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Summer 2016
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Summer CME
Chronic Kidney Disease – An Update
By Nabeel Aslam, MD, FASN

Chronic kidney disease (CKD) is a general term used to describe a wide variety of disorders affecting the kidney structure or function for more than three months. Several studies have demonstrated the association of CKD with an increased risk of all-cause and cardiovascular mortality, dialysis requirement and development of acute kidney injury.

Summer CME
Pediatric Hypertension – Pearls for Diagnosis
By Mohammad Ilyas, MD, Asad Telaymat, MD

Hypertension (HTN) can begin in childhood and adolescence, and it contributes to the early development of cardiovascular disease (CVD). Autopsy studies have shown an association of high blood pressure (BP) with atherosclerotic changes in the aorta and heart in children and young adults. Based upon these observations, identifying children with HTN and successfully treating their HTN should have an important impact on long-term outcomes of CVD. One of the most important components of the successful management of childhood HTN is determining whether or not there is an underlying cause that is amenable to treatment.

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From the Editor’s Desk

Summer is the time when many physicians take vacation; spend less time in the office, and more time on the golf course. It is the time of year when school is out, traffic is bearable, and meetings and activities are limited.

However, as a physician, summer is also the most important time of year. Every July, newly minted interns, residents and fellows begin their long journey toward becoming a practicing physician. It is the time of year when enthusiasm and hope for our profession should be the greatest. It is the time of year that every physician should remember that moment of excitement, fear, and anticipation stepping out onto the wards for the first time. For those of us in private practice, we should take the time to recollect our journey into our profession. Though much has changed, we all share that common bond of being an intern on July 1. Take this time to remember why you became a physician. Take the time to honor the hard work, sacrifice, and dedication you made to care for your patients.

For my colleagues in our city’s residency and training programs, this day brings renewed hope and promise to teach the next generation of physicians. Your guidance, mentorship, and knowledge will help guide our community’s new physicians as they are challenged mentally, emotionally, and physically like never before. July is the only time of year that morning reports, teaching rounds, conferences, and calls will be on time, 100% attended, and without complaint.

Year after year we evolve and adapt to the tumultuous change within our healthcare system. Despite this change, we need to remind ourselves it is our relationship with our patients that is the backbone of our lives, profession, and healthcare system.

As I wrote about in the Spring issue of the Journal, the summer of 2016 is going to be a heated political season. From the presidential election to electing our state representatives, summer is the time when the political climate will become heated and cantankerous. On the national stage, the Republican and Democratic national conventions should provide for ample entertainment and political theater. Locally, the departure of Ander Crenshaw in the House opens the political stage to many up and coming candidates. In the US Senate, Florida will have to elect a new senator to replace Marco Rubio. As usual, the Florida House and Senate will have a wide range of candidates vying to represent Northeast Florida in Tallahassee. It is tempting to tune out politics until the fall, but many of the candidates that will go on to win will come out of the summer political gauntlet. As physicians, be sure you are aware of the candidates and issues that will affect our ability to practice medicine on a day-to-day basis. If you can, spend not only your time, but your dollars on making sure physicians are a loud and powerful political voice.

Summer is also the biggest time for the Florida Medical Association. The FMA annual meeting will be held this year from July 29-31 in Orlando. This is the time where hundreds of physicians gather to help set the policies and priorities of the FMA. Physicians in the FMA House of Delegates are the heart and soul of medicine in Florida. With resolutions and votes, FMA delegates help shape legislative, public health, and physician centered policies. I encourage all of our DCMS physicians to learn more about the annual meeting and find ways to become more involved in Florida Medicine.

Finally, summer is the time for all our DCMS physicians to spend time enjoying family and friends. Take the opportunity to take a day off mid-week to enjoy the wonderful outdoor activities in our community. Even consider ending your day early to enjoy an evening walk on our miles of beaches. Fire up the grill, jump into the pool, and enjoy your summer as a valuable member of the NE Florida Physician Community. Avoid your summer doldrums!!!

Ruple Galani, MD
Editor-in-Chief
Northeast Florida Medicine

Summer Doldrums...or not?
We are fortunate to live in a beautiful part of the country. The Northeast Florida area has great weather, pristine beaches, numerous nature trails and a river whose widest track flows right through the middle of a bustling and growing downtown. We have a lot to be proud of.

However, our community has many troubling concerns as well. The much publicized Robert Wood Johnson Foundation’s annual county health rankings were released in March. The Foundation listed Duval County as 48 out of 67 Florida counties in overall health. Of the many factors that are included in these rankings, some are very broad and include a larger social concern such as violent crime, injury related deaths, children in poverty and high school graduation rates. These are critical areas that must be addressed but will take a grassroots effort over many years to reverse.

Fortunately, there are many other factors that can be changed relatively quickly. Duval County is rated at or worse than the state average for certain health behaviors including smoking, obesity and physical inactivity just to name a few. There is no reason why these numbers can’t be improved upon relatively quickly.

As Florida’s oldest and largest medical society, the DCMS and its Foundation are working closely with Jacksonville Mayor Lenny Curry’s office on a comprehensive plan to encourage healthy physical activities. Getting off the couch to walk after dinner, run laps at the nearest track or ride a bike in the neighborhood are simple and inexpensive ways to get Jacksonville moving. But our plan will be much more than that. We are encouraging all corners of this wonderful region to make Northeast Florida healthier. It is time for our big and small businesses, professional sports franchises, media outlets, colleges, hospitals, churches and restaurants to get on board. This is a mission that we will be taking to all parts of the metropolitan area from Arlington to Mandarin, from Orange Park to Callahan, from Ponte Vedra to Middleburg, from Fernandina to the Beaches and from Macclenny to the Northside.

Our mission is for the region to collectively lose one million pounds. However, we will not stop there. We also are encouraging groups to burn one million calories, walk one million miles, jog one million laps on a track or swim one million laps in a swimming pool. It really does not matter. We want businesses, church groups, radio/television stations, newspapers, political leaders and health professionals to form teams to compete with each other and track their results so that we can achieve Jacksonville’s Mission One Million. This is a very unique project that will encourage appropriate behaviors and habits that will allow Duval County to move up the rankings but more importantly improve the health of the entire community.

It is critical to note that we will not be utilizing any tax payer dollars for this initiative. However, in order to properly get the message out and to encourage organizations and businesses to participate, we will need to spend money. We are enlisting the help of our local business community, but we must start by showing our own support for this very meaningful project. We must lead by example, before expecting others to follow. Once the business community sees that we, the physicians, have committed not only our money but also our time to this worthwhile region-wide initiative they will feel more compelled to participate as well.

We are fortunate that we have a Mayor who believes very strongly in improving the health of the community and has enlisted the expertise of the Duval County Medical Society to make this happen. This mission can only be accomplished with a strong public/private partnership and we have just that.

Now we have to make it happen. When we do, not only will we be a healthier county, but we will also set an example for the rest of the country to follow. We will be an even more attractive area for businesses to relocate and for families to settle. So fellow physicians I ask you: What is your mission?
April 7th, 2016 was the culmination of years of work for the Duval County Medical Society Foundation, its leaders, and myself, when Jacksonville Mayor Lenny Curry announced Mission One Million: The 904 in Motion. The challenge from Mayor Curry is for our community to lose one million pounds. To achieve this goal, people will need to work together in their homes, at work and at play.

This ambitious goal is part of an effort to improve the overall health of our community. Jacksonville ranked 48th out of 67 counties in the most recent Robert Woods Johnson Foundation County Health Rankings (www.countyhealthrankings.org). St. Johns County, on the other hand, ranked #1.

For more than two years, I have been an ambassador of this program, working with dozens of community partners in helping to establish a strong network of partners to make the program successful. I served as the Chair of the Mayor’s Council on Fitness and Well-being for two years, and this organization is a key part of bringing the program to life.

The problem is…well…me. I’m part of the problem. On April 7th, I weighed 313 pounds. I am slightly taller than average at 6’3”, but by any measure, I was (am) obese. I joked about my weight during the lead-up to the program saying that I was simply “stockpiling” so that I’d have more weight to lose. The line captured a laugh in most meetings, but the simple fact is that it is hard for me to lead from the front as the CEO of an organization driving to reduce obesity in the community, while I remain obese.

So now the Mission for me is clear. I need to be one of the first and major contributors to the Mission One Million program. One of the great things about Mission One Million is that while not everyone needs to lose weight, everyone can benefit from a healthy lifestyle goal. DCMS President Dr. Sunil Joshi does not need to lose any weight, but his Mission Pledge is to run the Gate River Run in 2017. For me, the Mission is much more specific.

OK, so I might not have any control over whether or not I get selected to go on SURVIVOR, but I can control my weight using the simple guidelines established by the Department of Health: 

- Move more
- Eat less
- Set goals

The goal setting is done, now it’s up to me to move more and eat less. Since the start of the Mission One Million program, I am doing better on the food intake, but still have a ways to go in getting enough physical activity. I am definitely looking into creative ways to incorporate movement into my daily routine, including potentially getting a standing desk.

As of this writing, I am at 297 pounds. Not great, but it’s a 16 pound start on my 80 pound goal. Just like the journey to one million pounds will be a long one, my journey will take time. I know that it’s not just about getting to the finish line, but also about what I do when I get there. Thank you to all of you who have already reached out and given me signs of encouragement. I know that I will have moments of weakness. I am still addicted to pizza, and we’re getting closer and closer to football season and its myriad of unhealthy food and beverage choices. I welcome your support, and I am excited to learn about what YOUR Mission is. Please feel free to share your Mission with me at bcampbell@dcmsonline.org. Whether it’s a personal one, or a commitment to share the message of the Mission with your patients, together we can truly help improve the health of our community.

Bryan Campbell
DCMS Executive Vice President

My Mission is to lose 80 pounds, and to be healthy enough to participate in the reality TV show SURVIVOR.
The 2015-2016 academic year has been exciting for the Naval Hospital Jacksonville Family Medicine Residency Program, one of the United States Navy's largest family medicine residencies. In the summer of 2015 we graduated a strong class of residents that have traveled throughout our country and the world to care for our sailors and marines. We also welcomed a large, dynamic class of interns and new faculty members to our ranks, some of whom graduated from Jacksonville and have "returned to roost." Overall, the year has been challenging and successful with many moving parts serving the mission to care for our patients and produce another quality group of residents.

Our program largely focused on scholarly activities with the goal of expanding research activity among our residents. Dr. Jed Siebel, our resident research coordinator, led a resident research workshop where residents learned the basic, practical principles of case studies, poster presentations, photo quizzes and letters to the editor. This motivated many of our residents to embrace research and a record number of residents attended the 2016 Uniformed Services Academy of Family Physicians Annual Meeting & Exposition in Denver, Co for a long weekend of education, fellowship and snow!

Naval Hospital Jacksonville was represented by six residents, with all three classes represented, and three faculty members presenting general audience breakout sessions on topics ranging from autism to nutrition in weight loss. We also sent an impressive contingent of 15 residents to the poster convention with inspiring posters on medicine and operational topics encountered in our own clinics and wards. One of our second year residents, Dr. Brittany Wiles, placed 3rd in the poster competition.

Our research coordinator also orchestrated a regional research symposium to benefit all the local family medicine residencies that will take place the 9th of June. The full-day event will feature residents from north Florida and Georgia as well as local and regional presenters including keynote presenter Dr. Christy Ledford from Eglin Air Force Base. Dr. Ledford will be speaking on cultivating physicians to contribute to research which, in turn, shape future practice. Having an entire day to focus on research and explore our faculty's scholarly activity will be fulfilling and memorable.

Naval Hospital Jacksonville's faculty worked extensively this past year to redesign our academic series, introducing a faculty spearheading monthly skills workshop series. Their hours of preparation were evident in the sessions, which combine academic and small group skill sessions. Residents' favorites from this year's series included the obstetrical ultrasounds, colposcopy, joint injections utilizing our anatomical simulation mannequins and cardiac risk stratification workshop exploring EKGs, ESTs and case studies. We are grateful and fortunate to learn from such passionate faculty and we appreciate all the extra time they dedicate to these sessions.

As a military residency, we typically have increased turnover in program leadership when compared to our civilian counterparts. Our program transitioned to a new program director (PD) this past March with Dr. James Keck handing the torch to Dr. Kristian Sanchack. Dr. Keck will be continuing his career in Navy Family Medicine in Rota, Spain. For the past five years, our residents have flourished under the nurturing leadership of Dr. Keck. In his welcome speech he greeted us as interns and introduced us to the “purposeful imbalance” of our daunting and rewarding graduate medical education adventure. His frequent updates on administration undertaking reassured us of the entire faculty’s dedication to our education. We will miss him and we always strive to incorporate his compassion for patients and commitment to service as we continue in our own family medicine journey.

We are equally excited to welcome our previous assistant program director, Dr. Kristian Sanchack, as our new program director. Dr. Sanchack is well known for his engaging and inspiring presentations in our academic session and we look forward to his tenure as program director!
Guest Editorial

The history of nephrology can be traced back to Galen (129-200 CE) when he first recognized the kidney as the source of urine formation. Progress in the field of kidney disease has been relatively stagnant until last century when tremendous advances began. This includes a better understanding of the fine structure of the kidney which provides insight into its function and formation of urine, to the realization that life can be extended in patients with end stage renal disease either by dialysis (Dr. W. Kolff - 1940) or renal transplants (Dr. Murray 1954).

These scientific breakthroughs in the field of medicine have given us great acumen in the understanding of kidney diseases, as well as the new modalities to manage them. The spectrum of evolution in the field of nephrology could not be covered in this “Nephrology” issue of Northeast Florida Medicine. However, in this issue we highlight information on current trends in nephrology practice that are relevant for primary care physicians and allied health professionals.

Did you know nephrolithiasis, more commonly known as kidney stones, are more common in the southeastern United States (called stone belt)? In their article, Dr. Ivan Porter and Dr. William Haley, address the key points in kidney stones. Due to its increased prevalence, kidney stones are a major health issue and great financial burden on medical economics. Understanding the risk factors and recognizing the early signs and symptoms associated with the disease can help physicians with early intervention. This will not only minimize suffering but also prevent long term consequences.

Acute Glomerulonephritis (AGN) commonly occurs as a result of previous sore throat due to streptococcal group A infections. Dr. Omar Tolaymat and I discuss the changing epidemiology, clinical and laboratory markers, and common pitfalls associated with the diagnosis and management of post strep AGN.

Dr. Muna Canales, Dr. Keerti Bhanushalli, Dr. Richard Berry and Dr. Rebecca Beyth elaborate on the complex association between sleep apnea and kidney disease. They also highlight the important aspect of kidney disease related to sleep disorder.

In Dr. Nabeel Aslam’s CME article, he takes an in-depth look at chronic kidney disease. He discusses the updated K/DOQI classification, evaluation of chronic kidney disease, advancement in measurement of GFR, the role of Cystatin-C in the measurement of GFR and specific interventions that halt the progression. He also addresses the complications resulting from renal replacement therapy.

Two articles in this issue cover the important topic of kidney transplantation. Dr. Alfonso Santos, Jr. focuses on the criteria for patient selection and assessment in kidney transplantation. Dr. Gil Cu addresses the issues related to renal transplants and the role of a primary care physician in the care of renal transplant patients.

In the CME article on Pediatric Hypertension, Dr. Asad Tolaymat and I provide an update on classifications of HTN and new techniques to monitor blood pressure, particularly the ambulatory blood pressure monitor (ABPM). This 24 hour BP monitoring device has brought a new understanding in the evaluation and management of hypertension. It has helped us to redefine prehypertension, white coat syndrome and masked HTN. Vital information such as BP load and nocturnal dip can only be obtained with ABPM.

Finally, Dr. Rajesh Mohandas, Dr. Girish Singhania and Dr. A. Ahsan Ejaz provide an update on the current management strategies in acute kidney injury. The article primarily focuses on preventive measures in contrast-induced nephropathy, cardiac surgery-associated acute kidney injury and dialysis modality and outcomes.

The kidney is not only affected by primary disease but can also be the victim of systemic diseases like diabetes mellitus, hypertension, lupus and others. Understanding the etiology leads to a quick diagnosis and prompt intervention can improve outcomes. This issue of Northeast Florida Medicine will give the reader a new appreciation of the nephrology world and its broad range of diagnoses, treatment options, and issues specific to this area of medicine.

I am greatly honored to serve as the guest editor for this issue devoted to Nephrology. I hope it will update health care professionals on recent advances while improving the care of those with kidney problems in Northeast Florida. In doing so, this issue will promote the mission of the Duval County Medical Society: “Helping physicians care for the health of our community.”
Key Points in Kidney Stones

By Ivan Porter, MD, and William Haley, MD

Division of Nephrology & Hypertension, Department of Internal Medicine, Mayo Clinic Florida

Abstract: There are few randomized, controlled trials (RCTs) or comparisons of active treatment regimens for kidney stones, despite its prevalence in the general public. An individualized approach to therapy and understanding of patient-related factors is paramount to successful prevention of kidney stone formation. Kidney stones are more common in men than women, but the incidence in women has increased over the past two decades. Stones are often found incidentally during abdominal imaging and up to a third of these patients can require some form of treatment or report a stone event within the next four years. Presentation is often accompanied by renal colic. Kidney stones smaller than 5 mm will usually pass spontaneously, while fifty percent of stones larger than 5 mm will require urologic intervention for removal. Consideration of hereditary causes of kidney stones is important in younger patients or those with recurrent stones. While ultrasound may indicate the presence of a stone or obstruction, a CT scan is much more likely to provide information for the optimization of acute and prospective treatment and prevention, including information about stone burden, location, size and alternative diagnoses. Due to the recurrent nature of this disease process, follow-up depends on the patient’s individual risk factors and periodic face-to-face counseling, during periods with and without stone formation.

Introduction

There are few randomized, controlled trials (RCTs) or comparisons of active treatment regimens for kidney stones, despite its prevalence in the general public.1 Anyone who has experience with the treatment of kidney stones understands the importance of an individualized approach to therapy and accepts that understanding patient-related factors is paramount to successful prevention of kidney stone formation.

Societal Burden

The cost of kidney stones to the general population is estimated to be over $10 billion annually.2,3 Urgent and emergency care, associated imaging and expensive surgical interventions make up these costs, much of which could be prevented by fostering the relationship between patients and their providers and providing better patient education and awareness. Managing expectations as a form of prevention is the most cost-effective strategy.

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Natural History & Epidemiology

Incidence

Kidney stones are more common in men than women, but the incidence in women has increased over the past two decades.4 Currently, the lifetime incidence is around 10-12 percent: 13 percent for men and seven percent for women.4,5 Additionally, stones are often found incidentally during abdominal imaging with varying significance, and up to a third of these patients can require some form of treatment or report a stone event within the next four years.5

Based on National Health and Nutrition Examination Survey (NHANES) data, the African American population has the lowest reported incidence followed by the Hispanic population.4 Non-Hispanic Caucasians have the highest incidence rates. Epidemiologic studies over the past two to three decades have suggested an increased frequency of kidney stone disease for every age group.4 The incidence in the southeastern United States has always been higher than the rest of the United States, and it is referred to as the stone belt. This has been variably related to dietary tendencies, sun exposure, and temperature.

Risk factors

Low urine volume is a very common finding in patients who develop kidney stones. Occupations that may limit access to fluid intake or emptying of the bladder create unique challenges to a successful prevention program. Truck drivers, business travelers, teachers, and certain service industry jobs are often at a higher risk of kidney stone formation.6,7 Urinalysis can also report symptoms that may increase risk: hyperoxaluria, hypercalciuria, hypocitraturia, hyperuricemia and hyperuricosuria. The intake of excessive vitamin D and calcium supplements are also associated with increased formation.8,9

Family history appears to be a large risk factor because a person who has a family member with kidney stone disease also may have three times the risk of kidney stones.10,11

Diet may impact the incidence of kidney stones and is evidenced by the increasing incidence of kidney stone formation in Japan, with the influx of the Western diet and lifestyle. Diet alone may not cause kidney stones; increased rates of metabolic syndrome, diabetes and obesity have also been seen and are correlated with these dietary tendencies.6,12

Clinical Features

While many stones are incidentally found, presentation is often accompanied by renal colic. This usually occurs when the stone is located within the ureter or distal urinary tract. In addition, pain, nausea and vomiting are associated with the disease. However, gross hematuria is not always present. In the setting of gross hematuria, papillary necrosis, renal tumors, urinary tract infections and renal emboli must be ruled out before diagnosis. Stones within the renal pelvis do not usually cause pain unless they trigger ureteral spasm or cause an obstruction.
Kidney stones smaller than 5 mm will usually pass spontaneously, but some require prolonged, conservative management. Fifty percent of stones larger than 5 mm will require urologic intervention for removal.13

Patients with a single stone episode should be assessed for systemic disorders, such as hyperparathyroidism, hyperoxaluria and certain tubular defects, along with an assessment of risk factors. For first-time stone formers, a conservative approach has been advocated in the past; however, current guidelines recommend evaluation of all patients with newly diagnosed kidney or ureteral stones to include a thorough medical and dietary history, blood chemistry, urinalysis, stone analysis and imaging to quantify stone burden.14 High risk and recurrent stones require additional metabolic testing with 24-hour urine kidney stone risk panels that assess supersaturation and stone forming factors.15

Stone Formation

Urinary supersaturation is dependent upon the concentration of stone-forming ions, the inherent properties of the ions, the chelators of the ions and the environmental pH.15 Stone minerals exist in a bidirectional process of precipitation and dissolution. This overall process has second to second variation in vivo. As crystals form, aggregation occurs. Urinary macromolecules are likely in a constant promoting and inhibiting further crystallization and aggregation. This is evidenced by the fact that, while crystalluria may occur in many patients, not every patient produces stones.

