Fluid and Electrolyte Metabolism/
Renal and Urologic Disorders

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Disclosures

- I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity.
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

• Evaluate and plan treatment for various etiologies of hyponatremia and their associated fluid and electrolyte abnormalities
• Distinguish between the causes of and initiate evaluation for glomerular and non-glomerular hematuria
• Interpret which markers of severity in the setting of acute glomerulonephritis warrant evaluation and treatment
• Review the causes of and management approaches for nephrotic syndrome and asymptomatic proteinuria in children
Major Concepts in Sodium Handling

• Why is the sodium low?**
  – Too much water
  – Too little salt

• What aids in this decision?**
  – Patient volume status clinically
    • Weight changes
  – Urine Na\(^+\) [Fractional Excretion of Na\(^+\) (FENa)]
  – Urine Osmolality
Major Concepts in Urine Na⁺ Evaluation

• Kidney preserves circulating volume with highest priority!
• $U_{Na^+}$ reflects renal perfusion** independent of Serum$_{Na^+}$:
  
  – Low $U_{Na^+}$ (<20 mEq/L) or Low FeNa (<1%)
    • Renal Perfusion is decreased**
  – High $U_{Na^+}$ (>50 mEq/L) or High FeNa (>2%)
    • Renal Perfusion is normal or increased
    • Defect in tubule reabsorption**
  – If $U_{Na^+}$ elevated in clinical circumstance when renal blood flow is expected to be decreased → suggests renal tubular dysfunction**
Major Concepts in Urine Osm Evaluation

- $U_{\text{OSM}}$ reflects $H_2O$ removal from tubule fluid**
  - When $U_{\text{OSM}}$ is high $\rightarrow$ water retained by body
  - When $U_{\text{OSM}}$ is low $\rightarrow$ water is being excreted in urine
  - Normal $U_{\text{OSM}}$ can range from 50-1200 mOsm/L
  - SG in urine $1.010 = U_{\text{OSM}}$ 300 mOsm/L
Major Concepts in Urine Osm Evaluation

• ADH secretion stimulated by
  – Increase serum osmolality ($S_{\text{OSM}}$)
  – Decrease circulating volume
  – ADH secretion results in increases in $U_{\text{OSM}}$ (any increase can be related to ADH secretion)
  – However, when $U_{\text{OSM}} > S_{\text{OSM}}$ by >1.5 X or more, the only way that can happen is by ADH acting on collecting duct

• If $U_{\text{OSM}}$ is increased without increased $S_{\text{OSM}}$ or decreased intravascular volume:
  – ADH secretion is non-physiologic (SIADH)—irrespective of urine output or urine volume**
Hyponatremia Case One

- 9 month old girl
- 3 days of fever, non-bilious, non-bloody vomiting, and watery diarrhea
- Decreasing urine output over past 2 days, only once in past 24 hours
- 3 lb weight loss since health maintenance visit 2 weeks ago. She has some tachycardia but is interactive, cranky but consolable by mother, good peripheral perfusion
Case One Labs**

- Na 127
- K 3.0
- Cl 100
- HCO3 16
- BUN 24
- Cr 0.3
Questions Case One

- What do you suspect the FENa and Urine Osmolality are?
Case One Urine Labs**

- Urine Na <10 mEq/L
- FENa <0.2%
- Urine Osm 800 mosm/L
- In this case and the others, use Serum Sodium to estimate calculated Serum Osmolality
  - unless the serum BUN or Glucose values given are elevated, in which case use the formula:
    - $2 \times Na + \frac{BUN}{2.8} + \frac{Glucose}{18} = \text{Calculated Serum Osm**}$
Questions Case One

• What is the diagnosis?**

• Does the patient seem to have more vomiting or diarrhea?**

• Explain the hypokalemia and how would you treat it?**
Hyponatremia Case Two

• The same 9 month old girl is given oral rehydration. Over next 24 hours, vomiting persists, intake is poor, and diarrhea is increasing. No urine output.

