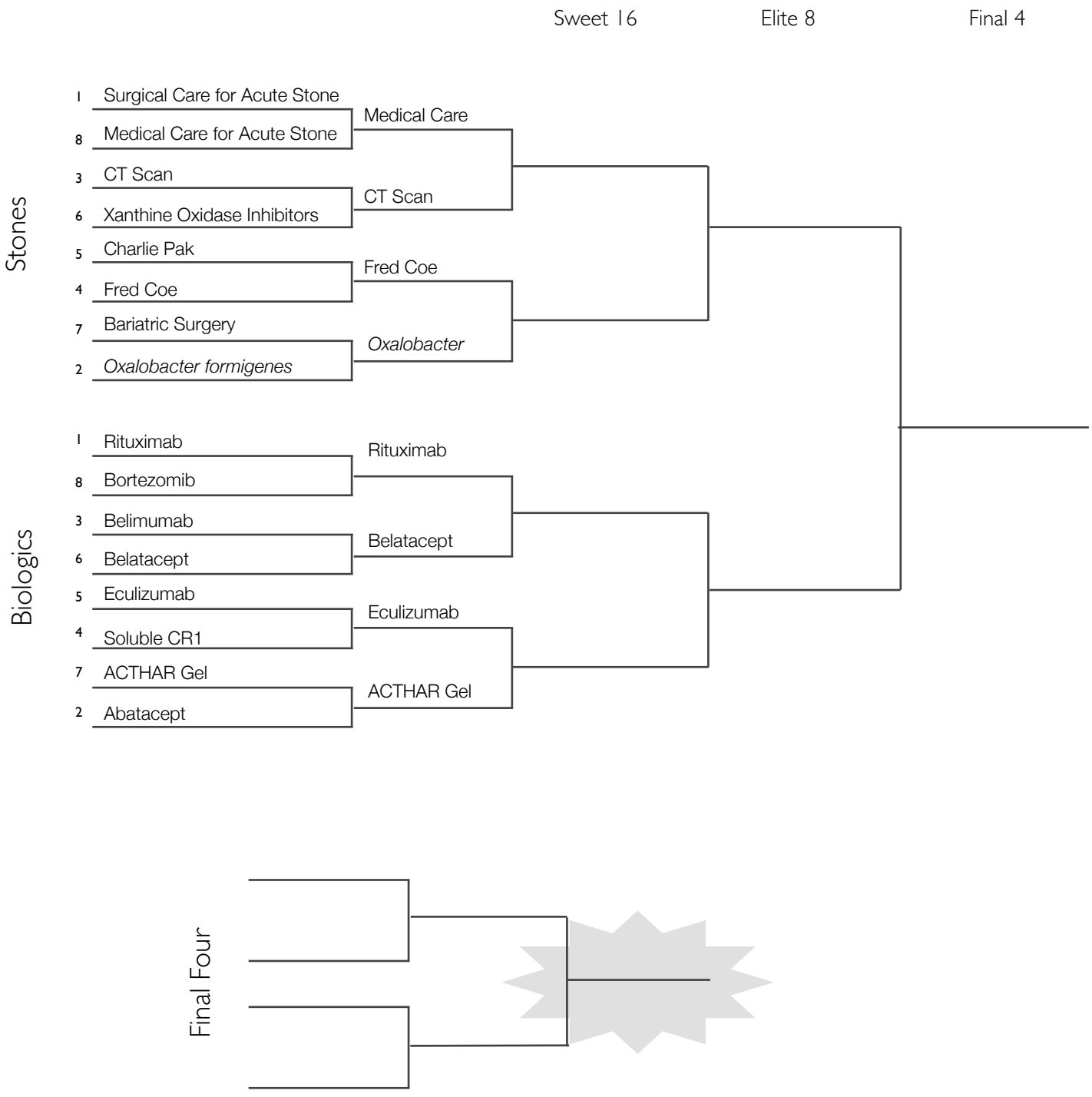
-Written and Edited by Kenar Jhaveri and Jonathan Hogan

Brackets: First Round Results




Sweet 16
Elite 8
Final 4
Renal Replacement Therapy
1 Convective Clearance
8 Diffusive Clearance
Diffusive Clearance
3 Buttonhole Technique
6 Residual Renal Function
RRF
5 Fistula First
4 Urgent Start Peritoneal Dialysis
Urgent Start PD
7 DreamRCT: Intermittent vs CRT
2 DreamRCT: Peritoneal vs Hemo
PD vs Hemo
Regeneration
1 Parietal Epithelial Cells
8 Renin Lineage Cells
Parietal Epithelial Cells
3 Renal Pericytes
6 EMT
Renal Pericytes
5 Tubule Self-Duplication
4 Resident Stem Cells
Tubule Self-Duplication
7 Hypertrophy
2 Bioartificial Kidney
Bioartificial Kidney


Sweet 16
Elite 8
Final 4
AKI
1 Contrast Nephropathy
8 Remote Ischemic Pre-Conditioning
Contrast
3 U/A and Indices
6 Acute Kidney Injury Biomarkers
U/A and Indices
5 Balanced Solutions
4 Normal Saline
Balanced Solutions
7 KDOQI AKI Guidelines
2 KDIGO AKI Guidelines
KDOQI AKI
Electrolytes
1 Hypertonic Saline
8 Vaptans
Hypertonic Saline
3 Serum Anion Gap
6 Urine Anion Gap
Serum Anion Gap
5 ZS-9
4 Kayexalate
ZS-9
7 Bicarb in Chronic Kidney Dis.
2 Bicarb in Acute Met. Acidosis
Bicarb in CKD


Sweet 16
Elite 8
Final 4
Stones
1 Surgical Care for Acute Stone
8 Medical Care for Acute Stone
Medical Care
3 CT Scan
6 Xanthine Oxidase Inhibitors
CT Scan
5 Charlie Pak
4 Fred Coe
Fred Coe
7 Bariatric Surgery
2 Oxalobacter formigenes
Oxalobacter
Biologics
1 Rituximab
8 Bortezomib
Rituximab
3 Belimumab
6 Belatacept
Belatacept
5 Eculizumab
4 Soluble CR1
Eculizumab
7 ACTHAR Gel
2 Abatacept
ACTHAR Gel
Final Four

First Round Results

Toxins

Aristolochic Acid versus Hemoperfusion

Winner: Aristolochic Acid

It was a senior class of alkylation, mutation and profibrogenesis that propelled Aristolochic Acid to a decisive first round victory over Hemoperfusion. Now considered to be one of the leading causes of CKD in China and Taiwan, Aristolochic Acid was completely resistant to all forms of defensive adsorption and binding attempted by Hemoperfusion. Using a new "undeclared" player strategy, Aristolochic Acid secretly put extra toxins on the court without checking in at the referee table and notifying Hemoperfusion. As these toxins were not obvious because they weren't listed on the standard player personnel sheet, Aristolochic acid pummeled Hemoperfusion relentlessly. Hemoperfusion was limited in its availability and became too saturated as the game went on to continue at a continuous high level of play. This new "undeclared" strategy and the direct toxicity of Aristolochic Acid puts them in a formidable position to advance beyond the second round.

Toxic Metals versus Fomepizole

Winner: Fomepizole

This is why the game is played on the court and not on paper! An early favorite to advance, Toxic Metals clearly overlooked the enzymatic potential of their opponent, Fomepizole and were eliminated in the first round. Fomepizole exposed the weakness of Toxic Metals as having a one dimensional offense focusing almost exclusively on the proximal tubule. In contrast Fomepizole demonstrated a wide variety of versatility being able to inhibit the metabolism of multiple alcohols: ethyl alcohol, ethylene glycol, methanol, isopropyl alcohol, and propylene glycol. In addition, toxic metals proved vulnerable to the metallothionein defense which is widely available to all opponents. Fomepizole proved that indeed money can buy the best team and now heads into the second round with momentum and confidence.

Glycyrrhizic Acid versus Chelation Therapy

Winner: Glycyrrhizic Acid

In the most exciting game of the first round, Glycyrrhizic Acid came back from a huge first half deficit to shock Chelation Therapy at the buzzer. From the first tipoff, Chelation Therapy bound their way to a quick lead. EDTA, DMSA and BAL combined to leave nothing "free" on the court and it appeared that Chelation Therapy was poised to cruise into the second round. But then after halftime, as time passed, the avidity of Chelation Therapy began to wane and dissociate. Glycyrrhizic Acid took full advantage of this momentum shift and attacked the Na-K ATPase pump repeatedly. With the game tied and only seconds remaining, Glycyrrhizic Acid called a timeout to map their final play. Inbounding into the

serum, Glycyrrhizic Acid quickly entered the cytoplasm and set up the perfect screen on 11-betahydroxysteroid dehydrogenase completely neutralizing it. This allowed the “backdoor play” to materialize as cortisol came off the bench and rushed untouched straight into the aldosterone receptor and sealed the victory. A true ESPN top 10 play of the day! Glycyrrhizic Acid, the crowd favorite, moves on to inhibit another day in the tournament!

DSHEA versus Osmolar Gap

Winner: DSHEA 1994

As expected, DSHEA 1994 proved that even after 20 years, it remains the most important factor influencing the sale, control, and advertisement of Alternative Medicines in the US. Osmolar Gap put up the best effort it could but it has a complex mathematical formula to remember on calculating serum osmolality and a dependence on the ordering of additional tests: measured serum osmolality made it slow and unable to keep up with DSHEA 1994. In addition, Osmolar Gap proved too nonspecific and a variety of toxic and nontoxic alcohols constantly tricked it. As a last gasp effort, the Osmolar Gap even tried to bring in 2 new players, the FDA and Congress, off the bench but DSHEA 1994 wasn’t deterred at all and continued it’s powerful permissive role in the favor of all the manufacturers of herbal and vitamin supplements. DSHEA 1994 may require the election of a brand new House of Representatives and Congress in order to derail it’s anticipated march into the finals.

Hypertension

Combination RAS inhibition vs Renal artery therapies

Winner: Renal artery therapies

This was a battle of disappointments, RAS inhibition’s season was reeling from ALTITUDE and ONTARGET. The last hope for salvaging the season came with the VA NEPHRON-D study and again, combination therapy dropped the ball. Combo RAS blockade began with the disgraced and retracted COOPERATE trial and closed with the definitive shutter of multiple RCTs. Put a fork in dual RAS inhibition, it is done.

However, this disappointment cannot hold a candle to the grand daddy of disappointments that was renal artery therapies. This package includes two potential all-conference players: a power forward playing renal revascularization and a point guard playing renal sympathetic denervation.

Revascularization is the type of therapy that makes so much intuitive sense that it would be pretty easy to accept without evidence. If atherosclerosis is choking the kidney’s blood supply, opening up the artery with a balloon and stent should preserve renal function and reverse or at least improve renal vascular hypertension. Talk to an old nephrologist for an hour or two and she will tell a story of a patient with progressive renal failure that was saved by a well-timed revascularization or a patient with resistant hypertension that was reversed by a cath cowboy. The rub is that multiple studies have tried and failed to show a consistent benefit from the procedure. Four times RCTs have tried to protocolize who would benefit from revascularization and four times they have failed to show improvement in blood pressure or renal survival:

1. CORAL
2. ASTRAL
3. DRASTIC
4. EMMA

The other half of the renal artery duo is radiofrequency ablation of the renal artery. Blocking sympathetic stimulation of the kidney in order to lower peripheral blood pressure. It worked in two trials but in the pivotal third trial in order to get licensed in the US, it was unable to lower blood pressure. The early work was impressive enough for the procedure to be approved in Europe and get the nephrology community excited for this novel approach. The shock and disappointment when Symplicity-3 was halted secondary to futility was palpable. This Saturday at the American College of Cardiology we will get the first data on the halted Symplicity-3 trial since the press release.

In the end this shock is what turned the tide in favor of renal artery therapies being more important than combination therapy. Renal Artery therapies come from the eighth seed to upset combination RAS inhibition.

Systolic blood pressure versus diastolic blood pressure

Winner: Systolic blood pressure
The selection committee tries to separate in-state rivals, so they don't meet in the opening round but this battle must have slipped through a loop hole.

Systolic blood pressure has long ruled this rivalry. Increases in systolic blood pressure are associated with increased stroke risk and interventions that lower systolic blood pressure reduce strokes. Diastolic pressure is more nuanced, especially among people over the age of 65 where diastolic blood pressure has a U-shaped curve, so that low diastolic blood pressures are associated with cardiovascular events. This u-shaped phenomena is also seen in post MI patients.

It was hard scrapped fight but the linear reduction in CVA with reductions in SBP helped SBP drain a three at the buzzer to avoid overtime and advance to the next round.

Chlorthalidone versus hydrochlorothiazide

Winner: Chlorthalidone
Chlorthalidone and HCTZ used to be single team, in fact in the MRFIT trial patients randomized to the Special Intervention group could be given either diuretic. A few years into the study the investigators noticed a mortality difference based on which thiazide they were given with the advantage tilting towards chlorthalidone.

This difference became more important after the publication and impact of ALLHAT, the largest hypertension trial ever. The supremacy of thiazides as initial management of hypertension was sealed in the publication of JNC7. ALLHAT used chlorthalidone but JNC7 advised use of any thiazide, most of which turned out to be HCTZ.

This choice began to look foolish when in ACCOMPLISH HCTZ plus an ACEi was inferior to amlodipine and an ACEi. Was this finding due to the superiority of the amlodipine or the weakness the specific thiazide used, HCTZ.

The HCTZ versus chlorthalidone debate has spawned an academic industry of authors writing papers examining the difference but for this contest, chlorthalidone takes it.

Blood pressure guidelines: JNC8 versus KDIGO

Winner: JNC8
If you think clinical practice guidelines are a snooze, try to watch the authors of said guidelines play basketball. Pathetic. Neither team could shoot, dribble or pass. The final score was football-like 17 to 14. These codgers better step it up or it will be a short tournament for the winners.

Both teams emerged in the last days of 2013 and have been eating up publicity since publication. The JNC8 is the last guideline to be initiated by the National Heart Lung and Blood Institute, NHLBI (but in a confusing twist, the NHLBI does not endorse these blood pressure guidelines) and it is a doozy. This is massive simplification of blood pressure management. No more splitting hairs for diabetes, or proteinuria. The JNC 8 guidelines are pretty simple, especially in regards to CKD patients:

		KDIGO	JNC8
NON DIABETIC CKD	albuminuria <30 mg/d	>140/>90 (1B)	>140/>90 • E for SBP • A for DBP if over 30 • E for DBP if under 30 ACEi or ARB for all CKD regardless of diabetic or proteinuric status
	albuminuria 30-300 mg/d	>130/>80 (2D) ACEi or ARB (2D)	
	albuminuria >300 mg/d	>130/>80 (2C) ACEi or ARB (1B)	
DIABETIC CKD	albuminuria <30 mg/d	>140/>90 (1B)	
	albuminuria >30-300 mg/d	>130/>80 (2D) ACEi or ARB (2D)	
	albuminuria >300 mg/d	>130/>80 (2C) ACEi or ARB (1B)	

Reading the KDIGO guidelines, one is overwhelmed by the amount of opinion based recommendations. 2C and 2D recs pepper the guidelines. Too often policy makers adopt guidelines with no regard to the strength of the evidence and it is time that guideline authors realize that and try to limit themselves to strong, high quality evidence based recommendations.

This round goes to JNC8.

Renal Replacement Therapy

Convective Clearance versus Diffusive Clearance

Winner: Diffusive clearance

Convective clearance is really interesting and has some tantalizing results but nephrology has been burned too often by big sounding ideas that have come back to bite us. We are still licking our collective wounds from increased eKt/V, normalization of hemoglobin and every angle of mineral bone metabolism. In all of these areas preliminary, low quality data propelled us forward to expensive drugs, changes in procedures and alternative philosophy. In order for us to

rewrite the rules of ESRD, we will need to see clean, repeatable wins in randomized controlled trials. For now convective clearance can't deliver the mail but its time maybe coming.

Residual Renal function versus Buttonhole technique

Winner: Residual renal function

It seems that the time is right for nephrology to start paying attention to the very last few nephrons, even after patients start dialysis. We need to start studying the effect of RRF and the interventions that we can preserve it. RRF feels like it is in his infancy but it also feels like the sort of thing that could turn on a dime and be a critical factor in nephrology.

On the other hand, the buttonhole technique is having an off year. This is still an important technique that will likely have a role in the future of dialysis.

Urgent Start PD versus Fistula First

Winner: Urgent start PD

In the United States we are witnessing the collapse of peritoneal dialysis as a major modality in the US. Urgent start PD is a way to reverse this. PD might be the best way for patients that need to start dialysis urgently.

Fistula first, like buttonhole technique had a bad year. As nephrology tries to become more patient centered, we will need to change from thinking fistula first to patient first and answer the question, what is best for our patient and not blindly follow protocol.

DreamRCT: ESRD versus AKI

Winner: ESRD

Figuring out if PD or HD offer a survival benefit should be a top priority of nephrology. If PD offers worse survival, then initiatives like Urgent start PD starts to look foolish.

DreamRCT AKI has been done on multiple occasions with usually no clear advantage for either modality. We may be getting to the point that we begin to realize that the reason there is no detected difference is that there is no difference.

Regeneration

Parietal epithelial cells versus Renin lineage cells

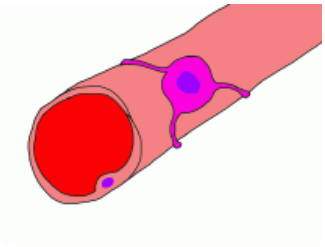
Winner: Parietal epithelial cells

The parietal epithelial cells (PECs) migrate their way to victory over the upstart renin lineage cells. This was an up and down game but the PECs proved dominant and took over this contest in the second half. The youth and inexperience of the renin-lineage cell team proved too much of a hurdle to overcome. The proliferative capacity of the PECs were in full display. The tipping point came with evidence that a subpopulation of proliferative PECs may lead to collapsing FSGS in humans. Renin-lineage cell put up a good fight. Interestingly, evidence of renin-lineage cells becoming PECs has been reported. So, I guess you could say that the renin-lineage cell's top player transferred to the PEC team in order to advance. How PECs function in physiology and disease is still a matter of debate. It is likely that PECs in some instances are good and useful as a progenitor pool to damaged podocytes and other cells. While, in certain circumstances, such

as collapsing FSGS, PECs can actually be harmful. The PECs are now in the kidney spotlight and more research will help to elucidate their role in kidney disease. The PECs move on to round 2 of NephMadness 2014 to face the formidable team renal pericytes.

Renal pericytes versus Epithelial to mesenchymal transition

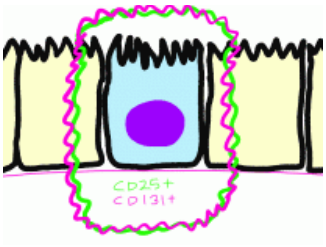
Winner: Renal pericytes



Team pericytes wins against team EMT in what will for sure go down as one of the greatest first round matchups of NephMadness history. The anticipation was palpable for this one. Team EMT had all of the tradition going for it (like a John Wooden led UCLA). However, team pericyte as the Cinderella of NephMadness showed how much versatility this niche cell type has. Fibrosis is a hot topic in multiple areas of medical research and this is proving to be true in the kidney field as well. The end-game for all forms of kidney damage is persistent fibrosis and understanding the mechanisms governing fibrosis will be critical in order to successfully target progressive kidney failure. EMT has been studied for the longest duration in the field of kidney regeneration. This matchup by far is the most controversial in the regeneration bracket. Several groups have demonstrated by lineage tracing that the bulk of fibroblasts that accumulate in the kidney after ureteral obstruction in the mouse (an experimental model of CKD) are of renal tubular cell origin. However, Lin et al demonstrated that it is the pericyte that transforms into the collagen-producing myofibroblast. I'm sure we haven't heard the last of this battle. EMT has been around for a while and I'm sure they will be back to NephMadness soon. Team pericytes will have a tough matchup with the PECs. Both have youth and the ability to migrate and potentially differentiate into either podocytes or fibroblasts. This will be an interesting matchup.