Stone Type and Associated Medical Conditions

The most common stone type is composed of calcium. Calcium oxalate, calcium phosphate or a mixture of the two account for around 80 percent of all kidney stones. Uric acid and infection-related (struvite) stones are seen to account for 10-15 percent of all kidney stones, while the remaining stones are attributed to rarer genetic conditions, such as cystinuria.16,17

Up to 20 percent of patients with primary hyperparathyroidism may form kidney stones.16 Elevated or normal serum parathyroid hormone level with high or high normal calcium and low serum phosphorus helps to diagnose primary hyperparathyroidism. In the setting of non-elevated urine calcium, the physician should check for familial hypocalciuric hypercalciemia. In cases of normal serum calcium without another cause of increased calcium excretion, idiopathic hypercalciuria, a familial syndrome, can be a cause.16

Hyperuricosuria can promote stone formation by decreasing the solubility of other minerals. However, most uric acid stones are not associated with hyperuricosuria; rather, uric acid stones are more frequent in patients with diabetes, obesity and metabolic syndrome, all of which are associated with a more acidic urine.17,18

Increased oxalate excretion in urine, also known as hyperoxaluria, is common in individuals who develop kidney stones. Hyperoxaluria can be caused by low calcium intake.17 Additionally high doses of ascorbic acid (vitamin C) are converted to oxalate, and increased absorption of dietary oxalate occurs in pancreatic, biliary and small bowel disease. Inflammatory bowel diseases, such as Crohn’s disease or ulcerative colitis, are associated with up to fivefold increase in incidence of stones.18 Additionally, any condition resulting in intestinal malabsorption, especially Roux-n-Y gastric bypass, can increase the risk for stone formation. With the increasing popularity of bariatric surgery, the implications of stone disease should be anticipated and addressed.

Hypocitraturia can occur due to potassium depletion or systemic acidosis. Citrate naturally chelates calcium, forming a soluble complex which prevents calcium stone formation. While treatment with citrate raises pH, an increase in pH above 6.5 can increase the risk for calcium phosphate stones in the setting of high urine calcium.17

Struvite stones are a mixture of magnesium ammonium phosphate and carbonate apatite caused by bacteria using the enzyme urease. Effective treatment requires removal of the stone and antibiotic therapy, as bacteria live within the stone material.

Anatomic abnormalities are likely to have complicated treatment requirements that affect both the likelihood of formation and treatment strategies. These conditions include malrotated kidneys, congenital variants and pathology of the collecting system.

Hereditary Causes of Kidney Stone Formation

Consideration of hereditary causes of kidney stones is important in younger patients with recurrent stones because these causes can often be associated with chronic kidney disease. Nascent metabolism problems are often associated with kidney stone formation.19 However, the following disorders are important to exclude:

Cystinuria

One of the most common inherited causes of kidney stones, cystinuria is caused by a defect in transport protein SLC7A9 or SLC3A1 and affects the reabsorption of filtered cystine. Treatment strategies include reducing the supersaturation of urinary cystine via urinary pH, cystine concentrations and absolute cystine levels. Goal concentration of less than 1 mmol/L can be attempted with up to 5L of fluid intake daily. Limiting animal source protein and lowering sodium intake are associated with less cystine excretion. Increasing urinary pH to a goal of 7.5 with potassium citrate reduced the supersaturation of cystine. For success the goal is alkalinization for the full 24 hours which requires frequent dosing. Cystine-binding thiold drugs such as tiopronin and penacillamine produce soluble cystine drug complexes which can be excreted.20

Primary hyperoxaluria (PH)

Primary hyperoxaluria (PH) is an inherited autosomal recessive disorder that impacts hepatic function leading to oxalate overproduction. High urinary concentration overcomes the capacity of the kidney for excretion, resulting in local injury and stone formation. Three types have been described based on the affected enzyme: PH1 AGXT, alanine-glyoxylate aminotransferase (most common, 80 percent); PH2 (10 percent) due to mutations in GRHPR glyoxylate reductase/hydroxyl pyruvate reductase; and PH3 HOGA1 4-hydroxy-2-oxoglutarate aldolase (10 percent). Many other patients who have hyperoxaluria likely have abnormalities in oxalate metabolism that have yet to be identified. The diagnosis can be confirmed.
by genetic testing. Reduction of urinary oxalate is the mainstay of therapy. Outcomes in this disease process correlate with the degree of hyperoxaluria. Pyridoxine has been shown to reduce oxalate secretion, but its effects are not successful for all types of PH. As kidney function declines, oxalate can deposit in many organs (systemic oxalosis) necessitating kidney transplantation. Liver transplantation addresses the genetic defects that cause PH. \textsuperscript{21,22}

**Dent disease**

This is a rare X-linked renal tubular disorder associated with mutations in the CLCN5 and OCRL genes on the X chromosome. It affects the kidneys of male patients. The disease is associated with low molecular weight proteinuria, hypercalcuria, nephrocalcinosis, nephrolithiasis, aminoaciduria, hypophosphatemia and osteomalacia. The disease presents in early adult or childhood with progression to chronic kidney disease (CKD) in the third or fourth decade of life. While the presentation can be variable, low molecular weight proteinuria (retinol binding protein, alpha 1 microglogulin) is the pathognomonic feature. Specific effective treatment strategies are currently lacking.\textsuperscript{23}

**Familial hypomagnesemia with hypercalcuria and nephrocalcinosis (FHHNC)**

This is a rare autosomal recessive disorder with mutations in the CLDN16 on chromosome 3 and the CLDN19 gene on chromosome 1. These genes encode integral membrane proteins of the claudin family, which are involved in calcium and magnesium reabsorption in the thick ascending limb of the loop of Henle. Presenting features vary from recurrent and relapsing UTIs to hematuria, in addition to manifestations of electrolyte abnormalities. All affected patients will have hypomagnesemia, hypercalcuria and nephrocalcinosis at diagnosis. One third of patients will have ESRD prior to their second decade of life.\textsuperscript{19} There are few effective treatment strategies, but those strategies are focused on the prevention of renal disease progression.

**Adenine phosphoribosyltransferase (APRT) deficiency**

This is a rare autosomal recessive disorder causing large amounts of 2,8-dihydroxyadenine (DHA), contributing to the formation of stones. Often, individuals in their first decade of life are seen with bilateral stones. The stones are usually radiolucent (as are uric acid stones), but urine pH is often increased (decreased in uric acid stone formation). Treatment is with xanthine dehydrogenase inhibitors, such as allopurinol or febuxostat.

**Evaluation of the Stone Former**

Stone analysis should be performed on any passed material. Multiple imaging modalities are capable of answering clinical questions on the management of stone disease. Some data has suggested that ultrasound and computerized tomography (CT) scans are interchangeable; however, this is controversial.\textsuperscript{24} Many clinical questions can be answered with less invasive, less expensive tests, such as ultrasound. Often, patients who receive ultrasound require a subsequent CT scan. While ultrasound may indicate the presence of a stone or obstruction, a CT scan is much more likely to provide information for the optimization of acute and prospective treatment and prevention, including information about stone burden, location, size and alternative diagnoses.\textsuperscript{25} Indeed, the sensitivity and specificity of an ultrasound for diagnosis of kidney stones is reported to be 25-40 percent compared to CT at 90-100 percent.\textsuperscript{24} Follow-up CT scans allow assessment of treatment success and also provide patients with information regarding stone growth.

It is difficult to estimate radiation risk, but the use of comparisons allows patients to make informed decisions about their care (Figure 1).\textsuperscript{26}

**Figure 1:** Visual representation of probability of death from various causes, compared to dying from a radiation-induced malignancy from abdominal or head CT, using risk assumptions as delineated in BEIR VII and linear no-threshold hypothesis. Reused with permission from Fletcher et al and Springer Publishing.

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**Management**

Prevention of further stone formation is the ultimate goal. This is often a moving target, as patient situations can change on a day-to-day basis, inhibiting consistent adherence to prevention strategies.

Evaluation of the stone type is paramount to successful medical management, because this may affect the responsiveness of a stone to a specified treatment.

**Acute Renal Colic**

Emergency evaluation and prompt urological consultation is warranted based on presence of signs of systemic infections (chills, fever), intractable pain, and vomiting (preventing control of symptoms). Careful attention to symptoms is warranted for patients who have a solitary kidney or cases of anuria, obstructing stone with fever, sepsis or UTI, acute kidney injury, leukocytosis, gross hematuria, diabetes, immunologic disorders, pregnancy or volume depletion.
Pain control can often be achieved with analgesics, such as non-steroidal anti-inflammatory drugs, or narcotics, if needed. While increasing hydration is normally recommended, exclusion of an obstructing stone is appropriate.

Medical expulsive therapy with alpha blockers such as tamsulosin may be effective for the spontaneous passage of stones, in addition to encouraging fluid intake and straining urine to collect stone material.

**Large Stones**

Following stone passage trials with medical expulsive therapy, delayed or immediate surgical intervention with ureteroscopy, shock wave lithotripsy, laser lithotripsy and/or percutaneous nephrolithotomy are commonly employed. The choice and timing of urological intervention may depend on a variety of factors including insurers, facility, provider capabilities, stone size/location and patient preference.

**Maintenance & Prevention**

A 24-hour urine profile should be performed prior to the initiation of therapy in order to allow assessment of the success of therapeutic interventions. Studies have also shown that our urine composition changes with age. This means one test may not be sufficient. Repeat testing should be performed months after initiation of treatment and dependent upon the patient’s response.

Given the relationship between urine concentration and urine supersaturation, fluid intake should be a mainstay of therapy. Fluid intake should be encouraged to maintain urine volume of no less than 2.5 L per day. Beverage choices are important; lower sodium, lower carbohydrate fluids can be substituted for water, as well as beverages containing citrate. The avoidance of beverages containing phosphoric acid and fructose may also be helpful.

Sodium intake affects hypercalcuiiria, and the reduction in sodium intake leads to lower urinary calcium excretion. Limiting salt intake is a safe, effective preventive measure. High salt intake reduces citrate excretion, which increases the risk for formation.

Randomized control trials with normal calcium intake reported a reduction in stone formation compared to those with a calcium-restricted diet. In contrast to dietary calcium, the use of calcium supplements and supplements of vitamin D are associated with increased stone formation. Low-fat dairy products provide dietary calcium, whey protein and vitamin D for fortification, decreasing the need for additional supplements, promoting bone health and reducing kidney stone formation. Further reduction of calcium may reduce bone mineral density, increasing the risk of bone fractures.

Foods high in oxalate, especially if accompanied by low dietary calcium, can cause hyperoxaluria. Spinach, rhubarb, granola, beets, soy and almond milk are a few foods on this list; however, there is no comprehensive list of oxalate foods and their respective values as growing properties and preparation can vary the concentration. High-dose supplements of vitamin C or ascorbic acid should be avoided because they can also increase the excretion of urinary oxalate.

Dietary reduction of non-dairy protein results in less urinary acidification and lessening of hypocitraturia, as well as a reduction in calcium.

**Pharmacologic Management**

Thiazide diuretics decrease urine calcium and have reduced stone recurrence in randomized controlled trials. Chlorthalidone and indapamide are favored over hydrochlorothiazide due to their longer duration of action.

Potassium citrate benefits patients with calcium kidney stones, because it chelates calcium and improves urinary citrate levels. It also acts as an alkalinizing agent in the treatment of uric acid stones. Caution is recommended in patients who have calcium phosphate stones, because the increase in urinary pH may increase the supersaturation of calcium phosphate crystals.

In one small study, allopurinol was shown to decrease stone recurrence in patients with hyperuricosuria and a lack of hypercalciuria.

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**Figure 2:** The Recurrence of Kidney Stone (ROKS) nomogram can be easily applied in first time symptomatic stone formers. First, determine the total points based on the sum of 11 predictors (A). Second, estimate recurrence risk at 2 years, 5 years, and 10 years based on the total points (B). Risk of recurrence at 2, 5, and 10 years is \(1 - e^{-0.936 + 0.00942 \times \text{points}}\), where 0.936, 0.871, and 0.785, respectively. An electronic version of the ROKS nomogram is available on the QxMD app “Calculate” (iOS: http://qx.md/qx; Android: http://qx.md/android; and web tool: http://qxmd.com/ROKS). N, no; Y, yes.
Risk of Recurrence

Following passage or treatment for a stone, the risk of recurrence during the next five years ranges from 35-50 percent. There are clinical tools to aid caregiver assessment of kidney stone recurrence. The Recurrence of Kidney Stone (ROKS) nomogram was developed to identify first-time stone formers who were at high risk and needed more intensive interventions and specialty care. This calculator takes into account the patient’s age, gender, family history, symptoms with first stone event, stone composition, imaging and other clinical features and is used to assess the 2-, 5- and 10-year recurrence of symptomatic stone events in first-time stone formers (Figure 2).24

Conclusion

Successful treatment of kidney stones requires an individualized strategy and avoidance of a one-size-fits-all approach. Follow-up depends on the patient’s individual risk factors and periodic face-to-face counseling, even during periods without stone formation. Maintenance and successful prevention of this common, expensive and often preventable condition is critical. ⊖

References

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Acute Post Streptococcal Glomerulonephritis – An Update

By Omar Tolaymat, MD1, Mohammad Ilyas, MD2

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2Assistant Professor, University of Florida, Jacksonville, FL

Abstract: Acute post streptococcal glomerulonephritis (APSGN) is caused by prior infection with specific nephrogenic strains of group A beta-hemolytic streptococcus. The clinical presentation of APSGN varies from asymptomatic microscopic hematuria to the full-blown acute nephritic syndrome, characterized by gross hematuria, proteinuria, edema, hypertension, and acute kidney injury. The long term outcome is generally favorable, especially in children, but rare cases may progress to chronic renal failure.

Introduction

Acute Glomerulonephritis is defined as proliferation and inflammation of renal glomeruli. Acute post streptococcal glomerulonephritis (APSGN) is the most common form of glomerulonephritis in children in the United States.1 It is rare in children younger than three years of age; the mean age at onset is six to seven years. The true incidence is unknown, because many cases are subclinical.

Etiology

APSGN is known to follow infections of the skin or upper respiratory tract with certain nephrogenic strains of group A beta-hemolytic streptococcus. APSGN is associated with pharyngitis, most commonly occurring in winter months and pyoderma, most commonly occurring in summer months. Pyoderma-related APSGN used to be more common in the southern regions of the United States;2 however, over the last two decades it has declined. Now pharyngitis is the most frequent cause of APSGN, as seen in the northeast Florida region for the period of 1996-2006 when compared to 1959-1973.3 Characteristically, there is a latent period between the onset of streptococcal infection and the onset of nephritis (usually 8 to 14 days for pharyngitis and 14 to 21 days for pyoderma).4 APSGN can occur as sporadic cases or in well-organized epidemics. Early death is extremely rare in children (<1 percent).2 In elderly patients with debilitating conditions (e.g. malnutrition, alcoholism, diabetes and chronic illness), the incidences of azotemia (60 percent), congestive heart failure (40 percent) and nephrotic-range proteinuria (20 percent) are high.5 Death may occur in 20-25 percent of these patients.5

Pathophysiology

Although many morphologic, clinical and serologic features suggest that APSGN is an immune complex disorder, the precise nature of the antigen-antibody interaction is undefined. Proposed theories have suggested that glomerular entrapment of circulating immune complexes contain a streptococcal antigen in the affected glomerulus. In situ immune complex formation at glomerulus is also observed, either from antibodies reacting with streptococcal antigen deposited in the glomerulus or with the glomerulus itself.6 (Figures 1, 2 and 3 show histopathology). In either case, antigens localize on the glomerular capillary wall, activate the complement system and then initiate a proliferative and inflammatory response.6

The glomerular inflammation impairs microcirculation leading to a reduction in glomerular filtration rate (GFR). This results in an increase sodium in and water retention, leading to volume overload. The amount of water retention is variable, but in severe cases, may result in hypertensive crisis and pulmonary edema.7

Clinical Presentation

The clinical presentation varies, it depends upon the intensity of the disease, but many patients are not markedly ill. Hematuria and edema are the most common complaints. Gross hematuria (tea-colored urine) has been reported in 70 percent of hospitalized patients, and microscopic hematuria is present in virtually all children with the disease.2 The initiating streptococcal infection usually has resolved by the time of the illness presentation, although impetigo may still be present. Table 1 lists the clinical manifestations in patients with APSGN in order of frequency. Table 2 summarizes a variety of laboratory and radiographic abnormalities that are observed in these patients.

Many patients have no symptoms and their disease is discovered only by examination of their urine. Most commonly, the patient will be seen because of a sudden change in urine color. However, patients can present with acute distress, such as a child with severe systemic involvement manifested by lower extremity edema, hypertension, oliguria, azotemia and seizure. When obtaining a patient’s history, it is important to include questions about previous upper respiratory tract illness or skin infection, as well as medications. Additionally, a detailed history should be obtained about the change in urine color. Hematuria in children with APSGN is typically described as “coke” or “tea” colored. Bright red urine is likely a consequence of anatomic problems such as urolithiasis, rather than glomerulonephritis.8

The physical exam should begin with a full set of vital signs. Hypertension if accompanied by altered mental status demands prompt attention. The glomerular filtration rate is usually reduced, reflected in decreased urine output. Signs of circulatory overload, such as peripheral edema, are common findings. In severe cases, pulmonary edema may manifest as respiratory distress.

Laboratory Assessment

Laboratory abnormalities vary with the severity of the disease. Hematuria is the most consistent urinary abnormality, but the uri-
nalysis can be normal.² The urinary sediment reveals red blood cell casts. Pyuria and hyaline granular casts are common. Proteinuria may be present, but is usually less than 2g/m2/24h.

In a small number of patients, there are profound elevations of blood urea nitrogen (BUN), serum creatinine and serum inorganic phosphate, that signify a reduction of glomerular filtration.² Hypertension, hyperkalemia and metabolic acidosis also can occur. The complete blood cell count may show a dilutional anemia. Rising antistreptolysin O (ASO) titers suggest previous streptococcal infection; however, anti-DNase B is more appropriate to be increased following streptococcal infection; however, anti-DNase B is more appropriate to be increased following streptococcal pyoderma. The C3 component of complement is decreased in most patients due to consumption at the glomerular mesangial level.² Cultures from the throat and skin should be obtained to isolate a nephrogenic strain of Streptococcus.

The findings on chest radiography could include cardiomegaly, pulmonary edema, pleural effusion and edema of the soft tissues.¹⁰

**Differential Diagnosis**

Entities that may mimic the presentation of post-infectious glomerulonephritis are listed in Table 3, with some differentiating features. It is important to recognize that a patient with APSGN could possibly develop a life-threatening complication, such as hypertensive encephalopathy and hyperkalemia.

**Management**

In most cases of acute post-streptococcal glomerulonephritis, there is no specific therapy that influences healing of the glomerular lesions. Antibiotics do not alter the course of the disease but may decrease the spread of nephrogenic strains of Streptococcus in patients with positive cultures.²

Appropriate therapy, as listed in Table 4, should be instituted promptly for the child who presents with acute renal failure, hypertension, hyperkalemia, hyponatremia and congestive heart failure.

Patients with renal insufficiency should be assessed by a nephrology specialist. When APSGN is accompanied by a nephrotic syndrome, the additional diagnostic and therapeutic interventions are also beyond the typical primary care practice.

Symptoms suggestive of hypertensive encephalopathy such as headache, nausea, vomiting, seizures and transient cortical blindness require prompt attention and control of blood pressure.

Beyond these situations many such patients can be managed in the primary care setting, but this entails a commitment to serial examination. The major threat to such patient is hypertension and its complications, and this may evolve over a few days. In otherwise typical post streptococcal glomerulonephritis with stage I hypertension and no renal failure, therapy with dietary restrictions, along with a loop diuretic and daily blood pressure rechecks are reasonable.²⁻⁷

The urinary abnormalities in post-streptococcal glomerulonephritis may persist for a long time, even up to a year. The best indicator of resolution of renal inflammation and proliferation is the return of C3 level back to normal. This generally occurs within six to eight weeks. A persistent decrease in C3 after eight weeks merits referral, as this could be an indicator that “glomerulonephritis” was

**Table 1: Clinical Findings in Acute Post-Streptococcal Glomerulonephritis**

<table>
<thead>
<tr>
<th>Most Frequent Presenting Manifestations</th>
<th>Less Frequent Associated Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Edema (periorbital-anasarca)</td>
<td>• Urinary Tract Syndrome</td>
</tr>
<tr>
<td>• Hematuria (microscopic-gross)</td>
<td>– Flank-loin pain, dysuria, frequency</td>
</tr>
<tr>
<td>• Hypertension (mild-moderate)</td>
<td>• Circulatory congestion</td>
</tr>
<tr>
<td>• Oliguria</td>
<td>– Mild symptoms of congestive heart failure</td>
</tr>
<tr>
<td>• Nonspecific systemic symptoms (Anorexia, nausea, fever, malaise, abdominal pain and pallor)</td>
<td>• Hypertensive encephalopathy (Headaches, vomiting, confusion, somnolence, visual disturbances, aphasia, convulsions)</td>
</tr>
</tbody>
</table>

**Table 2: Laboratory Investigations**

<table>
<thead>
<tr>
<th>U R I N E - S e d i m e n t</th>
<th>BLOOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria, red blood cell casts ± hyaline granular casts, proteinuria</td>
<td>Biochemistry</td>
</tr>
<tr>
<td></td>
<td>BUN: ?</td>
</tr>
<tr>
<td></td>
<td>Creatinine: N or ?</td>
</tr>
<tr>
<td></td>
<td>Sodium: N or ?</td>
</tr>
<tr>
<td></td>
<td>Potassium: N or ?</td>
</tr>
<tr>
<td></td>
<td>Chloride: N or ?</td>
</tr>
<tr>
<td></td>
<td>Albumin: N or ?</td>
</tr>
<tr>
<td></td>
<td>Serology</td>
</tr>
<tr>
<td></td>
<td>Antistreptolysin-O: ?</td>
</tr>
<tr>
<td></td>
<td>(with pharyngitis)</td>
</tr>
<tr>
<td></td>
<td>Anti-DNase: B ?</td>
</tr>
<tr>
<td></td>
<td>Anti-hyaluronidase: ?</td>
</tr>
<tr>
<td></td>
<td>Complement Components</td>
</tr>
<tr>
<td></td>
<td>C3: ?</td>
</tr>
<tr>
<td></td>
<td>C4: N or rarely minimally ?</td>
</tr>
<tr>
<td></td>
<td>H e m o l y t i c C o m p o n e n t s</td>
</tr>
<tr>
<td></td>
<td>Activity: ?</td>
</tr>
<tr>
<td></td>
<td>H g b and Hct: N or ?</td>
</tr>
<tr>
<td></td>
<td>P l a t e l e t s: N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C U LT U R E S</th>
<th>R a d i o g r a p h i c  S t u d i e s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throat</td>
<td>Chest</td>
</tr>
<tr>
<td>Skin</td>
<td>± Cardiomegaly</td>
</tr>
<tr>
<td></td>
<td>± Pulmonary Congestion</td>
</tr>
<tr>
<td></td>
<td>± Pleural Effusion</td>
</tr>
<tr>
<td>Abdomen</td>
<td>± Ascites</td>
</tr>
</tbody>
</table>
actually the initial presentation of a more chronic process, such as membranoproliferative glomerulonephritis (MPGN).