• Weight is further decreased. She has worse tachycardia. She is lethargic and doesn’t respond much to examination. Cap refill is now prolonged
Case Two Labs**

- Na 125
- K 6.5
- Cl 92
- HCO3 9
- BUN 45
- Cr 0.9
Questions Case Two

• What do you suspect the FENa and Urine Osmolality are?
Case Two Urine Labs

- Urine Na 60 mEq/L
- FENa 2.3 %
- Urine Osm 250 mosm/L
Questions Case Two

• The patient appears more volume depleted but based on urine sodium and FENa, the kidney thinks renal perfusion is adequate. What is causing this discrepancy?**

• Explain the low bicarbonate?**

• What management would you provide for the high potassium?**

• What do you think her GFR is?**
Hyponatremia Case Three

- Five year old male presents with periorbital edema, abdominal distension, and ankle swelling.
- He has a weight gain of 5 lb over the past 4 days.
- Notable in his history are a recent URI, and decreased urine output only 1-2 times per day.
- His HR is borderline tachycardia, Blood Pressure 92/54.
Case Three Labs**

- Na 128
- K 4.9
- Cl 90
- HCO3 26
- BUN 12
- Cr 0.5
Questions Case Three

• What do you think the child’s diagnosis is?**
• What do you suspect the FENa and Urine Osmolality are?**
• Why is hyponatremia associated with his condition?**
• How do you fix the hyponatremia?**
Hyponatremia Case Four

- 12 month old male with neuroblastoma receiving chemotherapy including cyclophosphamide
- He is prescribed 1 and ½ Maintenance fluid rate with ½ NS for 3 days
- He has no edema but a slight weight gain over this time, normal heart rate, blood pressure
Case Four Labs**

- Na 128
- K 3.6
- Cl 96
- HCO3 22
- BUN 5
- Cr 0.3
Questions Case Four

• What do you suspect the FENa and Urine Osmolality are?
Case Four Urine Labs**

- Urine Na 95 mEq/L
- FENa 2.1 %
- Urine Osm 780 mosm/L
Questions Case Four

• What is the child’s diagnosis is?**
• What will your management be?**
Hyponatremia Case Five

- 6 year old female develops polyuria and polydipsia
- Her weight is decreased and she has an increased respiratory rate
Case Five Labs**

- Na 128
- K 5.8
- Cl 94
- HCO3 10
- BUN 20
- Cr 0.7
- Glucose 450
Questions Case Five

• Why is the serum sodium low?**
### Various Etiologies of Hyponatremia**:

**Clinical Utilization of $U_{Na}$ and $U_{osm}$**

<table>
<thead>
<tr>
<th>Increased Weight</th>
<th>$U_{Na}$</th>
<th>$U_{osm}$</th>
<th>Decreased Weight</th>
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<tr>
<td>Hyypoalbuminemia</td>
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<td>Diabetes Insipidus</td>
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<td>Non-Physiologic ADH</td>
<td>&gt;50</td>
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<td>Osmotic Diuretics</td>
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Take Home Points for Practice

• The etiology of hyponatremia can be determined through assessment of clinical volume status, urine sodium excretion (FENa), & urine osmolality
• If the renal response to a suggested clinical volume state appears inappropriate, consider renal tubular pathology—tubular injury, tubular dysfunction, or inappropriate hormone secretion (e.g. SIADH)
• Treatment of low volume states respond well to volume and electrolyte repletion; treatment of excess volume states respond to management of underlying disorder (e.g. nephrotic syndrome) and thoughtful supportive restrictions (e.g. SIADH)
Hematuria Case 1

- 7 year old male presents with tea colored urine
- Otherwise well, no known trauma, URI symptoms 1 month ago, now better. +Headache, otherwise ROS negative
- PMHx—well managed Type 1 DM dx’d 4 years prior
- On Insulin, acetaminophen as needed
- Soc Hx, Fam Hx: non-contributory
- Exam
  - BP 150/80, vitals otherwise normal for age
  - 95% ht, 97% wt (mom noted weight is up 5 pounds from a week ago)
  - exam otherwise normal, fundi wnl, no edema, normal abdomen and lungs
What is the next step?
What is the next step?