Self-duplication of tubules versus Tubule regeneration from resident stem cells

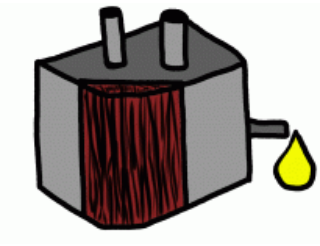
Winner: Tubule regeneration from resident stem cells



Team stem cell defeats self-duplication of tubules for a spot in the second round against bioartificial kidney. This was a close one. Stem cells have continued to garner a lot of attention and this is rightfully so. Will resident stem cells hold the key to successful kidney regeneration? How did stem cells defeat direct tubule regeneration? First, evidence of a stem cell population capable of tubule differentiation has been identified in close proximity to the renal proximal tubule and distal convoluted tubule. The self duplication fans can hang their hats on the study by kusaba et al that show that a majority of cellular proliferation of injured tubules was from reduplication of terminally differentiated tubular cells and not from expansion of a progenitor cell population. This matchup will likely continue for years to come. However, with the recent momentum of stem cells it could be fight to the finish. The next match for stem cells will be a dangerous one. The mighty bioartificial kidney is lurking.

Bioartificial kidney versus Hypertrophy

Winner: Bioartificial kidney



Hypertrophy was no match for bioartificial kidney. Bioartificial kidney won hands down as team hypertrophy was stuck in the 80s with half court offense and an inability to run to court. Team bioartificial kidney was still riding high from the Nature Medicine report of the functional bioartificial kidney. This was quite a feat as the reproduction of a complex 3-dimensional kidney still seemed years away. The report by Song et al was years ahead of its time. However, whether or not this bioengineered kidney would be able to sustain the life of the rat for an extended period of time is unknown. The other exciting story was from Taguchi et al. This group reconstituted nephrons in vitro and implanted these beneath the renal capsule of mice and new vascularization commenced. Team hypertrophy was just happy to be in the big dance this year it seemed. Too many injuries. The fundamental principle of hypertrophy is how an individual cell enlarges, by increasing its protein content, without an increase its DNA content. Is bigger always better? Wiggins et al demonstrated that podocytes when lost due to cell death, their neighbor podocyte will undergo hypertrophy to cover the bare area. This is called compensatory hypertrophy. However, with time, these large cells produce an excess of deleterious factors such as cytokines, and augment rather than reduce disease. This was the Achilles heal of team hypertrophy and was their ultimate undoing. Team bioartificial kidney will go up against kidney stem cells in what will be a great matchup as far as skill is concerned. It is anyone's guess who will win this battle.

Acute Kidney Injury

Contrast Nephropathy vs Remote Ischemic Preconditioning (RIPC)

Winner: Contrast Nephropathy

Contrast nephropathy took home the win in convincing fashion. Team Contrast Nephropathy, also known as the Cath Cowboys, came with a deadly one-two punch: contrast nephropathy is both common and lethal. Contrast nephropathy is sparking fear throughout the tournament and a hefty amount of research devoted to its prevention. This research is culminating with the ongoing PRESERVE trial, weighing in at over $23 million, it will enroll 8,680 patients to a 2×2 factorial design in order to determine whether NAC or sodium bicarbonate are any better than normal saline for the prevention of contrast nephropathy.

By far the most impressive part of the trial is the (relatively) hard-end point they will be using:

Source of original image.

	BICARBONATE	SALINE
NAC	bicarbonate + NAC	saline + NAC
PLACEBO	bicarbonate + placebo	saline + placebo

- **primary endpoint**: composite of 90-day mortality, need for dialysis, persistent decline in renal function
- **secondary endpoint**: development of contrast induced nephropathy, 90-day hospitalization for acute coronary syndrome, heart failure or stroke, 90-day all-cause hospitalization, individual primary endpoints,
- **tertiary endpoint**: ESRD and mortality at one year

This trial will become, by far, the largest randomized controlled clinical trial conducted in nephrology (recall that the very large ATN and RENAL trials enrolled 1,124 and 1,508 patients, respectively).

Despite the loss, remote ischemic pre-conditioning showed its potential. In a recent review, 7 studies with a total of 4,689 patients were studying the use of remote ischemic preconditioning for the prevention of AKI in adults or children undergoing cardiothoracic surgery.

Urinary indices versus biomarkers

Winner: Urinary indices
Probably the sloppiest game of the first round, traditional urinalysis and urinary indices eked out a win over, oh so trendy, biomarkers – yet both teams played poorly.

The biomarker team needs to learn the fundamental truth that there is no "I" in team. Pregame, the players touted their individual achievements all saying that they were the best – but when it came to game time, they just couldn't work together and that led to their downfall.

Close analysis reveals that the individual biomarkers may have been over-hyped. Indeed, in one of the largest studies thus far, the best performing biomarker, urine IL-18, had only a sensitivity of 54% and a specificity of 82% in adults to

predict AKI (Urine NGAL had a sensitivity of 46% and specificity of 82%; plasma NGAL with a sensitivity of 50% and specificity of 82%).

source

Dick Vitale was adamant, that for biomarkers to get over the hump (especially NGAL, IL-18, KIM-1, L-FABP, Cystatin C, and urine enzymes) "Baby! They need to learn to work together as a team!" Some are good post-cardiac surgery, some are good early, some are good later, and some are good in sepsis – but one biomarker isn't going to be able to carry the team. Once they start playing together, the potential to predict and accurately stage AKI might finally be realized.

Despite the loss, there is great hope and optimism for the future for biomarkers. The red-shirt freshman, cell cycle arrest markers, will play next year and the scouting report looks good for these markers to predict AKI in patients admitted to the intensive care unit; we wonder if the cell cycle arrest markers should try to get catchier names, though, as tissue inhibitor of metalloproteinases (TIMP)-2 and insulin-like growth factor binding protein 7 (IGFBP7) don't go well in cheers.

The biomarkers also need to play in the right context. Similar to troponin only being checked when there is chest pain or suspicion for an MI, a similar "renal angina index" is being tested and developed to guide the clinical scenario in which measuring AKI biomarkers might be most useful.

The traditional team played as usual: many brilliant calls and many predictable mistakes. Urine sodium was low and correctly identified the pre-renal patient, but was also low in contrast-induced AKI and sepsis in whom balanced electrolyte solution resuscitation did not lead to improved kidney function. FeUrea worked in patients receiving diuretics, but had a poor performance in the ICU with a sensitivity of 63% and specificity of 54% (with a cutoff of 35%) (6). But, by sticking to what they know and dealing with what they didn't know, they managed to pull off the win.

Despite the loss, remote ischemic pre-conditioning showed its potential. In a recent review, 7 studies with a total of 4,689 patients were studying the use of remote ischemic preconditioning for the prevention of AKI in adults or children undergoing cardiothoracic surgery.

Normal Saline vs Balanced solutions

Winner: Balanced solutions

It wasn't even close. Balanced electrolyte solutions trounced normal saline in a game that had fans bored and even booing the poor performance of normal saline at the end. The distaste for normal saline was intense. Said one fan: "normal saline isn't even normal! 154 mEq/L of sodium and 154 mEq/L of chloride – who ever heard of a serum chloride of 154 mEq/L? That's 48 mEq/L off! They're just a bunch of liars."

Being associated with hyperchloremic metabolic acidosis and AKI in patients were just two of the major downfalls of "normal" saline that lead to its loss. Sealing the deal was a study from the near future (publication date, April 2014) comparing balanced solution and normal saline for resuscitation in rats with sepsis; compared to balanced electrolyte solution, rats resuscitated with normal saline had increased serum chloride, decreased pH, increased AKI severity, and increased mortality.

Despite the victory here, normal saline remains the most widely used isotonic crystalloid in North America. One wonders, about the chances of balanced electrolyte solutions moving forward in the tournament, given that a head to head comparison of balanced solutions and saline has not been performed in patients. DreamRCT anyone?

AKI Guidelines: KDIGO versus KDOQI

Winner: KDOQI

In the closest match of the AKI bracket, KDOQI guidelines edged out KDIGO guidelines. Despite the US homefield advantage, KDOQI was the underdog. Some had predicted that with its thin 23 pages that KDOQI would be no match for the behemoth KDIGO's 138 pages and international experience. In many ways, though, KDOQI was playing with the same play book as KDIGO – essentially copying and agreeing with most of their plays, but adding just enough improvements to get the win. Notably, KDOQI agreed with:

1. all of the level 1 recommendations for the prevention and treatment of AKI (KDIGO chapter 3)
2. the majority of recommendations for contrast-induced AKI (KDIGO chapter 4)
3. all of the level 1 recommendations for dialysis management in AKI (KDIGO chapter 5)

The winning formula for KDOQI relied on a number of key plays at the end, especially exploiting the KDIGO trip up regarding the appropriate dose of intermittent dialysis. In recommendation 5.8.3 (the second to last recommendation of the document), KDIGO states "We recommend delivering at least a Kt/V of 3.9 per week when using intermittent or extended RRT in AKI. (Level 1A)". Of course, everyone knows what they meant – that dialysis dose should be a Kt/V of 1.3 per treatment in AKI patients receiving thrice weekly hemodialysis, and KDOQI agreed with this recommendation. But KDOQI called them out on how they said it by noting that "3.9 is based on the arithmetic sum of the dose per individual treatment. Kinetic modeling suggests that this is erroneous and that prescription of intermittent hemodialysis to provide a Kt/V of 1.3 three time per week or a Kt/V 0.65 six times per week are not equivalent." This technical foul was one of the factors that played into the win for KDOQI, even though both groups essentially agree on this issue and also agree that delivered dose of dialysis should be assessed frequently in AKI since delivered dose is typically lower than prescribed dose.

Sealing the win were KDOQI's recommendations about the definition of AKI. KDOQI's rejected the use of urine output to define AKI and they rejected KDIGO's use of weight based definition of AKI. Using KDIGO's formula would mean that a urine output of 40 mL/hr in a 90 kg patient for 12 hours, 480 mL, would be classified as stage 2 AKI. Lastly, KDOQI rejected the addition of yet another definition, namely: acute kidney disease, to bridge the nomenclature between AKI (48 hours or so) and CKD (3 months).

Overall, however, these teams were extremely well matched and the game was conducted with dignity, respect, and poise. "We are really very similar teams" noted one member of the KDIGO team humbling accepting the unexpected defeat.

Moving forward – the KDOQI AKI recommendations are looking pretty tough to beat. Their lean and mean team covers the range of evidence for defining, preventing, and treating AKI. Given that AKI is the most common reason for inpatient nephrology consultation in the US, KDOQI is looking unbeatable.

Electrolytes

Hypertonic Saline versus Vaptans

Winner: Hypertonic Saline

Hypertonic saline squeezes out Team Vaptan with a buzzer beater to sneak into the next round of NephMadness. This was the big matchup in the first round in the Electrolyte region and it didn't disappoint. The big man Tolvaptan, likely still hurting from its surprise preseason loss to the FDA for approval in APKD, just didn't deliver. In TEMPO 3:4, despite reaching its primary endpoint by slowing the increase in total kidney volume (& the decline in kidney function) over a 3-year period there were issues. A higher dropout rate (23 v 14%) versus placebo limited its power (and hence P value) and the higher rate of "clinically significant" rises in LFTs ultimately ruined its chances against the FDA (4.95 vs 1.2% for ALT). The veteran Hypertonic saline proved its critics wrong and will fancy its chances to a run deep in NephMadness. Hypertonic saline, as the only agent capable of rapidly increasing the serum sodium, can be a lifesaver. The types of situations where it can be invaluable include precipitous drops in serum sodium associated with primary polydipsia, ingestion of MDMA ("ecstasy") and exercise-induced hyponatremia, as occurs in marathon runners. The common mechanism here is a marked increase in water intake with failure to adequately suppress ADH. The risk for osmotic demyelination is lower with acute hyponatremia (and risk for cerebral edema due to the low sodium is high) meaning we should not be afraid of using hypertonic saline when indicated. However, it must be noted that such patients may autocorrect quickly, by excreting a dilute urine, when the stimulus for ADH suppression is removed.

Serum Anion Gap versus Urine Anion Gap

Winner: Serum Anion Gap

Hypertonic Saline will now face off against Serum Anion Gap (SAG) who won its local rivalry with Urine Anion Gap by some distance. The hyped "Battle of the Gaps" turned out to be one way traffic as the wealth of physician experience and familiarity with SAG made the difference. In our NephMadness scouting report of SAG, we concentrated on its versatility and application in different situations (high, normal, low gap; acidosis, non-acidosis) which is an obvious strength. It must be noted, however, that sometimes the SAG is an oversimplification. For example, the degree of change in SAG for each unit change in HCO3 is not always uniform, being more with lactate than other anions such as ketoacids. This may be important when using SAG in conjunction with other tools, such as delta HCO3 (expected HCO3 may be different depending on the cause of the acidosis). A nice review of the current use of SAG for nephrologists can be found here. The urine anion gap (UAG) or sometimes referred to as the urine cation gap or the urine net charge. The point of measuring the UAG is to measure the NH4 content in the urine. This is because with hyperchloremic metabolic acidosis, NH4 is excreted in the urine usually with Cl. Thus, urine Cl usually exceed the sum of the urine Na and urine K. This results in the negative UAG. Why? Urine NH4 is difficult to measure so this is a surrogate of NH4 content. The problem with UAG is that when the relationship between urine NH4 and Cl is disrupted then the UAG may be misleading. This is when another unmeasured urinary anion is present (NON-CHLORIDE).

Examples include

- Beta-hydroxyburyrate
- acetoacetate in ketoacidosis
- hippurate following toluene inhalation (glue-huffing)
- bicarbonate with proximal RTA is treated with alkali

- D lactate
- 5-oxoproline (with acetaminophen ingestion)

In these situations it may be better to perform a urine osmolal gap (UOG). This is another indirect measure of urinary NH4 excretion. The difference between the directly measured and the calculated urine osmolality is termed the UOG. Urine osmolality is generally made up of ammonium salts such as NH4Cl and NH4+other anions. Thus, the UOG, in contrast to the UAG, is still useful when unmeasured anions are excreted in the urine. For these reasons UAG just couldn't keep up with SAG and, unfortunately, their season comes to an end. How with SAG fare against Hypertonic Saline. We shall see.

Kayexalate versus ZS-9 (novel potassium binder)

Winner: ZS-9 (novel potassium binder)
ZS-9 entered the competition with lots of momentum and hype (despite little substance as yet) and wins over Kayexalate, its unloved opponent. ZS-9/zirconium silicate works as an inorganic cation exchanger and has high selectivity for potassium. It appears to be well tolerated in its early studies, with no diarrhea reported. It has a cool name, novel mechanism, and was always going to beat Kayexalate. However, it needs hard data to back it up from here so my prediction is it will struggle from here in this years tourney.

Bicarbonate in CKD versus Bicarbonate in Acute Metabolic Acidosis

Bicarbonate in CKD
Bicarb in CKD beats Bicarb in Anion Gap Acidosis in what was a contest of emerging evidence versus no evidence. Certainly, the idea of treating CKD-associated acidosis with NaHCO3 (or equivalents such as sodium citrate) is gaining traction with exciting evidence suggesting retardation of progressive renal dysfunction. Another approach to this is by using dietary interventions with high fruit and vegetable intake to counteract the systemic acidosis. A recent study has demonstrated this can work over one year in a CKD stage 4 population. A potential worry with this diet is the risk for hyperkalemia although this was not evident in the cited study despite universal ACE inhibitor use. In patients with ESRD, acidosis is generally corrected by their dialysis. Persistent acidosis can be be managed by altering bicarbonate concentration of the dialysate from the standard 35 mEq/L. KDOQI guidelines suggest midweek pre-dialysis bicarb levels >22 mEq/L which is consistent with recent survival data in hemodialysis patients. ZS-9 versus Bicarb in CKD will showcase two up and coming teams but my pick is the team that is slightly more established with more evidence to back up the hype.

Kidney Stones

Acute Stone: Surgical Care versus Medical Care

Winner: Medical Care
Surgical care has long been dominant to the point that conference officials were thinking about removing medical care from nephrologists altogether but stone clinics are gaining ground and frequent stone formers are learning the tricks to helping themselves pass stones without intervention. Teaching a patient about medical stone care is a way to empower them to take ownership of their disease.

Xanthine oxidase inhibitors versus the CT Scan

Winner: CT Scan

Kidney stones are generally a non-lethal condition. When I was a fellow, Fred Coe used to call it civilian nephrology. Well there is nothing civilized about iatrogenic cancer. Over use of radiology is going to be a bigger and bigger issue in medicine due to cost and radiation exposure. Kidney stones are likely to be the canary in the coal mine. This is another issue where properly educated patients can be empowered to advocate their own case. CT scans have among the highest exposures to radiation, yet a KUBs paired with an U/S has similar sensitivity and specificity for clinically relevant stones.

Dr. Pak versus Dr. Coe

Winner: Coe

Coe versus Pak is a Sophie's choice. Both are legends and neither would out of place advancing to the next round, however Pak is held back by his classification of hypercalciuria. His focus on different categories hypercalciuria is not clinically useful. Coe wins for defining the natural history of kidney stones.

Oxalobacter formigenes versus Bariatric Surgery

Winner: Oxalobacter

The microbiome will be one of the major themes in the twenty-first century. Medicine will learn to appreciate the prokaryotic population within us and hopefully leverage it for therapeutic benefit. Kidney stones are on the leading edge of this fascinating topic.

Biologics

Rituximab versus Bortezomib

Winner: Rituximab

Rituximab versus bortezomib was a tough battle. Both agents are borrowed from our oncology colleagues. They also affect similar cell types. For ritux it's the B cell and for bortez it is the plasma cell. They have really made a significant addition to the nephrology drug arsenal in transplantation. Bortezomib is an anti-plasma cell agent that has made some progress in acute kidney rejection but unfortunately we are still awaiting its widespread use in glomerular diseases. On the other hand, rituximab has the upper hand in both transplantation and glomerular diseases. Let's take a look at some adverse effects regarding both these agents. While cardiac arrest and anaphylactic reactions have been reported with rituximab, the major concern is development of progressive multifocal leukoencephalopathy (PML). PML, although rare, has been reported in patients treated with rituximab in both cancer and with lupus. Whether this is a drug effect or a net immunosuppression effect is hard to differentiate. Infectious complications are common with rituximab as well. What about bortezomib? Bortezomib is associated with peripheral neuropathy in 30% of patients. Occasionally, this neuropathy can be painful. It seems to be a side effect of proteasome inhibitors. The myelosuppressive side effects of bortezomib appear to be minor. Rituximab advances to the next round given the vast use of this agent in the nephrology world for various disorders. However, there is hope for bortezomib for the future as reducing the production of pathologic antibodies via plasma cells sounds like an attractive approach to a number of glomerular diseases. Bortezomib is a team for the future, but unfortunately the future is not yet here. We have more experience with rituximab but this could be the peak of its run.

Belimumab versus Belatacept

Winner: Belatacept

A post-hoc analysis of the BLISS-52 trial showed that many indices of kidney involvement and serologic activity favored the use of belimumab in patients with lupus. Remember belimumab works by inhibiting B cell activation by blocking the B cell activating factor (BAFF). However, the differences seen between groups (mycophenolate vs. mycophenolate + belimumab) in a majority of kidney outcomes were not statistically significant. This suggested that there might be some kidney benefit with this agent but we have to keep in mind that severe lupus nephritis patients were excluded from the trial. It is possible that in patients with more severe kidney involvement with lupus that belimumab might be more effective. On the other hand, belatacept is on a roll in kidney transplantation. And this is where the difference was made in NephMadness 2014. A quick search of ongoing clinical trials shows several ongoing studies on use of belatacept in transplantation. Calcineurin inhibitors allowed us to think of "steroid free" protocols in transplantation. While belatacept has provided the potential for "calcineurin free" protocols? What is most common cause of CKD in the post transplantation world? That would be calcineurin inhibitor toxicity. Has the era begun for calcineurin-free care? Belatacept clearly wins this round to match up against the almighty rituximab.