**Common Pitfalls**

- Hematuria is the most common urinary abnormality, but the presence of polymorphonuclear leukocytes and renal epithelial cells may be the only abnormalities early in the disease. Thus, the patient may be mistakenly diagnosed as having a urinary tract infection.

- It is extremely important to differentiate between AGN and the nephrotic syndrome, because the management may be entirely different. Patients with nephritis may have signs of fluid overload and should be fluid restricted. Diuretics should be used in the management of circulatory congestion. Those with the nephrotic syndrome may also present with edema, despite intravascular volume depletion. The use of diuretics here, however, should be done with great care, because it may lead to a decline in effective circulatory volume.

- It is important to remember that too rapid correction of the elevated blood pressure can also be dangerous and lead to hypoxic ischemic insult. It is therefore essential that the patient should be monitored closely during treatment of hypertension. The mean arterial blood pressure should be lowered no more than ≤25 percent of the initial value in the first hour and then gradually reduced over the next 24–48 hours to normalize blood pressure.¹¹

**Conclusion**

Acute post-streptococcal glomerulonephritis (APSGN) primarily affects children, with spontaneous recovery occurring in almost all patients, including those who develop renal insufficiency during the acute phase. Irreversible renal failure likely occurs in less than one percent of all pediatric patients, however, the percentage is slightly higher in adults. Despite sporadic outbreaks, the incidence of APSGN has decreased over the last few decades. Although the reasons for this decline have not been clearly delineated, the widespread use of antibiotics, changes in etiological pathogens, altered susceptibility of the host, better health care delivery and improved socioeconomic conditions clearly play a major role. ✤

### Table 3: Differential Diagnosis of Acute Post-Streptococcal Glomerulonephritis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute exacerbation of chronic glomerulonephritis</td>
<td>• Absence of latent period</td>
</tr>
<tr>
<td>Idiopathic hematuria (focal Nephritis, benign hematuria, IgG/IgA nephropathy)</td>
<td>• Significant azotemia and anemia</td>
</tr>
<tr>
<td></td>
<td>• History of known renal disease</td>
</tr>
<tr>
<td></td>
<td>• Usually hematuria without edema, hypertension, or azotemia</td>
</tr>
<tr>
<td></td>
<td>• Coincides with infection or exercise</td>
</tr>
<tr>
<td>Nephritis of Henoch-Schonlein Purpura</td>
<td>• History of preceding upper respiratory tract infection</td>
</tr>
<tr>
<td></td>
<td>• Abdominal pain, purpuric rash, arthralgia</td>
</tr>
<tr>
<td>Lupus Nephritis</td>
<td>• Rash, arthralgia, lupus serology (antinuclear, antibody Anti-DNA)</td>
</tr>
<tr>
<td></td>
<td>• Prolonged hypocomplementemia, hemolytic anemia common</td>
</tr>
<tr>
<td>Membranoproliferative</td>
<td>• Most likely if C3 still decreased after 6-8 week and</td>
</tr>
<tr>
<td></td>
<td>• Glomerular filtration rate still decreased after 3 week</td>
</tr>
<tr>
<td></td>
<td>• Rising antistreptolysin-O titers favors post-streptococcal</td>
</tr>
<tr>
<td></td>
<td>• glomerulonephritis, but 25% of patients with MPGN have preceding streptococcal</td>
</tr>
<tr>
<td>Nephritis secondary to toxins (e.g. lead, mercury, hydrocarbons)</td>
<td>• Suggested history and other clinical findings of suspected toxins</td>
</tr>
</tbody>
</table>

### Table 4: Management of Complications of Acute Glomerulonephritis

<table>
<thead>
<tr>
<th>Category</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Acute Renal Insufficiency</td>
<td></td>
</tr>
<tr>
<td>1. Fluid restriction</td>
<td>a. Insensible water loss (300 mL/m2/24 h) + urine output – planned weight loss</td>
</tr>
<tr>
<td>2. Diet</td>
<td>a. Low sodium (1-2 NaCL/m2/24h)</td>
</tr>
<tr>
<td></td>
<td>b. Low protein: 0.5 g/kg/24h (if BUN &gt;75)</td>
</tr>
<tr>
<td>3. Correction of metabolic acidosis (serum bicarbonate &lt;12)</td>
<td>a. 0.6 x weight x (desired – observed HCO3) given i.v. over 4-6 h</td>
</tr>
<tr>
<td>B. Hypertension</td>
<td>1. Encephalopathy</td>
</tr>
<tr>
<td></td>
<td>a. Oxygen</td>
</tr>
<tr>
<td></td>
<td>b. Nicardipine 1-4 mcg/kg/min iv infusion</td>
</tr>
<tr>
<td></td>
<td>c. Furosemide 1 mg/kg per dose i.v.</td>
</tr>
<tr>
<td>2. No encephalopathy</td>
<td>a. Nifedipine 0.10-0.50 mg/kg per dose PO or SL; may repeat in 400 hr</td>
</tr>
<tr>
<td></td>
<td>b. Hydralazine 0.1-0.2 mg/kg i.v.</td>
</tr>
<tr>
<td></td>
<td>c. Isradipine 0.05-0.15 mg/kg per dose PO Maximum dose 0.8 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>d. Captopril 0.15-3 mg/kg dose TID, Max 6 mg/kg/day</td>
</tr>
<tr>
<td>C. Hyperkalemia – If serum K &gt;6.5 mEq/L with ECG changes</td>
<td>1. Calcium: 10-15 mg/kg of elemental calcium i.v. over 15-30 minutes with continuous ECG monitoring</td>
</tr>
<tr>
<td></td>
<td>2. Bicarbonate: 1-3 mEq/kg (short term effect)</td>
</tr>
<tr>
<td></td>
<td>3. Glucose and insulin: 1 mL/kg D50 with 0.2 U insulin per gram of glucose given</td>
</tr>
<tr>
<td></td>
<td>4. Kayexalate: 1 g/kg with dextrose and water (enema) or with sorbitol (oral)</td>
</tr>
<tr>
<td></td>
<td>5. Dialysis if above measures are unsuccessful</td>
</tr>
<tr>
<td>D. Hyponatremia</td>
<td>1. Fluid restriction</td>
</tr>
<tr>
<td>E. Congestive Cardiac Failure</td>
<td>1. Oxygen</td>
</tr>
<tr>
<td></td>
<td>2. Fluid restriction</td>
</tr>
<tr>
<td></td>
<td>3. Correct hypertension</td>
</tr>
<tr>
<td></td>
<td>4. Diuretics (i.e. furosemide)</td>
</tr>
<tr>
<td></td>
<td>5. Dialysis</td>
</tr>
<tr>
<td></td>
<td>• May exacerbate hypertension</td>
</tr>
<tr>
<td></td>
<td>• Causes profound hypotension in adults</td>
</tr>
</tbody>
</table>
References


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Chicken or Egg? The Complex Association between Sleep Apnea and Kidney Disease

By Keerti Bhanushalli, MD1, Richard Berry, MD1,2, Rebecca Beyth, MD, MSc1,2, and Muna Canales, MD, MS1,2

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2 Malcom-Randall VA Medical Center, Gainesville, FL

Abstract: Sleep apnea and chronic kidney disease (CKD) are two highly prevalent and costly diseases with numerous negative health consequences. Because sleep apnea is more common among CKD and end-stage renal disease (ESRD) patients, it is hypothesized that they may be related. There is epidemiological evidence for an association between sleep apnea and CKD and complex mechanisms that link these two disorders. However, there are still gaps in our knowledge of sleep apnea and CKD, and studies are ongoing to address these gaps.

Introduction

Sleep apnea disproportionately affects patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) when compared to the general population. The association between sleep apnea and kidney function is complex and may be bidirectional. Three theories to explain this association exist. Reduced renal function may lead to dysregulated breathing and sleep apnea. Secondly, sleep apnea and kidney disease share common risk factors. Finally, sleep apnea may drive or accelerate kidney disease development or progression. Ultimately, treatment of sleep apnea may represent a novel tool to slow the progression of kidney disease and related complications.

CKD is common, costly and deadly

CKD is a disorder marked by decreased estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m2 or other evidence of kidney damage. Over the last decade there has been a marked increase in the prevalence of CKD globally and it appears that trend is likely to continue. In the United States, it is estimated that CKD, as defined by eGFR less than 60 ml/min/1.73m2 and/or albuminuria, affects more than one in 10 adults, and the prevalence increases with age; one in three people >60 years of age have CKD. Approximately 400,000 Americans require dialysis and more than 185,000 have functioning kidney transplants as of December 2011.

CKD has numerous negative health consequences. Beyond progression to end-stage kidney disease requiring dialysis, CKD is associated with a spectrum of complications including bone and mineral metabolism disorders, electrolyte abnormalities, acid-base disturbances, anemia, cognitive impairment and hypertension. Most importantly, CKD is a well-known independent risk factor for cardiovascular disease (CVD) and death. For example, a retrospective cohort study of more than one million integrated health plan members found that subjects with eGFR 45-49 ml/min/1.73m2 versus eGFR ≥ 60 ml/min/1.73m2 had a 40 percent increased risk of cardiovascular events and a 20 percent increased risk of death during the median follow up of 2.8 years, despite multivariate adjustment. This risk rose exponentially with reduced eGFR. Indeed, patients with CKD who are not on dialysis are more likely to die prematurely of CVD than to progress to dialysis or transplantation. Furthermore, CKD impairs quality of life independent of other co-morbid conditions. For example, a large population-based cross-sectional study of more than 10,000 subjects found that eGFR <60 versus >60 ml/min/1.73m2 was associated with impaired quality of life despite adjustment for age, body habitus and co-morbid conditions; this finding has been echoed in other studies.

It is therefore not surprising that CKD confers considerable cost burden on our health care system. CKD accounts for nearly 24 percent of Medicare expenditures and more than $22,000 is spent per person per year in the management of CKD and related complications. Once on dialysis, more than $88,000 is spent per person per year. In the year 2011 alone, more than $45 billion was spent on CKD in the United States.

Given the epidemic of CKD and its attendant consequences and cost of care, novel, treatable risk factors are being sought to attenuate the risk of CKD development, progression and related adverse outcomes. One such factor is sleep apnea.

Sleep apnea is common and associated with negative health outcomes

Sleep apnea is a disorder characterized by repeated episodes of apnea (cessation of airflow) and hypopnea (reduction in airflow) lasting at least 10 seconds and accompanied by some level of oxygen desaturation. The apnea-hypopnea index (AHI) summarizes the severity of sleep apnea and is defined as the number of apneas and hypopneas (with oxygen desaturation) per hour of sleep as determined from polysonography (PSG). PSG, also known as an overnight sleep study, is the gold standard for diagnosis of sleep apnea. The American Academy of Sleep Medicine Task Force defines an AHI of less than five events per hour as “normal,” whereas mild, moderate and severe sleep apnea are diagnosed when the AHI is 5-14.9 events/hour, 15-29.9 events/hour and ≥ 30 events/hour, respectively. Sleep apnea may be obstructive as a result of airway collapse during inspiration, central as a result of decreased respiratory drive or a mix of both central and obstructive events. Treatment of sleep apnea consists of a variety of measures including weight loss, surgery, sleep position adjustment, medications, oral appliances and, most commonly, positive airway pressure (PAP) therapy. Sleep apnea (AHI ≥ 5) affects one in five Americans and at least one in 15 have moderate to severe sleep apnea. The majority
of sleep apnea in the general population is obstructive. Key risk factors for sleep apnea include male gender, obesity and older age.

Sleep apnea, much like CKD, is associated with an array of negative health consequences including hypertension, insulin resistance, cognitive impairment, reduced quality of life, cardiovascular disease and death. More specifically, data from the Wisconsin Sleep Cohort Study, a large population-based prospective study of middle-aged community-dwelling men and women, found that over a range of follow-up time (4-14 years), PSG-diagnosed severe sleep apnea at baseline was associated with a threefold increased risk of incident hypertension, a fourfold greater incidence of stroke, a threefold increased risk of all-cause mortality and a fivefold increased risk of cardiovascular death. The mechanistic underpinnings of the cardiovascular consequences of sleep apnea begin with the sleep apnea event. Sleep represents a time of increased parasympathetic tone, drop in blood pressure and heart rate, and body repair. However, during sleep apnea, with cessation of airflow, hypoxemia and hypercapnia ensue, accompanied by intra-thoracic pressure changes, as attempts are made to breathe against a closed airway. Ultimately, arousal occurs in order to open the airway. The combination of hypoxia, hypercapnia and arousal lead to sympathetic activation, endothelial dysfunction, vascular oxidative stress, inflammation, hypercoagulability and metabolic dysregulation which conspire to increase cardiovascular risk. Notably, treatment with PAP therapy has been shown to reverse many of these intermediary mechanisms.

**Sleep apnea disproportionately affects CKD and ESRD patients**

Growing evidence supports a higher prevalence of sleep apnea in both CKD and ESRD patients. Reports from 1989-2007 have shown a prevalence of 30-90 percent for sleep apnea in ESRD (dialysis) patients, with the majority of studies reporting a prevalence of over 40-50 percent. The range in prevalence is related to variability in the definitions and cut-points for sleep apnea that have evolved over time. Other studies have examined the prevalence of sleep apnea in non-dialysis-requiring CKD. For example, a recent study of individuals with a spectrum of renal function found that the prevalence of sleep apnea rose progressively with worsening renal function. Among the 55 participants with eGFR > 60 ml/min/1.73m2, 27 percent had moderate to severe sleep apnea, whereas among those with CKD (n=124) and on dialysis (n=75) the prevalence of moderate to severe sleep apnea was 41 percent and 57 percent, respectively. Interestingly, though obstructive sleep apnea predominated in all three groups in this cohort, the proportion with central sleep apnea was higher with worsening level of kidney function. Furthermore, the prevalence of nocturnal hypoxia, defined as ≥12 percent of total sleep time spent at less than 90 percent oxygen saturation, increased with the presence of CKD or ESRD. These findings have since been confirmed in other studies of sleep apnea prevalence in CKD.

The reason for the high prevalence of sleep apnea in CKD and ESRD is not clear but three possible explanations exist and may not be mutually exclusive.

**A confluence of co-morbidities may explain the high prevalence of sleep apnea in kidney disease**

Patients with advanced CKD and ESRD have a high burden of co-morbid conditions, such as diabetes and cardiovascular disease, compared to the general population that predispose them to sleep apnea. The relationship between co-morbid conditions is complex and may be related to confounding, mediation or modification along a potentially bidirectional pathway between sleep apnea and kidney disease. Notably, a case-control study of 46 dialysis patients compared to 137 age-, sex- and BMI-matched controls from the Sleep Heart Health Study found that dialysis patients had fourfold greater odds of severe sleep apnea and nocturnal hypoxemia even after adjustment for co-morbid conditions. Other studies have found associations between sleep apnea and/or related nocturnal hypoxia and kidney disease independent of co-morbid conditions. This suggests that other factors may underlie the high prevalence of sleep apnea in CKD and ESRD.

**Factors “retained” with advanced CKD and in dialysis patients may explain the high prevalence of sleep apnea in kidney disease**

A second hypothesis to explain the high prevalence of sleep apnea in kidney disease is that something “retained” with advancing CKD and ESRD dysregulates breathing and leads to sleep apnea (Figure 1). Putative factors include uremic toxins, volume excess, enhanced chemo-reflex activity in the setting of hypocapnia related to chronic metabolic acidosis and others. There has been some evidence to support this hypothesis. First, Hanly et al performed sleep studies on 15 conventional hemodialysis (three times per week) patients, then repeated the sleep studies after transitioning to several months of nocturnal hemodialysis, which provides more clearance of uremic toxins. The authors found that among the seven patients with sleep apnea, the AHI was reduced significantly from mean AHI 44 ± 22 to 9 ± 9 events per hour when PSG was performed on the day of dialysis; the reduction in AHI was not as marked when PSG was performed on the night before dialysis (AHI 46 ± 19 events per hour for conventional hemodialysis versus 19 ± 15 events per hour for nocturnal hemodialysis). The authors speculated that more aggressive clearance of uremic toxins and volume reversed processes that might promote sleep apnea. Specifically, volume excess and...
uremia predispose to upper airway collapse and central destabilization of ventilatory control which, in turn, lead to sleep apnea in dialysis patients. Other studies have supported these mechanisms. Another study demonstrated that dialysis patients with sleep apnea on conventional thrice-weekly dialysis displayed heightened sensitivity to hypercapnia (enhanced chemoreflex activity) which promotes periodic breathing and central events. More aggressive dialysis led to improvement in chemoreflex response among those whose sleep apnea improved. In addition, another study demonstrated that the reduction in AHI with more aggressive peritoneal dialysis was associated with a concomitant decrease in total body water as measured by bioimpedance. In this same study, those with more aggressive peritoneal dialysis exhibited a larger airway cross-sectional area as demonstrated by magnetic resonance imaging (MRI). Finally, while case reports have documented improvement (but not normalization) in the AHI after kidney transplantation, the largest study of kidney transplant patients (n=18) found that AHI did not change before and after kidney transplantation. Taken together, factors “retained” in advanced CKD and in dialysis patients, such as uremic toxins and volume, at least partially contribute to the high prevalence of sleep apnea observed in this population.

Sleep apnea may lead to faster progression of kidney disease

A third explanatory hypothesis is that presence of sleep apnea early in the course of CKD predisposes to faster decline in renal function and therefore high prevalence of SDB in late CKD. Several cross-sectional studies have found greater evidence of CKD as defined by a lower eGFR in sleep apnea. In addition, studies have found higher albuminuria, another marker of kidney injury, among individuals with severe sleep apnea. While this data is suggestive of an association, longitudinal data is required to establish causality. Recently, several papers have been published examining the association between sleep apnea and/or nocturnal hypoxia associated with sleep apnea and kidney function decline over time. Ahmed et al followed 858 middle-aged men and women who had undergone sleep studies as part of clinical care and had serial measurement of kidney function over 2.1 years follow up. Mean eGFR of this cohort was 71 ml/min/1.73m2. The researchers found that severe sleep apnea was associated with fourfold greater odds in rapid decline in kidney function, but this was largely explained by age, BMI, diabetes, heart failure and nocturnal hypoxia. However, presence of nocturnal hypoxia (≥ 12 percent of total sleep time < 90 percent) was associated with a nearly threefold greater odds of rapid decline in renal function (≥4 ml/min/1.73m2/year), even after adjusting for demographics, co-morbidities, independent of the presence of sleep apnea. Finally, most recently, among over 3 million veterans without CKD at baseline, Molnar et al found that veterans with incident untreated sleep apnea and treated sleep apnea, as determined using diagnosis and procedure codes had a 30 percent and 28 percent increased risk of rapid decline in eGFR, respectively (≥ 4 ml/min/1.73m2/year), despite multivariate adjustment. Of note, while this study indirectly examined the role of sleep apnea treatment on renal function trajectory, randomized trials are lacking in regards to the impact of PAP therapy or other sleep apnea therapies on kidney function trajectory.

When one considers that sleep apnea represents a disruption of the “turned down” status of the body during sleep by virtue of sleep disruption, sympathetic surges and hypoxic events occurring more than 30 times per hour in severe cases, it is plausible that sleep apnea might cause kidney injury. Indeed, hypoxia and sleep fragmentation in the form of arousals initiate a cascade of events that are hypothesized to lead to kidney injury (Figure 2). Hypoxia is known to cause oxidative stress which leads to endothelial dysfunction at the level of the glomerular capillaries which may cause injury. In addition, hypoxia, in concert with frequent arousals, triggers sympathetic activation and stimulation of the renin-angiotensin system. The consequences of sympathetic activation include nocturnal hypertension and conversion to a non-dipper blood pressure pattern at night which itself has been associated with rapid decline in renal function. It also promotes glomerular hyperfiltration which leads to overworking of individual nephrons and ultimately renal injury. Interestingly, glomerular hyperfiltration has been documented to improve with treatment of sleep apnea. Finally, activation of the renin-angiotensin system in response to arousals and hypoxia may promote glomerular fibrosis. Ultimately, all of these factors conspire to promote renal injury in sleep apnea.

Figure 2: Putative direct mechanisms by which sleep apnea causes renal injury. Adapted from Adeseun et al. Current Hypertension Reports 2010;12:378-83 with permission.

The rationale for the high prevalence of sleep apnea in kidney disease is multifactorial and likely bi-directional

As shown, three hypotheses exist to explain the high burden of sleep apnea in CKD and in dialysis patients. In reality, all three hypotheses may be correct but of variable relevance depending upon the stage of CKD (Figure 3). Early in CKD or pre-CKD, sleep apnea may promote development or progression of CKD. As renal function declines and approaches end-stage, factors related to uremia and volume excess destabilize breathing further and promote development of or exacer-
Sleep apnea is under-recognized in kidney disease

Sleep apnea is under-recognized in kidney disease. This is thought to be because kidney disease patients with sleep apnea may not present with the typical symptoms of sleep apnea seen in the general population. For example, CKD patients with sleep apnea may have less snoring, lower body mass index (BMI), less bed-partner reported apneas, less daytime sleepiness and greater prevalence of central sleep apnea as compared to sleep apnea patients with normal renal function. This makes the recognition of sleep apnea in CKD patients more challenging and the current risk prediction tools to identify sleep apnea less effective in the CKD population.

Identification and treatment of sleep apnea in kidney disease may be beneficial

The current strategies to prevent development or progression of CKD and related adverse outcomes include blood pressure and diabetes control as well as renin-angiotensin system inhibition. In the past 15 years, few interventions have been developed to affect CKD trajectory and complications. In an era where the burden of CKD and related cost of care is soaring, there is an urgent need for new therapies to attenuate CKD progression and related consequences. Regardless of the directionality of the association between sleep apnea and CKD, sleep apnea may represent a novel, modifiable risk factor for CKD progression and/or its complications. Identification and treatment of sleep apnea in CKD and dialysis patients may improve quality of life, reduce cardiovascular risk for these patients and slow the progression of CKD for those who are pre-dialysis, thus attenuating the risk of CKD-related complications. Providers of CKD and dialysis patients should be aware of the high prevalence of sleep apnea in this population and consider referral for sleep evaluation in high-risk individuals.