• First, confirm true hematuria**--
  – Is U/A + for blood?
    • If U/A neg blood—ingestion (beets, med)
• Next confirm RBC in urine**
  – Is Microscopy + for RBCs?
  – If Microscopy neg for RBCs then think:
    • Myoglobinuria
    • Hemoglobinuria
    • Old specimen or other false positive
DDx Gross Hematuria in Children**

- **Glomerular (Kidney)**
  - Systemic signs/sx
  - Brown or black color
  - RBC casts, dysmorphic RBCs

- **Glomerulonephritis**
  - Post-Infectious
  - MPGN, SLE
  - IgA Nephropathy, HSP
  - HUS
  - Alport’s, Thin BM Dz

- **Non-Glomerular**
  - Localized signs/sx
  - Pink/red urine +/- clots
  - eumorphic RBCs

- **Tumors, Trauma**

- **Infection, Inflammation**

- **Cystic disease, Congenital anomaly, Crystalluria (Calciuria)**

- **Stones, Sickle cell**
Patient’s Urinalysis
Acute Glomerulonephritis

• What next?
What are clinical indicators of a severe glomerulonephritis?

- Acute kidney injury/elevated creatinine
- Hypertension
- Severe proteinuria, nephrotic range proteinuria, in particular nephrotic syndrome
- Why and how can glomerulonephritis cause nephrotic syndrome?
Recap on Podocytes and Glomerular Basement Membrane

• Podocytes
  – Help create the negatively charged slit diaphragm that prevents many serum proteins (e.g. albumin) from filtering across the glomerulus

• Minimal Change Disease is a result of podocytes that are no longer functioning (they are “effaced”)
  – Negative charge slit diaphragm is gone
  – Serum proteins (e.g. albumin) filter into the Bowman’s Space
Severe Glomerulonephritis

- When there is severe involvement of the basement membrane, then one might think of the podocytes as innocent bystanders
- Therefore, Nephrotic Syndrome is a manifestation of severe proteinuria and a marker for a severe glomerulonephritis (GN)
- If such a GN goes untreated, or does not resolve spontaneously (e.g. post-infectious), then this results in a poor long-term prognosis
Serology Interpretation

• Let’s say you get C3 and C4 and ASLO titer
• Results show a + ASLO titer, but C3 and C4 are normal

• What is your diagnostic interpretation?**

**
Back to Patient

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<th>108</th>
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<td>4.2</td>
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<td>0.5</td>
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- CBC normal
- ANA Neg, C3 very low, C4 normal, Post-strep titers positive
- Pr/Cr ratio 7.2!
What is your presumptive diagnosis?**

A. IgA Nephropathy
B. Alport Syndrome
C. Membranoproliferative GN
D. Post-Infectious GN
How could you confirm this?**

A. Monitoring for spontaneous resolution and return of C3 to normal over next 2-3 months
B. Response to empiric treatment with Corticosteroids
C. Renal Biopsy
But what about his Hypertension?**

A. Provide reassurance. If this is post-strep GN, it will get better on its own so it does not require treatment

B. It is severely elevated for a 7 yo so warrants treatment with a low sodium diet and an ACE Inhibitor until the GN resolves

C. It is severely elevated for a 7 yo, so warrants treatment with a low sodium diet and thiazide diuretic until the GN resolves
Why did he gain weight?**

A. With his acute GN and HTN he was more sedentary, so this is increased body fat

B. With his acute GN, his GFR may be decreased so this is likely fluid weight from renal failure

C. With his acute GN, renin is stimulated and his nephrons are likely reabsorbing salt and water so this is fluid weight

D. With his acute GN and being sick, he probably actually lost weight, so this is measurement error
Hematuria Case 2

- 6 yo male presents with pinkish-red colored urine
- Otherwise well, no known trauma, no recent medications, in school but no obvious illness, ROS completely negative
- PMHx, Soc Hx, Fam Hx all Non-Contributory
- Exam
  - normal BP and vitals, 50% ht and wt
  - Exam otherwise completely normal
Next Step

Urine dip and microscopy to confirm whether this is hematuria? Glomerular vs. Non-glomerular?**

Patient’s results: U/A + blood, trace protein Many eumorphic RBC, no casts
How would you evaluate at this point?
How would you evaluate at this point?**

• DDx of non-glomerular hematuria**
  – Urine Ca/Cr and Renal U/S
    • If either positive for stones, consider 24 hour urine for stone chemistries
  – Any symptoms/signs of infection? If so, Urine Cx
  – Could consider Lytes BUN, Cr, CBC, Pr/Cr—if still need to be certain to exclude a GN etiology
Results