Eculizumab versus Soluble CR1

Winner: Eculizumab

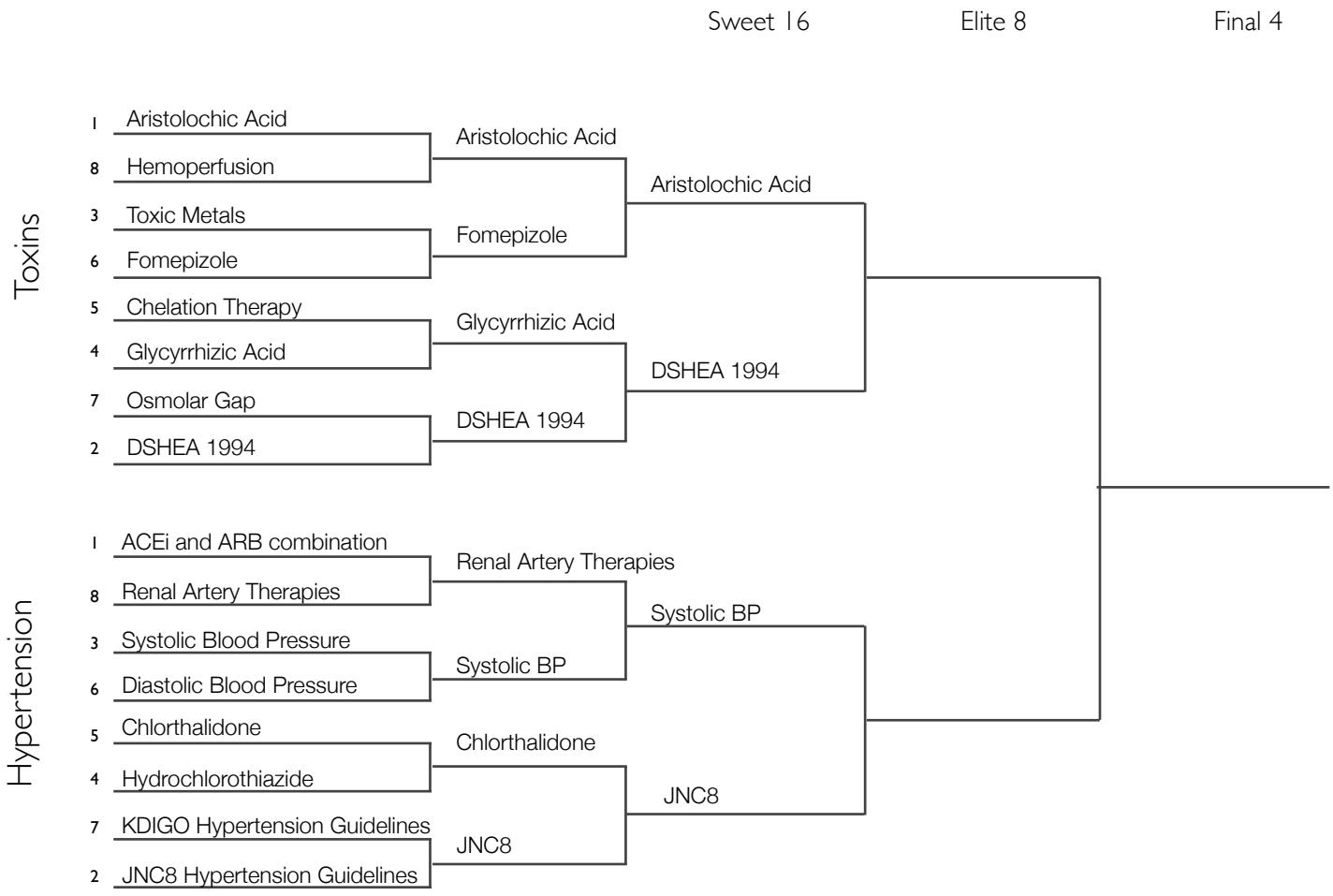
This was an interesting match-up. Complement inhibition versus complement inhibition. However, you have a more specific inhibition with soluble CR1. Soluble CR1′s youth and inexperience really showed against the almighty eculizumab. Eculizumab has taken the nephrology and hematology world by storm. With cases of Shiga toxin–associated HUS even treated, such a record landed this drug in NEJM and puts it right in the spotlight. The cases had such great recovery. Furthermore, NEJM also published a letter on a case of refractory MPGN, but it is the atypical HUS syndromes where this agent made its home. Soluble CR1 has a long way to go still as it is currently only being evaluated in basic science models. Great concept and more specific, but eculizumab takes this one with a landslide victory.

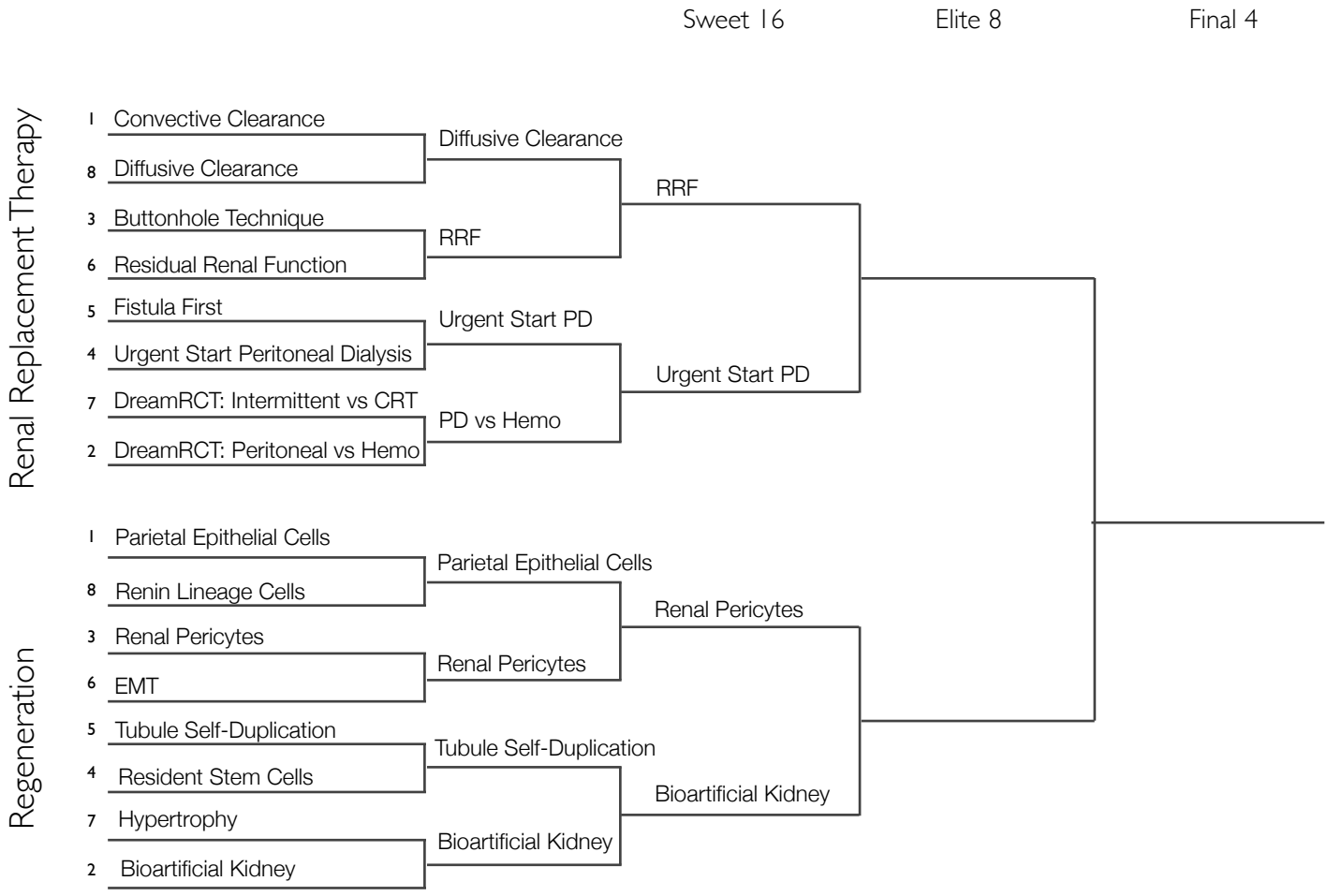
ACTHar gel versus Abatacept

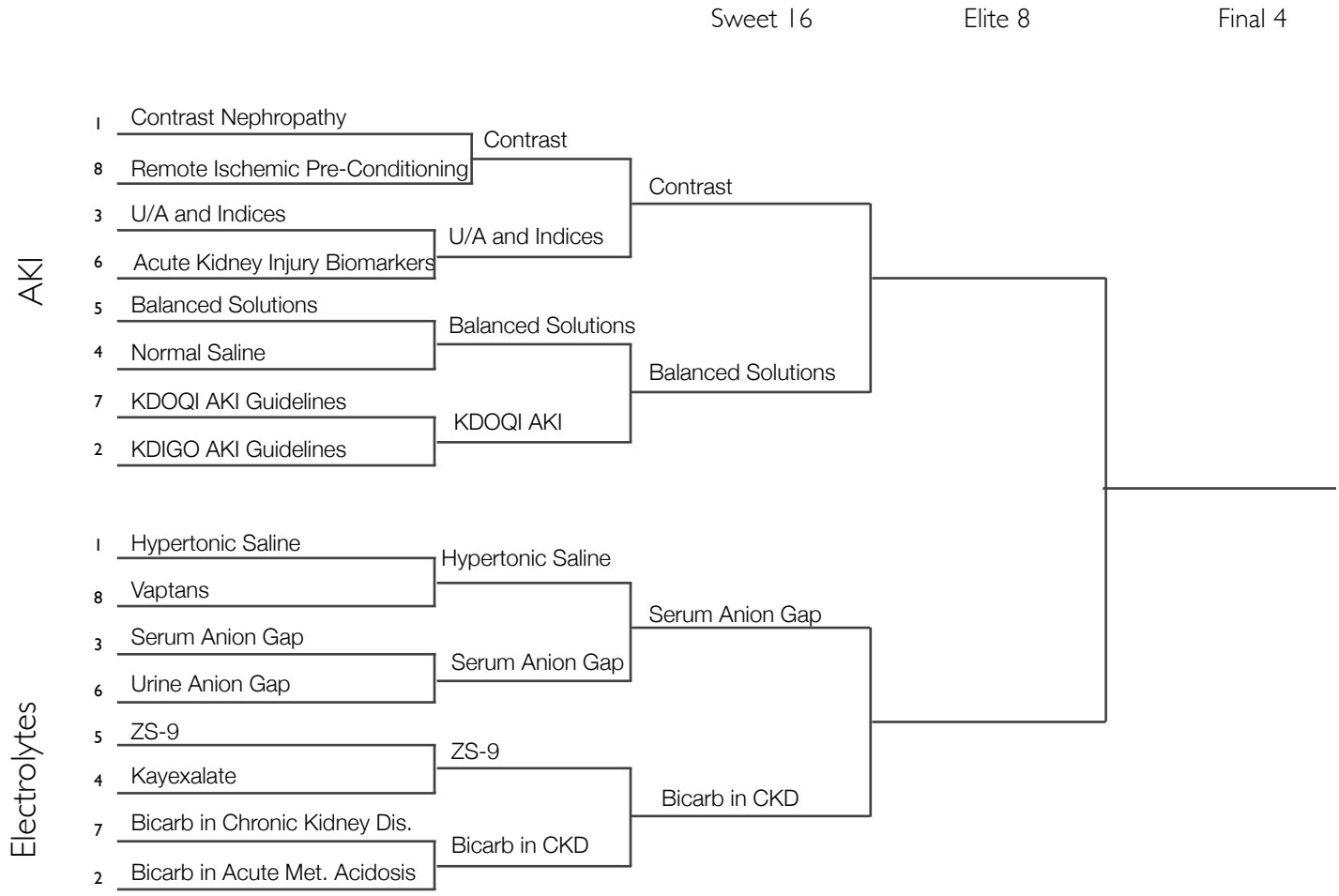
Winner: ACTHar Gel

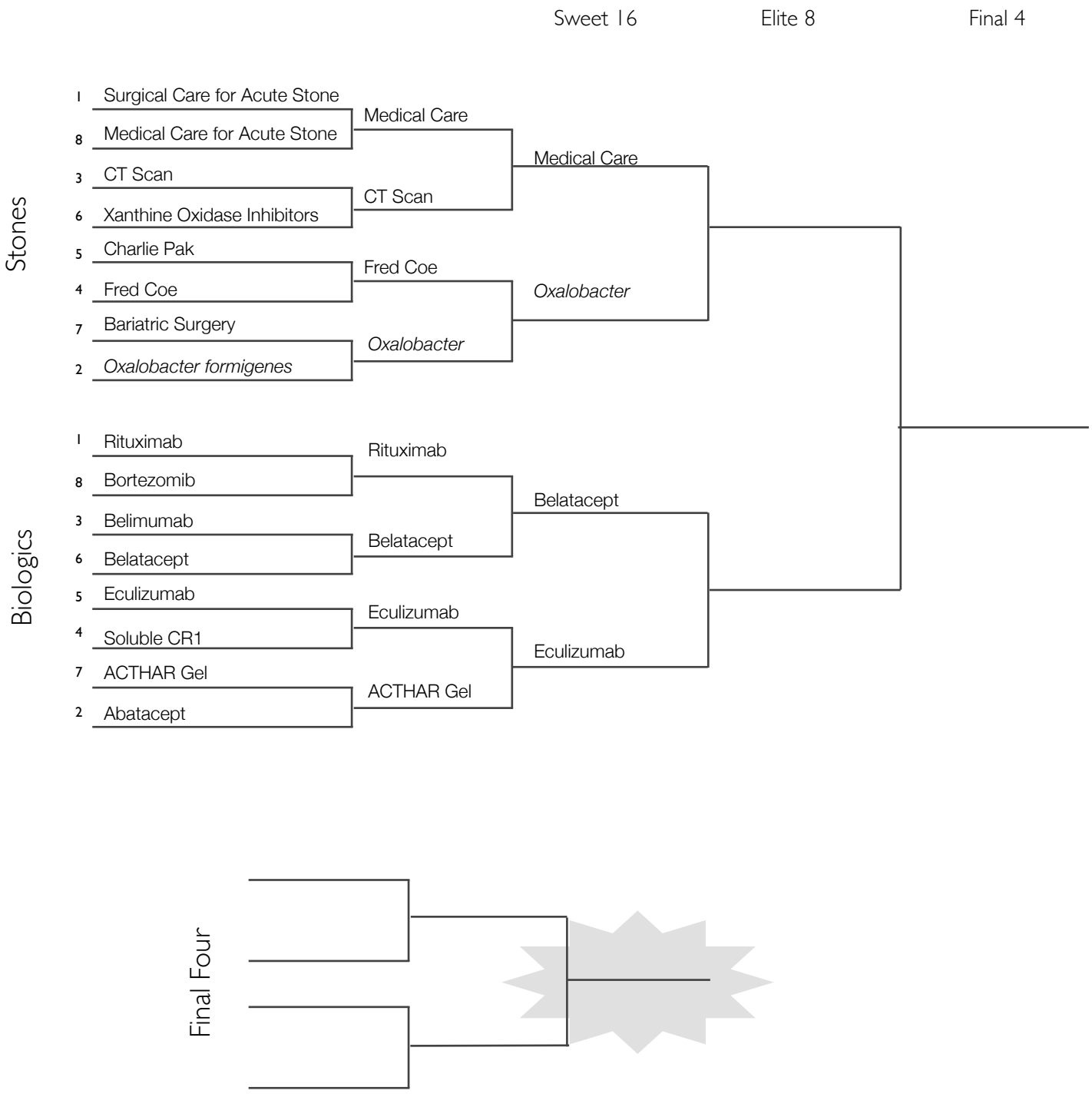
Abatacept made its big splash into the nephrology scene in 2013 in this NEJM paper. Success was seen in patients with glomeruli that stained positive for B7-1 in a variety of nephrotic diseases. While this agent is very specific and showing great promise in glomerulonephritis and posttransplant glomerulonephritis, ACTHar Gel upset this promising agent. One of the biggest reasons is the lack of properly conduced randomized clinical trials for Abatacept. Right now all we have is small case series. ACTHar Gel has its issues as well but it has been around for a long time and its use and study is starting to spread again. One of the earliest records of use of this dates to the 1950s in a historic paper from JAMA pertaining to children, as well as another report of cases from Canada in the same era. The landmark paper by Bomback et al showed that in 21 patients with nephrotic syndrome of various etiologies, ACTHar gel was capable of achieving remission. This brought the drug back to limelight in 2009 and rest is history. ACTHar gel upsets Abatecept in this match up.

Round Two Winners: The Sweet Sixteen




Sweet 16
Elite 8
Final 4
Renal Replacement Therapy
1 Convective Clearance
8 Diffusive Clearance
Diffusive Clearance
3 Buttonhole Technique
6 Residual Renal Function
RRF
RRF
5 Fistula First
4 Urgent Start Peritoneal Dialysis
Urgent Start PD
Urgent Start PD
7 DreamRCT: Intermittent vs CRT
2 DreamRCT: Peritoneal vs Hemo
PD vs Hemo
Regeneration
1 Parietal Epithelial Cells
8 Renin Lineage Cells
Parietal Epithelial Cells
3 Renal Pericytes
6 EMT
Renal Pericytes
Renal Pericytes
5 Tubule Self-Duplication
4 Resident Stem Cells
Tubule Self-Duplication
Bioartificial Kidney
7 Hypertrophy
2 Bioartificial Kidney
Bioartificial Kidney


Sweet 16
Elite 8
Final 4
AKI
1 Contrast Nephropathy
8 Remote Ischemic Pre-Conditioning
Contrast
3 U/A and Indices
6 Acute Kidney Injury Biomarkers
U/A and Indices
Contrast
5 Balanced Solutions
4 Normal Saline
Balanced Solutions
7 KDOQI AKI Guidelines
2 KDIGO AKI Guidelines
KDOQI AKI
Balanced Solutions
Electrolytes
1 Hypertonic Saline
8 Vaptans
Hypertonic Saline
3 Serum Anion Gap
6 Urine Anion Gap
Serum Anion Gap
Serum Anion Gap
5 ZS-9
4 Kayexalate
ZS-9
7 Bicarb in Chronic Kidney Dis.
2 Bicarb in Acute Met. Acidosis
Bicarb in CKD
Bicarb in CKD


Sweet 16
Elite 8
Final 4
Stones
1 Surgical Care for Acute Stone
8 Medical Care for Acute Stone
Medical Care
3 CT Scan
6 Xanthine Oxidase Inhibitors
CT Scan
Medical Care
5 Charlie Pak
4 Fred Coe
Fred Coe
7 Bariatric Surgery
2 Oxalobacter formigenes
Oxalobacter
Oxalobacter
Biologics
1 Rituximab
8 Bortezomib
Rituximab
3 Belimumab
6 Belatacept
Belatacept
Belatacept
5 Eculizumab
4 Soluble CR1
Eculizumab
7 ACTHAR Gel
2 Abatacept
ACTHAR Gel
Eculizumab
Final Four

Toxins

Aristolochic Acid versus Fomepizole

Winner: Aristolochic Acid

Graduates of the Aristolochic Acid college are enjoying quite a season. How is a Toxin able to fare this well in a tournament filled with remedies, guidelines, and therapies? How is this possible? Well, Aristolochic Acid is quite the demon that needs to be reined in. The International Agency for Research on Cancer and the World Health Organization (WHO) have labeled Aristolochic acid as a type I human carcinogen. This hasn't stopped its use. It is an undeclared ingredient in up to 20% of Chinese herbal products. You got that right. 20%. This is a crazy statistic as Aristolochic acid could be the cause chronic kidney disease in a majority of patients in Asia. And with the population of China being so large, this is a big deal. So Aristolochic acid is worth remembering as it is not just a "board question". Fomepizole was way to expensive of a drug to maintain. The use of alcohol itself to compete with ethylene or diethylene glycol, methanol or propylene glycol is really an option. For this reason, fomepizole just couldn't pull it out. Aristolochic Acid goes on to face its arch nemesis DSHEA 1994.