Gaps in our understanding of the association between sleep apnea and kidney disease exist

It is important for providers to understand that gaps in knowledge remain. First, well planned longitudinal studies with prospectively collected data and adequate sample size in populations with a range of renal function are needed to determine whether sleep apnea promotes development or progression of kidney disease. Furthermore, such studies are needed to determine whether sleep apnea magnifies the risk of heart disease, death and other negative outcomes related to kidney disease. Second, randomized controlled trials of sleep apnea treatment on kidney function trajectory and related consequences are needed. Finally, screening of all CKD and dialysis patients with sleep studies is not possible due to cost and burden on the health care system. Thus, simple-to-use screening tools for sleep apnea are necessary to assist providers in identifying high-risk patients for screening. Existing sleep apnea risk questionnaires may be inadequate to predict sleep apnea in CKD because, as discussed earlier, patients with CKD and sleep apnea have a different profile than sleep apnea patients in the general population.

To address these gaps in the literature, ongoing studies are addressing some of the remaining questions. First, the Sleep and Nephrology Outcomes Research (SNORE) Study is a United States Department of Veterans Affairs (VA)-funded study of 250 North Florida/South Georgia Health System veterans with moderate to severe CKD who are not undergoing treatment for sleep apnea. Veterans are enrolled prospectively to undergo full, unattended PSG at baseline. Participants are followed for three years with serial measurement of kidney function and quality of life. The goal of this study is to determine whether sleep apnea leads to faster kidney function decline and reduced quality of life. In addition, this study will validate an existing sleep apnea risk questionnaire for use in CKD. Another study that is ongoing at the University of Calgary will randomize 40 patients with moderate to severe CKD and sleep apnea to treatment with PAP therapy or no treatment for one year to determine the impact of PAP therapy on renal function trajectory in CKD.

Conclusion

Sleep apnea is common in patients with CKD and ESRD. The association between sleep apnea and kidney disease is complex and may be bidirectional. Identification and treatment of sleep apnea may be of benefit to CKD patients by attenuating risk of progression. In addition, among CKD and ESRD patients, treatment of sleep apnea...
may mitigate the risk of adverse kidney disease-related outcomes that may be magnified by sleep apnea. Further prospective studies are needed to confirm the association between sleep apnea and kidney disease, to determine whether treatment of sleep apnea is truly of benefit to this population and to provide guidance with respect to screening for sleep apnea in kidney disease.

**Acknowledgments**

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**References**


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Chronic Kidney Disease – An Update

Background:
The Duval County Medical Society (DCMS) is proud to provide its members with free continuing medical education (CME) opportunities in subject areas mandated and suggested by the State of Florida Board of Medicine to obtain and retain medical licensure. The DCMS would like to thank the St. Vincent’s Healthcare Committee on CME for reviewing and accrediting this activity in compliance with the Accreditation Council on Continuing Medical Education (ACCME).

This issue of Northeast Florida Medicine includes an article, “Chronic Kidney Disease- An Update” authored by Nabeel Aslam, MD, FASN, which has been approved for 1 AMA PRA Category 1 credits. For a full description of CME requirements for Florida physicians, please visit www.dcmsonline.org.

Faculty/Credentials:
Nabeel Aslam, MD, FASN, Chair, Division of Nephrology and Hypertension and Program Director, Nephrology Fellowship, Mayo Clinic Florida.

Objectives:
1. Discuss kidney disease: Improving global outcomes (KDIGO), the definition of chronic kidney disease and staging system.
2. Review various methods for estimation of glomerular filtration rate (GFR) and its limitations.
3. Describe steps in management of patients with chronic kidney disease.

Date of release: June 1, 2016  Date Credit Expires: June 1, 2018  Estimated Completion Time: 1 hour

How to Earn this CME Credit:
1. Read the “Chronic Kidney Disease- An Update” article.
2. Complete the posttest. Scan and email your test to Kristy Wolski at kristy@dcmsonline.org or mail it to 1301 Riverplace Blvd., Suite 1638, Jacksonville, FL 32207.
3. You can also go to www.dcmsonline.org to read the article and take the CME test online.
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Faculty Disclosure:
Nabeel Aslam, MD, FASN reports no significant relations to disclose, financial or otherwise, with any commercial supporter or product manufacturer associated with this activity.

Disclosure of Conflicts of Interest:
St. Vincent’s Healthcare (SVHC) requires speakers, faculty, CME Committee and other individuals who are in a position to control the content of this education activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly evaluated by SVHC for fair balance, scientific objectivity of studies mentioned in the presentation and educational materials used as basis for content, and appropriateness of patient care recommendations.
Chronic Kidney Disease – An Update
By Nabeel Aslam, MD, FASN

Introduction
Chronic kidney disease (CKD) is a general term used to describe a wide variety of disorders affecting the kidney structure or function for more than three months. Several studies have demonstrated the association of CKD with an increased risk of all-cause and cardiovascular mortality, dialysis requirement and development of acute kidney injury.1,2,3,4 Based upon conservative estimates, approximately 11 percent of the U.S. population has impairment of renal function.5,6 Chronic kidney failure requiring renal replacement therapy (dialysis or transplantation) develops in one percent of patients with CKD; however, the cost associated with renal replacement therapy is the highest among all of the chronic diseases, consuming six percent of the health care budget, and leads to a significant reduction in lifespan.8

Chronic Kidney Disease – Classification
Up until 2002, there was no uniform definition of chronic kidney disease. The National Kidney Foundation published guidelines through the Kidney Disease Outcome Quality Initiative (KDOQI) for a uniform definition of CKD.9 KDOQI guidelines define chronic kidney disease as an abnormality in the structure or function of kidneys that manifests as proteinuria, hematuria, radiologic abnormalities or a reduction in the glomerular filtration rate (GFR) that is persistent for at least three months. These guidelines led to the awareness of CKD among the medical community and changed the laboratory practices resulting in uniform reporting of the GFR. Since the publication of KDOQI, there has been a tremendous body of research highlighting the adverse effects of decline in GFR and albuminuria.1,2,3,4 Based upon this new evidence, the Kidney Disease: Improving Global Outcome (KDIGO) group updated the definition of CKD and proposed a new staging system.10

CKD is defined by KDIGO as abnormalities of kidney structure (abnormal imaging) or function (albuminuria – albumin to creatinine ratio - ACR >30mg/G, abnormal urine sediment, electrolytes disorder due to tubular dysfunction, histologic abnormalities, kidney transplantation, GFR <60 ml/min/1.73 m²) present for ≥ 3 months, with implications for health. CGA staging in KDIGO classification is based on Cause, GFR group and Albuminuria (Table 1). As an example, a patient with diabetic nephropathy with GFR of 25 ml/min/1.73 m² with albuminuria > 300 mg/G would be classified as CKD due to diabetic kidney disease G4 A3.

The rationale of using this staging system is that each CGA category with increasing severity is associated with a worse outcome. A patient with G3a A3 is more likely to have an adverse health outcome as compared to a patient with G3a A1. Thus, this new staging system provides better prognostic information about the outcome of CKD.

Table 1: Cause, GFR, Albuminuria (CGA) Staging10

<table>
<thead>
<tr>
<th>Cause of Kidney Disease</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular Disorders</td>
<td>Diabetes, autoimmune diseases, drugs</td>
</tr>
<tr>
<td>Vascular Disorder</td>
<td>Renovascular disorders, ANCA associated vasculitis</td>
</tr>
<tr>
<td>Tubulo-interstitial Disorders</td>
<td>Stones, obstruction, toxins, drugs</td>
</tr>
<tr>
<td>Congenital Disorders</td>
<td>Polycystic kidney disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GFR (ml/min/1.73 m²) Grouping</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>G 1</td>
<td>≥ 90</td>
</tr>
<tr>
<td>G 2</td>
<td>60-89</td>
</tr>
<tr>
<td>G 3a</td>
<td>45-59</td>
</tr>
<tr>
<td>G 3b</td>
<td>30-44</td>
</tr>
<tr>
<td>G 4</td>
<td>15-29</td>
</tr>
<tr>
<td>G 5</td>
<td>&lt; 15</td>
</tr>
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</table>

Persistent Albuminuria (albumin to creatinine ratio-ACR)

<table>
<thead>
<tr>
<th>Persistent Albuminuria (albumin to creatinine ratio-ACR)</th>
<th>A 1</th>
<th>A 2</th>
<th>A 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to mildly increased</td>
<td>&lt;30 mg/G</td>
<td>30-300 mg/G</td>
<td>&gt;300 mg/G</td>
</tr>
<tr>
<td>Moderately increased</td>
<td></td>
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<tr>
<td>Severely increased</td>
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Evaluation of Chronic Kidney Disease

Once the presence of CKD is suspected based upon estimated GFR <60 ml/min/1.73m² or urine analysis findings of hematuria/proteinuria, the first step is to confirm whether these findings are due to CKD or are transient in nature. This can be accomplished by reviewing the past measurements of the creatinine and/or urine analysis results to confirm the chronicity of the findings for > 3 months. Alternatively, a combination of the presence and duration of the risk factors known to cause CKD, imaging findings of the reduced renal size/increased echogenicity and repeated measurement in three months can be used to confirm the diagnosis of CKD in the absence of historical data. Chronicity of the kidney disease cannot be assumed based upon one measurement since acute kidney injury can present with similar findings.

Measurement of the GFR

There has been a considerable advancement in the measurement of GFR since the turn of the century. Serum creatinine alone is not used as the measure of GFR due to its inherent limitations. Several factors affect the serum creatinine value including the muscle mass, age, gender, race, diet and use of drugs inhibiting creatinine secretion. Therefore, GFR estimation needs to account for several of these variables. There are several equations that have been validated to estimate the GFR. The most known among these equations are the Modification of Diet in Renal Disease (MDRD) equation and the CKD-EPI equation. The MDRD equation is derived from data collected from 1628 patients who participated in the MDRD trial, in which the urine 125I-Iothalamate clearance was used as the standard. KDOQI guidelines recommended using the MDRD equation for an estimation of the GFR. There have been several attempts to enhance the accuracy of the MDRD equation in different ethnic groups. One of the limitations of the MDRD equation is that it tends to underestimate the GFR in patients with normal or near normal creatinine since the validation cohort had an average GFR of approximately 40 ml/min/173 m². To overcome this limitation, Levey et al analyzed the data from 8,254 subjects from six research studies and four clinical populations and derived the CKD-EPI equation for an estimation of GFR. The KDIGO guidelines recommend using the CKD-EPI equation for an estimation of GFR (eGFR). As a result, many clinical laboratories are now using the CKD-EPI equation for reporting eGFR. Knowledge of the equation being used by the laboratory is important since CKD-EPI results in higher GFR for patients with mildly elevated serum creatinine level.

Role of Cystatin C in Measurement of GFR

Cystatin C is a non-glycosylated protein that is produced by all nucleated cells at a constant rate. It is filtered by the glomeruli and reabsorbed/catabolized by the proximal tubular cells. Thus, serum level of cystatin C can be used as a marker of GFR. Cystatin C level increases in the blood as the GFR declines. Cystatin C is FDA approved for the measurement of GFR. Cystatin C-based equations perform better than the serum cystatin C level alone in estimating the GFR. However, there are several sources of error in GFR measurement using cystatin C including non-steady state in acute kidney injury (AKI), variation in cystatin C generation due to ethnicity, thyroid disorders and glucocorticoid administration. Cystatin C does not add to the clinical management of patients with advanced stages of chronic kidney disease (G3b to G5). There is a debate in the literature whether patients with estimated GFR 45-59 ml/min/1.73 m² (using creatinine-based equations) without albuminuria or renal imaging abnormalities are at increased risk of adverse health outcome or whether this level of measured GFR is due to the limitation of the creatinine-based GFR estimation equation without an increased risk of adverse health consequences. In this scenario, cystatin C is helpful in confirming the presence or absence of clinically meaningful CKD. KDIGO guidelines suggest measuring cystatin C in adults with eGFR<60 45-59 ml/min/1.73 m² who do not have other markers of kidney disease. It is recommended to use the cystatin C based eGFR equations rather than the cystatin C level alone to estimate the renal function. If eGFR<60 in a patient with eGFR<60 45-59ml/min/m² is less than 60 ml/min/1.73 m³, the diagnosis of CKD is confirmed. Cystatin C-based eGFR measurement is superior to 24 hours creatinine clearance in measuring the kidney function.

Once the presence of CKD is confirmed, the next step is to ascertain the cause of the chronic kidney disease since the management of CKD depends upon the cause. In the majority of patients, kidney damage is caused by diabetes mellitus, hypertension and vascular disease. Primary renal disease accounts for the minority of cases of CKD. The cause can usually be established by careful review of the history for risk factors for CKD, including comorbid conditions, use of nephrotoxic agents, family history of kidney failure, as well as detailed clinical examination. The baseline investigations for CKD include urine analysis with estimation of albumin to creatinine ratio, measurement of electrolytes, serum creatinine and ultrasound examination of the kidneys. Additional diagnostic studies are done based upon the history and physical examination findings. In patients with suspected primary renal diseases like primary glomerulonephritis or tubulointerstitial nephritis, additional serologic tests and kidney biopsy may be warranted.
Management of CKD

Management of CKD is comprised of the following:

A - Specific treatment of the cause
B - Measures to slow the progression of CKD
C - Addressing the complications resulting from CKD
D - Preparation for the renal replacement therapy

A - Treatment of underlying etiology

Treatment of the underlying cause is directed at stabilizing or reversing the pathologic process that results in kidney damage. As an example, control of hypertension to a target of <130/80 in patients with proteinuria and <140/90 among patients without proteinuria slows the rate of decline of GFR.10 Similarly, glycemic control with a target of HbA1c of 7.0 is recommended for patients with diabetic kidney disease.16

B - Measures to slow the progression of CKD

The management of CKD progression is targeted at addressing the risk factors known to be associated with a rapid decline in kidney function. These measures include individualized blood pressure (BP) targets, use of angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB), use of statins for cardiovascular risk reduction, avoidance of nephrotoxic agents, moderate protein restriction, avoidance of AKI episodes and smoking cessation.

Hypertension control is critical in slowing the disease progression.17 Several studies have shown that poor BP control leads to rapid deterioration of renal function. However, optimum BP target is unknown. Based upon available knowledge, KDIGO recommends a BP target of <140/90 among CKD patients (diabetic and non-diabetic) with albuminuria ACR <30 mg/G (A1) and a BP target of <130/80 (diabetic and non-diabetic) for patients with albuminuria ACR >30 mg/G (A2, A3).10 In addition, BP targets should be individualized based upon the age and comorbid conditions, especially among the elderly population. Measurement of orthostatic BP is essential while titrating the antihypertensive medicines since there is an increased risk of postural hypotension that can predispose to an adverse outcome.

Several studies have shown the beneficial effect of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) in slowing the progression of kidney disease.19,20,21 A Lewis et al. study in type 1 diabetes mellitus (DM)18 and a study by Brenner et al.21 in type II DM have conclusively demonstrated that ACEi and ARB have a beneficial effect on diabetic kidney disease. The available literature shows that ACEi and ARB are most effective in patients with proteinuric kidney disease. KDIGO guidelines for the management of CKD suggest using ACEi/ARB for diabetic kidney disease (albuminuria A2, A3) and non-diabetic kidney disease (albuminuria A3).10 ACEi/ARB are preferred antihypertensive agents in patients with all stages of CKD. However, careful monitoring of the electrolytes after initiation and with each subsequent up-titration of the dose is highly recommended. A rise in serum creatinine of up to 25 percent is acceptable after initiation of renin angiotensin aldosterone system (RAAS) inhibitors since it reflects expected reduction in intra-glomerular pressure that is associated with a favorable long-term outcome. A rise of >25-30 percent in serum creatinine after the initiation of RAAS inhibitors may indicate underlying renovascular disease and, therefore, ACEi/ARB should be discontinued. There is insufficient evidence of the beneficial effect of the combined use of ACEi and ARB, but there is some data to suggest a higher risk of hyperkalemia and AKI with the combined use.22 Therefore, combined use of ACEi and ARB should be avoided.

Agents that can deteriorate renal function such as non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycoside antibiotics and radiocontrast dyes should be avoided. The role of protein restriction in slowing CKD progression is controversial.23 In general, high protein intake is associated with an accelerated decline in GFR in the early stage of CKD.24 The trials using protein restriction have not shown convincing evidence that protein restriction slows the progression of CKD.23,25 However, based upon expert opinion, lowering of protein intake to 0.8 grams/kg/day can be considered for CKD G4 patients with appropriate nutrition counselling.10 Several studies have shown the harmful effect of smoking on kidney disease and active smokers are at an increased risk of renal function decline as compared to non-smokers.26 Therefore, CKD patients should be counselled about smoking cessation.

C - Manage Complications of CKD

Several studies have shown the independent association of cardiovascular disease and CKD.27,28 The cardiovascular events occur at a younger age among CKD patients as compared to non-CKD patients, indicating that chronic kidney disease accelerates the development of cardiovascular disease.28 Statins have been shown to reduce the cardiovascular events in the general and CKD population; therefore, it is recommended that all CKD patients should receive statins.29
Metabolic acidosis has several adverse consequences, including increased catabolism and worsening of bone-mineral disease. There is data to support that metabolic acidosis itself leads to decline in renal function. There is suggestive evidence to support that correction of acidosis with exogenous bicarbonate supplementation slows the decline in GFR. Therefore, it is recommended to supplement oral bicarbonate to keep serum bicarbonate level > 22 meq/L.

Anemia is an important complication of CKD and contributes to significant symptom burden. Patients with CKD G3 should be monitored for anemia on at least a yearly basis and more frequent monitoring of anemia is required with advanced stages of CKD. The target hemoglobin in patients with CKD is 9-11 grams/dL.

Reduced GFR leads to impaired excretion of phosphate, reduced conversion of 25 hydroxy vitamin D to 1,25 dihydroxyvitamin D, reduced calcium level and elevated parathyroid hormone (PTH) level, all of which contribute to bone-mineral disorders among CKD patients. Laboratory determination of calcium, phosphate, PTH, vitamin D and alkaline phosphatase help identify patients who are at risk for bone-mineral disorders. There is insufficient evidence to recommend the target PTH level for various stages of CKD. However, it is generally recommended to maintain calcium and phosphorus levels in the normal range among non-dialysis dependent CKD patients. Dietary counselling to limit daily phosphorus intake is recommended.

Dietary counselling by a trained renal nutritionist is recommended for patients with advanced stages of CKD. General recommendations include sodium restriction of 2 grams/24 hours, limiting high phosphorus food and moderate protein restriction, as previously outlined.

Figure 1 provides a summary of evaluation and management of CKD.

Timing of Referral to the Nephrologist

The majority of patients with CKD G3 can be managed by the primary care physician. One-time consultation with the nephrologist may be considered at the time of the diagnosis of CKD to help identify the etiology of the CKD and help address measures to slow the disease progression. Subsequent monitoring for the progression of CKD can be done by the primary care providers with at least yearly monitoring of the eGFR and albuminuria among patients with CKD G3. Patients with advanced stages of CKD may require more frequent monitoring based upon each individual patient’s characteristics. Specialized nephrology care is highly recommended for patients with CKD eGFR <30 ml/min/1.73 m², persistent albuminuria >300mg/G, progressive decline in GFR despite general measures to slow progression as outlined previously, resistant hypertension (>3 antihypertensive meds including a diuretic), hereditary renal disease and recurrent nephrolithiasis. Patient education regarding the potential need of renal replacement therapy is warranted when eGFR falls below 30ml/min/1.73 m². A frank and timely discussion should be had with patients about their prognosis and all management options, including conservative management short of dialysis. Referral to the transplant center is recommended for patients with eGFR <20 ml/min/1.73 m².

Conclusion:

CKD is a common condition affecting up to 11 percent of the U.S. population. Timely diagnosis with appropriate staging can help identify patients at high risk of progression. A systematic approach to diagnosis, institution of measures to slow the progression and timely referral to a nephrologist can improve prognosis and reduce the burden of end-stage renal disease and cardiovascular events.
References


Chronic Kidney Disease – An Update

CME Questions & Answers (circle one answer)/Free to DCMS Members/$55.00 charge non-members*

(Return by June 1, 2018  BY MAIL: 1301 Riverplace Blvd. Suite 1638, Jacksonville, FL 32207 or ONLINE: www.dcmsonline.org.)

1. Based upon conservative estimate, what percentage of the U.S. population has impairment of kidney function?
   A- 6%
   B- 11%
   C- 15%
   D- 19%

2. Chronic kidney disease is defined by KDIGO (Kidney Disease – Improving Global Outcome) as abnormalities of kidney structure or function present for which of the following durations:
   A- ≥ 1 month
   B- ≥ 3 months
   C- ≥ 6 months
   D- ≥ 12 months

3. A patient with membranous nephropathy with GFR of 25 ml/min/1.73 m2 and albuminuria > 300 mg/G would be classified by KDIGO (Kidney Disease – Improving Global Outcome) as which of the following:
   A - CKD due to membranous nephropathy G4 A3
   B- CKD due to membranous nephropathy G3 A2
   C- CKD due to membranous nephropathy G 5 A1
   E- CKD due to membranous nephropathy G4 A2

4. Serum creatinine alone is not used as the measure of GFR due to its inherent limitations. Which of the following factors affect the serum creatinine value?
   A- Muscle mass
   B- Age
   C- Gender
   D- All of the above

5. Which of the following equations to estimate glomerular filtration rate (GFR) is recommended by the Kidney Disease – Improving Global Outcome (KDIGO) guidelines?
   A- Modification of Diet in Renal Disease (MDRD) equation
   B- 24 hour urine creatinine clearance
   C- CKD-EPI equation
   D- Cockcroft-Gault equation

6. All of the following measures are recommended to slow the progression of chronic kidney disease EXCEPT:
   A- Blood Pressure Control
   B- Use of ACEi or angiotensin receptor blocker (ARB)
   C- Avoidance of NSAID
   D- Increase consumption of protein

7. Specialized nephrology care is highly recommended for which of the following patients with chronic kidney disease:
   A- CKD with eGFR <30 ml/min/1.73m2
   B- Persistent albuminuria >300mg/G
   C- Resistant hypertension (>3 antihypertensive meds including a diuretic)
   D- All of the above

8. Based upon the available evidence, combined use of ACEi and an angiotensin receptor blocker (ARB) should be avoided in patients with chronic kidney disease. The reason is:
   A- Increased risk of edema
   B- Increased risk of hyperkalemia and acute kidney injury
   C- Reduced risk of edema
   D- Reduced risk of hyperkalemia and acute kidney injury

9. Evaluation questions & CME Credit Information

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Introduction

As of 2012, the United States Renal Data System (USRDS) reported that there were 636,905 prevalent cases of end stage renal disease (ESRD) in the U.S. Based on prevalent ESRD treatment modalities, 65 percent were on hemodialysis, 6.5 percent were on peritoneal dialysis and 28.4 percent received kidney transplants. According to U.S. Organ Procurement and Transplantation Network (OPTN) data, 371,129 kidney transplants were performed in the U.S. between January 1, 1988 and February 28, 2015. Studies have shown that compared with dialysis, kidney transplantation is associated with lower mortality, reduced risk of cardiovascular events and improved quality of life. The relative benefits of transplantation over dialysis persist, despite increases in the age and comorbidity of transplant recipients. Due to the detrimental effect of prolonged dialysis treatment on transplant outcomes, early referral for transplantation in patients with advanced chronic kidney disease (CKD) is desirable; however, the timing of such referral depends on the CKD stage, clinical course and rate of progression. Currently, transplantation is allowed for qualified patients with CKD and estimated glomerular filtration rate (GFR) of less < 20 ml/min. Pre-emptive transplantation is associated with optimal outcomes. According to the Educational Guidance on Patient Referral to Kidney Transplantation OPTN Minority Affairs Committee March 2014 document, referral of medically appropriate patients for transplant is encouraged once a GFR of less than 30 ml/min is reached. Early referral affords enough time for pre-transplant education, thorough evaluation and workup of a potential live donor.

