Suggested Guidelines to Assist Primary Care Providers with Initial Renal-related Work-ups and Possible Nephrology Referral

Frequently Asked Questions regarding congenital renal anatomic anomalies
1. Congenital absence of a kidney
2. Horseshoe kidney
3. Duplicated collecting systems
4. Simple cysts

Congenital Absence of a Kidney
Having one normally functioning kidney requires no specific follow since there is essentially nothing to be done to change that circumstance, and much past experience tells us there are no particular sequelae.

In circumstances where there is the presence of a normally functioning kidney (generally of greater than normal size), but with the added radiographic report of the contra-lateral kidney described as either “Multicystic Dysplastic”, “Hypoplastic” or “Atrophic”, a common question is in regard to the appropriate follow, if any, for the “abnormal kidney”.

With documentation (normal serum creatinine) that normal kidney function is being provided by the “single, normal kidney”, there really is nothing to be gained by regular nephrology follow as one expects renal function to remain normal as provided by the single normally functioning kidney. The poorly formed kidney is expected to undergo further involution and may eventually not be at all radiographically demonstrable. Such congenitally poorly developed kidneys would not be expected to cause any particular problem to support their removal. On the other hand, a small, scarred kidney that has resulted from disease or injury may cause hypertension.

Horseshoe Kidney
This anatomic anomaly with normal renal function and no hypertension (rare) requires no input from Nephrology. If there is accompanying hydronephrosis, Urology should be consulted.

Duplicated Collecting Systems
Duplicated collecting systems (more than one ureter per kidney) are anomalies which if only associated with hydronephrosis suggest either vesicoureteral reflux or ureteric obstruction.

Simple Cysts
The radiographic report of a “simple cyst or cysts” in a kidney, is not the same as a diagnosis of polycystic kidneys. These are congenital defects that represent a one-time malformation of cysts, and thus progressively, more (and enlarging) cysts are not expected, in contrast to polycystic kidney disease. They require no intervention.

Considering a referral to Children’s Hospital Colorado Kidney Center?
Recommendations and helpful clinical data prior to considering a possible referral
To assist all providers with some of the most frequently asked questions pertaining to the work up of the most commonly encountered renal diagnoses in the primary care setting, the nephrologists at the Children’s Hospital Colorado Kidney Center offer the following guidelines for a work up pertaining to these more frequently encountered problems, the results of which will also be very helpful for the nephrologist should a referral be needed.

1. Microscopic Hematuria
2. Gross Hematuria
3. Proteinuria
4. Nephrotic Syndrome
5. Renal Tubular Acidosis
6. Hypertension
Microscopic Hematuria

It is recommended that a workup for possible renal (glomerular) related, asymptomatic, microscopic, hematuria not be pursued based solely on a urinary “dipstick” finding, since “false positive” readings are common. Microscopy of the urine sediment is the gold standard used to define hematuria and would be considered positive, if greater than 5 rbcs/hpf noted by urine microscopic exam on more than one occasion.

Relevant clinical data when considering a referral to the Nephrology department include:

- Complete urinalysis reports (greater than 5 rbcs/hpf)
- Serum BUN
- Creatinine and electrolytes
- C3 complement
- Urine calcium/creatinine ratio
- Renal ultrasound
- Documentation of hypertension, if noted

If Lupus is clinically suspected, results of ANA, Double Stranded - DNA, ESR and CBC would be included.

Note: If Henoch-Schoenlein Purpura (HSP) is known to be the cause of hematuria, and there is normal renal function and blood pressure with no significant proteinuria (protein creatinine ratio of less than 0.5), follow by PCP is reasonable as long as continued clinical improvement is noted.

Should the workup be normal except for the hematuria, continued follow by PCP is certainly acceptable and permits the passage of time, continued normal renal function and normal blood pressure to support a diagnosis of benign hematuria, but as stated the Nephrology department is available to discuss the possible significance of any questionable abnormality, but referral is certainly at PCP discretion or for parental reassurance.

Gross Hematuria

The two most common renal causes of acute onset gross hematuria (i.e. cola colored, tea colored, etc.) are generally asymptomatic, but may be associated with flank pain (see below). These are post streptococcal (or other infection related/presumed) glomerulonephritis and IgA nephropathy.