Glycyrrhizic Acid versus DSHEA 1994

Winner: DSHEA 1994

Team Dietary Supplement Health and Education Act of 1994 (DSHEA) represents the FDA's major defensive strategy in the management of the marketing and distribution of vitamin and herbal supplements in the US. DSHEA is a landmark federal legislation that guides the government's role in the regulation of herbal and vitamin supplements. The history of this act is important to truly evaluate the impact it has had on pharmaceutical safety and financial success of the supplement industry. Let's review some of the scouting report from Dr. Kupin:

> *Prior to 1962, the FDA was not required to evaluate the efficacy and claims of any drug or supplement marketed in the U.S. The 1938 Food, Drug and Cosmetic Act only mandated that the drug companies demonstrate to the FDA that their drug was safe. However there was no regulation of advertising claims or any requirement of efficacy. The tragic thalidomide birth defects in Europe, however, forced an overhaul on the operations of the FDA. The Kefauver Harris Amendment or "Drug Efficacy Amendment" of 1962 required all manufacturers to provide proof of effectiveness of all drugs sold. An exemption to the Kefauver Harris Amendment was passed in 1994 called the Dietary Supplement Health and Education Act (DSHEA). This change in the law allowed all vitamin and herbal supplement manufacturers to be exempt from FDA review.*

The DSHEA 1994 act remains the most important factor influencing the sale, control, and advertisement of Alternative Medicines in the US. We need to start regulating these agents as deleterious side effect are bound to continue. DSHEA 1994 moves to the next round to play Aristolochic Acid. This will be the test we have been waiting for. We need to find a way to regulate these and unfortunately DSHEA 1994 is not that way.

Hypertension

Renal Artery Therapies versus Systolic Blood Pressure

Winner: Systolic Blood Pressure

Systolic blood pressure takes the victory from the injury prone renal artery therapies. This was not really a surprise as systolic blood pressure has been the target of therapy and epidemiology studies since the beginning of medicine. Nobody can rival the dominance of systolic blood pressure in this field. Renal artery therapies has had a rough couple of years. First, we get the CORAL trial showing that revascularization of of renal arteries with stents did not confer a significant benefit compared to medical management. Then we have the SYMPLICITY trial. This was the biggest letdown of the year for hypertension research. The anticipation was palpable. A press release late last year hit with a thud. BP effect was not as great as anticipated. The results of the SYMPLICITY trial will be reported at ACC2014 on Saturday. We will update you on the results of this trial. Next up for Systolic BP is JNC8. The much awaited guidelines to reduce the prowess of Systolic BP.

Chlorthalidone versus JNC8

Winner: JNC8

The Chlorthalidone fan club will surely be disappointed with the demise of Chlorthalidone to JNC8. JNC8 was was way to "streamlined" to deal with. The guidelines shaved off considerable bulk from the JNC7 predecessor. JNC8 attempted to simplify management of hypertension buy recommending Systolic BP to be below 150/90 in those over the age of 60 and 140/90 for all others; similarly, they also simplified the drug regimen, that is, ACEi, ARB, calcium-channel blockers (CCB), and thiazide-type diuretics are reasonable choices, to get patients to goal SBP. In the era of personalized medicine some argues that this was a 'oversimplified approach.' JNC8 does a number of other things.

- define the target BP thresholds for initiation of pharmacological intervention, eg, decrease blood pressure to <150/90 mm Hg in patients aged ≥60 or older and a DBP <90 in those aged 30 to 59
- recommend a broader range of anti-hypertensive agents for initial treatment in non-blacks, including those with diabetes
- recommend ACEi or ARB for all patients with CKD with or without DM regardless of race.

Unfortunately, it was difficult for Chlorthalidone to dethrone a massive guideline document. This is unfortunate indeed. Chlorthalidone has a longer half-life and larger volume of distribution allowing the drug to achieve a more evenly distributed BP control throughout the day as compared to hydrochlorothiazide. This is why they won round one. Now it is a battle of the beast (SBP) and the beast master (JNC8).

Renal Replacement Therapy

Diffusive Clearance versus Residual Renal Function

Winner: Residual Renal Function

Residual renal function is looking to really make waves in this years NephMadness. Seems like we are always preaching to other services to "preserve the residual renal function". This teams needs to be mainstream. Like avoiding NSAIDs, contrast if possible and keeping low blood pressure at a minimum. Interesting that residual renal function's arch nemesis contrast nephropathy is still alive and well. Why should we care about residual renal function. As discussed in detail in the original scouting report, residual renal function lowers B2 microglobulin, potassium, aluminum levels, raises bicarbonate and improves phosphate balance. Residual renal function is important contributor to patient health. Here is what Andrew Howard and Klemens Meyer, President Elect and President of the ESRD Networks, had to say:

> *The requirement to exclude residual renal function from reported Kt/V presents those facilities which choose to measure residual renal function with a dilemma: either accept a QIP penalty for supposedly (but not really) inadequate dialysis, or coerce the patient to accept a medically unnecessary prolongation of treatment time. This hardly sounds like patient-centered care, and we suggest that as written, the proposed Rule fails fairly to answer the question "How did the patient do?"*

Residual renal function is a contender to win it all. Unfortunately, diffusive clearance hit a wall. The convective clearance bandwagon was extremely disappointed to lose the first round against the wily diffusive clearance team. Diffusive clearance has been tinkered with for years without any improvements in mortality. Just look at the HEMO study. Middle molecule clearance is the future. Studies are starting to roll out. Like this study from Spain published in JASN in 2013. Unfortunately, the future is not yet here. We await big randomized trials for convective clearance. This is the end of the road for diffusive clearance. Up next for team residual renal function is Urgent Start Peritoneal Dialysis.

Urgent Start PD versus DreamRCT: ESRD

Winner Urgent Start PD

Urgent Start PD continues to dominate NephMadness. The ability to start patients on peritoneal dialysis immediately after placement of a peritoneal dialysis catheter has really increased the number of patients using this modality. This is especially good news in the US where the utilization rates of PD are much lower that other counties. This is described by Ghaffari et al in AJKD eloquently. PD is a great option for many patients as patients have much more freedom and autonomy and they can travel much easier. Urgent Start PD is starting to sweep the US. This is a much needed initiative and frankly quite opposite of many of the initiative performed before to try to boost interest in PD. The Sweet 16 battle of Urgent Start PD versus Residual will be something to watch for sure. Unfortunately, for the Dreamer's out there, DreamRCT: ESRD just couldn't knock off Urgent Start.

Kidney Regeneration

Parietal Epithelial Cells versus Renal Pericytes

Winner: Renal Pericytes

Team pericytes takes the victory over parietal epithelial cells (PECs). This is an interesting matchup as both of these cell types were the forgotten cell type a decade ago. Now there is renewed interest and much more research is being performed. This is a battle of the P's. How did the pericytes edge out the PECs? While is has been shown that PECs are starting to gain traction in a variety of glomerular diseases such as FSGS or rapidly progressive glomerulonephritis, team pericyte might be involved in the eventual march to fibrosis and end organ damage that are common to all of CKD including diabetes! This gives the edge to team pericytes. They also could play an important role in repair and the fibrotic response to acute kidney injury.

Tubule Regeneration from Resident Stem Cells versus Bioartificial Kidney

Winner: Bioartificial Kidney

Was there ever a doubt that Bioartificial Kidney wouldn't make it to the Sweet 16. Team Bioartificial Kidney is an amalgam of everybody in the regeneration bracket all rolled into one superstar team. They are the Kentucky of NephMadness. A team filled with one-and-dones. The problem with team Bioartificial Kidney is that the initial report, however impressive, fell short of actually being able to sustain the life of the animal it was implanted into. Also, the results have not been replicated. We are still a long way off from being able to even think of doing something like this in humans. Resident Stem Cells of the kidney barely squeaked by its first round contender Self-duplicating Tubules. This is because mounting evidence has been mounting that self-duplication might be the process that occurs instead of the the proliferation of resident stem cells. Next up for Bioartificial Kidney with be the prolific fibroblast-making team Pericyte. This will be a prime-time battle that will surely not disappoint. Vegas is a buzz about this one.

Acute Kidney Injury

Contrast Nephropathy versus Urinalysis and Indices

Winner: Contrast Nephropathy

Contrast Nephropathy takes the win over Urinalysis and Indices. The first thing done when you receive a consult is to graph out the creatinine and place times where contrast was given. See if it lines up. From the round 1 game analysis:

> *Contrast-Induced AKI leaves a long lasting impact on its opponents who are rarely able to completely recover and perform back at their full capacity accompanied by an accelerated development of CKD in their future. Both short and long term mortality is markedly increased after Contrast-Induced AKI is present.*

It is clear that Contrast Nephropathy is something for its opponents to fear. Urinalysis and Indices are a staple for nephrologist. Everyone with AKI gets these. In fact, we demand they be done well in advance. Here are some of the weakness in team Urinalysis and Indices as noted in the scouting report.

> *Once considered to be the star player FENa has had a challenging time when faced against a team that uses diuretics, CKD, or heme pigment toxins. In addition, FEUrea has similarly slowed down over the years having a very difficult time in sensitivity (61%) and specificity (59%) in ICU patients.*

So what is next for Contrast Nephropathy. Next up is Balanced Solutions. What, no Normal Saline? I know, I know. Duke and Normal Saline lost in the first round. Just not their year. Balanced Solutions have a new coach and their critics are starting to like them again.

Balanced Solutions versus KDOQI AKI

Winner: Balanced Solutions

Now, what is up with Balanced Solutions. Are they really all that? Lets look at the scouting report:

> *This team has labored in the shadow of Fluid Resuscitation: Normal Saline for years and has yet to breakthrough into the mainstream. In order to change the prescribing patterns of physicians, Balanced Solutions knows that they will need concrete evidence and a blockbuster study to support their cause. So far things are looking promising at the bench research level. Compared to their arch nemesis Normal Saline, Balanced Solutions resulted in improved renal blood flow and a reduced risk of AKI. Clinically, even better news is on the horizon as Balanced Solutions own an early victory in comparison with Normal Saline in critically ill patients for the prevention of AKI.*

Team Balanced Solutions still has a long way to go in order to gain widespread popularity. They are from an outside conference looking in. We need a large randomized controlled trial comparing different solutions. KDOQI AKI had a great run but ultimately fell short. Ultimately, AKI guidelines just couldn't beat the recent surge of Balanced Solutions. Up next is a battle with Contrast Nephropathy.

Electrolytes

Hypertonic Saline versus Serum Anion Gap

Winner: Serum Anion Gap

This was a very interesting matchup. It is true that hypertonic saline has been a life-saving therapy in the treatment of hyponatremic emergencies; however, the sky is the limit when you think about the uses one can give to serum anion gap: uncovering acid-base disorders even when the pH is normal (eg, pH=7.4, pCO_2= 40, HCO_3=24, Na=140, Cl=80), alerting us of the hidden toxic alcohol ingestion, diagnosing a monoclonal gammopathy when low or negative values are found. There is no comparison! One must still consider the limitation of SAG. This round goes to serum anion gap.

ZS-9 (novel potassium binder) versus Bicarbonate in CKD

Winner: Bicarbonate in CKD

Even though ZS-9 seems to be the long-sought solution to the problem of dealing with hyperkalemia in a safe manner, their lack of use in practice makes ZS9 just an illusion for now. On the other side, bicarbonate comes highly recommended since it has been around for decades. Its minimal sodium retention properties and recent evidence for its use in slowing progression of CKD makes bicarbonate in CKD the winner of this matchup. I'm sure we will hear from ZS-9 soon. Frankly, I'm a little surprised that the results still haven't been published. Next on the chopping block from Bicarb in CKD is the venerable team SAG. Can bicarb stuff the gap and move on to the Elite 8? You will have to tune in to see.

Kidney Stones

Medical Care of Acute Stones versus CT scan

Winner: Medical Care of Acute Stones

To everyone's pleasure Medical Care of Acute Stones (MET) is still alive. This is important and often overlooks topic in the Stone world. Let's go back to the scouting report by Dr. Goldfarb and see exactly what we mean about this.

> *One of the primary concerns of MET is pain control. Opioids and NSAIDs both can be used. In a single center RCT, the combination of ketorolac and morphine was better than either drug alone. NSAIDs may have an additional benefit by reducing ureteral edema than can impede stone expulsion.*
>
> *Additional agents include alpha blockers (tamulosin, doxazosin) and calcium channel blockers (typically nifedipine) which are both effective at increasing the success and reducing the time until the stone is cleared. In a meta-analysis of 9 studies (693 patients) use of these drugs had a number-needed-to-treat of only 4 to get an additional stone expulsive. In addition, steroids may have a role, either alone, or more commonly in conjunction with one of the above agents. The steroids, may have act just like to NSAIDs to reduce the edema and ease stone passage.*

This is an important topic to highlight and discuss as it can really impact the life of a patient. The radiation exposure of the CT Scan was its limiting factor in allowing to continue in NephMadness. It's overuse cannot be understated and it was time to put an end to its dominance. MET did just that. Next up is Oxalobacter formingenes. This will be a true test.

Dr. Fred Coe versus Oxalobacter formigenes

Winner: Oxalobacter formingenes

Oxalobacter formigenes beats out Dr. Coe. Dr. Coe led to a revolution in how we think of stones and his influence continues. No disrespect from the NephMadness team. Team Oxalobacter are the new kids on the block. Lets look at the scouting film:

> *Oxalobacter are anaerobic gut bacteria that metabolize oxalate, the critical urinary metabolite in calcium oxalate stones. If you are colonized with these bacteria, you absorb less oxalate than someone with a similar diet who is not colonized with oxalobacter. People colonized with oxalobacter can plow through cans of spinach like Popeye on a bender and their urinary oxalate doesn't budge. Siener et al found a tight dose response, such that patients with stone recurrence are much less likely to be colonized with Oxalobacter and the relationship becomes tighter and tighter as the number of stone episodes rises. Unfortunately, attempts to seed stone formers with oxalobacter have not shown consistent benefit.*

The addition of this probiotic could become a major player in the kidney stone prevention world. For these reasons they won the first and second rounds. Next up is MET in the Sweet 16.

Biologics

Rituximab versus Belatacept

Winner: Belatacept

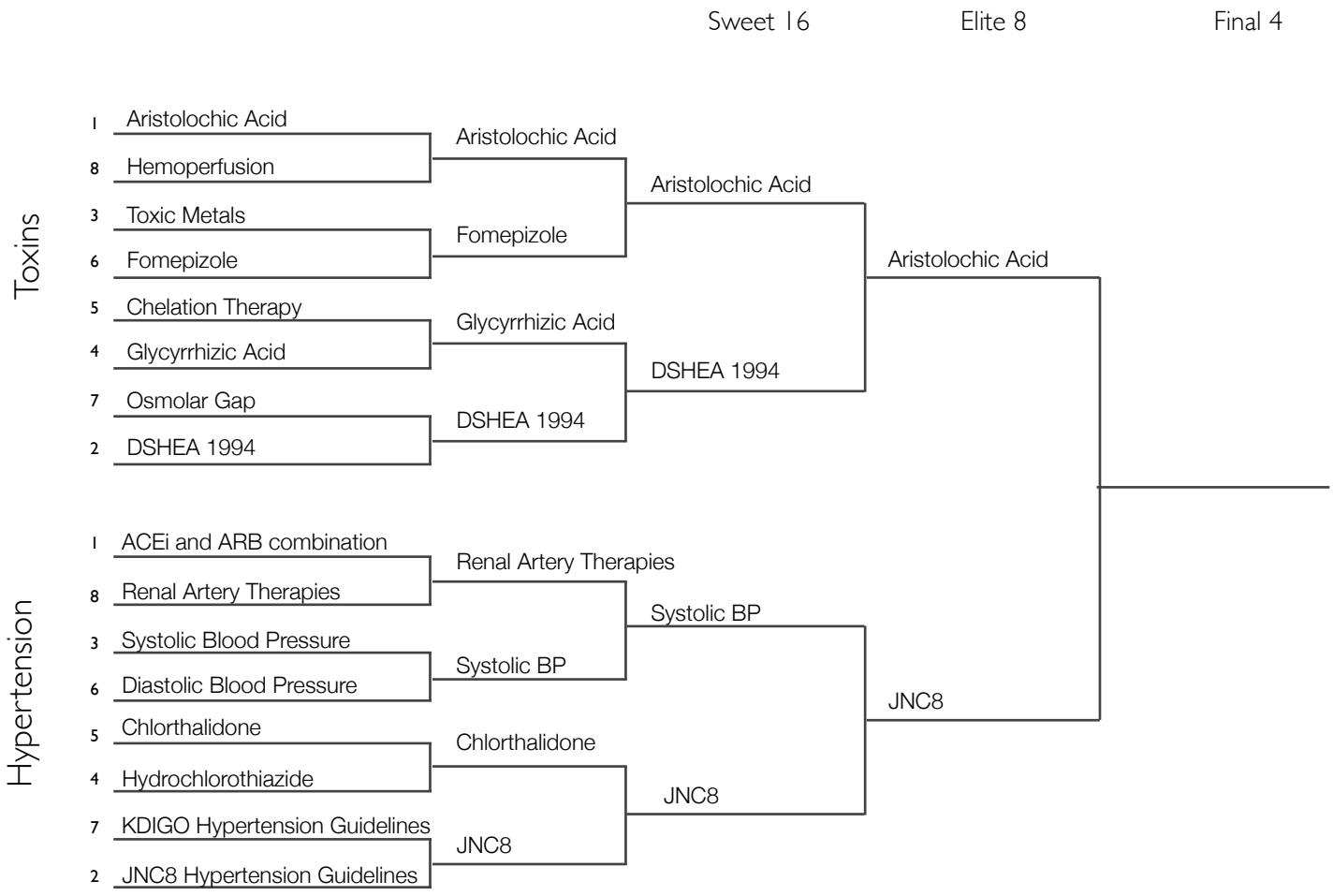
This is the big biologic battle that you have been waiting for! Yes, the favorite of many in Nephmadness is rituximab. At this point, it is the most popular contender in the contest. But let's bring to light some major newer side effects this agent can lead to. Newer studies now showing rituximab-induced lung disease, rituximab induced coronary spasms and a vast review of long term side effects with this agent. While rituximab is used in transplantation, it's more of a rescue agent. In general nephrology, it has become a major player. In the last 10 years, belatacept has been a true breakthrough in the transplant literature. It is the only way to minimize calcineurin-related CKD in our transplant patients (seriously, there isn't anything else out there). And it's sister drug (abatacept) is making recent news again in NEJM this week. It can be upsetting to see the Yankees lose to the Mets or Brazil get beat by a new team in the FIFA world cup or Duke getting beat in the first round by Mercer. It has happened now in NephMadness: Belatacept out does Rituximab in this round to march on to the next round to face Eculizumab.