- Ca/Cr 0.47 (Nml <0.2)
- Renal U/S neg, other screens normal

- 3 months later—presents with flank pain and passes stone!
Hypercalciuria

- **Why care?**
  - Presence of hematuria worrisome to parents
  - Risk for stones** — VERY PAINFUL!!!
  - Can be associated with nephrocalcinosis**
    - deposits of calcium within tubulointerstitial parenchyma
    - can cause progressive scarring and loss of function

- **Who develops?**
  - Idiopathic (probably multifactorial—genetics, diet, etc...)
  - Certain ‘tubulopathies’ (e.g. Dent’s disease, Bartter’s syndrome)
  - Medication induced
When Infants and children develop stones
  – Stone is not the disease. It’s a sign of the disease

Every child with kidney stones or nephrocalcinosis should have a thorough evaluation as to the cause**
  – H&P into systemic disorders
    • Growth and development, blood pressure, bone related signs/symptoms
    • Dietary history (attention to excess or deficiency), fluid intake, meds including vitamins and supplements
  – Fam Hx of stones, hematuria, renal failure
  – Urinalysis, urine and serum chemistries, imaging
  – STONE analysis (send the stone for chemical analysis)
Clinical Constellation of Childhood Kidney Stones*

- Acute Flank Pain not the rule, though is the presenting finding in majority
- Often difficult to diagnose in infants and young children**
  - nonspecific discomfort, may be in abdomen or hip
- Hematuria-microscopic or macroscopic
  - Stones or crystalluria (eg hypercalciuria) or nephrocalcinosis
- Dysuria and frequency (bladder irritation)
Causes/Risks of Stones in Children**

- **Calcium Oxalate**—radioopaque—50-70%
  - Risks are hypercalciuria, hyperoxaluria, and/or hypocitraturia
- **Calcium Phosphate**—radioopaque –15-30%
  - Form in alkaline urine, common in children with metabolic bone disease or immobilization
- **Struvite**—radioopaque –15%
  - Form in alkaline urine, associated with urinary tract infection with urease producing organisms
- **Cystine**—radioopaque—5%
  - Form in acidic urine, hereditary proximal tubule transporter defect
- **Uric Acid**—5%
  - Radiolucent and form in acidic urine
- **Other**—5%
How do you treat idiopathic (most common form) hypercalciuria (and prevent nephrolithiasis)?**

A. Drink lots of fluids to make a dilute urine  
B. Low Sodium Diet  
C. High Citrate Diet  
D. Thiazide Diuretic
Hematuria Case 3

• 14 year old Caucasian boy presents with maroon urine
• He is otherwise healthy, playing touch football with friends earlier that day. Denies obvious trauma or rough tackle.
• ROS otherwise NEG
• Soc Hx – Athlete, starting 9th grade, doing well, no substance use, not sexually active
• Fam Hx—Mother with hypertension
• Exam—HR 60; BP 138/84; tall and thin, athletic build; otherwise completely normal, no abd masses or tenderness, no edema
Next step--Urinalysis

• 1.025, pH 6, trace protein, large blood, many dysmorphic RBCs/hpf, no casts
Discuss the top three diagnoses on your differential**
What would your evaluation be?**
Evaluation**

- Urine Calcium/Cr normal
- Basic Metabolic Panel normal
- Renal Ultrasound reveals b/l enlarged kidneys with multiple cysts

- Diagnosis—Presumed Autosomal Dominant Polycystic Kidney Disease (ADPKD)
ADPKD in children**

• A significant minority of cases of ADPKD present in childhood**
  – Occasionally on prenatal imaging, especially with known family history
  – More commonly with acute onset gross hematuria (often in setting of trauma or exertion)
  – Hypertension is a common presentation

• Asymptomatic screening of children of parents with ADPKD is not currently recommended**
  – Screening of these children’s Blood Pressure and a urinalysis for protein at health maintenance is generally recommended
  – Presence of hypertension and/or proteinuria are associated with progression of chronic kidney disease, and can be treated to delay progression**
Name three things you might do as far as clinical management**
ADPKD Management**