1. Acute post infection glomerulonephritis is associated with a depression of serum C3 complement. However, C3 can resolve so quickly that it may be normal at first testing. If it is depressed when first obtained, it may take up to a month’s time to normalize. Initial workup other than serum C3 includes serum BUN, creatinine and electrolytes and assessment of blood pressure. ASO titers or streptozyme testing, although of interest, do not contribute significantly to the diagnosis or management, since infections other than streptococcal have been associated with the immune mediated “post-infection” response noted in the kidney. Clinically present infectious symptoms noted at the time of presentation would, however, warrant treatment of the underlying illness.

Associated hypertension should also be treated, and the drug of choice would be the ACE inhibitor class of antihypertensive medication (e.g. lisinopril) provided that renal function is not significantly compromised. If so a calcium channel blocker like amlodipine may be used.

Presentations with the association of nephrotic range proteinuria or 50% reduction in creatinine clearance (doubling of normal serum creatinine for patient size) and/or emergent levels of blood pressure support initial inpatient management. However, mild, uncomplicated acute glomerulonephritis can otherwise, for the most part, be managed in the outpatient setting with a Nephrology department phone consultation.

Cases with worsening clinical features or the persistence of depressed serum C3 beyond 30 days from onset warrant earlier referral to the Nephrology department.

In the severely ill-appearing child especially one presenting with significantly compromised renal function or severe hypertension, hospitalization is usually necessary. It remains true that 85% of cases resolve without sequelae. Many cases resolve without need for specific Nephrology referral or follow, but referral remains at the discretion of the PCP. It is not uncommon for hypertension to require treatment for several months post recovery of the glomerulonephritis.

2. IgA Nephropathy typically presents as recurrent episodes of grossly bloody urine, often at the time of unrelated minor acute illness (fever, viral syndrome, URI, etc.), however, episodes can present with no other associated symptoms. The gross hematuria may last from 1 to 7 days, after which the urinalysis may demonstrate either persistent microhematuria, or complete resolution. Since the first episode can mimic possible acute post infection glomerulonephritis, a similar initial workup is conducted. Significantly, there is no associated serum C3 depression. In 85% of cases in children there will be no poor prognostic indicators which include associated impairment of renal function, hypertension or persistent, significant proteinuria. Some children may experience flank pain or dysuria caused by the "chemically induced" irritation of the genitourinary tract mucosa by the presence of blood itself.

After each subsequent episode of gross hematuria, follow-up includes documenting continued normal serum creatinine,
blood pressure and the absence of persistent significant proteinuria after the gross hematuria resolves (microhematuria may persist indefinitely). However, should any undesirable abnormalities develop (increasing serum creatinine, chronic hypertension and/or defined, persistent proteinuria, nephrology referral is warranted. Renal histologic confirmation (biopsy) may be helpful for prognosis, but therapeutic intervention would be attempted based on the clinical situation, regardless of the renal histology, given the serious consequences of progressive renal failure. There is no universally accepted treatment, but corticosteroids and other immunosuppressive medications are widely employed. There exists some compelling evidence that fish oils (omega-3 fatty acids) may have a beneficial effect. Fortunately, as previously indicated, only about 15% of IgA nephropathy cases are the severe form, therefore renal biopsy is often deferred in the 85% with clinically mild disease, since the absence of poor prognostic features would not indicate specific treatment. Therefore many children with IgA nephropathy are followed by their PCP with input from a nephrologist, however, as previously stated, the Nephrology department is always available for referral.

Proteinuria

It is recommended that a workup for possible proteinuria not be pursued solely on the basis of a positive urine “dipstick” finding, since “false positive” readings are common.

Suspected proteinuria should be confirmed with a urine protein/creatinine ratio (random urine sample in which urine protein mg/dl and urine creatinine mg/dl are measured, and the ratio is then calculated by dividing the urine protein by the urine creatinine) normal being 0.2 or less.

Caveat: if the laboratory reports the result as albumin per gram of creatinine, normal is 200 or less.