Transplant referral and evaluation process

The referral to a kidney transplant center is usually made by the primary nephrologist providing CKD care or dialysis treatment to the medically appropriate renal patient. However, dialysis unit social workers and nurses can also play important roles in educating the potential transplant candidate and facilitating the referral process. After clearance by the patient’s insurance provider, the patient is scheduled for an evaluation at the transplant center. Their evaluation may entail single or multi-day visit(s). The kidney transplant candidate evaluation involves patient education, medical and surgical assessments and investigation of the patient’s psychosocial situation and support. The potential impact of co-existing illness on perioperative and post-transplant morbidity and mortality is assessed during the pre-transplant evaluation. The determination of transplant eligibility is often a complex and difficult process that typically follows a multidisciplinary model involving transplant surgeons, nephrologists, nurses, social workers, financial counselors, pharmacists, psychologists, referring physicians and the patients. During the evaluation process, the patient and his or her caregiver are counselled regarding the goals of transplantation, the wait-listing process and wait time, transplant surgery and recovery period, immunosuppression and its potential complications, the short and long-term follow-up protocol of the transplant center and important financial or insurance-related repercussions of transplantation.

Medical and Surgical Considerations of Transplant Evaluation

Contraindications to transplantation

There are few conditions that are generally accepted as contraindications to kidney transplantation:

1. Possibility of non-compliance: Evidence that the recipient...
will be non-compliant with the recommendations of the transplant team is a contraindication because non-compliance will lead to graft rejection and subsequent failure. Patients with a history of non-compliance or substance abuse would be carefully screened before transplant.

2. Serious active infection: Post-transplant immunosuppression could either worsen or make the eradication of a pre-existing serious active infection difficult, likely impairing the patient’s recovery from the transplant procedure.

3. Active malignancy under treatment: Patients with an active malignancy that is still under treatment are excluded from transplantation until the likelihood of residual cancer and recurrence is low. The time interval between treatment and transplantation depends on the type, stage and grade of cancer, and the type of treatment given.

4. Certain severe, uncontrollable medical problems: Certain medical problems are contraindications when they are severe and not amenable to improvement. In any of these cases, the condition could sharply diminish the patient’s life expectancy, regardless of whether a transplant is done or not, and would reduce the chances of survival after transplant surgery. Examples include severe, uncontrollable heart disease, lung disease, or liver disease, and irreversible limitation of rehabilitative potential.

5. Uncontrollable psychiatric disorders: An uncontrollable psychiatric disorder that impairs the patient’s ability to give informed consent and their ability to comply with prescribed treatment regimen is a contraindication.

6. Pregnancy: Pregnant women are not transplant candidates. A suitable period of time should elapse after delivery before transplantation.

Advance age and obesity

Published data have demonstrated that transplantation provides survival benefits, even for recipients of advanced age. Advanced age, per se, is not a contraindication for transplantation and listing decisions are based on medical criteria rather than age. However, transplant candidates should have a reasonable probability of surviving beyond current waiting times for transplantation.

Listing criteria relating to obesity may vary between transplant centers. Some centers will accept all patients irrespective of their weight, some assess patients on a case-by-case basis, while others have strict exclusion criteria based on body mass index (BMI). As an example, some centers may refuse transplant candidacy if BMI is > 40 kg/m2 and recommend consideration for gastric bypass. Those same centers may allow the transplant listing for patients with a BMI > 35 kg/m2 under a provision that the patient will lose weight to achieve a BMI < 35 kg/m2 over a reasonable period of time.

Evaluation for Infections

Pre-transplant screening frequently includes serological tests to rule out infection. Testing includes the following: Human immunodeficiency virus (HIV) antibody, herpes simplex (HSV) IgG antibody (at some centers), cytomegalovirus (CMV) IgG antibody, Hepatitis C (HCV) antibody, Hepatitis B (HBV) surface antigen (HBsAg), Hepatitis B core antibody (HBcAb IgM and IgG, or total core antibody), Hepatitis B surface antibody (HBsAb), rapid plasma reagin (RPR), Toxoplasma antibody (especially in heart recipients), purified protein derivative (PPD) or interferon gamma release assay (IGRA) for latent TB infection in recipients, Epstein–Barr virus (EBV) antibody (EBV VCA IgG, IgM), varicella-zoster virus (VZV) antibody and West Nile virus serology or nucleic acid test (NAT). Optional screening measures may include HHV-8 serology and Strongyloides, Coccidioides and (or) Trypanosoma cruzi serology for recipients from endemic areas. All patients are required to be free of active serious infection at the time of transplantation because immunosuppression would hamper the eradication of an infection that is present at the time of transplant, and could negatively impact the recipient’s post-transplant recovery. If without medical contraindication, transplant candidates should be vaccinated against infections that are prevalent or potentially life-threatening.

Due to the efficacy of highly active antiretroviral therapy (HAART) and acceptable one- and 3-year transplant outcomes in stable patients receiving a transplant, HIV infection does not disqualify a patient from consideration for kidney transplantation. HIV-specific inclusion criteria for kidney transplant listing include the following: (1) CD4>200 cells/µL for at least six months, (2) undetectable HIV viremia (< 50 copies/mL) for at least six months, (3) demonstrable adherence to a stable HAART regimen for at least six months (managed in conjunction with an Infectious Disease specialist), (4) absence of AIDS-defining illness following successful immune reconstitution after HAART and (5) available antiretroviral treatment options in the future (this must be discussed and confirmed with the specialist treating the HIV). Patients with HIV are counseled during the transplant evaluation process that due to significant drug-to-drug interactions between some antiretroviral medications and immunosuppressants, including calcineurin inhibitors (such as cyclosporine and tacrolimus) or mammalian target of rapamycin (sirolimus and everolimus), a close post-transplant follow-up by the transplant nephrologist, in conjunction with an Infectious Disease specialist, is imperative.

Cardiovascular evaluation

Cardiovascular disease is a leading cause of morbidity and mortality after kidney transplantation. It is also a major cause of death with a functioning renal allograft. Therefore, careful screening for cardiovascular disease and risk factors thereof is an integral part of the renal transplant candidate evaluation. The history and physical examination should focus on identifying active cardiac conditions, such as unstable coronary syndromes (unstable angina,
severe angina or recent myocardial infarction, decompensated heart failure, significant arrhythmias and severe valvular disease. All of these conditions are associated with high rates of perioperative cardiovascular morbidity and mortality and may require delay or cancellation of surgery. Other chronic cardiac conditions that may also require further assessment before wait-listing include the following: chronic limiting angina, a myocardial infarction that is more than 30 days old but without symptoms of unstable angina, a prior history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), decompensated heart failure, moderate valvular disease or prior valve surgery or stable arrhythmias. For transplant candidates with no “active cardiac conditions,” the American Heart Association and the American College of Cardiology Foundation guidelines recommend the consideration of noninvasive stress testing in the presence of three or more of the following risk factors: diabetes mellitus, prior cardiovascular disease, more than one year on dialysis, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension and dyslipidemia. Although noninvasive testing for CAD has imperfect sensitivity and specificity in patients with renal failure, the accuracy of inotropic stress echocardiography for the purpose of screening to identify high-risk anatomy may be somewhat superior to that of vasodilator stress nuclear perfusion imaging.

Kidney transplantation candidates with a left ventricular ejection fraction (LVEF) less than 50 percent, evidence of ischemic left ventricular dilatation, exercise-induced hypotension, angina or ischemia in the distribution of multiple coronary arteries should be referred to a cardiologist for evaluation and long-term management.

Echocardiography is used to assess left ventricular function and to monitor ESRD patients with moderate aortic stenosis for progression. The echocardiogram could also be used to make an initial assessment of right ventricular pressure. Patients with echocardiographic evidence suggestive of significant pulmonary hypertension, defined as right ventricular systolic pressure >45 mm Hg, may warrant a right heart catheterization to confirm the diagnosis. Those with confirmed pulmonary hypertension and no apparent underlying secondary cause (such as obstructive sleep apnea, left heart failure, etc.) will need referral for expert pulmonary arterial hypertension management.

In patients with a recent history of transient ischemic attack or stroke, kidney transplantation should be deferred for at least six months. Although the presence of peripheral vascular disease per se is not a contraindication for transplant surgery, its presence would be assessed in the context of other co-existing comorbidities in determining eligibility for transplantation. Vascular conditions that will contraindicate transplantation include large uncorrectable abdominal aneurysms, severe occlusive common iliac disease, active gangrene or recent athero-embolic events.

Evaluation for malignancy

Immunosuppression increases the risk of malignancy and the progression of pre-existing malignancy in transplant recipients. With few exceptions, a renal transplant candidate with a previous history of malignant disease should be cancer-free before proceeding with transplantation. The wait-time between successful cancer treatment and transplantation will depend on the type, stage and grade of the cancer prior to treatment. The prognosis of each malignancy in terms of five-year survival rates should be considered and should not fall below the general five-year life expectancy after solid-organ transplantation. Based on consensus recommendations from the American Society of Transplantation (AST), Canadian Society of Transplantation (CST), Caring for Australians with Renal Impairment (CARI) and the European Renal Best Practices Guidelines (EBPG), cancers that would require a 5-year disease-free wait time prior to transplantation include the following: Duke C colorectal cancer (AST, CST, CARI), large or invasive renal cancer (AST, CST, CARI), advanced breast cancer (AST), melanoma stage 1A or higher (AST, CST, CARI), and invasive cervical cancer (CST). Cancers that would not require a disease-free waiting period before transplantation include non-invasive basal skin cancer (AST, CST, CARI, EBPG), incidental small renal cell carcinoma (AST, CST, CARI), in situ bladder cancer (AST, CST, CARI) and low grade/localized prostate cancer (AST, CST, CARI). For squamous cell skin cancer, CARI recommends no waiting time, while CST and EBPG recommends a wait time of two years. Screening recommendations for the general population, according to current guidelines, is typically followed in evaluating transplant candidates for cancer for the purpose of wait-list enrollment.

Patients with previous transplant

Declining graft function in renal transplant recipients should be recognized early because re-transplantation can be associated with an 88 percent reduction in mortality in these patients. A patient with a previous transplant that is failing and who is medically appropriate should be referred for re-listing when GFR is approaching CKD stage 4. Allograft nephrectomy generally is not indicated except in those with ongoing uncontrolled rejection, severe hematuria or malignancy, as it may be may be associated with a resurgence of donor-specific antibodies. Evidence comparing patients with a failed transplant with and without allograft nephrectomy is insufficient and conflicting, precluding a consensus guideline addressing this clinical issue. In patients approaching CKD stage 5 with a potential living donor, consideration should be given to maintaining adequate immunosuppression, promptly followed by re-transplantation to avoid immune activation.

Conclusion

Kidney transplantation generally provides superior survival and quality of life benefits over dialysis. Shorter time on dialysis is associated with better patient and graft outcomes post-transplantation. Early referral for transplant evaluation affords sufficient time for pre-transplant education, thorough evaluation and workup of potential live donors. The transplant evaluation is a complex process...
that utilizes a multidisciplinary approach in order to determine if a patient is an appropriate transplant candidate. The goal of the evaluation process is to identify and, whenever possible, provide guidance in the correction of medical, surgical or psychosocial factors that may increase the risk for adverse post-transplant patient and graft outcomes.

References


Caring for the Kidney Transplant Patient in the Primary Care Setting

By Gil A Cu, MD, FACP

Abstract: About three months post transplantation, the primary care physician and primary nephrologist are tasked to resume care of the patient. Adequate knowledge of the post-transplant course, immunosuppression and possible complications is imperative to maintain the allograft function. Constant communication with the transplant center is encouraged to avoid certain pitfalls in the management of post-transplant complications.

Introduction

The prevalence of end-stage renal disease has been increasing over recent decades. As of December 31, 2011, there were almost 615,899 patients enrolled in Medicare for end-stage renal disease, compared to 10,000 patients in 1973. About $49.3 billion is being spent on these patients annually. It is calculated that about $87,945 is being spent on a hemodialysis patient per year compared with $32,922 per year on a kidney transplant. With these expenditures, there is an impetus for patients to get a kidney transplant as soon as possible. More importantly, kidney transplant recipients enjoy a better quality of life. They can tolerate a more liberal diet, travel without restrictions, are able to bear children and can get involved in athletic activities.

Unfortunately, not all end stage renal disease patients are eligible for transplantation. Age is no longer a contraindication. Major contraindications include the presence of malignancy, liver cirrhosis, severe myocardial dysfunction, active mental illness, chronic infection, active substance abuse and extreme obesity. Of late, patients with HIV are now considered for kidney transplantation if they have undetectable viral loads and are compliant with their antiviral regimen.

Referral for kidney transplantation is usually initiated by a patient’s nephrologist. Patients can be referred when their glomerular filtration rate (GFR) reaches 20ml/min. Due to the paucity of available deceased donor organs, living donation is being encouraged. Otherwise, the patient is listed under the United Network for Organ Sharing (UNOS) and the average wait time to transplant is 3.6 years.

Pre-transplant screening

Routine pre-transplant screening includes a full history and physical examination, complete blood count, comprehensive metabolic panel, prothrombin time/partial thromboplastin time, blood type, Hepatitis B and C tests, HIV screen, Cytomegalovirus test, pelvic exam and Papanicolaou smear, chest X-ray, electrocardiogram, human leukocyte antigen (HLA) tissue typing and cytotoxic antibodies, and Venereal Disease Research Laboratory (VDRL) test. Elective pre-transplant workup includes voiding cystourethrogram, cardiac stress test, cardiac catheterization, echocardiogram, mammogram, non-invasive vascular studies, endoscopy, prostate specific antigen, immunoelectrophoresis, Epstein-Barr virus screen, Herpes simplex virus screen, Varicella-zoster virus screen, Toxoplasma titer, lipid profile and purified protein derivative (PPD) skin test.

Living Versus Deceased Donor Kidney Transplantation

Living donor kidney transplantation is favored by many transplant centers over deceased donor kidney transplantation. In addition to a shorter waiting time, living donor transplantation can offer better short and long-term outcomes including minimal delayed graft function, less aggressive immunosuppression and emotional gains for the donor. In contrast, there is a higher incidence of delayed graft function and shorter longevity of the kidney in deceased donor kidney transplantation.

Matching donor and recipient

The first determinant for matching donor and recipient is ABO blood matching in living donor kidney transplantation (ABO compatible) and deceased donor kidney transplantation (ABO identical). HLA matching involves the three antigens located on the white blood cells (HLA-A, HLA-B and HLA-DR). The cross match tests whether the recipient has anti-HLA antibodies to potential donors. A negative cross match would allow the transplantation to proceed while a positive crossmatch will cause accelerated rejection of the donor kidney. Over time, recipients can develop anti-HLA antibodies from pregnancy, blood transfusion and previous organ transplantation. The plasma reactive antibody (PRA) assay represents the amount of anti-HLA antibodies present in the serum of recipients. The recipient's serum is tested against a panel of 60 different persons with different HLA antigens. If the recipient has about 67 percent or greater reactivity to the panel of antigens, there is a strong likelihood of a positive crossmatch. This would preclude kidney transplantation.
**Immunology in kidney transplantation**

The human immune system is designed to thwart foreign antigens from invading our body. In addition to defending against bacteria, viruses, fungi and parasites, the immune system recognizes transplanted organs as foreign. For donor organs to be accepted, it is imperative that the immune system is not activated to cause rejection. Current immunosuppression drugs are designed to decrease responsiveness of the immune system to allow engraftment.

Figure 1 illustrates the mechanisms of several different drugs being used by transplant centers.\(^5\)

Immunosuppressive agents are classified as follows:

1. **Induction agents** - These are usually monoclonal agents (daclizumab, basiliximab, muromonab-CD3 and alemtuzumab) and polyclonal (rabbit or equine anti-thymocyte globulins) antibodies administered during the preoperative period. These are designed to eliminate all immune function for a short period of time while delaying the initiation of calcineurin agents until allograft function is improved.

2. **Primary immunosuppressants or maintenance agents** - The introduction of cyclosporine in the early 1960s revolutionized organ transplantation. Over the past decade, however, tacrolimus has become the primary agent for immunosuppression. This is usually combined with mycophenolate and oral steroids. There is now a trend for steroid-sparing protocols. The latter three drugs shown in the figure are often called adjuvant agents.\(^5\)

**Allograft rejections**

Allograft rejection is defined as acute deterioration of kidney transplant function associated with specific pathologic changes noted on kidney biopsy. Rejection can have a significant impact on the longevity of the transplanted kidney, even if the patient recovers allograft function.

There are three types of rejection that occur in kidney transplantation.\(^5\)

1. Hyperacute antibody-mediated rejection is caused by preformed donor-specific antibodies (DSA) such as ABO isoagglutinins, anti-endothelial antibodies and anti-HLA antibodies. This results in graft loss within 24 hours.

2. Acute cellular rejection is mediated by T cells causing tubulitis, arteritis and interstitial infiltration with T lymphocytes. If not reversed, this can result in graft loss or chronic rejection characterized by chronic allograft arteriopathy (intimal fibrosis and mononuclear cell infiltration).

3. Antibody-mediated rejection is due to the presence of circulating anti-donor antibodies with C4d deposition in the parenchyma of the transplanted organ. Histological findings can range from acute tubular necrosis to arterial inflammation and fibrinoid changes.

Hyperacute rejection inevitably will cause graft loss. Acute cellular rejection can be reversed by the same agents used for induction or by pulsed methylprednisolone (1 g daily x 3 days), rituximab (anti-CD 20) or alemtuzumab (anti-CD52) are used for antibody-mediated rejection. There is a consensus that if allograft rejection occurs during the first year post-transplant, the longevity of the transplanted kidney diminishes.

**Common medical problems following transplant**

About three months post-transplantation, the patient is returned to the nephrologist and primary care physician for post-transplant care. Medical problems occurring post-transplant can be classified into two groups. The first group is related to immunosuppression and the second group is related to the original kidney disease. It is also related to end-stage renal disease and chronic kidney disease preceding kidney transplantation.\(^1\)

1. Increasing creatinine: The majority of deceased donor transplanted kidneys do not achieve a normal GFR and therefore have underlying renal dysfunction. This is worsened by volume depletion, calcineurin toxicity, rejection, recurrence of glomerulonephritis (e.g. focal sclerosing glomeulocerosis), drug-induced interstitial nephritis, renal artery stenosis and viral infection (e.g. BK virus).

2. Microalbuminuria: Proteinuria following transplantation portends decreased allograft function and mortality. Urinary protein excretion can be monitored by the urine protein/creatinine ratio. This finding may signify recurrence of previous disease (IgA nephropathy, focal segmental glomerulosclerosis or diabetic nephropathy). Protocol biopsy is usually indicated for allograft dysfunction.

3. Hypomagnesemia: Magnesium (Mg) deficiency occurs post transplantation due to calcineurin-induced down regulation of renal expression of Mg channels. Patients will need long-term Mg supplementation to prevent muscle weakness and cardiac arrhythmia.

4. Diabetes mellitus: Patients may develop diabetes mellitus following kidney transplantation, termed new-onset diabetes after transplantation (NODA). This is attributed to increased metabolism and excretion of insulin in the newly transplanted kidney, which causes uncontrolled hyperglycemia. Calcineurin inhibitors (especially tacrolimus) and prednisone are diabetogenic. It is important to obtain weekly fasting blood sugars for the first four weeks post-transplantation and later an HbA1c to confirm diabetes. Pharmacologic treatment is usually indicated in addition to diabetic diet. Immunosuppression dosage can be altered or decreased with caution.

5. Common infections: Common infections like upper respiratory infections and urinary tract infections are treated like those in the normal population. Opportunistic infections that occur post-transplant include cytomegalovirus (CMV), BK virus and Pneumocystis pneumonia. The patient usually receives anti-CMV prophylaxis (valcylovir) and PCP prophylaxis (Bactrim DS or pent-
Figure 1: Illustrates the mechanisms of several different drugs being used by transplant centers.5

References

Wardrobe
A wardrobe is a piece of furniture used for storing clothing and personal items. It typically consists of a series of drawers or compartments for organizing and accessing clothes, as well as a hanging space for storing long garments such as jackets or dresses. Wardrobes can be made from various materials such as wood, metal, or plastic, and they may have different styles and designs depending on the intended use and personal preference. In some cases, wardrobes may also serve as a decorative element in a room, complementing the overall interior design and adding a touch of elegance or practicality to the space.
amidine) for six months post-transplant. Live virus vaccinations are contraindicated like varicella zoster, intranasal influenza, live oral typhoid, BCG, measles, mumps, rubella, oral polio, live Japanese B encephalitis vaccine, yellow fever, smallpox and meningococcus. Inactivated vaccines are acceptable.

6. Anemia: Anemia usually improves post-transplant. However, in those patients who develop anemia post-transplant, it may be attributed to immunosuppression (especially when the patient is on mycophenolate or azathioprine as these can suppress bone marrow function), antiviral agents, active infections and the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Anemia caused by these agents can be corrected with Epoetin alpha injection.

7. Cardiovascular disease: Cardiovascular disease occurs frequently post-transplant manifested as hypertension, hyperlipidemia, obesity and cardiac disease. Worsening dyslipidemia is most noted with the use of sirolimus, calcineurin and steroids. This requires aggressive treatment with statin drugs and diet. Cardiac diseases are managed accordingly.