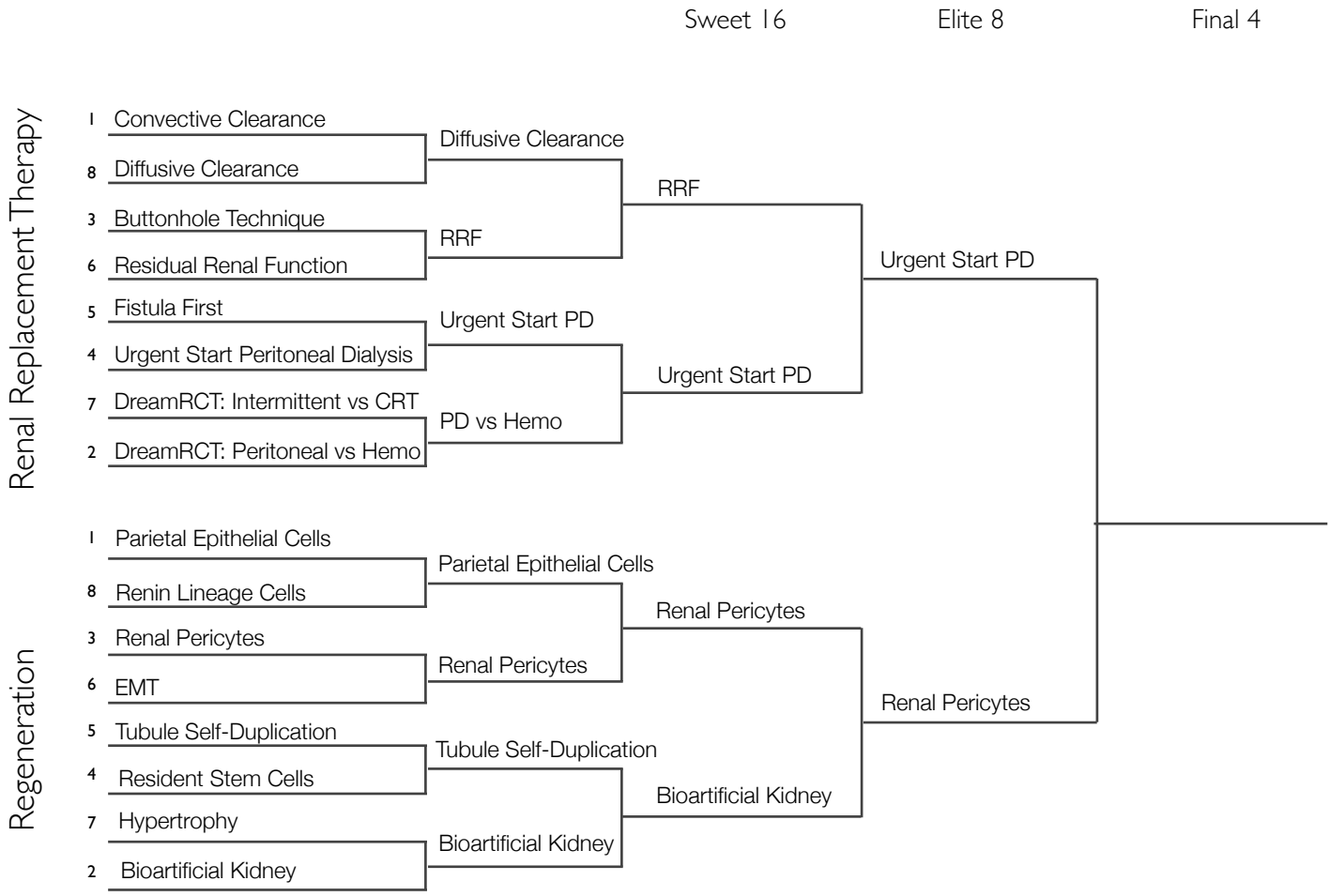
Eculizumab versus ACTHar Gel

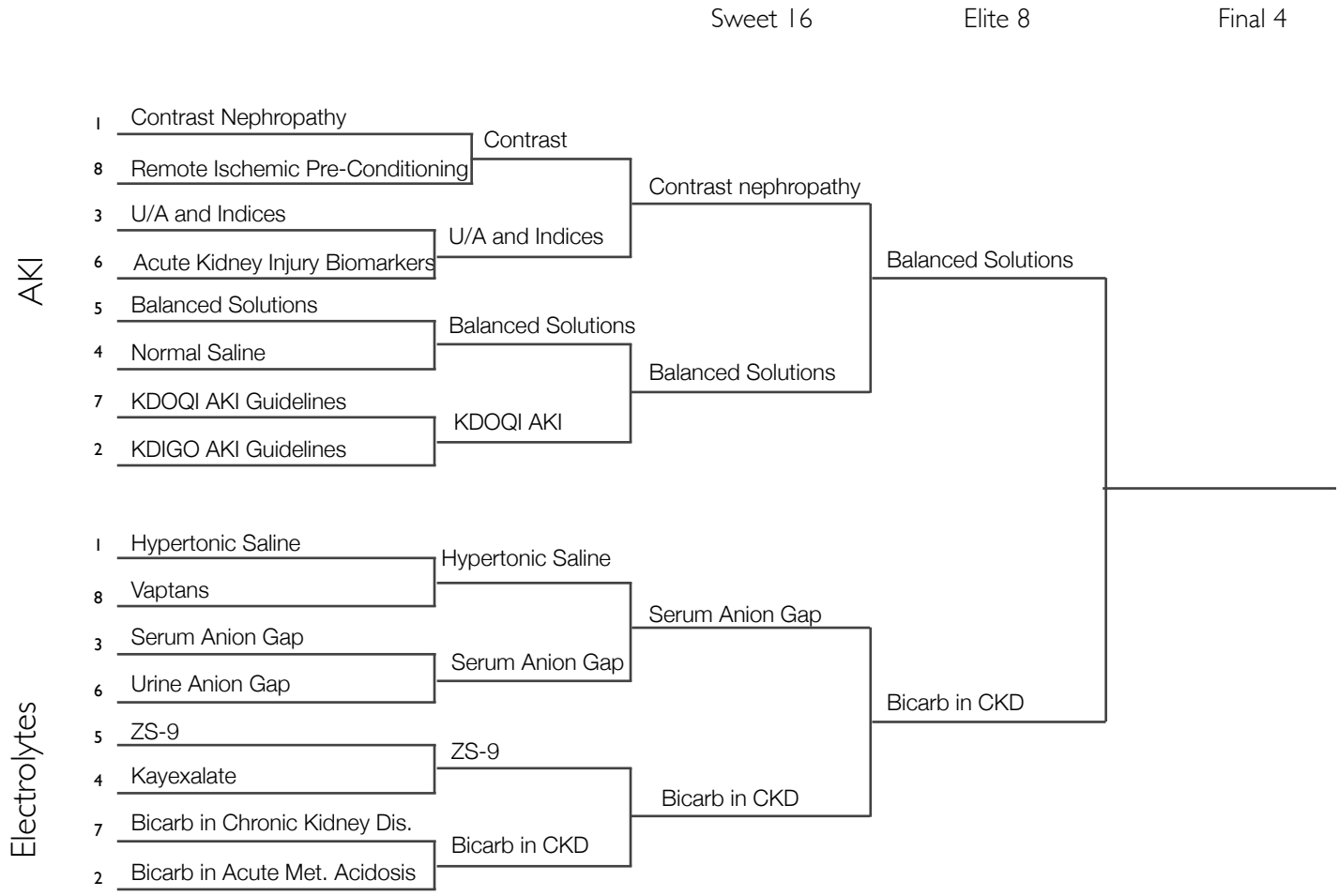
Winner: Eculizumab

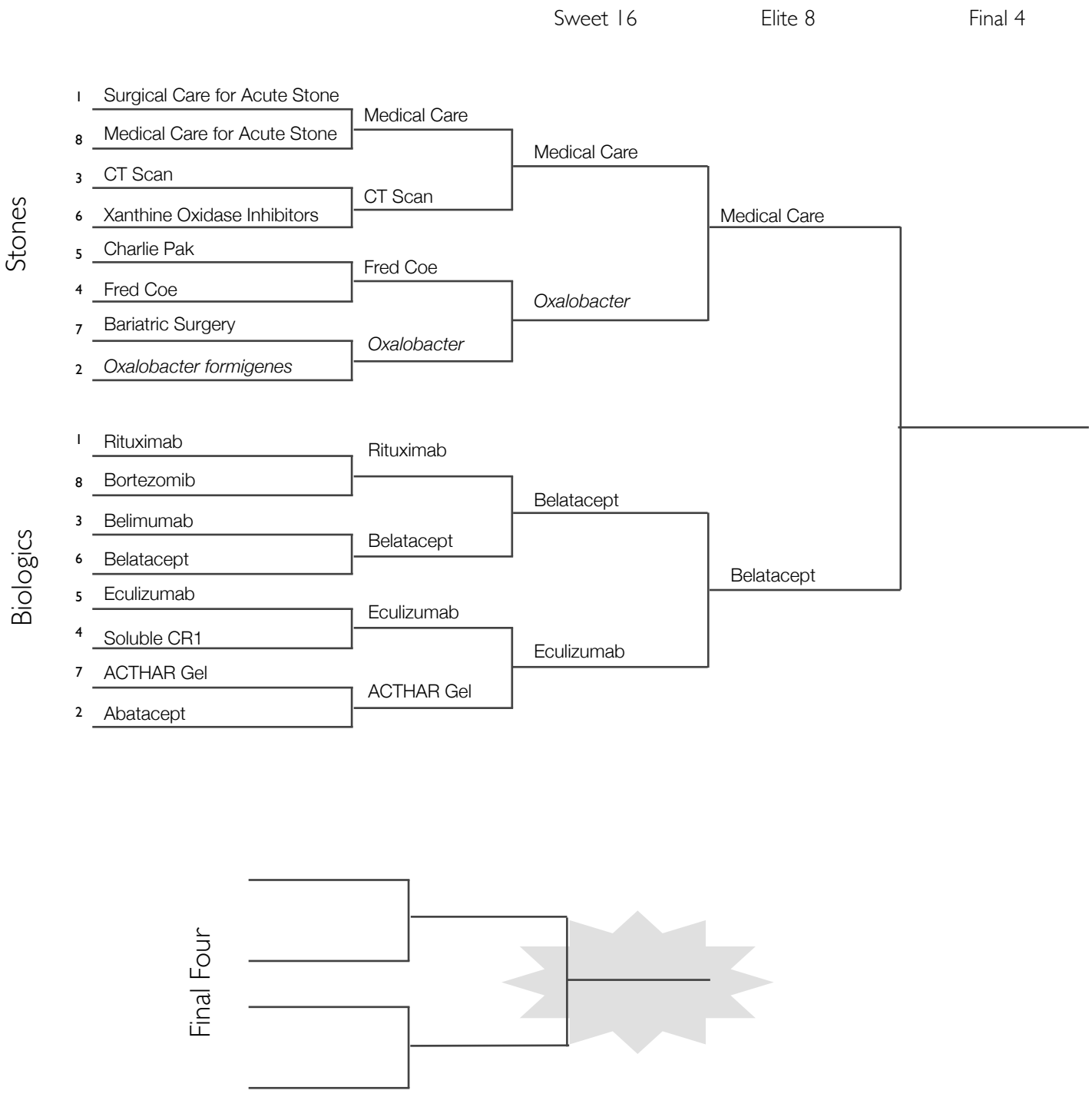
Should we shock you more?? ACTHar Gel while had some earlier success in Italian studies, the use in US has been based on few observational trials only in proteinuric diseases. Eculizumab on the other hand has really changed a pathway of treating diseases: use of the alternative complement inhibition to combat many autoimmune diseases: atypical hemolytic uremic syndrome, membranoproliferative GN, C3 glomerulopathy, and dense deposit disease. And many more to come? Given it's role in complement inhibition, we won't be surprised that it can be used in transplant rejection, ANCA-associated kidney disease and other autoimmune disorders. Clearly, a new class of agents that has more long term potential than ACTHar Gel. Eculizumab wins over and proceeds to the next round to face Belatacept.

Round Three Winners: The Elite Eight




Sweet 16
Elite 8
Final 4
Renal Replacement Therapy
1 Convective Clearance
8 Diffusive Clearance
Diffusive Clearance
3 Buttonhole Technique
6 Residual Renal Function
RRF
RRF
5 Fistula First
4 Urgent Start Peritoneal Dialysis
Urgent Start PD
7 DreamRCT: Intermittent vs CRT
2 DreamRCT: Peritoneal vs Hemo
PD vs Hemo
Urgent Start PD
Urgent Start PD
Regeneration
1 Parietal Epithelial Cells
8 Renin Lineage Cells
Parietal Epithelial Cells
3 Renal Pericytes
6 EMT
Renal Pericytes
Renal Pericytes
Renal Pericytes
5 Tubule Self-Duplication
4 Resident Stem Cells
Tubule Self-Duplication
7 Hypertrophy
2 Bioartificial Kidney
Bioartificial Kidney
Bioartificial Kidney


Sweet 16
Elite 8
Final 4
AKI
1 Contrast Nephropathy
8 Remote Ischemic Pre-Conditioning
Contrast
3 U/A and Indices
6 Acute Kidney Injury Biomarkers
U/A and Indices
Contrast nephropathy
5 Balanced Solutions
4 Normal Saline
Balanced Solutions
7 KDOQI AKI Guidelines
2 KDIGO AKI Guidelines
KDOQI AKI
Balanced Solutions
Balanced Solutions
Electrolytes
1 Hypertonic Saline
8 Vaptans
Hypertonic Saline
3 Serum Anion Gap
6 Urine Anion Gap
Serum Anion Gap
Serum Anion Gap
5 ZS-9
4 Kayexalate
ZS-9
7 Bicarb in Chronic Kidney Dis.
2 Bicarb in Acute Met. Acidosis
Bicarb in CKD
Bicarb in CKD
Bicarb in CKD


Sweet 16
Elite 8
Final 4
Stones
1 Surgical Care for Acute Stone
8 Medical Care for Acute Stone
Medical Care
3 CT Scan
6 Xanthine Oxidase Inhibitors
CT Scan
Medical Care
5 Charlie Pak
4 Fred Coe
Fred Coe
7 Bariatric Surgery
2 Oxalobacter formigenes
Oxalobacter
Oxalobacter
Medical Care
Biologics
1 Rituximab
8 Bortezomib
Rituximab
3 Belimumab
6 Belatacept
Belatacept
Belatacept
5 Eculizumab
4 Soluble CR1
Eculizumab
7 ACTHAR Gel
2 Abatacept
ACTHAR Gel
Eculizumab
Belatacept
Final Four

Toxins

Aristolochic Acid versus DSHEA 1994

Winner: Aristolochic Acid

Aristolochic acid's connection to medicine began as a curious case series out of Belgium. A series of middle-aged women who developed kidney failure due to what was initially called Chinese herb nephropathy. This outbreak, traced to a slimming clinic who's recipe was contaminated with Aristolochia instead of Stephania tetrandra as the herbalist prescribed. A handful of years after the outbreak of kidney failure the victims began to develop unusual transitional cell cancers. They occurred in low risk patients like a 28 year old and in unusual locations, the renal papilla of 42 year old and multifocal disease of the ureters. This lead to the discovery that aristolochic acid covalently binds to the DNA and triggers adenine to thymine mutations.

These unusual cancers and the DNA adducts triggered the realization that Aristolochia was responsible for Balkan Endemic Nephropathy, a 50 year old medical mystery responsible for tens of thousands of cases of end-stage renal disease and urogenital cancers in southeastern Europe.

The same clues also led to the possibility that the reason that Taiwan leads the world in both ESRD and GU cancer was the high use of Aristolochia in Chinese herbal therapies. Forty percent of the population of Taiwan has been exposed to Aristolochia at an average dose of 100g per person.

The last piece to this puzzle and the reason Aristolochia is walking all over the Toxins region is the likely possibility that use of Aristolochia is causing kidney failure and cancer in China, where herbal medicine is ubiquitous. Aristolochia is probably the most important public health discovery of the 21st century. Read about this dramatic story here.

Click on the NephMadness Recommended Article for Aristolochic Acid

Hypertension

Systolic Blood Pressure versus JNC8

Winner: JNC8

JNC8 was introduced this past December to a storm of controversy but it represents both a first and a last. It is the last guideline that began its journey under the auspices of the National Heart, Lung and Blood Institute but famously, just as the guidelines were finishing, the organization announced it would no longer be involved in guideline development and would leave that to specialty societies. It represents a first in that the guideline development adhered to the Institute of Medicine's standards on guideline development. Because of this adherence to the IOM standards, JNC8 is a very different document from JNC7. It is a narrower document that doesn't attempt to be a comprehensive guide to hypertension. Its use of IOM guidelines and its reliance on only RCT shows the future of clinical guidelines. For more info see this.

Click on the NephMadness Recommended Article for JNC8

Renal Replacement Therapy

Residual Renal Function versus Urgent Start PD

Winner: Urgent Start PD

Urgent Start PD represents a new way of thinking about how patients are started on renal replacement therapy. This is important as the US has a problem with too few patients on PD versus HD compared to other nations. The notion of starting a patient with progressive CKD with no access on PD seemed unthinkable a few years ago. Now this trend is starting to catch on and as a result we are seeing more and more patients on PD. This is a good thing. Residual renal function should be proud of the deep run they had in this year's NephMadness. Residual Renal Function is no doubt one of the most important factors contributing to mortality and morbidity in patients with ESRD. Every effort should be taken to preserve this.

Click on the NephMadness Recommended Article for Urgent Start PD

Kidney Regeneration

Renal Pericytes versus Bioartificial Kidney

Winner: Renal Pericytes

Team Renal Pericytes take the Kidney Regeneration bracket title and earn a spot in the Sweet 16. Team Bioartificial Kidney put up a good fight; however, this is still more of a dream than a reality. While the Nature Medicine paper published a year ago was a major breakthrough, we still have a long, long way to go. On the other hand, team Pericytes is really starting to create a buzz and hopefully we will start seeing real therapies aimed at pericytes soon.

If you could only read one article on the subject, then this would be it.

Click on the NephMadness Recommended Article for Renal Pericytes

Acute Kidney Injury

Contrast Nephropathy versus Balanced Solutions

Winner: Balanced Solutions

Balanced solutions marches on. Sorry Contrast Nephropathy, but we had to go with the renewed study of intravenous solutions as this is a nephrology staple and has the potential to really be a game changer in nephrology. Our NephMadness one article to read recommendation is below.

Click on the NephMadness Recommended Article for Bicarbonate in CKD

Electrolytes

Serum Anion Gap versus Bicarbonate in CKD

Winner: Bicarbonate in CKD

While we have no doubt that team Serum Anion Gap is arguably one of the most useful formulas in nephrology it couldn't take down team Bicarb in CKD. Large definitive studies still have not been performed but smaller studies have been encouraging. We have highlighted a recent study in CJASN on this topic.

Click on the NephMadness Recommended Article for Bicarbonate in CKD.

Kidney Stones

Medical Care of Acute Stones versus Oxalobacter formigenes

Winner: Medical Care of Acute Stones

Medical care for acute stones is a way to empower both nephrologists and patients. During Bruce Molitoris' president address at the ASN he implored nephrologists not to limit their practice to dialysis. He emphasized the need for nephrologists to fight limitations to their scope of practice. Acute kidney stone management is one of the fronts in this battle. Nephrologists should not retreat from kidney stones but fight to keep it. Learn more about acute management of kidney stones here.

Click on the NephMadness Recommended Article for Medical Care of Acute Stones

Biologics

Belatacept versus Eculizumab

Winner: Belatacept

Belatacept represents a new era in transplantation. The potential for a calcineurin-inhibitor free regimen. This is the last remaining transplant-related entity left in NephMadness. Eculizumab has a lot of potential for a variety of glomerular diseases that are complement related. Belatacept on the other hand, has a seat at the table in transplantation. However, cost issues, long term infection concerns, and administration issues (IV only) have hampered their widespread adoption. We link to the pivotal BENEFIT trial published in the American Journal of Transplantation.

Click on the NephMadness Recommended Article for Belatacept

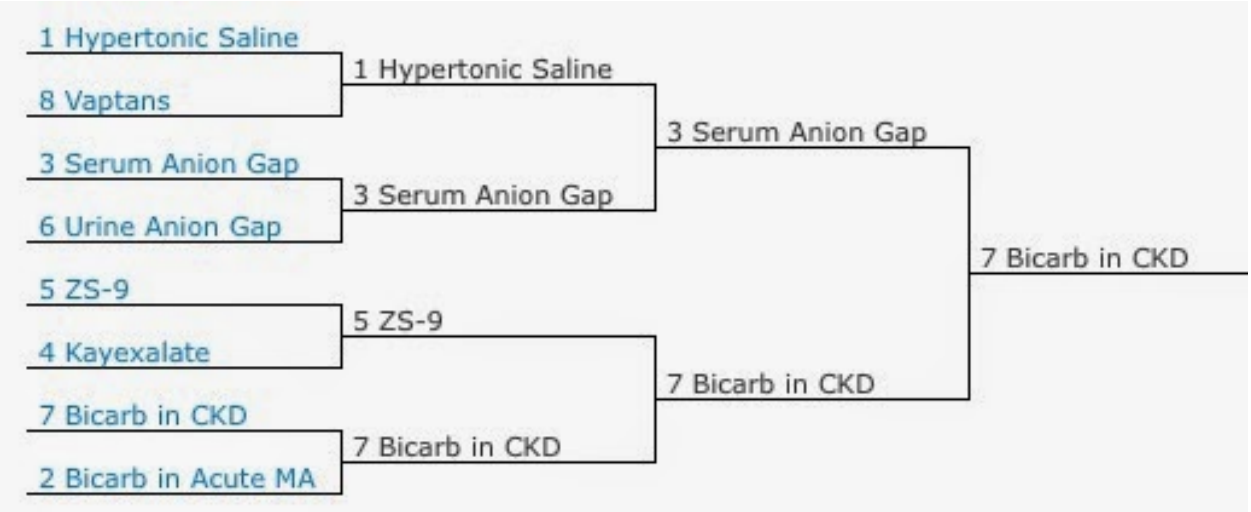
Editorials on the Elite Eight

The Fall of the Serum Anion Gap

from PBFluids.com

The serum anion gap was an entry on the electrolyte region of NephMadness. It won it's opening round over urine anion gap and advanced to the Sweet 16 by beating hypertonic saline but failed to win the electrolyte region when it fell to

Bicarbonate in CKD.