NOTE: Orthostatic or postural related proteinuria, a benign condition with associated normal serum creatinine, normal renal ultrasound and absence of hypertension, should be excluded by the calculation of the urine protein/creatinine ratio on a “first morning” void. If postural proteinuria is documented and renal ultrasound, and creatinine are normal, and the child has a normal blood pressure, the condition requires no further follow. Should there be no postural relationship with persistent proteinuria and a renal ultrasound reveals hydronephrosis, Urology referral is warranted. With associated hypertension nephrology referral is indicated.

Caveat: In obtaining a “first Morning” void, instruct child/parent regarding the understanding that the bladder must be emptied just prior to going to bed, not just “some time” before, since, subsequent to that void, the urine collecting in the bladder must be done while the child is supine, permitting proper comparison of “upright” (ratio elevated) to “supine” (ratio normal), thus demonstrating the postural relationship. Furthermore, upon awakening the child should immediately obtain the urine specimen prior to any other activity.

Relevant clinical data when considering nephrology referral for proteinuria include:

• non postural related (persistent) urine protein/creatinine ratio greater than 0.2
• serum BUN
• creatinine
• electrolytes
• albumin
• renal ultrasound without evidence of hydronephrosis
• documentation of hypertension, if noted

Should the workup be essentially normal, save for the persistent, non-orthostatic proteinuria, follow by PCP is still certainly acceptable, since treatment would not be immediately indicated, and permits the passage of time (proteinuria may improve), continued normal renal function and blood pressure to support a diagnosis of benign proteinuria. However, an increasing protein/creatinine ratio and/or increasing serum creatinine and/or the development of hypertension warrant referral to nephrology.

Nephrotic Syndrome

When nephrotic syndrome (significant proteinuria resulting in hypoalbuminemia with varying degrees of edema/ascites) is diagnosed, initial follow is commonly done through PCP office. Referral to nephrology occurs any time at PCP discretion or parental request.

An extremely ill child with the nephrotic syndrome, or one whose clinical condition and management is deemed complex, should be hospitalized for initial management.

Here is a brief description of the typical corticosteroid (prednisone) treatment regimen for nephrotic syndrome in children:

1. Initial prednisone dose is 2 mg/kg/day (maximum 60 mg - for anyone over 70 kg, maximum is 80 to 100 mg) as a single daily dose for 6 weeks, followed by the same dose every other day for another 6 weeks.

2. After that, for children taking 40 mg or less, begin decreasing the alternate day dose of prednisone by 5mg every 2 weeks, and discontinue prednisone after a final 2 weeks at 5mg per dose every other day. In those initially taking 60 mg or greater, the dose reduction may proceed by 10mg every 2 weeks, until discontinued.
Please note: This regimen assumes the patient continues to remain in remission, i.e. trace to negative urine protein, throughout the course including the taper.

Discussion with nephrology is recommended if initial response does not occur within the initial 6 weeks of the starting dose, or at any time during the tapering of prednisone. Having achieved successful response and tapering, only to again relapse requires restarting the course from the beginning, but for subsequent courses initial maximum dose time course is 4 weeks daily, 4 weeks every other day, followed by the usual taper.

The utility of 25% albumin infusion and diuretics and guidelines for administration:
The time to response to prednisone will vary (average 2 weeks), and commonly the patient may acquire more edema while waiting. Therefore, the need may arise to provide diuretic control of edema (realizing the effect will be blunted by the low serum albumin).

Diuretics may be prescribed with caution, as long as there are no signs of intravascular volume depletion. However, diuresis alone may not achieve satisfactory results especially when serum albumin is below 2.5 gm/dl. Cautious intravenous infusion of 25% albumin (1 gm/kg over 4-5 hours) --- to allow vascular volume compliance while obviating hypertension (which may still need to be addressed anyway) --- is administered to temporarily restore the serum oncotic pressure, aiding in the mobilization of compromising edema back into the intravascular compartment, where it can be delivered to the kidney for excretion. This intervention is indeed temporary while the patient continues to demonstrate massive proteinuria, until there is a response to prednisone. However, depending on the serum albumin level at the outset, increasing the serum oncotic pressure a “degree” may not result in all the desired diuresis, and it is likely that several 25% albumin infusions would be needed to “normalize” the serum albumin oncotic pressure. But a serum level of 2.5 gm/dl is a reasonable goal for practical, management purposes.