8. Malignancy: Renal transplant recipients are three times more likely to develop cancers than the normal population, especially lymphoproliferative disorders (e.g. lymphoma). Skin cancers are prevalent, accounting for about 40 percent of all malignancies that develop post transplantation. The most common cancers are squamous cell carcinoma, basal cell carcinoma, melanoma and Kaposi sarcoma. Patients are advised to perform monthly self skin examinations and are advised to have six month or yearly examinations by a dermatologist. They are advised to avoid excessive sun exposure and to use sunscreens.

9. Bone diseases: Kidney transplant recipients are prone to renal osteodystrophy due to secondary hyperparathyroidism which may began while they are on dialysis or in an advanced chronic kidney disease stage. This condition may persist after kidney transplantation due to the effects of immunosuppression on bone remodeling. Prolonged intake of steroids may cause osteoporosis. Calcium and vitamin D deficiencies are also seen after transplantation. Appropriate use of supplements is indicated. Monitor for hypercalcemia, as resolution of previously noted hyperparathyroidism may be incomplete.

10. Pregnancy: Fertility in female transplant patients typically returns within a few months post-transplant and a consequent pregnancy is considered high risk. Pregnancy is encouraged if the graft function is optimal (serum creatinine <1.5 mg/dl, there is no concurrent CMV infection and teratogenic drugs are avoided (e.g. sirolimus, everolimus, mycophenolate, ACE inhibitors or ARBs).

Conclusion:
Caring for renal transplant recipients can be both challenging and rewarding. It is imperative that primary care providers and primary nephrologists are attuned to the indications and side effects of immunosuppression. Anticipation of both unique and usual medical problems related to kidney transplantation is good practice. Constant communication with the transplant centers is crucial to avoid pitfalls that may affect the longevity of the transplanted kidney as well as the well-being of the patient.

Bibliography
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- Developmental pediatrics
- Genetics
- Infectious diseases and immunology
- Nephrology and rheumatology
- Pain management and palliative care
- Rehabilitation
- Weight management
Pediatric Hypertension – Pearls for Diagnosis

Background:
The Duval County Medical Society (DCMS) is proud to provide its members with free continuing medical education (CME) opportunities in subject areas mandated and suggested by the State of Florida Board of Medicine to obtain and retain medical licensure. The DCMS would like to thank the St. Vincent’s Healthcare Committee on CME for reviewing and accrediting this activity in compliance with the Accreditation Council on Continuing Medical Education (ACCME).

This issue of Northeast Florida Medicine includes an article, “Pediatric Hypertension – Pearls for Diagnosis” authored by Mohammad Ilyas, MD and Asad Tolaymat, MD, which has been approved for 1 AMA PRA Category 1 credits.™ For a full description of CME requirements for Florida physicians, please visit www.dcmsonline.org.

Faculty/Credentials:
Mohammad Ilyas, MD Assistant Professor, of Pediatric Nephrology/Rheumatology, College of Medicine University of Florida, Jacksonville and Asad Tolaymat, MD, Professor and Chief, Division of Pediatric Nephrology and Rheumatology.

Objectives:
1. Understand that childhood hypertension prevalence is increasing, particularly in overweight and obese children.
2. Understand that early detection and management of childhood hypertension can prevent or minimize the long-term sequelae.
3. Understand the role of Ambulatory Blood Pressure Monitor (ABPM) in the management of childhood hypertension.

Date of release: June 1, 2016 Date Credit Expires: June 1, 2018 Estimated Completion Time: 1 hour

How to Earn this CME Credit:
1. Read the “Pediatric Hypertension – Pearls for Diagnosis” article.
2. Complete the posttest. Scan and email your test to Kristy Wolski at kristy@dcmsonline.org or mail it to 1301 Riverplace Blvd., Suite 1638, Jacksonville, FL 32207.
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Faculty Disclosure:
Mohammad Ilyas, MD, and Asad Tolaymat, MD, report no significant relations to disclose, financial or otherwise, with any commercial supporter or product manufacturer associated with this activity.

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Pediatric Hypertension – Pearls for Diagnosis

By Mohammad Ilyas, MD, Asad Tolaymat, MD

Division of Nephrology/Rheumatology, Department of Pediatrics
University of Florida/Health Sciences Center, Jacksonville, Florida

Abstract: Hypertension (HTN) can begin in childhood and adolescence, and it contributes to the early development of cardiovascular disease (CVD). Autopsy studies have shown an association of high blood pressure (BP) with atherosclerotic changes in the aorta and heart in children and young adults. Based upon these observations, identifying children with HTN and successfully treating their HTN should have an important impact on long-term outcomes of CVD. One of the most important components of the successful management of childhood HTN is determining whether or not there is an underlying cause that is amenable to treatment.

Definition of Hypertension in Children

In children, the definition of hypertension is based upon the normative distribution of BP in healthy children. The BP percentiles are based upon gender, age and height of the child. The systolic and diastolic BP are of equal importance; if there is a disparity between the two, the higher value determines the BP category. The National High Blood Pressure Education Program Working Group (NHBPEP) established guidelines for the definition of normal and elevated blood pressures in children.

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1. Normal BP – Both systolic and diastolic BP <90th percentile.

2. Pre-hypertension – Systolic and/or diastolic BP ≥90th percentile; but <95th percentile, or if BP exceeds 120/80 mmHg (even if <90th percentile for age, gender and height).

3. Hypertension – Hypertension (HTN) is defined as either systolic and/or diastolic BP ≥95th percentile measured on three or more separate occasions. Based on severity, HTN is further delineated by the two following stages:
   a. Stage 1 HTN – Systolic and/or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile.
   b. Stage 2 HTN – Systolic and/or diastolic BP ≥99th percentile plus 5 mmHg.

**Measurement of Blood Pressure**

Measuring BP in children is a challenging task. The younger the child, the more difficult it is to obtain an accurate BP. Routine measurement of BP in children is recommended from three years of age. Several factors impact the correct reading of BP. The cuff size depends on arm size. BP should be measured in the right arm of a relaxed and seated child (Figure 2). BP measurement by auscultation is the gold standard. BP by automated device correlates reasonably well with auscultation, but if the BP is high by automated device, the measurement should be repeated by auscultation.

Ambulatory blood pressure monitoring (ABPM) has become a helpful tool in evaluating hypertension in children. It is increasingly used to assess patients with white coat hypertension (i.e. high BP in medical office and normal at home), masked hypertension (i.e. normal BP at medical office and high at home), and secondary forms of hypertension, associated with underlying secondary cause e.g. chronic kidney disease. ABPM uses a portable automated device that records BP over a specific time period (usually 24 hours). ABPM monitors most commonly used in children are small oscillometric devices, which are worn on a belt in a pouch (Figure 3). Oscillometric ABPM devices directly measure the mean arterial pressure and calculate the systolic and diastolic BP using an algorithm that is unique to each device manufacturer. Development of normative data for pediatric ABPM has been difficult because of the variation of each algorithm.

The information obtained by the ABPM gives a detailed description of blood pressure over a period of 24 hours. ABPM provides unique information that otherwise would not be available. It not only provides average BP during the awake period, sleep period and overall, but also helps determine BP load (percent of BP reading above normal) and nocturnal dip (the difference between awake and sleep BP). An ABPM graph is shown in Figure 4. This information (i.e. BP load and nocturnal dip) is more strongly correlated with...
renal damage (i.e. albuminuria) than clinic BP. Albumin to creatinine ratio correlates most strongly to diastolic BP (DBP) variability, which can only be measured with ABPM. ABPM also associates more strongly with left ventricular mass (LVM) than clinic BP.

**Evaluation of Hypertension**

The evaluation of the child with hypertension includes history, physical examination, laboratory tests and procedures, in selected cases. There are three goals of the initial evaluation of the hypertensive child or adolescent; First, to search for an underlying cause of hypertension, second, to identify other co-morbid risk factors for cardiovascular disease (CVD) and third, to classify children who should be treated with anti-hypertensive drug therapy.

**History and physical examination (Silent Killer)**

Most children who present with a modest elevation in blood pressure (stage 1 hypertension) have no clinical signs of cardiovascular disease or target organ damage that would usually delay the diagnosis of hypertension. The diagnosis of hypertension is made, in this setting, only after an elevated and properly measured blood pressure that has been confirmed at least three separate occasions.

Two aspects of the initial evaluation of the hypertensive child deserve emphasis; there is a need for more accurate measurements of blood pressure in the office, with the addition of out-of-office measurements, either at home by self-measurement or by ambulatory monitoring.

The symptoms consistent with hypertensive emergencies include headaches, seizures, mental status changes, focal neurologic complaints, visual disturbances and cardiovascular complaints (such as chest pain, palpitations, cough or shortness of breath). These children require emergent evaluation and treatment. Pharmacologic therapy should be initiated without delay in children with stage 2 HTN, especially those with a hypertensive emergency.

Rare symptoms include fatigue, decreased activity tolerance, dizziness, palpitations, angina and dyspnea. The physical examination should include a retinal examination to detect retinal vascular changes due to HTN. Cardiac heave or laterally displaced point of maximal impulse (PMI) may indicate left ventricular hypertrophy (LVH).

**Primary versus secondary hypertension**

An important initial step in the assessment of hypertensive children is distinguishing between primary and secondary HTN. Correction of the underlying disorder may cure the HTN in children with secondary causes. There are many diagnostic clues for secondary hypertension (Table 1). The following factors can help differentiate secondary from primary HTN:

- Pre-pubertal children generally have some form of secondary HTN, while adolescents and post-pubertal children usually have primary HTN.
- Severe HTN (i.e. stage 2 HTN) is usually associated with secondary HTN, while primary HTN is associated with prehypertension or stage 1 HTN.

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**Figure 4: ABPM graph showing rise in BP with stress and nocturnal dip during sleep phase**

![ABPM graph showing rise in BP with stress and nocturnal dip during sleep phase](image_url)
Diastolic and/or nocturnal HTN detected by ambulatory blood pressure (BP) monitoring is more likely to be associated with secondary HTN than primary HTN.

Primary HTN is usually associated with obesity and/or a positive family history of HTN.

Symptoms or signs suggestive of an underlying systemic disorder indicate secondary HTN.

**Co-morbid risk factors and diseases**

There are several risk factors that increase the risk of premature atherosclerosis. These are HTN, obesity, dyslipidemia and a family history of premature CVD. These factors may occur concurrently, which further increases the likelihood of premature atherosclerosis and CVD. In addition, several childhood diseases such as type 1 and type 2 diabetes mellitus and chronic kidney disease are associated with accelerated atherosclerosis and CVD.

Current recommendations by the national high blood pressure education program (NHBPEP) are to target BP goals below the 90th percentile for age, height and gender in children and adolescents with one or more of the above risk factors. As a result, the evaluation of childhood HTN needs to systematically identify the presence of these factors and diseases.

The history and physical examination should assess for other cardiovascular disease (CVD) risk factors or diseases associated with CVD, in addition to hypertension. It is important to obtain a family history of premature CVD and/or strokes and identify overweight and obese children by calculating body mass index (BMI). The provider should also obtain a history of smoking, diabetes mellitus, chronic kidney disease, organ transplantation, cardiac disease, Kawasaki disease, autoimmune disease, familial hypercholesterolemia and cancer. In children, data also suggest an association between sleep-disorders and HTN. Based upon this information, the NHBPEP Working Group recommends that a sleep history be obtained in a child with HTN, especially if he or she is overweight. If a history of either sleep apnea or loud and frequent snoring is obtained, polysomnography should be considered to identify a sleep disorder.

### Laboratory Evaluation

The initial laboratory evaluation in all children with persistent HTN is directed at determining the etiology of HTN, identifying other CVD risk factors and detecting target-organ damage. The following approaches are recommended by the 2004 NHBPEP:

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**Table 1: Diagnostic clues for secondary hypertension**

<table>
<thead>
<tr>
<th>History</th>
<th>Possible cause of hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of Hypertension, early MI, diabetes, stroke</td>
<td>Essential hypertension</td>
</tr>
<tr>
<td>Excessive weight gain</td>
<td>Obesity</td>
</tr>
<tr>
<td>Excessive weight loss or change in growth percentiles</td>
<td>Thyroid dysfunction</td>
</tr>
<tr>
<td>Stress factors at home and school</td>
<td>Stress</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Neonatal history of umbilical artery catheters</td>
<td>Reno-vascular hypertension</td>
</tr>
<tr>
<td>Recent pharyngitis or impetigo</td>
<td>Post-infectious glomerulonephritis</td>
</tr>
<tr>
<td>Exposure to sources of enterohemorrhagic E. coli</td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Medications: Sympathomimetics, oral contraceptives, corticosteroids and others</td>
<td>Side effect of medication</td>
</tr>
<tr>
<td>Illicit drug use: Cocaine, amphetamines, anabolic steroids, phenycyclidine, ephedra-containing alternative medications, caffeine</td>
<td>Drug-mediated effects</td>
</tr>
<tr>
<td><strong>Physical Finding</strong></td>
<td><strong>Possible cause of hypertension</strong></td>
</tr>
<tr>
<td>Skin Rash</td>
<td>Renal vasculitis, HSP, SLE</td>
</tr>
<tr>
<td>Recurrent UTIs, abnormal urine color, enuresis, flank pain, dysuria</td>
<td>Reflux nephropathy</td>
</tr>
<tr>
<td>Sweating, pallor, palpitation, irregular pulse</td>
<td>Catecholamine excess, Thyroid dysfunction</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Alport syndrome, Lead poisoning</td>
</tr>
<tr>
<td>Head trauma, headache, visual disturbance, lethargy, seizures, tremors, morning vomiting</td>
<td>Elevated intracranial pressure</td>
</tr>
<tr>
<td>Edema, hematuria, proteinuria</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Hemoptysis, hematuria</td>
<td>AGN, Goodpasture syndrome</td>
</tr>
</tbody>
</table>

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- Diastolic and/or nocturnal HTN detected by ambulatory blood pressure (BP) monitoring is more likely to be associated with secondary HTN than primary HTN.
- Primary HTN is usually associated with obesity and/or a positive family history of HTN.
- Symptoms or signs suggestive of an underlying systemic disorder indicate secondary HTN.
1. Measurement of serum blood urea nitrogen (BUN), creatinine and electrolytes, and urinalysis. These tests permit quick assessment of renal function and abnormalities in glucose (e.g., diabetes mellitus) or potassium homeostasis (e.g., chronic kidney disease or congenital adrenal hyperplasia). An abnormal urinalysis and/or an elevation in serum creatinine is suggestive of underlying renal disease.

2. Complete blood count to look for anemia that may reflect chronic diseases such as vasculitis and chronic kidney disease, or polycythemia.

3. Measurement of fasting plasma glucose and lipids to identify children with diabetes mellitus and dyslipidemia. These tests should also be performed in pre-hypertensive children who are obese, have a family history of premature CVD or have chronic kidney disease.

4. An echocardiogram to identify children with left ventricular hypertrophy (LVH) because clinical parameters, such as the severity of HTN, and electrocardiography do not accurately predict LVH. LVH is the most prominent manifestation of target-organ damage from HTN. LVH has been reported in 30 to 40 percent of children and adolescents with HTN and, if present, is an indication to initiate or intensify antihypertensive therapy.

5. Renal ultrasonography is used to determine the presence of bilateral normal kidneys and the presence of any other congenital anomaly, hydronephrosis, cystic kidney disease or discrepancy in renal size.

Further Evaluation

Based upon the initial history, physical examination and laboratory evaluation, the clinician should be able to establish whether the hypertension (HTN) is primary or secondary. This distinction will determine whether further evaluation is performed for a potentially reversible cause of secondary HTN.

Primary Hypertension

Hypertensive children who fit the primary HTN profile may need no further laboratory evaluation beyond the initial testing cited above.

The NHBPEP recommends renal ultrasonography for all hypertensive children and adolescents. While some clinicians continue to obtain renal ultrasounds in all patients with HTN, other institutions do not routinely perform this study in patients who strongly fit the profile of primary HTN. These patients include post-pubertal adolescents with stage 1 HTN, obesity, strong family history of primary HTN, and those showing no signs or symptoms suggestive of secondary HTN.

Among obese children with primary HTN, measurement of hemoglobin A1c may be indicated, particularly if there is a strong family history of type 2 diabetes mellitus. Of note, being overweight does not preclude the small possibility of secondary etiology. This was illustrated in a retrospective study of overweight, (i.e. BMI >85 percentile) hypertensive children in which 15 out of 166 patients (9 percent) had secondary hypertension, while the remaining 91 percent were diagnosed with primary HTN. White coat hypertension is also prevalent among the children with increased BMI.

There is little data on the usefulness of plasma levels of uric acid, homocysteine and lipoprotein in the evaluation of pediatric primary HTN. Elevation of these substances has been reported to be associated with an increased risk of cardiovascular disease in adults. The NHBPEP does not recommend these studies unless there is a strong family history of an abnormality.

Secondary Hypertension

Further evaluation is required in patients with findings suggestive of secondary HTN to determine the underlying cause. The following diagnostic studies may be performed in hypertensive children with a high degree of suspicion that an underlying disorder is present.

1. Renal imaging — Renal ultrasound is useful to determine the presence of both kidneys or the presence of any congenital anomaly, hydronephrosis, cystic kidney disease or discrepancy in renal size.

2. Plasma renin activity — Plasma Renin Activity (PRA) may be useful in patients suspected to have one of the following conditions:

   a. Excess mineralocorticoids (e.g., aldosterone) secretion – Patients with mineralocorticoid excess are usually hypokalemic, have metabolic alkalosis and their PRA is low and often unmeasurable.

   b. Congenital adrenal hyperplasia is a frequent cause of excess mineralocorticoid secretion in children. Affected patients may also present as a neonate with ambiguous genitalia due to the excess secretion of androgens.
c. Aldosterone-secreting tumors are rare in children. Primary hypersecretion of aldosterone may also result from the rare genetic disorder glucocorticoid-remediable hyperaldosteronism. Hypokalemia is absent in more than half of these patients. In the absence of hypokalemia at presentation, the diagnosis may be suspected from the family history of early HTN (before age 21 years) and the frequent development of marked hypokalemia after the administration of a thiazide diuretic.

d. Renin-secreting tumor – Renin-secreting tumors are rare both in children and adults. Patients generally present with severe HTN, hypokalemia, metabolic alkalosis and markedly elevated renin levels.19

e. Renovascular disease – The plasma renin activity may be elevated in children with renovascular HTN, but it is a relatively insensitive test. Approximately 15 percent of children with arteriographically evident renal artery stenosis have normal plasma renin activity.20

3. Plasma and urine catecholamines — Patients with HTN due to disorders with catecholamine excess, such as pheochromocytoma and neuroblastoma, will have elevated levels of both plasma and urine catecholamines and metabolites. In addition to HTN, affected patients may present with headache, sweating and tachycardia. In patients with symptoms of catecholamine excess and elevated plasma and urine catecholamines, further evaluation is required.

4. Renovascular imaging — A very limited number of patients may require renovascular imaging, especially infants and children who have known predisposing factors or findings associated with renal artery stenosis, such as prior umbilical artery catheter placements, family history or findings for neurofibromatosis, an abdominal bruit or a significant size discrepancy on renal ultrasonography. In addition, renovascular imaging may be required in patients with stage 2 HTN, when no other cause has been identified.

Standard intra-arterial angiography is the gold standard for evaluating renovascular disease in children. The following noninvasive tests are used to screen for renal vascular diseases:

- a. Magnetic resonance angiography (MRA)
- b. Computed tomographic angiography (CTA)
- c. Duplex Doppler ultrasonography

If renovascular evaluation is required, a radiological center with pediatric experience in these screening techniques should be considered. The selection of the screening modality is dependent upon the expertise of the clinical staff, the availability of appropriate equipment and the development of safe and useful protocols.21

Practical Approach

In practice, the initial evaluation of HTN should include measurement of serum BUN, creatinine, electrolytes, a complete blood count, urinalysis, renal ultrasonography and an echocardiogram to evaluate left ventricular mass and to diagnose coarctation of the aorta. Other studies may be performed depending on the specific signs and symptoms suggesting secondary HTN. Thus, more extensive evaluation is reserved for pre-pubertal children (usually less than 10 years of age), and those with stage 2 HTN and/or findings indicative of a specific underlying cause:

- Plasma renin and aldosterone are obtained in all pre-pubertal children, any patient with stage 2 HTN and any patient with hypokalemia and/or metabolic alkalosis.

- Plasma and urine catecholamines are obtained in patients who exhibit symptoms of catecholamine excess (eg, headache, sweating and/or tachycardia) or who are at risk of pheochromocytoma, such as in patients with neurofibromatosis.

- Screening for renovascular disease is performed in any patient, particularly with stage 2 HTN if no other cause is identified, or if there are predisposing risk factors (eg, prior umbilical artery catheterization, neurofibromatosis or abdominal bruit).

- A 99mTc-dimercaptosuccinic acid (DMSA) renal scan is performed in patients with a strong suspicion for renal scarring based upon the history (i.e. recurrent urinary tract infection). A DMSA scan is also obtained to confirm a suggestive but unspecified finding on renal ultrasound.

- Other tests that may be performed to determine an etiology for secondary hypertension based on the clinical setting include:
  - Echocardiography for suspected coarctation of the aorta (i.e. differential between upper and lower extremity pulses and blood pressure).
  - For patients in whom renal parenchymal disease is suspected, a renal biopsy may be considered.

Conclusion

Prevalence of hypertension in the young population is increasing and is associated with a positive family history, obesity and life-style factors. Childhood hypertension is a risk factor for later cardiovascular disease. Early detection and evaluation is essential for identifying the underlying cause and to prevent long-term complications. ✪
References


# Pediatric Hypertension – Pearls for Diagnosis

## CME Questions & Answers (circle one answer)/Free to DCMS Members/$55.00 charge non-members*

(Retrieve by June 1, 2018 BY MAIL: 1301 Riverplace Blvd. Suite 1638, Jacksonville, FL 32207 or ONLINE: www.dcmsonline.org.)

1. What is hypertension, i.e. high blood pressure?
   a. A condition where low oxygen carrying capacity of blood leads to left ventricular failure.
   b. A condition where increased force of blood pumping in the walls of the arteries causes health problems.
   c. A condition where the heart pumps blood too fast, causing high pulse pressure and stroke volume.
   d. None of the above

2. What is the normal blood pressure for a child less than 18 years?
   a. Readings lower than 140/90mmHg.
   b. Readings between 50% and 95% for age, gender and height.
   c. Readings below 90% for age, gender and height.
   d. Readings between 90/60mmHg to 120/80mmHg
   e. Readings less than 75% for age, gender and the height.