- Strict Blood Pressure Control using RAAS inhibition—target <120/80 has illustrated slower decline of renal function
- Control of proteinuria with RAAS inhibition—similarly, this delays progression of CKD and may prevent future development of ESRD
- If kidneys >15cm— may need to restrict from high impact sports/activities (risk of trauma and cyst rupture—massive bleeding)
- High Fluid intake-- ADH is associated with cyst growth, so suppressing ADH with super-hydration may slow progression
- Patient Education and connections with resources/networks
Hematuria Case 4

- 16 yo female with diarrheal illness x 2 weeks presents with brown colored urine
- No recent travel or new foods, no emesis, but crampy abd pain results in decreased intake
- At first thought urine was just super-concentrated, but now dark brown
- Medications—took some Cipro after 1 week of illness, acetaminophen and ibuprofen prn pain
- PMHx healthy, Soc Hx non-contrib, Fam Hx notable for Grave’s Disease
- Exam
  - BP normal, vitals normal, Ht 50%, Wt 10%
  - Otherwise completely normal, no edema, mild non-specific diffuse abd tenderness
Next step

- Real hematuria? Upper vs. Lower?**
  - U/A + blood, 2+ protein, MANY RBC Casts (very impressive)
- What is your DDx Acute GN** (of note—also w/diarrheal illness and abd pain!)
Results of evaluation...

- Chems WNL
- CBC WNL
  - No HUS
- Pr/Cr ratio 0.9
- ANA, Strep-titers, ANCAss all NEG
  - No SLE, PAN
- C3 borderline, C4 WNL
  - Unlikely PIGN or MPGN
Hmm..

• Diagnosed with C. Diff Colitis
  – Treated with Flagyl and her diarrhea & abd pain resolved within 1-2 weeks
  – Never developed purpura or arthritis (no HSP)
  – Hematuria and proteinuria resolved
  – C3 completely normal 2 months later

• IgA Nephropathy? PIGN (can occur with chronic infections)
  – What to do?
  – What’s the treatment for IgA Nephropathy?
Answers

• Watchful waiting—she’s in spontaneous remission
  – If she relapses again with another GI illness or Resp illness, then likely IgA Nephropathy**
  – If never happens again, then likely PIGN**
• Only proven treatment for IgA Nephropathy is ACE-Inhibitor to relax glomerular capillary bed/decrease filtration pressure and prevent scarring
  – Fish Oil has a promising study, but not confirmed
  – For severe clinical presentations, steroids +/- other immunosuppressants
    • Some subjective experience, but no RCT yet to show benefit
Proteinuria Case 1

- 4 yo girl presents with eye swelling
- Pediatrician first thought allergies, tried anti-histamine, but it’s getting worse and now with abd distension and anasarca. She is active, has good appetite, no nausea/vomiting/diarrhea/fever, no hematuria or dysuria, +URI last week, now resolved
- PMHx eczema, Meds anti-histamine and topical moisturizer
- SocHx, FamHx Non-contributory
- Exam
  - Vitals Nml, Weight 90%, Height 50%, BP normal
  - Exam –Anasarca

- Can a Diagnosis of Nephrotic Syndrome be made?**
What’s missing?**

• Urinalysis
  – 1.030, moderate blood, 4+ Protein
  – Microscopy 10-20 RBCs, no RBC casts
• Serum Albumin—1.2
• Cholesterol elevated
• Now – we can confirm diagnosis of nephrotic syndrome**
  – Edema, Nephrotic range proteinuria, hypoalbuminemia, elevated cholesterol
DDx Nephrotic Syndrome in Children**

- **Primary Nephropathy**
  - Minimal Change Disease**—by far the most common, especially in young children
  - Focal Segmental Glomerulosclerosis (FSGS)
  - Membranous Nephropathy
- **Secondary Nephropathy (systemic illness causing nephrotic syndrome)**
  - Systemic Lupus Erythematosus
  - Hepatitis associated nephropathy
  - HIV associated nephropathy
- **Glomerulonephritis (severe GN complicated by nephrotic syndrome)**
- **Hereditary causes**
Case 1—What Next??