Typically, to achieve a more immediate diuresis in the face of some increased, but still subnormal serum albumin, the infusion is generally followed by intravenous furosemide of 2-4 mg/kg/dose (maximum 200 mg).

High doses are not uncommonly required in nephrotics, whose response to the action of Lasix may be quite “blunted”.

Blood pressure measurements are needed during the infusion to address any hypertension related to the oncotic infusion. Acute undesirable increases should be treated by interrupting the infusion and administering the intravenous furosemide “earlier”. If severe, hypertension is treated also with sublingual nifedipine.

Associated hypertension in nephrotic syndrome is common and should be treated, generally beginning with an ACE-inhibitor.

Generally, most pediatric-age patients with nephrotic syndrome are initially suspected to have minimal change disease (85% of cases), with its attendant good prognosis, as the underlying cause. Therefore renal biopsy is not of immediate need. Furthermore, even if the there is so-called steroid dependence or resistance, a renal biopsy, although able to specifically provide the histologic diagnosis, would not be expected to alter the course of treatment, as the treatment is directed towards the elimination of the nephrotic syndrome with all its attendant complications. Thus the renal histology provides more prognostic information than it contributes to specific drug management.

In cases of poor prednisone response or relapses of 3 per year, or during a prednisone taper, Prograf (tacrolimus) is added to the prednisone course. It is taken every 12 hours and the dose is established, through first initiation with 1 mg every 12 hours, verifying the resulting AM trough dose, and increasing each dose by 1 mg every 3-5 days to achieve a serum trough level of between 6 and 11.

The first level should be done after 3-4 days of taking the medication and 3-4 days of every adjustment to the dose. Once that is established prednisone should then hopefully be able to be more successfully tapered. Once remission is so achieved, maintaining therapeutic Prograf for at least 6 months is advisable before attempting to taper that drug. Even then relapse may again occur, and if so the maximum dose of prednisone and therapeutic dose of Prograf are once again initiated.

These courses may be repeated as long as needed awaiting the time for spontaneous resolution. This is generally well tolerated provided significant corticosteroid side effects are not noted nor problems with the Prograf (tremors, hyperglycemia).

For those children who either require so much exposure to steroids that side effects (such as osteoporosis, vertebral compression fractures, e.g.) are deemed present or eminent, and despite continuing to be responsive the steroids, or those who completely fail treatment with prednisone and Prograf, the next recommended step is a course of intravenous rituximab (once a week for 4 weeks).

Many uncomplicated cases of nephrotic syndrome are followed primarily by the child’s PCP, even after the need to add tacrolimus to the treatment, and phone consultation from nephrology is always available.
However, anytime during the course of nephrotic syndrome a child may be referred to nephrology at the PCP’s discretion or parent’s desire.

At some point in the course, especially if tacrolimus is deemed necessary, it is certainly appropriate for nephrology to become more directly involved, and see the patient at least periodically.

Given our geographic location and wide referral area, we do not insist on the burden of frequent visits here and are very willing, and appreciative of working at a distance with all PCPs.

Renal Tubular Acidosis

The so called “Type 2”, or “proximal” form of renal tubular acidosis (RTA), accounts for greater than 95% of all of the types of all RTAs seen in the pediatric population. It presents in early infancy and is expected to resolve with time (by age 2-6 years) and renal maturation.

The work-up of RTA includes: documentation of a low serum bicarbonate (HCO3 < 20 mEq/L) level in the presence of no anion gap, and a simultaneous urine pH above 5.5

NOTE: In proximal (type 2) RTA, where the kidney has a lower threshold at which to retain HCO3, if there is cause for the serum HCO3 to fall below that threshold, the kidney will acidify the urine, and the urine pH can drop anywhere below 6.5. Whereas in Type 1, or distal RTA, the urine can never acidify, i.e. fall below 6.5.

Caveat: Borderline levels of serum HCO3 (e.g. 17-19mEq/L) may contribute to an over-diagnosis of the presence of true acidosis. In such cases is recommended that one obtain a venous blood gas (VBG) to verify acidosis, along with evidence of respiratory compensation. Interpretation of a decrease C02 can be confounded in a crying child, however.