3. Which of the following children do NOT need routine BP monitoring?
   a. Children > 3 years of age who are seen in a medical setting.
   b. Children < 3 years of age with history of neonatal complications (Premature birth).
   c. A child with organ transplant.
   d. A child taking over the counter drugs that are known to cause hypertension.
   e. A two-year-old with family history of overweight or obesity.

4. Which of the following is the most important component of pediatric hypertension evaluation?
   a. History
   b. Accurate BP measurement
   c. Physical examination
   d. Laboratory testing
   e. Electrocardiogram

5. The following conditions are required for accurate measurement for pediatric patient blood pressure, EXCEPT?
   a. The use of appropriate equipment
   b. The use of appropriate cuff size
   c. The ambulatory BP monitor
   d. The pressure of the stethoscope on the artery
   e. The rate of deflation

6. In an adolescent, hypertension is correlated with an increased risk of the following, EXCEPT?
   a. Stroke
   b. Heart attacks
   c. Diabetes
   d. Kidney failure
   e. Premature death

7. The ambulatory BP monitoring helps in recognizing each of the following, EXCEPT?
   a. White coat hypertension
   b. Risk for end organ injury
   c. Apparent drug resistance
   d. Weight related hypertension
   e. Masked hypertension

8. All of the following statements are FALSE, except?
   a. Most hypertensive patients have mild clinical sign and symptoms.
   b. Most hypertensive patients will develop signs of hypertension-related target organ damage.
   c. Secondary HTN is the most common cause of hypertension in adolescents.
   d. The diagnosis of HTN is made only after an elevated and properly measured blood pressure and confirmed on at least three separate occasions.

9. The following routine laboratory tests are required for initial evaluation of HTN, EXCEPT?
   a. Urinalysis
   b. Complete blood count
   c. Blood chemistry (potassium, sodium, glucose, BUN and creatinine)
   d. Micro albuminuria
   e. Fasting lipid profile

10. The following noninvasive tests are used to screen for renal vascular diseases, EXCEPT?
    a. Magnetic resonance angiography (MRA)
    b. Magnetic resonance Imaging (MRI)
    c. Computed tomographic angiography (CTA)
    d. Duplex Doppler ultrasonography

11. Plasma Renin Activity (PRA) may be useful in patients suspected to have the following conditions, EXCEPT?
    a. Excess mineralocorticoids (e.g., aldosterone) secretion
    b. Congenital adrenal hyperplasia
    c. Wilms’ tumor
    d. Renin-secreting tumor
    e. Renovascular disease

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Perspectives on Current Management Strategies in Acute Kidney Injury

By Rajesh Mohandas, MD1, Girish Singhania, MD2 and A. Ahsan Ejaz, MD1

1Division of Nephrology, Hypertension and Transplantation, University of Florida, Gainesville, Florida
2Division of Nephrology and Hypertension, University of Utah, Salt Lake City, Utah

Abstract: This article summarizes recent changes in the terminology and definition of acute kidney injury and highlights the changing epidemiology based on these newer recommendations. The evidence regarding current prophylaxis and treatment strategies, especially with regards to timing of initiation of renal replacement therapies and modalities of dialysis are discussed. A silver bullet is not available in the treatment of acute kidney injury but survival in critically-ill patients is actually improving due to increased awareness, intensive monitoring and early interventions.

Introduction

Acute kidney injury (AKI) develops following a sudden, transient decrease in renal perfusion and culminates in renal functional impairment and parenchymal damage. Clinically this can manifest as oliguria, mild to severe uremia, metabolic derangements and downstream extra-renal organ involvement. Attempts to define AKI, based on the variable severity of the signs and symptoms, have resulted in over 35 different definitions of acute kidney injury. Currently, the Acute Kidney Injury Network defines AKI as an abrupt (within 48 hours) reduction in kidney function, characterized by an absolute increase in serum creatinine >0.3 mg/dL (>26.4 mmol/L) and a percentage reduction in kidney function: >50 percent (1.5-fold from baseline). The incidence of AKI, based on these criteria, is estimated to be 15,325 per 100,000 persons in the United States.4,5

Prevention of acute kidney injury

Contrast-induced nephropathy

The incidence of contrast-induced nephropathy (CIN) is less than two percent in the general population, yet it receives the most attention when considering interventions to prevent acute kidney injury. This is attributable to the high incidence of CIN (20-30 percent) in patients with diabetes mellitus, heart failure, impaired renal function, paraproteinemia syndromes and advanced age. Prevention involves identification of the vulnerable subgroup of patients, stringent adherence to accepted indications for the procedures, use of low-osmolar contrast agents, adequate fluid resuscitation strategy and anti-oxidant therapy. Radiocontrast agents have undergone dramatic transformations from ionic, hyperosmolar formulations (1400-1800mosmol/kg) to nonionic, iso-osmolar (290mosmol/kg) formulations. In the NEPHRIC (Nephrotoxic effects in high-risk patients undergoing angiography) study, the use of iso-osmolar agents was associated with a lower incidence of CIN than with low-osmolar agents.7 Another mainstay of most prophylaxis strategies is pre-procedural hydration, but ambiguity persists regarding the type of fluid to be administered. Current data suggests that infusion of isotonic saline for 24 hours (at a rate of 1 ml/kg/h), beginning 12 hours prior to scheduled procedure, is superior to one-half isotonic saline8 and isotonic sodium bicarbonate.9,10,11,12

Another contentious issue is renal replacement therapy for the prevention of CIN in chronic kidney disease (CKD) patients. Contrast media induces vasoconstriction and causes an immediate and progressive decline of both glomerular filtration rate and renal plasma flow in the absence of hypovolemia.13 Much enthusiasm was generated by the demonstration that the reduction rate of contrast agent,
i.e., iodine, by hemodialysis after angiogram was 46.6 percent at 1 hour, 65.2 percent at 2 hours and 75.1 percent at 3 hours in CKD patients.38 Despite initial enthusiasm, current cumulative evidence does not support a role for prophylactic dialysis. A recent meta-analysis of nine randomized controlled trials, involving 751 patients, failed to demonstrate that prophylactic renal replacement therapy reduces the incidence of CIN in CKD stage 3 patients.19

Cardiac surgery-associated acute kidney injury

Among the many types of acute kidney injury, AKI associated with cardiac surgery usually represents a distinct timeline and mode of injury. In the United States, over 400,000 coronary artery bypass graft surgeries and over 100,000 cardiac valve procedures are performed annually.20 The incidence of cardiac surgery-associated acute kidney injury ranges from 7-26 percent21 and increases when high-risk procedures, such as cardiac valve and thoracic aortic aneurysm surgeries, are performed. Among the many strategies to prevent postoperative acute kidney injury, the simplest are avoiding nephrotoxins, delaying elective surgery following cardiopulmonary bypass (contrast exposure) and ensuring adequate preoperative hydration, especially in patients with CKD. However, data on the favorable effect of hydration for the prevention of AKI in cardiac surgery (in contrast to contrast nephropathy) is not robust, nor is there evidence for the superiority of colloid solutions (synthetic or natural) versus crystalloid solutions (high or low chloride content).22,23,24 Hemodynamic optimization may be of benefit,25 but routine use of pulmonary artery catheters to reach that goal is not recommended.26 Furthermore, early goal-directed therapy did not reduce all-cause mortality in cardiac surgery,27 nor in critically-ill septic patients.28 Diuretics are important tools for the management of fluid overload, but they are not recommended for the prevention or treatment of AKI.29,30 Extensive studies with dopamine, fenoldopam31,32,33 and natriuretic peptides have not proven to be renoprotective in cardiac surgery.34 Natriuretic peptides reduced the incidence of postoperative AKI, but did not reduce all-cause mortality or need for dialysis. The renoprotection provided by natriuretic peptide (nesiritide) in the immediate postoperative period did not translate into improved long-term survival in these patients.35 More innovative efforts, such as remote ischemic preconditioning, did not significantly reduce the incidence of acute kidney injury in patients undergoing coronary artery bypass graft and/or valve surgery.36 In the EARLYARF study (early intervention with erythropoietin does not affect the outcome of acute kidney injury), early intervention with erythropoietin-stimulating agents to prevent acute kidney injury were unsuccessful.37

Prognosis of acute kidney injury

Most patients recover from AKI within a month. The mean duration is 14 days and 50 percent of patients recover within two days.38 However, recovery may take as long as three months.39 In general, 11 percent of patients with AKI require renal replacement therapy, but this number exceeds 70 percent in severe cases. AKI requiring dialysis is associated with >50 percent in-hospital mortality.39,40 The majority of deaths occur within the first two weeks.41 Studies have shown that 65-94 percent of AKI survivors had independent kidney function at discharge from hospital.42,43,44 These data rekindle the debate on the optimal timing of initiation of dialysis, an answer to which may be provided by the ongoing IDEAL-ICU study (initiation of dialysis early versus delayed in the intensive care unit) study.45 In the interim, retrospective, observational studies suggest that early implementation of renal replacement therapy improves the prognosis for these patients.46,47,48

Dialysis modality and outcomes

More dialysis may not be better in the management of AKI. The superior adequacy of small solute clearance with continuous renal replacement therapy (CRRT) compared to intermittent hemodialysis (IHD) provided the impetus for the preferential use of CRRT in the management of AKI in the intensive care unit.49,50 However, several studies have demonstrated that the initial technique of renal replacement therapy (RRT) was not a predictor of hospital survival or dialysis-free hospital survival.51,52,53 Moreover, more intense (higher delivered dose) RRT did not provide survival benefits, improve recovery of kidney function or reduce the rate of nonrenal organ failure, as compared with less-intensive therapy involving a defined dose of intermittent hemodialysis three times per week and CRRT at 20ml/kg/hr.54,55 The data is similar in extended daily dialysis versus high volume peritoneal dialysis (24 hours of dialysis with sessions performed 7 days/week). Despite faster metabolic control and higher dialysis dose and ultrafiltration with extended daily dialysis, there were no survival benefits when compared to high volume peritoneal dialysis.56

Conclusion

After decades of differing terminology and definitions, a consensus statement is emerging regarding the complex entity of AKI. Study designs are starting to reflect a common standard of identification of participants based on characteristic risk factors, a standardized protocol for the management of the patients and a uniform method of reporting of findings that will allow for the comparison of results of intervention to prevent or treat AKI. A recent report suggests that despite the lack of effectiveness of a single intervention, survival in critically-ill patients is actually improving due to increased awareness, intensive monitoring and early interventions.57 The lack of a silver bullet to cure AKI may be disappointing, but emerging biomarkers of AKI and the discovery of molecular signaling and cellular regeneration pathways hold promise for more effective therapies in the near future.
References


INDICATIONS

Adult Ulcerative Colitis (UC)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for inducing and maintaining clinical response, inducing and maintaining clinical remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission.

Adult Crohn’s Disease (CD)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission.

IMPORTANT SAFETY INFORMATION

- ENTYVIO (vedolizumab) for injection is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.

- Infusion-related reactions and hypersensitivity reactions including anaphylaxis have occurred. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.

- Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.
ENGINERED FOR UC AND CD

- Provides remission for patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD)\(^1\)
  - Studied in patients who have failed conventional therapies or a biologic
  - Individual results may vary

- Clinical trials evaluated safety in more than 3300 adults on Entyvio\(^1\)
  - Including more than 800 patients who received Entyvio for more than 2 years

- A distinct mechanism of action that specifically blocks lymphocyte migration that is a key contributor to inflammation in the gut\(^1\)

- Entyvio specifically binds to \(\alpha 4\beta 7\) integrin, blocking its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells\(^1\)

- 300-mg dose for adult patients\(^1\)

IMPORTANT SAFETY INFORMATION (continued)

- Although no cases of PML have been observed in ENTYVIO clinical trials, JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue ENTYVIO dosing permanently.

- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.

- Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.

- Most common adverse reactions (incidence \(\geq 3\%\) and \(\geq 1\%\) higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

Please see brief summary of Prescribing Information on adjacent pages.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ENTYVO (vedolizumab) for injection, for intravenous use

INDICATIONS AND USAGE

Adult Ulcerative Colitis (UC)

ENTYVO (vedolizumab) is indicated for:
- inducing and maintaining clinical response,
- inducing and maintaining clinical remission,
- improving the endoscopic appearance of the mucosa, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Adult Crohn’s Disease (CD)

ENTYVO (vedolizumab) is indicated for:
- achieving clinical response,
- achieving clinical remission, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

CONTRAINDICATIONS

ENTYVO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVO or any of its excipients (such as dextran, bronchosperm, urtica, flushing, rash and increased heart rate) [see Warnings and Precautions and Adverse Reactions].

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions and Hypersensitivity Reactions

In UC Trials I and II and CD Trials I and III, hypersensitivity reactions occurred including a case of anaphylaxis (one out of 1434 patients [0.07%]) [see Adverse Reactions]. Allergic reactions including dyspnea, bronchosperm, urtica, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to ENTYV0 may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion. If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVO immediately and initiate appropriate treatment (e.g., epinephrine and antihistamines).

Infusions

Patients treated with ENTYVO are at increased risk for developing infections [see Adverse Reactions]. The most commonly reported infections in clinical trials occurring at a rate greater than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis. ENTYVO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with ENTYVO. Exercise caution when considering the use of ENTYVO in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice. For progressive multifocal leukoencephalopathy (PML) [see Warnings and Precautions].

Progressive Multifocal Leukoencephalopathy

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised.

In ENTYVO clinical trials, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. No claims of comparative safety to other integrin receptor antagonists can be made based on this data.

Monitor patients on ENTYVO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVO and refer to a neurologist; if confirmed, discontinue dosing permanently.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVO should be discontinued in patients with jaundice or other evidence of significant liver injury [see Adverse Reactions].

Live and Oral Vaccines

Prior to initiating treatment with ENTYVO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVO [see Adverse Reactions].

ADVERSE REACTIONS

The following topics are also discussed in detail in the Warnings and Precautions section:

- Infusion-Related Reactions and Hypersensitivity Reactions [see Warnings and Precautions]
- Infections [see Warnings and Precautions]
- Progressive Multifocal Leukoencephalopathy [see Warnings and Precautions]
- Liver injury [see Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ENTYVO in 3,326 patients and healthy volunteers in clinical trials, including 1,386 exposed for greater than one year and 835 exposed for greater than two years.

The safety data described in Table 1 are derived from four controlled Phase 3 trials (UC Trials I and II, and CD Trials I and II); data from patients receiving open-label ENTYVO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included. In these trials, 1,434 patients received ENTYVO 300 mg for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis and 962 patients had Crohn’s disease. Patients were exposed for a mean duration of 259 days (UC Trials I and II) and 247 days (CD Trials I and III).

Adverse reactions were reported in 52% of patients treated with ENTYVO and 45% of patients treated with placebo (UC Trials I and II: 49% with ENTYVO and 37% with placebo; CD Trials I and III: 55% with ENTYVO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with ENTYVO compared to 4% of patients treated with placebo (UC Trials I and II: 8% with ENTYVO and 7% with placebo; CD Trials I and III: 12% with ENTYVO and 9%, with placebo).

The most common adverse reactions (reported by ≥3% of patients treated with ENTYVO in the UC Trials I and II and CD Trials I and III combined group and ≥1% higher than in combined placebo group) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain and pain in extremities (Table 1).
### Table 1. Adverse Reactions in ≥3% of ENTYVO-treated Patients and ≥1% Higher than in Placebo (UC Trials I and II* and CD Trials I and III*)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ENTYVO† (N=1434)</th>
<th>Placebo† (N=2397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Cough</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Influenza</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Back pain</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Rash</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Pain in extremities</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Data from patients receiving open-label ENTYVO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

**Patients who received ENTYVO for up to 52 weeks.

†Patients who received placebo for up to 52 weeks.

Safety data for patients (n=279) in UC Trials I and II and CD Trials I and III who received ENTYVO at Weeks 0 and 2 were then randomized to placebo at Week 6 for up to 52 weeks, and for patients (n=416) in CD Trial II, a 10 week Crohn's disease trial, are similar to those listed in Table 1.

### Infusion-Related Reactions and Hypersensitivity Reactions

Serious infusion-related reactions and hypersensitivity reactions including anaphylaxis have been reported following ENTYVO administration in clinical trials (see Warnings and Precautions). In UC Trials I and II and Crohn's Trials I and III, one case of anaphylaxis [one of 1434 patients treated with ENTYVO (0.07%)] was reported by a Crohn's disease patient during the second infusion (symptoms reported were dyspnea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate) and was managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone.

In UC Trials I and II and CD Trials I and III, 4% of patients treated with ENTYVO and 3% of patients treated with placebo experienced an infusion-related reaction (IRR). The most frequently observed IRR in the patients treated with ENTYVO (reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting (each of these adverse reactions occurred in <1% in all patients treated with ENTYVO) and no individual adverse reaction reported occurred at a rate above 1%. These reactions generally occurred within the first two hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment. Less than 1% of patients treated with ENTYVO had IRRs assessed by the investigator as severe, and IRRs requiring discontinuation of study treatment occurred in <1%.

In clinical trials, for patients with mild IRRs or hypersensitivity reactions, physicians were allowed to treat with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) prior to next infusion.

### Infections

In UC Trials I and II and CD Trials I and III, the rate of infections was 0.85 per patient-year in the patients treated with ENTYVO and 0.7 per patient-year in the patients treated with placebo (see Warnings and Precautions). The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued ENTYVO due to infections.

In UC Trials I and II and CD Trials I and III, the rate of serious infections was 0.07 per patient-year in patients treated with ENTYVO and 0.06 per patient-year in patients treated with placebo. Serious infections were more common in Crohn's disease patients than ulcerative colitis patients, and all abscesses were the most frequently reported serious adverse reaction in Crohn's disease patients. Over 48 months, there was no increase in the rate of serious infections.

In controlled- and open-label long-term extension trials in adults treated with ENTYVO, serious infections have been reported, including an abscess, sepsem (some fatal) tuberculosis, salmonella sepsis, Listeria meningitis and giardiasis and cytomegaloviral colitis.

In UC Trials I and II and CD Trials I and III, sepsis, including bacterial sepsis and septic shock, was reported in four of 1434 (0.3%) patients treated with ENTYVO and in two of 297 patients treated with placebo (0.7%). During these trials, two Crohn's disease patients treated with ENTYVO and one patient reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open label long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock were reported. The rate of sepsis in patients with ulcerative colitis or Crohn's disease receiving ENTYVO was two per 1000 patient-years.

In clinical trials, all patients were screened for tuberculosis. One case of latent pulmonary tuberculosis was diagnosed during the controlled trials with ENTYVO. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the United States, and none of the patients had extrapulmonary manifestations.

### Liver Injury

There have been reports of elevations of transaminases and/or bilirubin in patients receiving ENTYVO (see Warnings and Precautions). In UC Trials I and II and CD Trials I and III, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five ENTYVO doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with ENTYVO and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

### Malignancies

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1434 (0.4%) patients treated with ENTYVO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary neuroendocrine carcinoma, renal cancer and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

### Live and Oral Vaccines

There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVO.

In a placebo-controlled study of healthy volunteers, 61 subjects were given a single dose of ENTYVO 750 mg standard treatment (2.5 times the recommended dose), and 62 subjects received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with ENTYVO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to ENTYVO did have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

### Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. In UC Trials I and II and CD Trials I and III, in patients who received ENTYVO, the frequency of antibodies detected in patients was 1% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose). During treatment, 56 of 1434 (4%) of patients treated with ENTYVO had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. None of 56 patients were persistently positive (at two or more study visits) for anti-vedolizumab antibody and 55 of 56 patients developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced.
by several factors, including sample handling, timing of sample collection, concomitant medications, presence of vedolizumab, and underlying disease. For these reasons, comparison of the incidence of antibodies to ENTYVIO with the incidence of antibodies to other products may be misleading.

**DRUG INTERACTIONS**

**Natalizumab**
Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab.

**TNF Blockers**
Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO with TNF blockers.

**Live Vaccines**
Live vaccines may be administered concurrently with ENTYVIO only if the benefits outweigh the risks (see Warnings and Precautions).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Exposure Registry**
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTYVIO during pregnancy. Information about the registry can be obtained by calling 1-877-TAKEDA7 (1-877-825-3327).

**Pregnancy Category B**

**Risk Summary**
There are no studies with ENTYVIO in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefits to the mother outweigh the risk to the unborn child.

**Clinical Considerations**
Any adverse pregnancy effect from ENTYVIO would likely be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

**Animal Data**
A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

**Nursing Mothers**
It is unknown whether vedolizumab is present in human milk. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

**Pediatric Use**
Safety and effectiveness of ENTYVIO in pediatric patients have not been established.

**Geriatric Use**
Clinical trials of ENTYVIO did not include sufficient numbers of subjects aged 65 and over (45 Crohn's and ulcerative colitis patients aged 65 and over were treated with ENTYVIO during controlled Phase 3 trials) to determine whether they respond differently from younger subjects. However, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

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Inflammatory Bowel Disease: Past, Present and Future Therapies

By Mark R. Fleisher, MD

Introduction

Inflammatory bowel disease (IBD) is a spectrum of illnesses within the universe of Immune Mediated Inflammatory Diseases (IMID). These seemingly unrelated illnesses share a common aberrant overexpression of cytokines and leukotrienes yet have variable phenotypic expression. Among these illnesses are psoriasis, rheumatoid arthritis, Wegener’s granulomatosis, sarcoidosis and pyoderma gangrenosum, and while they have seemingly little in common with Crohn’s disease (CD) and ulcerative colitis (UC), they’re cousins. Even though this article may focus upon the therapies for IBD, much of the content can also be applied to IMID. UC always involves the colon and only involves the colon. UC always starts in the rectum, ascends proximally and is contained within the colon without skip lesions. CD can be found throughout the GI tract. The majority of CD resides within the ileum (40 percent), but a large percentage is within the colon (30 percent). A certain percentage resides purely within the small intestine (25 percent). The remaining small percentage (5 percent) is purely extraintestinal. This may be hard to conceptualize. However, one may have IBD and yet have no intestinal or colonic activity. Moreover, disease activity is hard to define. For example, endoscopically, the tissue may appear to be normal but biopsies may show disease activity. As such, it is quite a conundrum to define when someone is in remission. Several questions remain: Is someone in remission because they have no clinical symptoms? Is someone in remission because they have no endoscopic appearance of activity? Is someone in remission because they have no histologic activity? Is someone in remission if the GI tract is quiescent yet the extraintestinal manifestations (i.e. joint pains) and constitutional symptoms (i.e. fatigue) are still burgeoning?

Parameters

IBD is defined by several parameters. The first is location and is probably the most important.