A. Renal Biopsy is needed to confirm Minimal Change before treating

B. Wait 2-4 weeks before treating to see if it spontaneously resolves

C. Begin empiric treatment with Corticosteroids and suspect Minimal Change if there is a good treatment response
Answer

• Minimal Change Disease is the predominant cause
  – If everything consistent with minimal change (e.g. age, not a glomerulonephritis), can make presumptive diagnosis based on treatment response**
    • Age under 1 year suggests higher possibility of alternate causes (like hereditary causes)
    • Age above 10 years or so with broader differential (increasing likelihood for FSGS or in teenage years, Membranous Nephropathy)

• If anything presents atypically, or fails to respond to treatment, then further evaluation may be necessary, often including biopsy necessary
Minimal Change Disease

• Presumptive treatment, 2mg/kg or 60mg Prednisone Daily**
  – Usual response in 2-4 weeks, small number may take longer
  – Treat intercurrent infections/triggers
• Majority recur**
  – Significant minority one and done (up to 40%)
  – Others may develop frequent relapsing or steroid dependent nephrotic syndrome and require steroid-sparing therapy (e.g. cyclophosphamide)
  – If develops steroid resistance—reconsider other etiologies (e.g. FSGS)
• Consistent treatment response suggests an ultimately good prognosis, even if having recurrences**
Nephrotic Syndrome—Which of the following are other considerations?**

A. Low Sodium Diet
B. Albumin—Furosemide Infusion
C. Infectious concerns
D. Hypercoagulopathy
• All of them!
• Low Sodium Diet is helpful—high sodium intake results in worsening edema (fills interstitial volume)**
• When fluid overload/edema is causing symptoms (resp distress) or complications, albumin-furosemide infusions can help mobilize edema**
  – If this is needed, should be done at center with experience with this treatment approach
  – Acute intravascular mobilization of this edema can lead to pulmonary edema, and risk for respiratory failure or congestive heart failure
Answer

• Nephrotic syndrome is associated with an increased risk for infection**
  – Loss of IgG in urine—hypogammaglobulinemia
  – Fluid can get infected, in particular, cellulitis and Strep pneumo peritonitis or pneumonia

• Nephrotic syndrome is associated with a hypercoaguable state and at increased risk for venous thrombosis**
  (especially with membranous nephropathy)
  – Loss of pro-coagulants and anti-coagulants in urine but balance of these losses in a hypercoaguable state
Proteinuria Case 2

• 15 year old girl presents with asymptomatic proteinuria identified at sports physical (volleyball)
• PMHx negative, Meds/Supps/Drugs denies, SHx, FHx NC
• ROS completely neg
  – No hematuria, no dysuria, no abd pain, no cvat, no h/a, no fever
• Exam
  – Vitals Normal, normal BP, Ht 90%, Wt 50%
  – Otherwise 100% neg, no edema
  – U/A—1.025, 2+ Protein, otherwise negative
What to do next?
What to do next?**

• Quantitate proteinuria and assess positional pattern**

• If anything concerning then further evaluation needed

• The following would be concerning for more significant pathology:
  – >1gram/day (or Pr/Cr >1.0)
  – No orthostatic variation
  – Elevated blood pressure
  – Elevated serum creatinine (if measured)
DDx Proteinuria in Children**

• Benign
  – False positive (concentrated specimen)
  – Recent exercise, dehydration, physical stress
  – Orthostatic (benign positional) proteinuria
    • Classic is tall adolescent or 20-something

• Pathologic
  – FSGS, Membranous GN
  – SLE, Hepatitis Infection of HIV associated
  – Diabetic Nephropathy may start with asymptomatic proteinuria even in teens
  – Glomerulonephritis
  – Hereditary
Case 2 cont’d

- First morning Pr/Cr 0.16; afternoon Pr/Cr 0.76
  - Normal orthostatic pattern
- Treatment: Reassurance
- Cont to monitor for progression/worsening for a few years**
  - rarely asymptomatic proteinuria, even with reassuring initial eval, can be an early presentation of a pathologic lesion (e.g. FSGS)
Take Home Points for Practice

• Gross Hematuria may be a manifestation of
  – Glomerulonephritis, presenting with RBC casts, hypertension, and proteinuria or
  – Non-glomerular causes such as infection, hypercalciuria or congenital or acquired structural anomalies (stones, cysts, urinary tract dilation), presenting with urinary and/or abdominal/flank symptoms

• Elevated serum creatinine, hypertension, and nephrotic syndrome are clinical indicators of severity for an acute glomerulonephritis and warrant evaluation and treatment

• Nephrotic syndrome due to minimal change disease is most often responsive to steroids and has an excellent long-term prognosis, but is associated with serious complications requiring vigilence and support
Suggested Reading


NARRATIVES ARE PROVIDED AS A REFERENCE FOR THE CASE PRESENTATION SESSIONS.