CJASN did a recent review of the anion gap and they were frank with its limitations:

> *We conclude that the common definition of an abnormal gap as one that exceeds the upper limit of the normal anion gap or exceeds 2 SD above a specific mean value can lead to a failure to identify some cases of metabolic acidosis, to underestimate the severity of the acid load, and to misidentify complex acid-base disorders. In addition, the nature of the putative retained acid can have an important effect on the magnitude of the increase in the anion gap, and therefore should always be considered in the interpretation of acid-base data.*

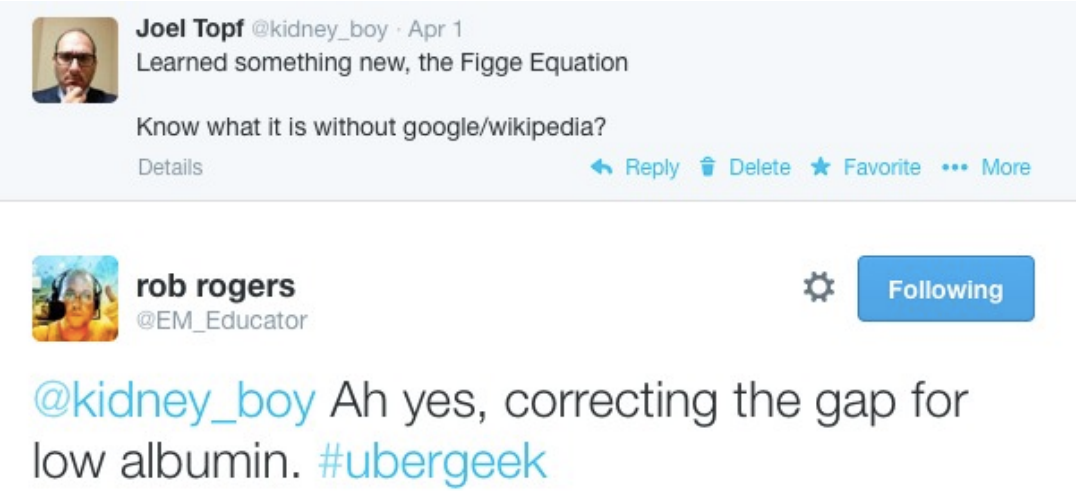
Some interesting notes about the anion gap: though the serum potassium was included in the original derivation of the calculation, none of the major U.S. textbooks include it. The upper limit of normal anion gap from the 8 sources included in the paper is much higher than I teach. I use 12 and after the ASN Board Review Class, I remember feeling that was too high.

	upper limit of anion gap
Fluid, Electrolyte and Acid-Base Physiology, 4th Ed. Halperin et al	16
Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th Ed. Burton Rose	13 (11*)
Goldman's Cecil Medicine, 24th Ed. Seifter	12
Textbook of Nephrology, 3rd Ed. Salem and Batlle	12 (10*)
Brenner and Rector's The Kidney, 8th Ed. Dubose	15
Murray and Nadel's Textbook of Respiratory Medicine, 5th Ed. Effros and Swenson	16
UpToDate 2013 Emmett	13 (9*)
Henry's Clinical Diagnosis and Management by Laboratory Methods, 22nd Ed. Oh	16

* with ion selective electrodes

The article then discusses the fact that ion selective electrodes are more sensitive for chloride so they detect higher chloride concentrations so that average and pathologic anion gaps are lower.

The article discusses the importance of albumin in the normal anion gap. As albumin falls, either the limit for a pathologically elevated anion gap needs to fall or the calculated anion gap needs to be adjusted upwards. The article recommends the latter. The anion gap should rise 2.5 for ever 1 g/dL the albumin falls below normal (presumably 4 g/dL). The authors recommend that albumin adjustments be incorporated into laboratory reporting so clinicians do not need to worry about this.



The meat of the article is contained in table 3 where the authors review 5 studies that looked at the sensitivity of an increased anion gap for lactic acidosis. It's not a pretty picture.

Table 3. Sensitivity of increased anion gap in detecting hyperlactatemia

Population (*n*)	Range and Anion Gap Indicating Acidosis (mEq/L)	Corrected For Serum Albumin Concentration	Sensitivity and Comments	Reference
272 patients in emergency department	>12	Yes	58% 78% with corrected anion gap	Adams *et al.* (26)
438 patients with lactate measured	5–16 >12	No	44% with elevated lactate 2.5 mmol/L had abnormal AG	Levraut *et al.* (27)
56 patients with serum lactate >2.5 mmol/L	>12 and <16 >16	No	43% with serum lactate between 2.5 and 4.9 mmol/L 50% with lactate between 5 and 9.9 mmol/L had normal AG	Iberti *et al.* (25)
143 ICU patients with serum lactate >2.5 mmol/L	10–12 >12	Yes	63% with serum lactate >2.5 mmol/L 94% with serum lactate >2.5 mmol/L with corrected AG	Chawla *et al.* (29)
Retrospective analysis of 639 values from 356 hospitalized patients	5–12 >12	Yes	39% uncorrected 75% with corrected anion gap ROC values for uncorrected and corrected AG similar	Dinh *et al.* (28)

AG, anion gap; ICU, intensive care unit; ROC, receiver operating characteristic.

The anion gap is meant to be a screening test, if it is positive the specific cause of the increased anion gap can be investigated with specific assays. Screening tests are supposed to be sensitive so that if they are negative one can rule out that potential diagnosis. Here we see that the anion gap is wearing no clothes. Sensitivity can be as bad as 43%, but typically runs around 60-70%.

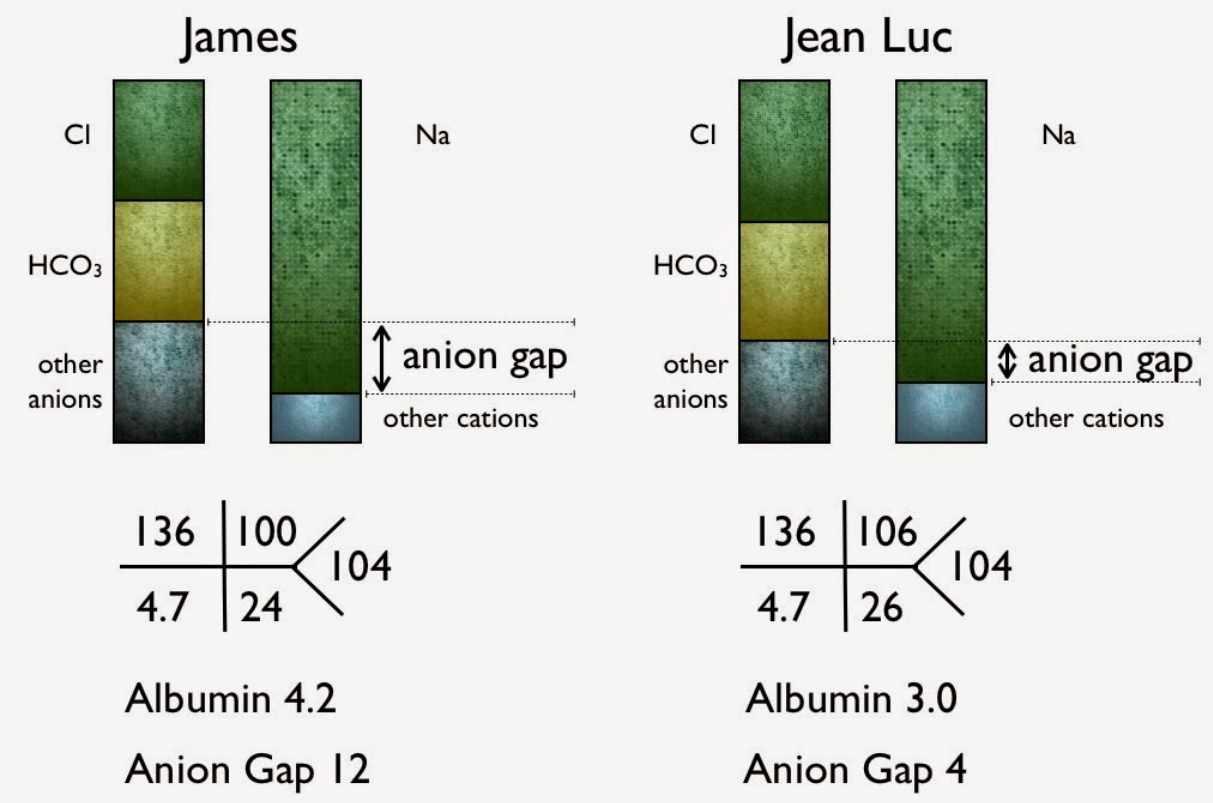
In Adams et. al's (PDF) analysis of emergency department patients, 50% of patents with a lactate level between 5 and 9.9 had an anion gap below 12!

We performed sensitivity analyses for both of the a priori established AG thresholds as to their overall performance in predicting lactic acidosis (table 2).

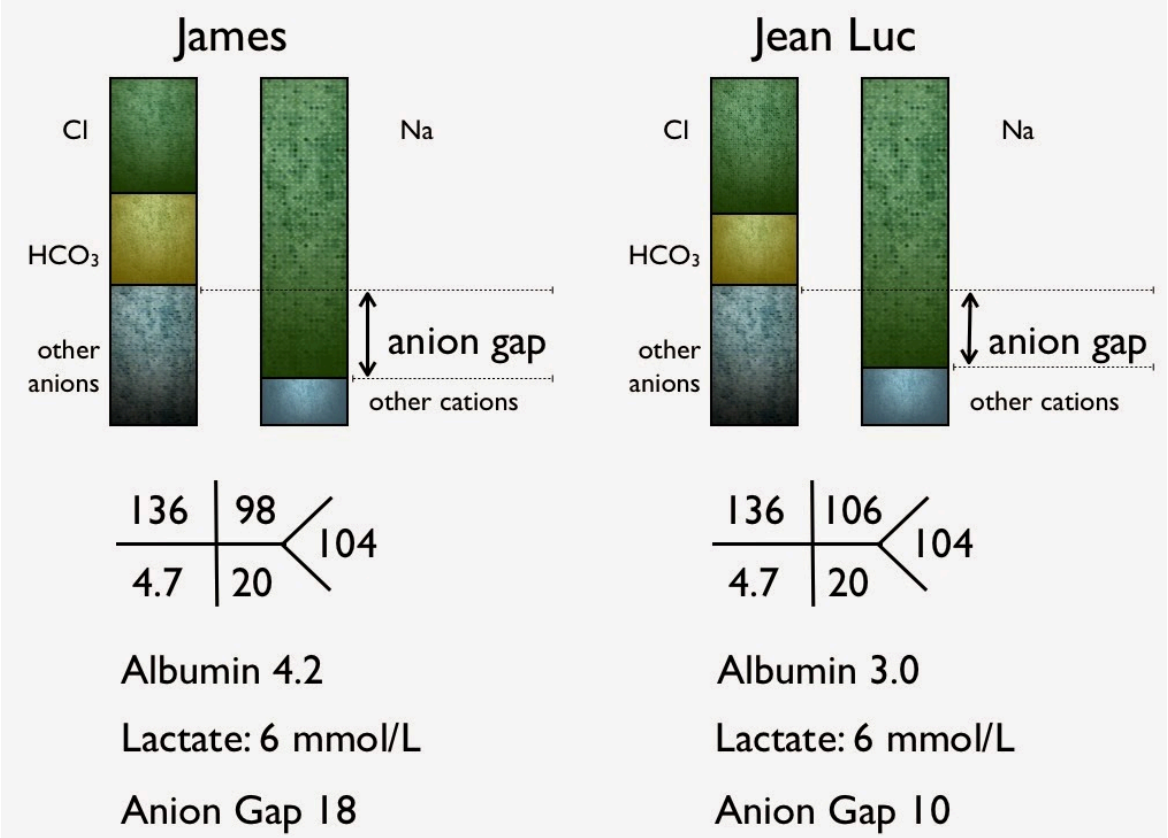
The AG threshold of 6 was most sensitive in predicting LA, with a sensitivity of 96.4% but a specificity of only 17.3%. The AG threshold of 12 was more specific at 81.0% but it yielded a sensitivity of only 58.2% (cases from our cohort of severe LA with a "normal" AG ,12 are detailed in table 3).

The accuracy of the AG threshold of 6 and 12 were 31.7% and 76.9% respectively (see table 2). By post hoc ROC analysis we determined that the optimal AG threshold to screen for the presence or absence of LA was 12.1.

The authors theorize that the anion gap fails due to the broad range of normal in the anion gap. The normal anion gap can range from 3 to 12, so suppose a patient is sitting at the low range of normal say 3 or 4, they could absorb an lactate level of 8 or 9 mmol/L while still maintaining a normal anion gap. See the illustrations with Gamblegrams below:



Both James and Jean Luc start with normal anion gaps, though James is at the upper limit and Jean Luc is at the lower limit of normal.



Both patients develop equivalent and significant lactic acidosis but only James develops an anion gap.

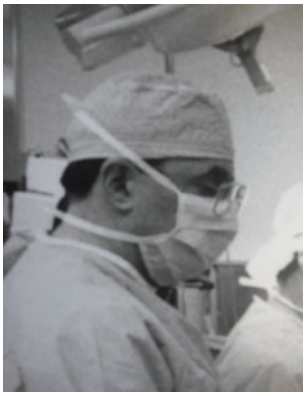
The article then describes some unusual behaviors of the anion gap. The first is that the anion gap can rise more than the bicarbonate falls. A basic tenet of the anion gap is that the ratio of the change of bicarb and the anion gap is 1:1, this is the theory that the delta gap equation rests on. In lactic acidosis apparently the the anion gap can rise 1.8 for every fall in the bicarbonate of one. The net result of this is patients can have significant lactic acidosis in the presence of a normal serum bicarbonate.

Additionally, patients with identified organic acidosis, the identified acid typically does not explain the entire gap.

The authors discuss some data on using personalized normal anion gap targets from previous labs. This would help the sensitivity of the test in patients who run low normal anion gaps and have a hard time cross the threshold for an increased anion gap (see Jean Luc above). However, the authors point to a study (Lipnick et al. 2013) which used this technique and still missed approximately 30% of lactic acidosis cases.

This is a good article but it does not address issues such as the the anion gap's usefulness in the diagnosis of the toxic alcohols and its use in the management of DKA.

Is normal saline bad for the kidneys? **Yes**



The Skeptical Scalpel has been a surgeon for 40 years and was a surgical department chairman and residency program director for over 23 of those years. He is board-certified in general surgery and a surgical sub-specialty and has re-certified in both several times.

He has over 90 publications including peer-reviewed papers, case reports, editorials, letters and book chapters. He blogs at SkepticalScalpel where he averages 1,400 page views a day. He has over 8,800 Twitter followers.

In October of 2012, JAMA featured a paper describing the effect of two intravenous fluids on the incidence of renal failure in critically ill ICU patients.

The paper compared normal saline (relative to human plasma, a high chloride-containing solution) administration to more physiologic, low chloride-containing IV fluids such as Hartmann's solution (very similar to Ringer's lactate) or Plasma-Lyte 148.

It found that using the low chloride intravenous infusions led to a statistically significant decrease in the incidence of acute kidney injury and the need for renal replacement therapy.

There was no significant difference in mortality rates related to the various solutions used.

The JAMA paper was based on research from a single hospital in Melbourne in 2008-2009 and was a before-and-after trial.

A 2012 randomized, double-blind crossover trial in 12 human subjects showed that compared to Plasma-Lyte 148, infusions of normal saline caused more sustained hyperchloremia and significantly decreased renal blood flow velocity and renal cortical perfusion.

Note that Plasma-Lyte 148 costs about 3 times as much as Ringer's lactate, about $12 vs. $4 respectively. That doesn't sound like much until you realize that 200 million liters of normal saline are used yearly in the US.

So what is a clinician to do? Normal saline is not really "normal." Solutions containing amounts of chloride closer to that of human plasma are the correct ones to use.

See the table for the amounts of sodium, chloride and buffer in standard IV solutions.

Concentration in one liter of solution (in Meq)

	Na	Cl	Buffer
Plasma	14	100	Bicarb 25
Normal saline	154	154	0
Hartmann's solution	131	111	Lactate 29
Ringer's lactate	130	109	Lactate 28
Plasma-Lyte 148	140	98	Acetate 23

In defense of JNC8

Dr. Susan P. Steigerwalt, MD, is the director of the hypertension clinic at St Clair Specialty Physicians and a member of the division of nephrology and hypertension at St John Hospital in Detroit, Michigan. She is also a clinical associate professor at Wayne State University. Her formal certifications are in internal medicine (ABIM), nephrology (ABIM) and Hypertension (ASH). Her particular research interests include the use of cognitive behavioral interventions to improve adherence in hypertensive women, resistant hypertension, primary aldosteronism and role of aldosterone in progression of kidney disease. She is delighted to be a St John site Principal Investigator for CRIC.

JNC-8 is a carefully crafted, conservative document which answers three very specific questions using RCT data and carefully rating the available evidence. It is far narrower in scope than JNC-7 and it is not a “how to” document. JNC-8 tells us what we do not have evidence for; what we do not know; and what we really need to know: ie, clear data on systolic BP goals. (I await SPRINT). A clear division within the JNC working group regarding goal BP age 60-80 was published March 15 in the Annals of Internal Medicine (PDF). This minority report looks at the evidence for those age 60-80 and concludes the goal systolic should be 140, NOT 150 as stated in the majority position

My choice for usable guidelines for the real world are the ASH-ISH guidelines and the AHA-CDC-ACC guidelines on systems approach to blood pressure control. Both are short, succinct and available on line, free of charge.

Medical Acute Stone Care

Dr. Goldfarb is the 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. He has a long-standing interest in kidney stone pathophysiology. His group established a registry of patients with cystinuria. The goal of this registry is to follow patients with cystinuria and learn more about the course of this disorder. He also is involved in new drug development for the treatment of cystinuria. The consortium also studies Dent disease, primary hyperoxaluria and APRT deficiency (a cause of dihydroxyadenine stones). Dr. Goldfarb is the associate editor of the Clinical Journal of the American Society of Nephrology (CJASN) and the founding editor of CJASN‘s eJournal Club.

Medical stone care, also known as “Medical Expulsive Therapy”, MET, continues to be a commonly practiced therapy.

A common misperception is the use of forced diuresis. It’s usual ER therapy and unlikely to ever have any benefit. If a patient with an obstructed kidney is given intravenous saline, the saline will be excreted by the contralateral kidney, the one that still has a GFR. It will NOT get to the obstructed kidney which quickly experiences a reduction in GFR. The best RCT on this subject was done by Preminger’s group at Duke.They gave patients with obstructed stones 2L NS over 2h, vs. 20 mL over 2h. There was no benefit of the aggressive fluid therapy in pain scores or stone passage rates. So we need additional therapies to promote stone passage.

Alpha blockers appear to be effective in numerous relatively small, if perhaps non-definitive RCTs. Presumably they cause ureteral relaxation and can be effective for stones up to 1 cm in size and even in a proximal location. I usually prescribe tamsulosin 0.4 mg qhs for 28 days assuming the patient does not have the sort of pain that requires hospitalization, and they can go to work or school or whatever. I warn them about hypotension, especially in younger women who have relatively low BP to begin with.

I also usually recommend some OTC NSAID (e.g., Aleve = naproxen 220 mg tabs, 2 tabs bid) since that adds some anti-inflammatory effect which might facilitate stone passage by reducing ureteral edema. Occasionally, in the NSAID-intolerant patient, I prescribe prednisone 20 mg qd instead.

Most of the European studies of calcium channel blockers, e.g., nifedipine, showed efficacy, and included concomitant administration of glucocorticoids, but whether these are independently useful has not been determined.

I also recommend for renal colic getting into a warm bath, turning down the lights and drinking some beer for maximal relaxation/dilatation; something like a Goose Island Lolita.