Let’s consider a patient with colitis. Biopsies may appear typical of UC. Geographically, it may appear to be a typical UC picture. However, the serologic markers, the second parameter, may point more towards CD. These markers include, but are not necessarily limited to, ANCA, ASCA, OMPC, CBIR-1, ACCA and ALCA. The first is most commonly associated with UC and the others with CD. These markers may point to the reason why a patient with what appears to be UC is not responding to medications for UC. Some patients may have symptoms more like CD and perhaps that is because they are serologically more like CD even though geographically and histologically, the third parameter, they appear more like UC. This example demonstrates that IBD is not easy to define. The fourth parameter, genetics is the most nefarious. The list of genes associated with IBD seems to swell every day.

Treatment

Defining the problem is the first step. Finding appropriate treatment is the second. When a patient has inflammatory bowel disease, one of the first therapies that may be given is prednisone. However, a study by Summers in 1979 noted that maintenance therapy with prednisone at a dosage of 0.25 mg/kg per day was not effective compared with placebo in maintaining remission. It is important to take a closer look at these numbers. One of the ways to do this is with the Absolute Reduction of Risk (ARR). This is also known as the Therapeutic Gain. Therapeutic gain (TG) is the following: drug minus placebo (drug – placebo). One can never talk about how well a drug works if there is no placebo arm. Most studies in IBD have an acceptable placebo arm of anywhere between 25 percent and 65 percent. The rest of this article will be discussed in terms of the therapeutic gains (TG) of medications. The study by Summers revealed that prednisone induced remission in 78 percent of patients with active Crohn’s disease compared with only 49 percent of patients treated with placebo. Some quick math reveals that steroids have a TG of 29 percent to induce remission. However, as mentioned earlier, there was no therapeutic gain compared with placebo in maintaining remission. Another study regarding prednisone was by Munkholm. In that study, 22 percent of patients with Crohn’s disease were off of steroids at the end of the second year. However, in the same time period, 20 percent were steroid refractory. The remaining 58 percent were steroid dependent. In essence, once a physician has given a Crohn’s patient a steroid, they have a 1 in 5 chance that they will not respond to them, a 1 in 5 chance that they will respond to them and be off of steroids in 2 years, and the rest will be stuck on steroids. With this in mind, steroid sparing drugs need to be at the ready as soon as an inflammatory bowel disease patient has been given steroids.

Physicians are often accustomed to prescribing Mesalamine for IBD. However, this pattern is not always the best for patients. Studies, such as the one done in 1997 by Gamma, have shown for years that patients who have been given steroids for Crohn’s disease are thereafter unable to maintain remission solely on mesalamine. In essence, mesalamine is not a steroid sparing drug. Another study by Modigliani corroborated this finding. This latter study also revealed that mesalamine will not help small bowel Crohn’s disease.

Knowing that steroids and 5ASA products are the hallmark of therapy, perhaps physicians need to keep in mind that these medications are not optimal. Physicians should never be surprised when a patient relapses after having been given steroids and a 5ASA product. Physicians need
to remember that the patient only has a 20 percent chance that once they are given steroids they will be able to maintain remission with a 5ASA product.7 Moreover, physicians need to keep in mind that 5ASA products may help colitis and Crohn’s disease but have never been demonstrated to be effective in small bowel disease.6,8 Perhaps that is why the FDA approval for 5ASA products is merely for colonic disease and not for small bowel disease.

The next category of therapy is immunotherapy. There are numerous studies regarding azathioprine and methotrexate when it comes to inflammatory bowel disease. A 1995 study by Candy revealed that azathioprine has a therapeutic gain of 35 percent as opposed to placebo.9 Another study by Markowitz from 1998 revealed a therapeutic gain of 31 percent as far as 6-MP and the treatment of inflammatory bowel disease.10 Figure 1 and Figure 2 summarize all the controlled studies for azathioprine and 6-MP when it comes to Crohn’s disease.

Methotrexate has also been used for Crohn’s disease. A study by Feagan in 1995 revealed that 39 percent of the patients were able to maintain remission at 16 weeks compared to placebo.11 Another study in 1999 by Feagan revealed a steroid discontinuation rate of 30 percent and a therapeutic gain to maintain remission of 26 percent when it came to methotrexate.12

There is also often discussion of the use of antibiotics for Crohn’s disease. One study revealed that ciprofloxacin and metronidazole had an efficacy of 80 percent to maintain remission on antibiotics. However, in the same study, 65 percent were able to do so with placebo. That’s a therapeutic gain of 15 percent when it comes to antibiotics for Crohn’s disease.13

The reader should note that the studies referenced thus far are from the 1990s. However, it is important to consider how we got to this point. Biologic therapies are now exploding on the market, because the last century’s drugs were not so great.

In 1997, the world of inflammatory bowel disease changed. Studies by Targan and Present in The New England Journal of Medicine presented the efficacy of infliximab for the treatment of Crohn’s disease with and without fistulae.14,15 In those studies, patients with steroid refractory Crohn’s disease had improvement within two weeks of infusion. Sixty one percent improved within two weeks of infusion. Within two weeks, 27 percent were in remission. The study showed a therapeutic gain of 64 percent. Infliximab therapy works by blocking antimuror necrosis factor. It is one of the cytokines that is part of the inflammatory cascade. Numerous trials followed. Accent I was a maintenance study for Remicade (infliximab) responders in nonfistulizing Crohn’s disease.16 The study showed a therapeutic gain of 23 percent for remission at week 8. Therapeutic gains of 27 percent were not draining at week 14.17

ACT I and ACT II trials were infliximab trials for induction and maintenance therapy in ulcerative colitis.18 Therapeutic gains for responsiveness of 40 percent were noted at week 8. Therapeutic gains of 25 percent was noted at week 54.

After those trials, there were questions regarding whether or not patients should be on infliximab with immunotherapy or without. Two trials followed. The SONIC trial and the SUCCESS trial revealed that combination therapy won the gold medal, infliximab won the silver, and immunotherapy was a distant bronze medal.19,20 However, with combination therapy came an increased risk of infections and neoplasms. As such, it is still a question whether or not a physician should pick the most

### Figure 1: Summary of Controlled Studies of Azathioprine or 6-MP for INDUCTION of Remission in Crohn’s Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Regimen</th>
<th>Key Findings</th>
<th>Analysis</th>
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<tbody>
<tr>
<td>Candy et al 1995</td>
<td>63 patients with active CD</td>
<td>AZA (Imuran) 2.5 mg/kg/d or placebo</td>
<td>At 12 wks, 75% and 68% of patients in the AZA and placebo groups, respectively, achieved and maintained remission, defined as CDAI&lt;150.</td>
<td>T.G. = 10% p = .60</td>
</tr>
<tr>
<td>Esw et al 1995</td>
<td>42 patients with active CD</td>
<td>AZA 2.5 mg/kg/d or placebo x 16 wks plus prednisolone 60 mg/d with a planned taper to a maintenance dose of 10mg</td>
<td>Of those who completed the crossover phase (n=39), 67% improved while receiving 6-MP and 8% improved while receiving placebo.</td>
<td>T.G. = 38% p=.03</td>
</tr>
<tr>
<td>Present et al 1980</td>
<td>83 patients with chronic active CD who failed to respond to sulphasalazine and steroids</td>
<td>6-MP 1.5 mg/kg or placebo x 1 year then the alternate treatment x 1 year</td>
<td>No significant difference between AZA and placebo, in terms of subjective (i.e. appetite, well-being) and objective parameters</td>
<td>No Gain</td>
</tr>
<tr>
<td>Summers et al 1979</td>
<td>136 patients with CD and CDAI &lt;150</td>
<td>AZA 2.5 mg/kg/d (max dose = 2500mg) or placebo x 17 weeks</td>
<td>At 17 wks, 36% and 26% of patients in the AZA and placebo groups, respectively, achieved CDAI&lt;150.</td>
<td>T.G. = 10%</td>
</tr>
<tr>
<td>Klein et al 1974</td>
<td>26 patients with active CD who were unresponsive to other therapies, had intestinal complications requiring extensive surgery, or were unable to tolerate steroids</td>
<td>AZA 5 mg/kg/d or placebo x 16 weeks, then the alternate treatment x 16 weeks</td>
<td>No significant differences between AZA and placebo in terms of subjective (i.e. appetite, well-being) and objective parameters</td>
<td>No Gain</td>
</tr>
<tr>
<td>Rhodes et al 1971</td>
<td>15 patients with CD and at least 1 severe symptom or 2 less severe symptoms</td>
<td>AZA (5mg/kg/d x 10d, then 2 mg/kg/d theretofore) or placebo x 8 wks, then the alternate treatment x 8 weeks</td>
<td>No significant difference between AZA and placebo in terms of symptomatic improvement, presence of colic, and bowel movement frequency</td>
<td>No Gain</td>
</tr>
</tbody>
</table>
potent therapy or a very potent therapy with less risk of neoplasms. After infliximab, other antitumor necrosis factor therapies came on the market with similar efficacies. It is important to note that all of these trials were not just in patients with UC and CD. The trials included patients who had already failed steroid therapy and SASA therapy and immunotherapy. These were the most recalcitrant IBD patients. As such, when evaluating a therapeutic gain or an absolute reduction of risk, one has to wonder as to the population being studied. In these studies of antitumor necrosis factor therapies, the opponent was quite formidable.

A new drug on the market is vedolizumab. Let’s review how this drug works. Lymphocytes have integrins. Some integrins bind to receptors on intestinal endothelial cells. These gut receptors are called MADCAM-1. When the lymphocyte integrin binds to the gut receptor, it is able to enter the intestines and create havoc. Vedolizumab is an IgG1 monoclonal antibody to alpha-4 beta-7 integrin located on the lymphocytes. When the lymphocyte tries to enter the gut, vedolizumab blocks the binding interaction of the integrin and the MADCAM-1 receptor. This prevents the lymphocyte from entering the intestine. In simpler terms, vedolizumab is a targeted antibody that hunts down a specific integrin on the lymphocyte and won’t let the coupling occur. Without this coupling, the lymphocyte can’t enter the intestine. Thankfully, this drug does not impact the alpha-4 brain receptor. Older anti integrins, such as natalizumab, block lymphocyte trafficking to the entire body including the brain. Patients were at grave risk for anti integrins, such as natalizumab, block lymphocyte trafficking to the entire body including the brain. Patients were at grave risk for PML, a fatal brain infection. Vedolizumab is better and safer due to its selectivity. In essence, lymphocytes stop entering the gut and the inflammatory cascade stops, yet lymphocyte surveillance is allowed to continue in the brain. Studies reveal that with vedolizumab there is a therapeutic gain of 31 percent in ulcerative colitis and 25 percent in Crohn’s disease at 52 weeks. The population studied in these trials were patients who had failed other treatments including anti-TNFs. Moreover, the data for vedolizumab is more robust than for the anti-TNF class of medications.

In 2000, there was a study by Subra Kugathasen. It revealed that earlier application of more aggressive therapy was able to prevent irrevocable deleterious consequences in a pediatric population. In essence, once a patient develops fistulae or strictures or abscesses, it is too late. The longer you delay applying appropriate therapy, the more difficult a patient’s IBD becomes. However, the earlier application of state of the art medication can change patient’s lives.

Moving Forward:
The Author’s Perspective

We have taken a look backwards and we have taken a look in the mirror, but now it is time to take a look forward. Where are we headed? Certainly, the obstacles are daunting, but I have always believed that our accomplishments are only limited by our imagination.

I believe that at some point we will have combination biologic therapy. Problems are multifactorial. Inflammatory bowel disease is the same way. I do not think it is just one cytokine or one leukotriene that needs to be fixed. It is often a host of problems. We have to keep in mind that the IMID patient has many branches to the uncontrolled arborization of the immune cascade. As such, I foresee that we will eventually order a profile that quarter. Instead of giving pa-

### Figure 2: Summary of Controlled Studies of Azathioprine for MAINTENANCE of Remission in Crohn’s Disease

<table>
<thead>
<tr>
<th>Study</th>
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<th>Regimen</th>
<th>Key Findings</th>
<th>Analysis</th>
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</thead>
</table>
| Candy et al 1995 | 65 patients with active CD (CDAI>200) | AZA (Imuran) 2.5 mg/kg/d or placebo x 15 months | At 15 mo, 42% and 7% of patients in the AZA and placebo groups, respectively, were in remission, defined as CDAI <175 | T.G. = 35%  
| Rosenberg et al 1979 | Part 1, Phase 1 136 patients with CD and CDAI>150  Part 2 155 patients in remission (CDAI<150) at study entry | Part 1, Phase 1 AZA 2.5 mg/kg/d (max dose = 250mg) or placebo x 17 weeks  Part 2 AZA 1.0 mg/kg/d or placebo as maintenance therapy | Treatment outcomes for both parts were similar between the AZA and placebo groups after a follow-up period of 1-2 years | No Difference |
| O’Donoghue et al 1978 | 51 patients with CD in good health during a >6 month course of AZA 2mg/kg/d | AZA 2 mg/kg/d or placebo x 12 months | 6-mo and 12-mo actuarial relapse rates were significantly (p = .01) lower in the AZA group (0% and 5%, respectively) compared to the placebo group (25% and 41%, respectively) | At 6 months  
| Rosenberg et al 1975 | 20 patients with CD who required >10mg prednisone per day during the previous 3 months | AZA 2 mg/kg/d or placebo x 26 weeks | Relapse rate and average reduction in steroid requirements were better in the AZA group compared to the placebo group | AZA > Placebo |
| Willoughby et al 1971 | 22 patients with CD and prednisone induced remission | AZA 2 mg/kg/d or placebo x 24 weeks | Relapse rate in the AZA and placebo group was 9% and 73%, respectively | T.G. = 64% |

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patients giant boluses every few months, perhaps they will just get a little drip of biologics all day long. I would not be surprised if patients are given some sort of biologic pump similar to those given to a diabetic for constant therapy of a baseline pancytokine inhibitor and then receive a quarterly booster of their designer drug to patch up the leaks.

On the horizon is stem cell therapy. Maybe IBD and all IMIDs need to be given an initial haymaker before the clean-up crew of anti-cytokines are brought in. Maybe these patients will undergo intense induction therapy to change the course of the illness.

Perhaps our colleagues will come up with a colon transplant. Maybe even a prosthetic colon is in our future.

Don’t be shocked if fecal transplants also play a role in the treatment of inflammatory bowel disease. It is hard to believe but fecal transplants may actually come in a pill one day soon.

All of these dreams are merely an expression of our patients’ hope prior to a cure. I may be wrong in where we are headed as far as specifics, but I do know we are headed in the right direction. Hopefully, this article has allowed you to see how we got here. As far as where we are headed: full steam ahead! ☄

References:


8 TOP QUESTIONS
a Patient Should Ask Their Nephrologist

By Franklin W. Maddux MD  Web ID: 1011

You have been referred to a doctor called a nephrologist. Here is what that means, and how to prepare for a successful and useful first encounter. The first thing to know is that a nephrologist is a physician trained in internal medicine or pediatrics and then additionally trained to understand and care for patients with kidney-related disorders that affect the kidney function as well as the other organs that rely on good kidney function. Before your appointment with the nephrologist, prepare by thinking about what you should understand. Don’t be shy about asking questions or expressing concerns you have about the condition for which your nephrologist has been asked to see you. These eight questions can start you on a path to a better understanding of your condition, but are by no means the only questions that might come up or be appropriate for your first visit.

WHAT ARE MY TREATMENT OPTIONS AND HOW DO I LEARN ABOUT THESE OPTIONS?
Depending on the degree of kidney function loss you have, and the speed to which that loss of function has occurred, there will be options offered to either stall, reverse or delay the progression of the kidney disease. The nephrologist can explain and prepare you for decisions about additional therapy needed if your kidney function deteriorates to the point that renal replacement therapy options should be considered.

WHO SHOULD I CALL WITH NEW PROBLEMS OR QUESTIONS?
By the end of the visit with your nephrologist, you should understand the role that she or he will play in your ongoing care. The nephrologist should be able to determine if and when they should be called for questions about the kidney disease or other problems. Many other medical conditions are affected by the fact that the kidneys are not working well, and these will influence the approach by your clinical care team.

WHAT DEGREE OF KIDNEY FUNCTION LOSS EXISTS NOW?
If your kidneys are not working properly, it is important for you to know how poorly they are functioning compared to normal. This is a reasonable question to ask and to track on your initial and subsequent visits to the nephrologist.

HOW RAPIDLY IS MY KIDNEY FUNCTION DECLINING?
Some causes of dysfunction of the kidneys are temporary, and some are permanent. Some conditions are associated with a continued loss of function over time. The rate at which this happens will be an indicator of the frequency and extent of attention needed to try to delay or slow kidney function decline.

WHAT CAN I DO TO SLOW, DELAY OR REVERSE THE DECLINE IN MY KIDNEY FUNCTION?
Preserving kidney function is the desire of every physician that is treating you for your kidney disease. This may or may not be possible depending on your individual health situation and medical condition. Your nephrologist can help you understand if your kidney function is likely to continue to decline over time or if certain therapies might preserve or even improve that function.

WHAT IS THE REASON MY KIDNEYS ARE NOT WORKING PROPERLY?
Kidney function is a measure of the ‘cleaning’ capacity of the kidneys, and the term “kidney dysfunction” primarily refers to: 1) kidneys’ reduced cleaning capacity in removing toxins from the body that build up from everyday living; and 2) kidneys’ reduced ability to balance fluid in the body. These two functions of the kidneys, among others, are frequently the focus of a visit when a patient’s kidney function is impaired or at risk of deteriorating. Other structural or functional aspects of the kidneys may have been the reason for a referral. Your nephrologist should know why you were referred, and their job with you is to further understand your condition so that they can assist in your care.

HOW CAN I SIMPLIFY THE MEDICINES, TESTS AND FOLLOW-UP NEEDED TO GET THE BEST BALANCE BETWEEN MY LIFE AND MY KIDNEY DISEASE CARE?
The management of kidney disease frequently requires multiple medicines, diet and activity changes and frequent interactions with the health care system. It is reasonable to have a discussion with your nephrologist about challenges you may have with taking multiple medications, and the about impact of your medical regimen on your daily life. Your nephrologist will work to help you adhere to a medical plan of care and avoid the known potential consequences resulting from the kidney disease.

Franklin W. Maddux MD, FACP is the Fresenius Medical Care Chief Medical Officer & Executive Vice President for Clinical & Scientific Affairs.
A lot can happen in twenty years. That’s how long it has been since I lived in New York City. After finishing fellowship training in gastroenterology at Lenox Hill Hospital, I left not for greener just safer pastures. I have always had trouble with self-confidence. I always took too long to ask out a girl. I always took even longer to kiss her. The same could be said about my career. I left NYC because I never thought I could compete. I never thought I could have a successful practice among the giants in Manhattan. I never thought anyone would choose me to be their doctor. When I was a little boy, my father showed me his tax return. Under occupation he wrote “salesman.” He told me that everything in life is sales. When you ask out a girl, you’re saying “pick me.” When you apply to college, you’re saying “pick me.” When you become a doctor, you’re asking other potential referring physicians to “pick me.” When you are looking for patients, you’re asking them to “pick me.”

And so lays my Achilles heel. Girls never picked me first. Captains of pick up punch ball games rarely picked me. They were merely left with me. American medical schools didn’t pick me. However, I persevered. I went overseas to medical school and I came home not just with a diploma in hand but a chip on my shoulder. At the end of my training, one of the finest men I ever met, Dr. Burton Korelitz, asked me what my goal was. I replied “to have the largest inflammatory bowel disease (IBD) practice in the nation.” And wouldn’t you know it, I do. In little Jacksonville I have been fortunate enough to direct the largest infusion center of biologic therapy in the world. Not too shabby. As a result, company after company asks me to speak for them. Finally somebody picked me. And yet I am the picky one.

I haven’t spoken in over a decade because I haven’t found any product worthy or compelling since I spoke about infliximab. When that drug came on the market, I knew it would change lives and careers. I spoke everywhere. However, when similar drugs came on the market I was instructed not to discuss them by the company hiring me. I had an epiphany. I was not to be an educator. I was a promoter. I would be PT Barnum with a stethoscope. I refused to discuss Burger King and not mention McDonald’s or Wendy’s. I would not lie to my colleagues. I would only speak if I was able to give a fair and balanced talk. My colleagues were counting on me. More importantly, their patients were counting on me. I decided to keep my integrity and stop going on tour.

Recently, a new drug, vedolizumab, came on the market for patients with IBD. It has a different mechanism of action. It is another weapon. More importantly it is a source of hope for patients who have run out of options. To them it screamed “pick me.” The company asked me to speak for them. As a former English minor I informed them that it was quite an honor to be asked to speak to my colleagues. I also reminded them that I will not speak for their company. I am not a marionette. However, I will speak as long as I can discuss every choice a patient and physician have. I will only go on tour if I am allowed to speak unencumbered by petty corporate competition. To my amazement they said “yes.”

Twenty years have passed since I fled my hometown. I have spoken in Memphis, Pittsburgh, Cleveland, Nashville, Buffalo, Detroit and even Paducah. I have to tell you, the medical teams in every city are all the same. Smart. Sincere. Hard working. Well meaning. Refreshing. Life affirming. I have stolen many a hotel bar of soap because that is the American way.

Recently I came to New York City having studied for weeks. I didn’t want to embarrass myself. I was afraid. I gave a lunch talk on William Street, It is just down the street from Peck Slip and a block from the Fulton Fish Market where my father worked as a longshoreman for 40 years. I spoke with doctors as young as my sons. We reviewed all the drugs for patients with IBD. We compared the numbers needed to treat and thereby the absolute reduction of risks. I told them that I was not in sales. My only job was to get them to think about their treatment paradigm and perhaps adjust it. It was the soft sell approach and I could feel their relief and respect.

A car was waiting for me downstairs. As we slowly made our way down William Street I saw spikes of silver and aluminum coming up from the ground. Dozens of metal slats lying sideways. Ground Zero. Traffic slowed as we passed the Memorial. It was as if this was an eternal funeral processional. I started to cry. My driver did, too. I couldn’t muster a word until we got to Greenwich Village. I told him, “You know, they flew me up here to talk but right now I have nothing to say.”

I gave a dinner talk that night. In the audience were two women from Mt Sinai. They were in their thirties. They both had their head covered. One Muslim and the other an Orthodox Jew. They worked together. They sat together. They ate together. They smiled at all of my stories. After my ride home that afternoon, they were just what I needed. I knew that my nation would be all right. I knew it before I had spoken one word.

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