IN ORDER FOR YOU TO ACHIEVE THE MOST BENEFIT FROM THESE SESSIONS, WE ASK THAT YOU DO NOT REFER TO THE NARRATIVES PRIOR TO ATTENDING THE CASE PRESENTATION SESSIONS.
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Renal and Urologic Disorders

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  - If $U_{Na⁺}$ elevated in clinical circumstance when renal blood flow is expected to be decreased $\rightarrow$ suggests renal tubular dysfunction**
Major Concepts in Urine Osm Evaluation

- $U_{OSM}$ reflects $H_2O$ removal from tubule fluid**
  - When $U_{OSM}$ is high $\Rightarrow$ water retained by body
  - When $U_{OSM}$ is low $\Rightarrow$ water is being excreted in urine
  - Normal $U_{OSM}$ can range from 50-1200 mOsm/L
  - SG in urine $1.010 = U_{OSM} 300$ mOsm/L
Major Concepts in Urine Osm Evaluation

• ADH secretion stimulated by
  – Increase serum osmolality ($S_{OSM}$)
  – Decrease circulating volume
  – ADH secretion results in increases in $U_{OSM}$ (any increase can be related to ADH secretion)
  – However, when $U_{OSM} > S_{OSM}$ by $>1.5 \times$ or more, the only way that can happen is by ADH acting on collecting duct
• If $U_{OSM}$ is increased without increased $S_{OSM}$ or decreased intravascular volume:
  – ADH secretion is non-physiologic (SIADH)—irrespective of urine output or urine volume**
Case One

• 9 month old girl
• 3 days of fever, non-bilious, non-bloody vomiting, and watery diarrhea
• Decreasing urine output over past 2 days, only once in past 24 hours
• 3 lb weight loss since health maintenance visit 2 weeks ago. She has some tachycardia but is interactive, cranky but consolable by mother, good peripheral perfusion
Case One Labs**

- Na 127
- K 3.0
- Cl 100
- HCO3 16
- BUN 24
- Cr 0.3
Questions Case One

• What do you suspect the FENa and Urine Osmolality are?
Case One Urine Labs**

- Urine Na <10 mEq/L
- FENa <0.2%
- Urine Osm 800 mosm/L
- In this case and the others, use Serum Sodium to estimate calculated Serum Osmolality
  - unless the serum BUN or Glucose values given are elevated, in which case use the formula:
    - $2 \times \text{Na} + \text{BUN}/2.8 + \text{Glucose}/18 = \text{Calculated Serum Osm}**$
Questions Case One

• What is the diagnosis?**

• Does the patient seem to have more vomiting or diarrhea?**

• Explain the hypokalemia and how would you treat it?**
Answers Case One

• Hyponatremic Dehydration**
  – the infant must have been getting hypotonic oral solution (juice, water, even pedialyte) as a treatment

• She has more diarrhea at this point, based on the normal anion gap (11) metabolic acidosis**
  – if vomiting were predominant, would expect a metabolic alkalosis**
Answers Case One

• The hypokalemia is in part from GI losses, but even more so, in the setting of volume depletion aldosterone is stimulated and causes high urinary excretion**
  – As she is rehydrated, her potassium may get lower as renal perfusion increases and acidosis is corrected**
    • High levels of H+ causes K to shift extracellular to allow H+ to move intracellular and reduce the acidemia
    • So as acidosis is corrected, K will shift back intracellularly, and serum K will drop
Repleting her potassium is particularly important to prevent symptoms such as weakness, paralysis, and arrhythmia.**

- Most safe and effective would be IV rehydration with NS solution with KCl (20 to 40 mEq/L) added in continuously
- If she were having symptoms from hypokalemia, then can give as IV K bolus– but important to be judicious and avoid prescribing K bolus except when absolutely needed due to serious complications from inadvertent hyperkalemia
Case Two

• The same 9 month old girl is given oral rehydration. Over next 24 hours, vomiting persists, intake is poor, and diarrhea is increasing. No urine output.