The first time I prescribed an alpha-blocker for a woman named Jackie was a memorable experience. At that time I was practicing at St. Vincents Hospital in New York, now closed. I called in the prescription and the pharmacist said “um, doc, Jackie does not have a prostate gland”. I replied, “I’m practicing here in Greenwich Village and YOU don’t know whether Jackie has a prostate gland or not!”

Belatacept

Dr. Prosek’s clinical interests include the CardioRenal Syndrome where he is working with his cardiology colleagues to define the role of ultrafiltration in acute decompensated heart failure, and the budding field of OncoNephrology, where he holds a clinic devoted to managing the toxicities of targeted chemotherapies such as VEGF-inhibitors and tyrosine kinase inhibitors.

Belatacept was put on the map in the 2010 BENEFIT trial, and efforts to define its role in transplantation are quickly ramping up. Belatacept is a CTLA-4 inhibitor, blocking the costimulatory pathways for T-cell activation. This is a welcome development, and its importance is best understood in the historical context of transplant immunosuppression. The role (and subsequent doses) of glucocorticoids has certainly diminished over the decades as additional medications for maintenance immunosuppression have been developed. Although there is disagreement on whether steroids should be stopped altogether (KDIGO Guidelines) or maintained at low doses, it’s clear that the toxicities related to exposure to higher doses over long periods of time have been greatly reduced. This has been accomplished mostly on the back of calcineurin inhibitors. While these drugs have a narrower side effect profile than steroids, they have one particularly unfortunate consequence, if not painfully ironic – chronic allograft nephropathy or calcineurin inhibitor toxicity.

Belatacept is being developed as a potential replacement for calcineurin inhibitors, and early studies have shown promise in this regard. The aforementioned BENEFIT trial compared two dosing regimens of belatacept versus cyclosporine. Although more acute rejection was seen in the belatacept arms, GFRs were significantly higher with the experimental

treatment. This study follow up has now reached five years with the belatacept arm benefiting from almost 25% higher GFR compared to the cyclosporine arm (77.2±22.7 with belatacept and 59.3 ±15.3 with CSA at 60 months). BENEFIT-EXT explored the "expanded criteria" donor population, a group perhaps even more sensitive to the risks of calcineurin inhibition. At twelve months graft survival was similar, but the belatacept group reached fewer "renal impairment endpoints" and benefited from an additional 4-7 mL/min of clearance.

The success of these two phase III trials have led to a proliferation of further trials which are ongoing. These investigations are wide-ranging including efforts to use belatacept in steroid-free protocols, kidney-pancreas transplantation, liver transplantation, and in renal recipients with delayed graft function.

What is holding belatacept back is cost, necessity of intravenous administration, but perhaps most concerning is a background rate of malignancy. In the 5 year follow-up of BENEFIT, there were 3 cases of PTLD with belatacept and one with CSA. Other cancers seemed to be more common with belatacept:

- 3 cases of PTLD with belatacept versus 1 with CSA
- 9 cases of non melanoma skin cancers versus 2 with CSA
- 1 Kaposi sarcoma versus none with CSA
- 1 prostate cancer versus none
- 2 breast cancers versus none
- 1 malignant melanoma versus none

Two cases of progressive multifocal leukoencephalopathy with belatacept have also occurred, the patients were taking higher doses at more frequent dosing intervals than recommended. See this page for a nice summary of the some of the safety issues. As the existing and forthcoming studies progress, we will more precisely quantify the incidence of these potentially devastating complications – only then will we truly know if we've reached the new age of transplant maintenance therapies.

Belatacept

Dr. Henderson is assistant director of peritoneal dialysis at SCSP. She has been instrumental in developing a successful acute PD program and growing their PD census for the first time in over a decade. Dr. Henderson went to Michigan State University Medical school and did residency at McLaren MaComb prior to doing her fellowship at St John Hospital and Medical Center.

Urgent start PD is the Michigan Wolverines of Nephmadness…forgotten for years but coming back with a vengeance. Unlike U of M, urgent start PD is dominating the Big dance. With only 7% of incident dialysis patients in the US initiated on PD and as high as 80% of incident patients starting with a tunneled venous catheter (which has the highest morbidity

and mortality), urgent start PD is a solution to a long standing problem. Since Ghaffari pioneered the urgent start PD movement there are now over 100 urgent start programs in the US…and gaining fans fast.

- Data from multiple centers show survival similar to HD with minimal complications
- More patients are given the opportunity to use PD as their modality
- Urgent start programs are showing high retention rates, which is essential to growing PD use in the US
- Urgent start PD prevents tunneled CVC placement
- It allows patient freedom and flexibility of choice in modality
- Helps maintain that residual renal function

It appears that Urgent Start PD has all the right elements to end up on top!

Treatment of Metabolic Acidosis in CKD

Dr. Jordan Weinstein is a nephrologist at St. Michael's Hospital in Toronto and Assistant Professor of Medicine at the University of Toronto. He is the founder and administrator of UKidney.com.

The treatment of metabolic acidosis whether acute or chronic has always been a controversial area. Over the years however, the role of bicarbonate supplementation in CKD has become increasingly important and is recommended in current clinical practice guidelines.

Metabolic acidosis has a number of potential consequences. These include muscle catabolism, insulin resistance, bone resorption, and enhanced systemic inflammation. Furthermore, as CKD progresses, nephrons lose function and their ability to participate in ammoniagensis declines. The burden on remaining nephron to maintain bicarbonate production via ammonium excretion rises. Some have argued that this increase in single nephron ammoniagenesis leads to fibrosis and accelerated loss of these remaining nephrons. Indeed, it has been observed that patients with CKD and metabolic acidosis have a faster rate of decline in renal function than those with normal serum bicarbonate.

Nevertheless, merely showing the impact of metabolic acidosis on patients with CKD does not prove that bicarbonate supplementation – even if the metabolic acidosis improves – is safe or effective. One of the early efforts that have shown benefit is the RCT by Ione de Brito-Ashurst et al. They randomized 134 patients with CKD stage 4 (average CrCl 20 mL/min) and metabolic acidosis (bicarbonate between 16 and 20, average 19.9 mmol/L) to usual care or 1.8 g of sodium bicarbonate (600 mg TID). The results were compelling. With two years of follow-up the bicarbonate group lost 1.88 mL/min of CrCl while the control group lost 5.93 mL/min. Four patients randomized to bicarbonate required dialysis compered to 22 randomized to usual care.

Phisitkul et al showed similar results in a 2-year study using sodium citrate as the exogenous alkali. This, however, is not a randomized study as the control group was made up of patients who refused the sodium citrate.

The theory of neutralizing acid and decreasing single nephron ammoniagenesis can also be achieved through diet changes. Goraya at al showed this during a year long trial of fruit and vegetable supplementation was able to reduce potential renal acid load. The intervention involved providing patients with:

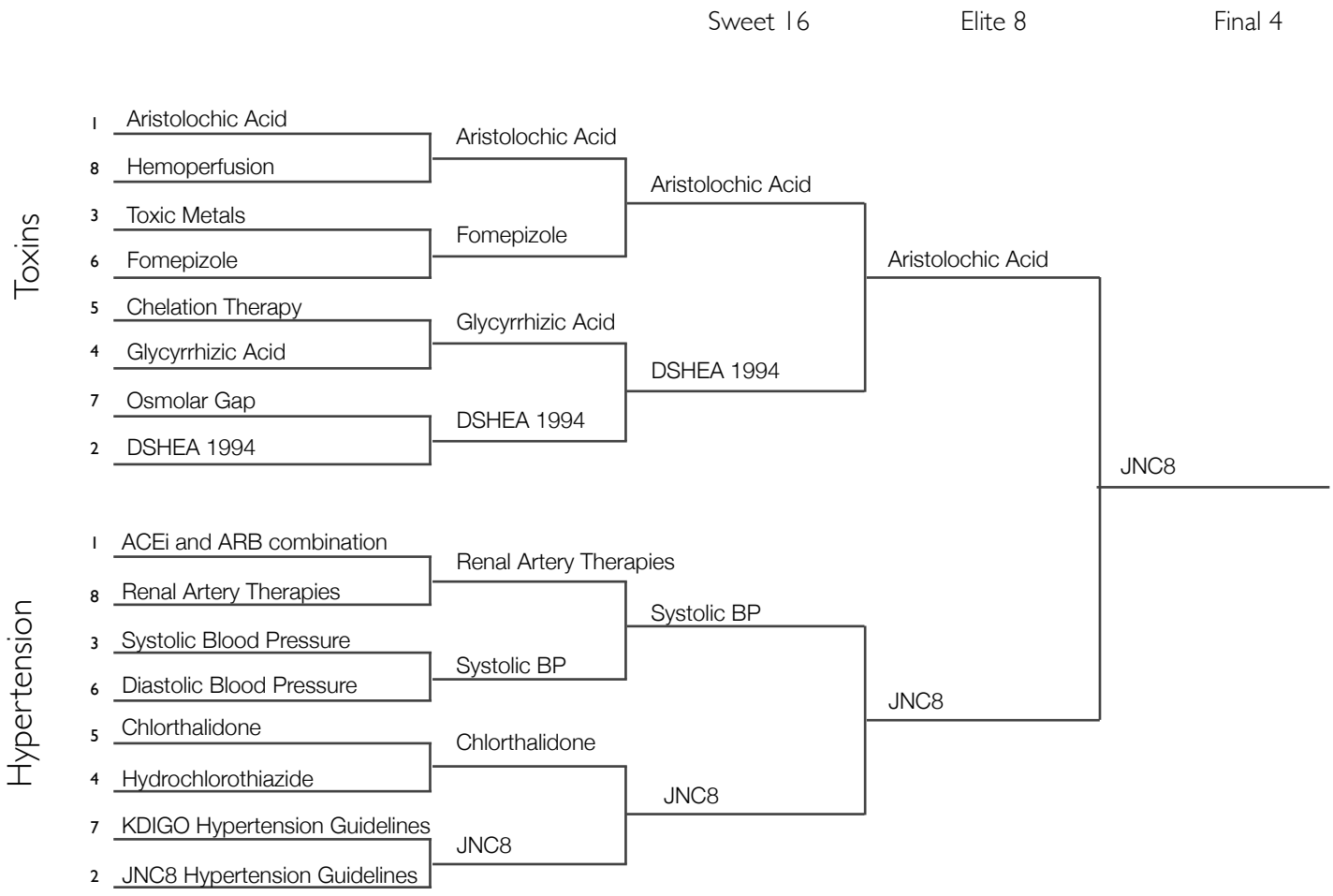
> *The 36 patients in the fruits and vegetables group received fruits and vegetables free of charge, prescribed by a dietitian and distributed from the food bank in amounts to reduce PRAL by half, as done previously (9). Prescriptions emphasized base-producing fruits and vegetables (14), such as apples, apricots, oranges, peaches, pears, raisins, strawberries, carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes, and zucchini.*

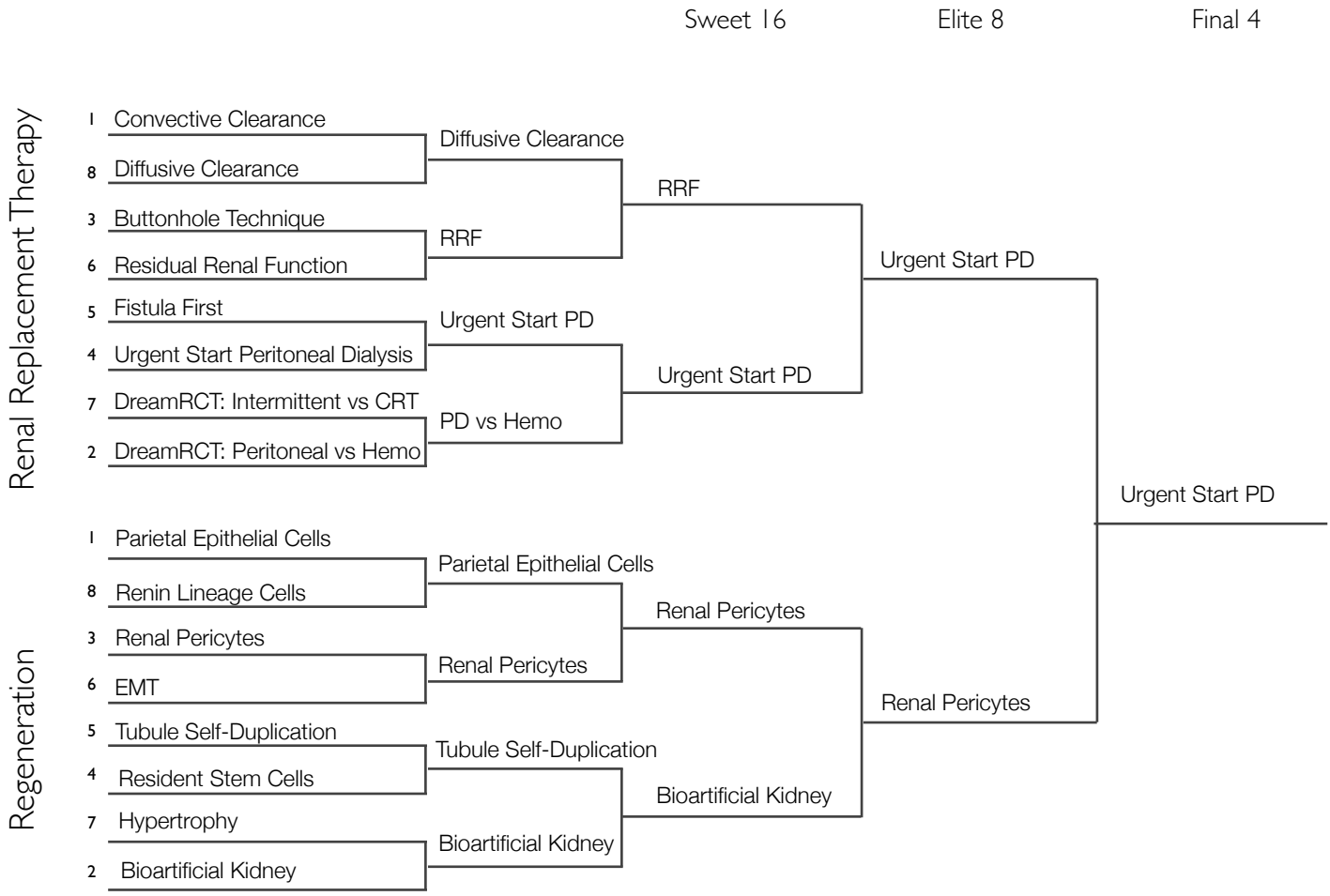
This intervention was able to increase serum bicarbonate (marginally), reduce blood pressure (by 4.3 mmHg systolic 6.4 mmHg diastolic versus sodium bicarbonate for alkalization), and reduce net ammonia production. There was increased potassium load and aldosterone levels but serum potassium remained unchanged at 4.1 mmol/L.

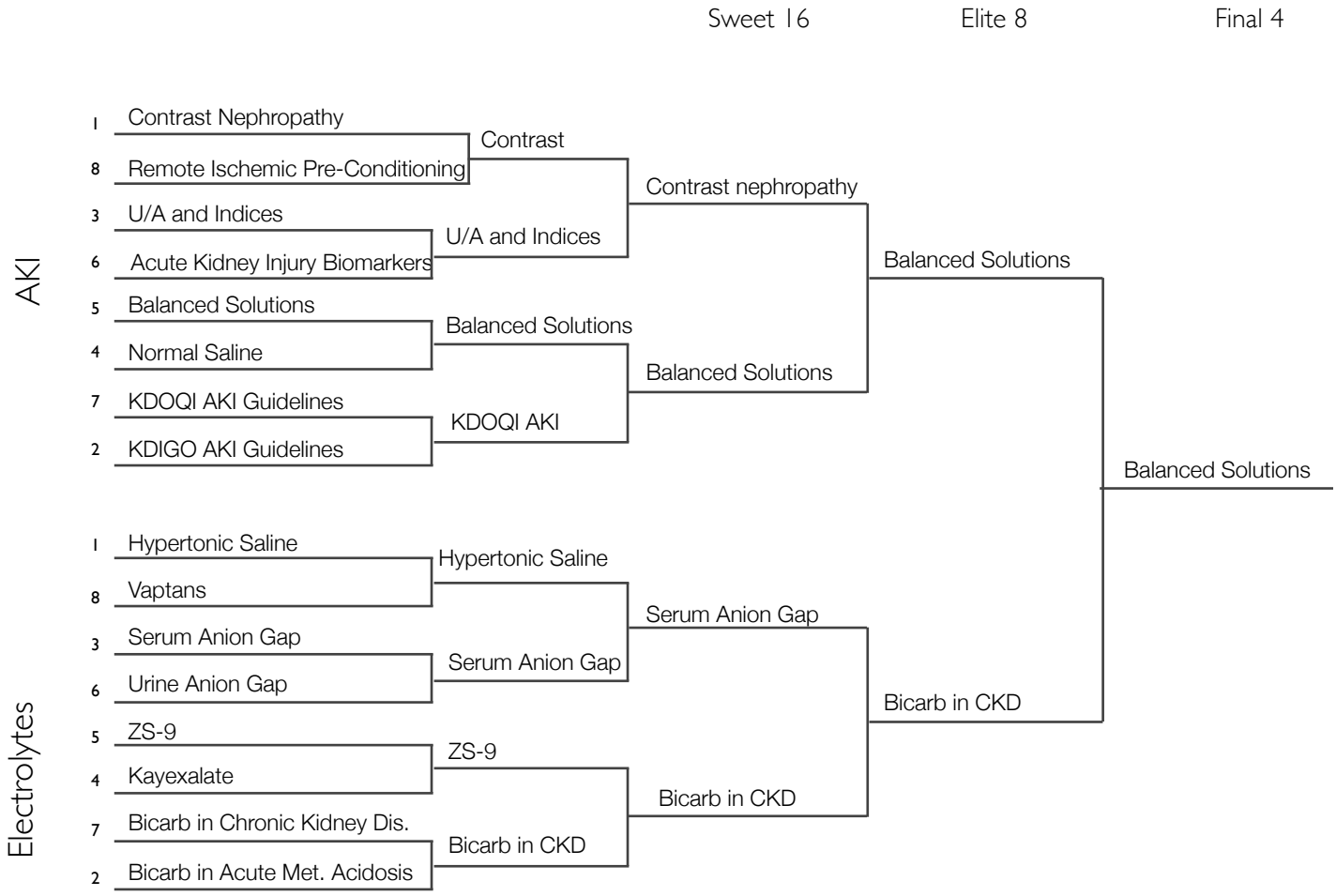
One intriguing line of study has been looking at lowering the potential renal acid load in the absence of metabolic alkalosis. Mahajan attempted this in a cohort of patients with CKD stage 2 (mean GFR 75 ml/min) and serum bicarbonate over 24.5 mmol/L. Patients were randomized to one of three arms: sodium bicarbonate, placebo, or sodium chloride. The GFR was better preserved with sodium bicarbonate than both alternatives after five years of follow-up.