Early childhood RTA Type 2 in the typical case is an isolated renal abnormality. It is the only thing that is (temporarily) wrong with the kidney, so serum creatinine and phosphorus should be demonstrated to be normal (e.g. if serum phosphorus is low then the renal tubule is wasting phosphorus as well as bicarbonate, suggesting a more extensive abnormality of the renal tubule (e.g. renal Fanconi Syndrome). A renal ultrasound is generally recommended to rule out the possibility of significant hydronephrosis, since RTA can be caused by urinary tract obstruction. Admittedly the yield is very low in children with no additional history or findings suggesting urinary tract anomalies (e.g. urinary tract infection). Sometimes nephrocalcinosis can be seen.

Because Type 2, is by far the most common type of RTA observed in the very young, it is rarely necessary to utilize the “classic” acid loading test (to see if the kidney can eventually create an acid urine) to separate it from Type I. The mere fact that the “bicarbonate wasting” aspect of proximal RTA necessitates much larger amounts of extra buffer, i.e. citrate, to correct the serum HCO3 level, is a more practical, less hazardous way, to obtain the clinical data in support of the more common diagnosis of proximal RTA, with its favorable prognosis.

As stated, most young children with RTA will have Type 2 RTA. The bicarbonate wasting results from an immaturity of the kidney resulting in the sole temporary defect of a lower bicarbonate threshold. It is expected to normalize anywhere from age 2 to 6 years. The other types are rare. The large amount (5-20meq/kg) of supplemental buffer (generally in the form of citrate) required to achieve an acceptable serum level (20meq/L) of bicarbonate (HCO3) supports bicarbonate wasting (Type 2). The total daily requirement is divided at least three times a day in order to try to maintain a more constant level in the blood, since there is continual loss via the kidneys. The taste of Bicitra (citrate = 1 mEq /ml) or Polycitra (2 mEq/ml) is citrus, or somewhat lemon, but can be improved by adding cherry flavoring or putting the dose in lemonade. Care should be taken not to add the medication to so much volume so that the child cannot consume a complete dose.

Unfortunately, there are no other medication choices currently available on the market. A reasonable initial dose is 3-5 mEq/kg/ day divided three times a day.

NOTE: Achieving a serum HCO3 level of 20 mEq/L with a dose of citrate lower than 2 mEq/kg suggests the possibility of Type 1 RTA.

As mentioned some of the difficulties encountered are due to the taste, at in some children there is associated diarrhea, which can sometimes be eliminated by further dividing the total daily dose into 4 or 5 times a day. After a week of initial dosing, assuming the child is taking the medication faithfully, a serum bicarbonate level should be checked to assure the goal of 20 mEq/L in the serum has been reached. If not at the desired level, each individual dose is increased by 3-5 ml (based on a TID schedule), and the blood level checked each week anytime the dose is changed.

Caveat: Blood HCO3 levels should always be checked at the same time relative to a dose, preferably a trough level, (i.e. before a given dose). That will eliminate the variations expected with continued renal excretion.

Once the serum level of 20 mEq/L is achieved, the need only be checked about every 3 months, while documenting possibly improved growth, so that at some point it can be determined that the medication is no longer required. When a subsequent HCO3 level is higher than expected (no dose increase having been made), the RTA has resolved, and treatment/follow-up for RTA may cease.
**Caveat:** Growth may improve, but often does not. However, an improvement in height is generally more impressive than weight gain. Children with this temporary disorder tend to burn more calories so weight gain is more nutritionally related. The most compelling reason to treat the acidosis has more to do with preventing renal rickets from increased need for buffer to come from the bones, hence the advisor to check venous blood gases to confirm the acidosis in order to justify the actual need for acidosis correction.

Since Type 2 RTA is expected to resolve with time, and in the absence of any other renal concerns, follow-up can be through the primary care provider’s office, but referral is always acceptable for problem cases and parental reassurance. If a type of RTA other than Type 2 is suspected after further discussion with nephrology, a referral is warranted.