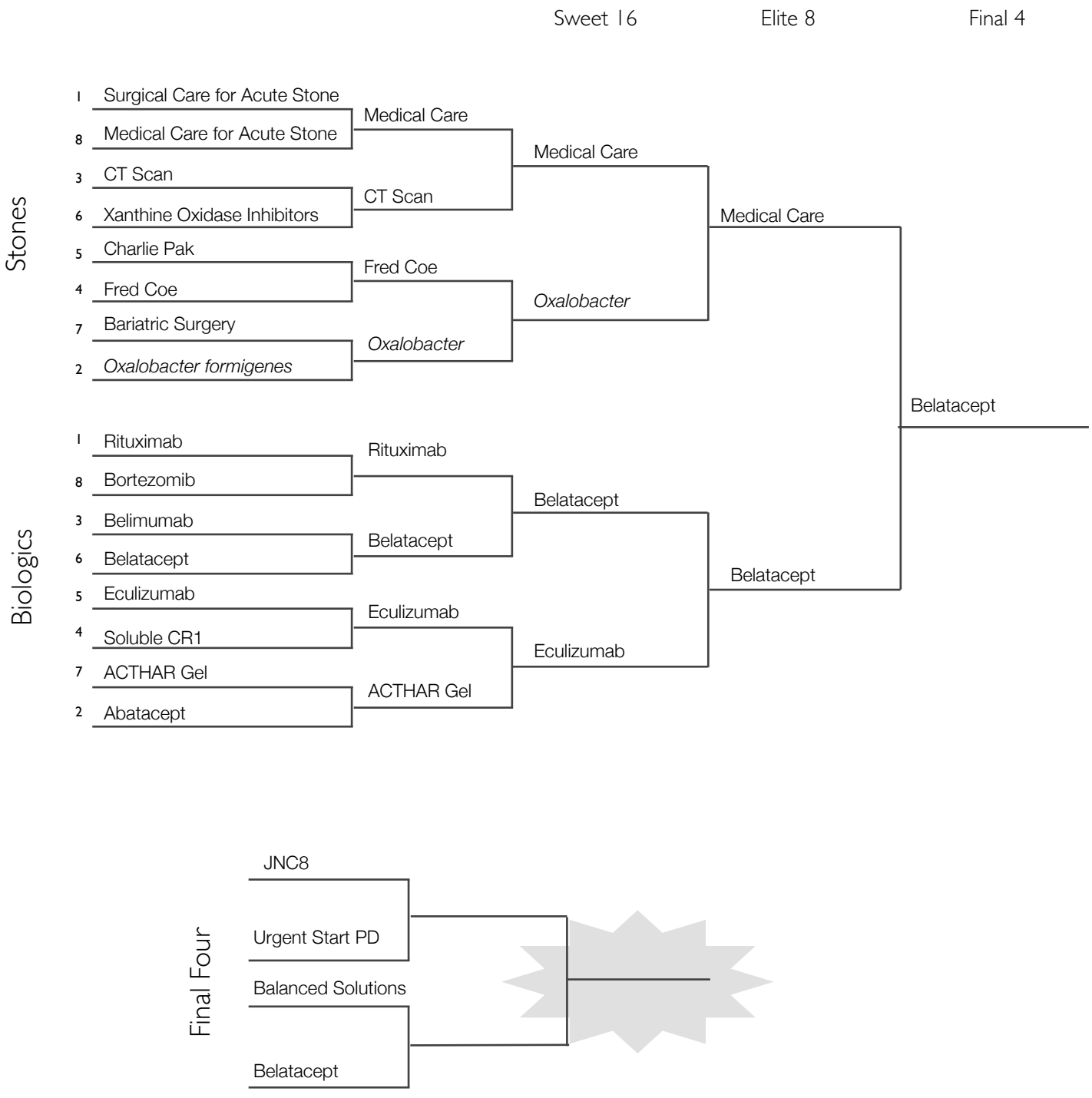
In the studies of alkali, adverse effects such as hypertension and edema have been uncommon and manageable. Alkali therapy still awaits a large, multicenter trial with hard end-points but the clinical data is building and the science looks sound. Sodium bicarbonate (or sodium citrate) supplementation should be strongly considered in patients with CKD and metabolic acidosis.

Round Four Winners: The Final Four




Sweet 16
Elite 8
Final 4
Renal Replacement Therapy
1 Convective Clearance
8 Diffusive Clearance
Diffusive Clearance
3 Buttonhole Technique
6 Residual Renal Function
RRF
RRF
5 Fistula First
4 Urgent Start Peritoneal Dialysis
Urgent Start PD
Urgent Start PD
7 DreamRCT: Intermittent vs CRT
2 DreamRCT: Peritoneal vs Hemo
PD vs Hemo
Urgent Start PD
Regeneration
1 Parietal Epithelial Cells
8 Renin Lineage Cells
Parietal Epithelial Cells
Renal Pericytes
3 Renal Pericytes
6 EMT
Renal Pericytes
Renal Pericytes
5 Tubule Self-Duplication
4 Resident Stem Cells
Tubule Self-Duplication
Bioartificial Kidney
7 Hypertrophy
2 Bioartificial Kidney
Bioartificial Kidney


Sweet 16
Elite 8
Final 4
AKI
1 Contrast Nephropathy
8 Remote Ischemic Pre-Conditioning
Contrast
3 U/A and Indices
6 Acute Kidney Injury Biomarkers
U/A and Indices
Contrast nephropathy
5 Balanced Solutions
4 Normal Saline
Balanced Solutions
7 KDOQI AKI Guidelines
2 KDIGO AKI Guidelines
KDOQI AKI
Balanced Solutions
Balanced Solutions
Electrolytes
1 Hypertonic Saline
8 Vaptans
Hypertonic Saline
3 Serum Anion Gap
6 Urine Anion Gap
Serum Anion Gap
Serum Anion Gap
5 ZS-9
4 Kayexalate
ZS-9
7 Bicarb in Chronic Kidney Dis.
2 Bicarb in Acute Met. Acidosis
Bicarb in CKD
Bicarb in CKD
Bicarb in CKD


Sweet 16
Elite 8
Final 4
Stones
1 Surgical Care for Acute Stone
8 Medical Care for Acute Stone
Medical Care
3 CT Scan
6 Xanthine Oxidase Inhibitors
CT Scan
Medical Care
5 Charlie Pak
4 Fred Coe
Fred Coe
7 Bariatric Surgery
2 Oxalobacter formigenes
Oxalobacter
Oxalobacter
Medical Care
Belatacept
Biologics
1 Rituximab
8 Bortezomib
Rituximab
3 Belimumab
6 Belatacept
Belatacept
Belatacept
Belatacept
5 Eculizumab
4 Soluble CR1
Eculizumab
7 ACTHAR Gel
2 Abatacept
ACTHAR Gel
Eculizumab

Final Four
JNC8
Urgent Start PD
Balanced Solutions
Belatacept

Toxins vs Hypertension

Aristolochic Acid versus JNC8

Winner: JNC8

Renal Replacement Therapy vs Regeneration

Urgent Start PD versus Pericytes

Winner: Urgent Start PD

Acute Kidney Injury vs Electrolytes

Balanced Solutions versus Bicarbonate in CKD

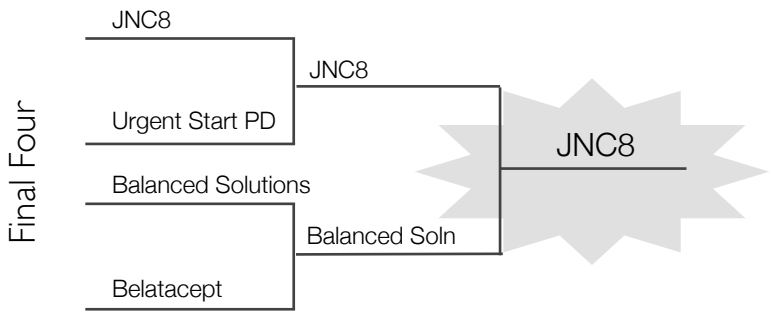
Winner: Balanced Solutions

Kidney Stones vs Biologics

Medical Care of Acute Stones versus Belatacept

Winner: Belatacept

Rounds Five and Six:



The Final Four Matches

JNC8 versus Urgent Start PD

Winner: JNC8

JNC8 continues to march through NephMadness 2014. This controversial team was just kicked out of the NIH league and is in search of a home. Also, a minority of the authors have published a call to decrease the BP threshold to less than 140 mmHg in patients over 60 without DM or CKD. There are supporters of JNC8 though. The guidelines simplify the treatment paradigm allowing for a much simpler approach to the care of patients with hypertension. JNC8 has also put the discussion of hypertension research and clinical care back in the national dialogue. This is a good thing. We are not picking JNC8 because it is the definitive document for approaching HTN. This is not the case. We still have many holes to fill in our understanding of how to properly manage this complicated condition. From JNC7 to JNC8 we have had several large trials published that have rocked the hypertension community. Namely, the ACCORD-BP trial which was published in NEJM in 2010. The dogma at the time of this trials inception was that the lower we go for BP control the better. Well, side-effects were notably higher in the lower BP arm of this trial (<120 vs. <140 mmHg SBP) without mortality benefit. We like team Urgent Start PD and the fact that it went this far in NephMadness is a testament to the much needed attention we need for peritoneal dialysis utilization in the US. We understand that Urgent Start PD is not the only answer to the low rates of PD use in the US. However, it is at least AN answer and it appears to be successful in boosting rates of PD usage in many programs in the US. Because of this we had to tip our hat to JNC8. Next up for JN8 is team Balanced Solutions. Couldn't ask for a match-up anymore different than this.

Balanced Solutions versus Belatacept

Winner: Balanced Solutions

The other side of the brackets pit team Belatacept versus team Balanced Solutions. This was an unlikely pairing. First, you have team Belatacept. The only remaining kidney transplant league participant. Why are they getting so much attention and success? It is true that Belatacept is not in common use throughout the world. However, the team offers potential solutions to one of the biggest problems we have in kidney transplant medicine – CALCINEURIN INHIBITOR (CNI) TOXICITY. This is a huge problem. With the success of the BENEFIT and BENEFIT-EXT trials and ultimate FDA approval, belatacept has been gaining momentum in its ability to avoid CNIs and potentially save GFR. However, problems with dosing (IV only), acute rejection, PTLD, and cost have limited their use. Team Balanced Solutions represents one of the most widely used therapies in all of ER, ICU, and inpatient medical care. Fluid resuscitation is an area often neglected in research. Normal Saline has been the hands down favorite for years. This is a nice review on "normal" saline (NS). A solution so far from actually being normal. The biggest issues with NS is its propensity to induce hyperchloremic metabolic acidosis and its high chloride content. See Skeptical Scalpel's post on eAJKD. Here comes team Balanced Solutions to save the day. With a neutral pH and near physiological Na and Cl content they could offer a paradigm shift in how we give patients fluids. Also, some interesting physiology about how low chloride solutions might be beneficial in certain situations is intriguing. Chloride delivery to the macula densa has shown to be an important mechanism for how the kidney reacts to certain stressors, such as ATN, where chloride delivery to the distal nephron is suddenly increased dramatically. Thus could occur during proximal tubule cell death during prolonged ischemia or cell death. Whether or not this mechanism in exacerbated in patients receiving high chloride solutions is hard to tell. Now we realize that definitive trials still have NOT been performed on this topic. The best example of a comparison between high and low chloride solutions was a study performed in the University of Melbourne published in JAMA. Here is what they did:

> *Prospective, open-label, sequential period pilot study of 760 patients admitted consecutively to the intensive care unit (ICU) during the control period (February 18 to August 17, 2008) compared with 773 patients admitted consecutively during the intervention period (February 18 to August 17, 2009) at a university-affiliated hospital in Melbourne, Australia. During the control period, patients received standard intravenous fluids. After a 6-month phase-out period (August 18, 2008, to February 17, 2009), any use of chloride-rich intravenous fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) was restricted to attending specialist approval only during the intervention period; patients instead received a lactated solution (Hartmann solution), a balanced solution (Plasma-Lyte 148), and chloride-poor 20% albumin.*

Here is what they found as taken from the RFN Top Story post back in 2012 (it came in at number 7 that year):

> *The primary outcome was looking at an increase in baseline creatinine to peak creatinine and AKI as dictated by RIFLE criteria. They reported that the chloride restrictive group had a lower change in creatinine (0.16) vs. chloride liberal group (0.25). Interestingly they found a significant reduction in AKI with a much lower need for acute dialysis (78 in the liberal vs. 49 in the restrictive). However, no differences were seen in mortality or length of ICU stay.*

Several issues still exist for team Balanced Solutions. First, this was a bundle-of-care study, so it is far from definitive. We really need to see a blinded randomized clinical trial. Also, we need to study this topic on general medical and surgical wards. Team Balanced Solutions has the potential to be a real game changer in every day medicine and for that reason was an unexpected winner in its field. Beating out Normal Saline, KDOQI AKI Guidelines, Contrast Nephropathy, Bicarb in CKD, and now Belatacept. Arguably, having an easier rode to the NephMadness Championship. Now the big battle against team JNC8. Tune in next week to find out who will win.

The Finals

JNC8 versus Balanced Solutions

NephMadness Champion: JNC8

The 2014 winner of NephMadness is JNC8. Since the publication of these guidelines in JAMA last December we have seen a proliferation of commentary and discussion about them. Prior posts chronicle some of this issues and concerns people and groups have had about the JNC8 guidelines. The win for JNC8 puts this very important topic square in the spotlight and deservedly so. Proper control of blood pressure is fundamental to maintaining kidney health. The JNC8 committee attempted to simplify the management of hypertension as below.

- 60 y/o or greater goal of 150/90 mm Hg (Strong Evidence)*
- 30 – 59 y/o DBP goal of <90 mm Hg (Strong Evidence), insufficient evidence for a SBP goal in this group so SBP <140 (Expert Opinion)
- <30 y/o, goal <140/90 mm Hg (Expert Opinion)
- goal <140/90 mm Hg hypertensive adults with diabetes or nondiabetic CKD (Expert Opinion)*
- Start drug treatment with an ACEi, ARB, calcium channel blocker, or thiazide diuretic in the nonblack patients, including those with diabetes. (Moderate Evidence)
- In the black patients, including those with DM, a calcium channel blocker or thiazide-type diuretic as initial therapy.

- Initial or add-on antihypertensive therapy with an ACEi or ARB in persons with CKD to improve kidney outcomes. (Moderate Evidence)
  *major changes from JNC7

What do the adoption of the JNC8 guidelines do to hypertension management in general population compared to JNC7? Here is a recent JAMA paper describing this exact issue utilizing NHANES data:

> *Compared with the JNC 7 guideline, the 2014 BP guideline from the panel members appointed to the JNC 8 was associated with a reduction in the proportion of US adults recommended for hypertension treatment and a substantial increase in the proportion of adults considered to have achieved goal BP, primarily in older adults.*

JNC8 guidelines do relax the blood pressure cut offs. However, this could mean less side-effects from over therapy especially in older patients. It also relaxes the goal BP in patients with DM2 or CKD from 130/80 to 140/90 mm Hg. The JNC8 guidelines adhere closely to the Institute of Medicine (IOM) standards for establishing guidelines. Because of this, JNC8 is a completely different document from JNC7. It is a narrower document that doesn't attempt to be a comprehensive guide to hypertension management. It's use of IOM guidelines and its reliance on only randomized controlled trials shows the future of clinical guidelines. JNC8 also shines a light onto areas in which we need to mature our understanding of hypertension. For these reasons, JNC8 is the champion of NephMadness 2014. Hypertension control is paramount to improving cardiovascular and kidney outcomes for patients. As more randomized clinical trials are performed and incorporated into guidelines we will continue to see our understanding of hypertension evolve. We still await the results of the SPRINT trial. Which according to ClinicalTrials.gov concludes in 2018. This compares BP goals in two groups: Standard arm and Intensive arm. Participants (no DM) are randomized into the Intensive BP arm will have a goal of SBP <120 mm Hg or age ≥75 years and SBP 130-139 mm Hg. Participants in the Standard arm will have a goal of SBP <140 mm Hg. Check out Clinical Trials.gov link for more information about this study. In conclusion, the JNC8 document is merely a guideline that was generated with information from well done clinical trials. It also included expert opinion in situations where information is lacking. The bottom line is that treating hypertension requires an individual plan and approach. No guideline will ever be able to do this. We have seen several disappointments in the last few years in hypertension therapy research: from renal denervation (see SYMPLICITY), to renal artery stenting (see CORAL), to combination ACEi/ARB therapy (see NEPHRON-D). The field of hypertension continues to change and mature. Look at how the ACCORD-BP trial demonstrated how intensive therapy can lead to more side effects without much mortality benefit. What about balanced solutions? While this was a formidable foe indeed we are waiting on more definitive studies with proper controlling of groups. Also, including a more diverse patient population (such as floor vs. ER vs. ICU) and replicating studies like this in different centers are needed before balanced solutions can really make major waves in medicine.

As this years NephMadness comes to a close we wanted to thank everyone for reading, commenting and contributing to the Madness. NephMadness is not about the winners and losers- its about learning nephrology – and pushing ourselves to share and engage about a topic we are all passionate about. The end product of NephMadness to create a dialogue and a community. Thanks- The NephMadness Team

Final Editorial on Guideline Medicine

Dr. Bakris currently serves as an Expert Consultant to the FDA Cardio-Renal Advisory Board and to CMS (Renal Medicare and Medicaid program). He has served on the JNC 6 and 7, ADA and the National Kidney Foundation (KDOQI) blood pressure and diabetes guideline committees. He is the immediate past-president of the American Society of Hypertension. He has published over 600 peer-reviewed publications in the areas of hypertension and diabetic nephropathy as well as 12 Books in the area of hypertension and diabetic kidney disease. He is the editor of American Journal of Nephrology and the hypertension, section editor of UpToDate, as well as an associate editor of Diabetes Care and Hypertension Research.

It is apparent from this competition of topics that people are enamored with guidelines. The reasons for this are unclear to this writer. However, the reader needs to be aware that guidelines are limited by the amount and quality of data available by which to make recommendations on specific topics. Thus, there are many issues in clinical medicine where there can be no guidelines since, the amount and quality of the data are poor or lacking. A good example is blood pressure guidelines in dialysis patients.

In 2014, the primary difference between the five “real and so-called” guidelines for blood pressure management in general medicine is the process used. The originators of the evidence-based approach to blood pressure guidelines emerged from the National Institute for Health and Clinical Excellence (NICE) committee in the United Kingdom. The group has a spectrum of epidemiologists and statistician as well as other professionals that evaluate data on topics of interest and relevance dictated by senior physicians in a given field. The guidelines are entirely based on the data available with no significant role for opinion.

The model used by NICE was similar to what the JNC 8 committee used. The other “guidelines” used a more traditional approach used by the JNC 7. The result of the guidelines using a traditional approach was a greater breadth of topics covered by more opinion and less evidence on which to base recommendations.

Physicians have lost sight of the fact that the word “guideline” refers to a general recommendation based primarily of evidence from the literature and is an informed suggestion evolved from the cohorts studied in the trials. Its relevance is restricted to that group. Moreover, because of people’s day to day behavior it has limitations even in that group. Hence, guidelines will never answer many specific clinical questions seen in practice. Nor should such guidelines be used in this context or the recommendation may not prove useful. The probability of a therapy proven successful in a trial is not identical in all the individuals treated even within that trial. This is because patient behavior is a key determinant variable associated with success in cardiovascular and renal trials, i.e. adherence. Therefore, the overall results of a trial cannot be assumed to apply to any particular individual, not even someone who corresponds to all the entry criteria for the trial.

This simply means that clinicians must still reason through the best choices for an individual because even in the absence of full and secure knowledge, clinical decisions must still be made. A recent article by Sniderman et.al., summarized guidelines by stating “Clinical reasoning is the pragmatic, tried-and-true process of expert clinical problem solving that does value mechanistic reasoning and clinical experience as well as randomized trials and observational studies. Clinicians must continue to value clinical reasoning if our aim is the best clinical care for all the individuals we treat.”

Medicine is not physics and even the laws of nature have the Heisenberg uncertainty principle. Since biology is a “softer” science than physics we should be even more careful when generalizing things from clinical trials that have much more

BP in mm Hg	NICE 2011	ESH/ESC 2013	ASH/ISH 2014	AHA/ACC/CDC 2013	JNC 8
Definition of Hypertension	≥140/90 and daytime ABPM (or home BP) ≥135/85	≥140/90	≥140/90	≥140/90	Not addressed
Drug therapy in low risk patients after non-pharmacologic treatment	≥160/100 or daytime ABPM ≥ 150/95	≥140/90	≥140/90	≥140/90	< 60 y. ≥140/90 ≥ 60 y. ≥150/90
beta-blockers - first line drug	No (Step 4)	Yes	No (Step 4)	No (Step 3)	No (Step 4)
Diuretic	chlorthalidone, indapamide	thiazides chlorthalidone, indapamide	thiazides chlorthalidone, indapamide	thiazides	thiazides chlorthalidone, indapamide
Initiate drug therapy with two drugs	Not mentioned	In patients with markedly elevated BP	≥160/100	≥160/100	≥160/100
Blood pressure targets	< 140/90 ≥ 80 y. < 150/90	<140/90, Elderly ≥ 80 y. SBP 140-150	<140/90 ≥ 80 y. < 150/90	<140/90 Lower targets may be appropriate in some patients, including the elderly	< 60 y. <140/90 ≥ 60 y. <150/90
Blood Pressure target in patients with diabetes mellitus	Not addressed	<140 /85	<140 /90	<140/90 Lower targets may be considered	<140 /90

uncertainty than nature itself.