**Hypertension**

Hypertension in children is frequently, but not exclusively, of renal origin. It is therefore anticipated in the setting of known renal parenchymal disease or scarring, but it may be incidental finding on routine physical examination in an otherwise normal child.

**NOTE:** Hypertension in the newborn will not be addressed here.

The average recorded systolic and diastolic blood pressures should be lower than the 90th percentile for age and sex. Careful measurement of blood pressure requires correct cuff size and reliable equipment. The cuff should be wide enough to cover two thirds of the upper arm and should encircle the arm completely without an overlap in the inflatable bladder. Although an anxious child may have an elevation in blood pressure, abnormal readings must not be too hastily attributed to this cause. However in an uncooperative child the measurements are not reliable.

Relevant initial clinical studies when considering nephrology referral for the otherwise well child with non emergent hypertension include a complete blood count, serum BUN, creatinine and electrolytes, serum renin and aldosterone levels, urinalysis, and renal ultrasound with Doppler flow studies. Ultrasonographic Doppler flow studies are used to reflect renovascular blood flow in determining the presence of renal artery stenosis, but further study with a renal magnetic resonance angiogram (MRA) may be needed if there remains continued question, largely driven by significant difficulty in achieving blood pressure control with medication.

If all the above tests are normal, it is not likely nephrology will recommend anything but continued treatment and monitoring. However, hypertension in the obese child should also be addressed with an attempt at weight reduction, and other “lifestyle” issues like caffeine and sodium ingestion or smoking, should be discussed as well. Treatment may be initiated prior to considering renal referral, after discussion with a nephrologist regarding drug choices, but the ACE-Inhibitor class of drug is frequently recommended, but the calcium channel blocker type of drug is also well tolerated.

**Caveat:** Emergent levels of blood pressure, or children with associated symptoms should either be considered for either direct hospitalization or prompt evaluation in an Emergency Department.

**Kidney Center overview**

The Kidney Center at Children’s Hospital Colorado in Aurora, Colorado is staffed by University of Colorado faculty pediatric nephrologists who see children with renal disease, including:

- Glomerular diseases (i.e. suspected by the presence of hematuria and/or proteinuria and/or renal insufficiency)
- Non-endocrine related electrolyte disorders (e.g. renal tubular acidosis, Bartter’s Syndrome, Gittleman’s Syndrome, pseudohypoaldosteronism)
- Metabolic kidney stone forming disease or predisposition (e.g. hypercalciuria, Hyperoxaluria or cystinuria)
- Hypertension
- Autosomal dominant or recessive polycystic kidney disease
- Chronic renal failure
- Need for dialysis
- Renal transplantation

The staff nephrologists welcome the sharing of patient care with their respective primary care provider (PCP), and depending on the clinical circumstances, many patients can be managed primarily by PCP follow with ongoing phone consultation with the Nephrology department.

Although a nephrologist will recommend a referral to the Kidney Center whenever advisable, a patient referral to the Kidney Center at any time remains at the discretion of the PCP, and of course may be at parental request to the PCP for reassurance.

When considering referral to nephrology, a copy of prior workup and results by PCP arriving in our hands prior to the visit is not only greatly appreciated, but also will make the initial visit more meaningful and gratifying for patient and family. This will also avoid unnecessary repetition of tests, as well as accommodate those patients whose circumstances require tests be done at places other than Children’s Hospital Colorado.

Urgent or emergent renal problems should be referred to an Emergency Department or considered for hospitalization.
Want to provide information to your patients and families? Tell them to visit childrenscolorado.org/kidney

**NOTE:** Urologic services are not available in the Kidney Center. Urology at Children’s Hospital Colorado in the Department of Pediatric Surgery should be contacted regarding disorders of the urinary tract per se such as hydronephrosis (concern for vesicoureteral reflux and/or urinary tract obstruction) and chronic urinary tract infection and/or dysfunctional voiding.

The Urology Department at Children’s Hospital Colorado can be reached at (720) 777-3926 or by email at urology.urology@childrenscolorado.org.

If such children also have renal insufficiency or hypertension as a result of any urinary tract abnormality, additional Nephrology referral is indicated to assist in the management of these problems.