• Weight is further decreased. She has worse tachycardia. She is lethargic and doesn’t respond much to examination. Cap refill is now prolonged
Case Two Labs**

- Na 125
- K 6.5
- Cl 92
- HCO3 9
- BUN 45
- Cr 0.9
Questions Case Two

• What do you suspect the FENa and Urine Osmolality are?
Case Two Urine Labs**

- Urine Na 60 mEq/L
- FENa 2.3 %
- Urine Osm 250 mosm/L
Questions Case Two

• The patient appears more volume depleted but based on urine sodium and FENa, the kidney thinks renal perfusion is adequate. What is causing this discrepancy?**

• Explain the low bicarbonate?**

• What management would you provide for the high potassium?**

• What do you think her GFR is?**
Answers Case Two

• She now has had such significant volume loss, her organ perfusion has suffered including perfusion to her kidney.**
  – She is in shock from fluid depletion**
  – This has resulted in intrinsic acute kidney injury due to acute tubular necrosis (ischemic injury)
  – Her renal tubules therefore, are no longer functioning or responsive
  – She needs immediate and aggressive iso-osmolar fluid resuscitation and if not immediately responsive, pressors**
# Differential Diagnosis of Acute Kidney Injury in Children**

<table>
<thead>
<tr>
<th>Inflow to Kidney (Circulating Volume)</th>
<th>Intrinsic to Kidney</th>
<th>Outflow from Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume depletion</td>
<td>Acute Tubular Necrosis (ischemic, toxic**—e.g. aminoglycosides)</td>
<td>Bladder Outlet Obstruction</td>
</tr>
<tr>
<td>Shock</td>
<td>Acute Interstitial Nephritis</td>
<td>B/L ureteral obstruction (or of solitary kidney)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>Tumor Lysis Syndrome</td>
<td>Renal Vein Thrombosis (b/l or in solitary kidney)</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>Hemolytic Uremic Syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute Glomerulonephritis (rapidly progressive GNs)</td>
<td></td>
</tr>
</tbody>
</table>
# Diagnostic Evaluation of Acute Kidney Injury in Children**

<table>
<thead>
<tr>
<th>Inflow to Kidney (Circulating Volume)</th>
<th>Intrinsic to Kidney</th>
<th>Outflow from Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment of hydration</td>
<td>Urinalysis with microscopy</td>
<td>Renal /Bladder Ultrasound</td>
</tr>
<tr>
<td>Urine Na, FENa (expect low)</td>
<td>Urine Na, FENa (expect elevated)</td>
<td>If applicable, Renal Venous Dopplers</td>
</tr>
<tr>
<td>Lytes, BUN, Cr, Serum Albumin</td>
<td>Lytes, BUN, Cr, Ca, Phos, Uric Acid</td>
<td></td>
</tr>
<tr>
<td>If applicable, assess heart, liver function</td>
<td>If applicable, renal biopsy</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** If applicable, also assess heart, liver function.
Answers Case Two

• Her bicarbonate level is lower suggesting worsened metabolic acidosis. Note that the anion gap is now elevated $(125 - (92 + 9) = 24^*)$
  – Given her volume depletion and poor perfusion this now represents and anion gap metabolic acidosis, likely from lactic acidosis**
  – With correction of her perfusion, then, this should improve
Answers Case Two

• Her potassium is now elevated, likely because of impaired renal excretion from low perfusion and tubular injury**
  – Hopefully correction of her perfusion will correct some tubular function and improve potassium excretion
  – If her kidney injury persists despite that, then additional measures are needed to prevent hyperkalemia complications (EKG changes ➔ fatal arrhythmia)**
    • IV Calcium to stabilize the cardiac myocytes
    • Albuterol (Beta-agonist), Insulin + Glucose, and/or Bicarbonate can all help K shift intracellularly
    • Means for excretion—renal excretion (if responsive to improved perfusion), GI excretion through Na-K resins, and/or dialysis
Answers Case Two

• Her GFR is currently ZERO**
  – In acute kidney injury, the GFR is based on the rate of rise of creatinine**
  – The creatinine level depends on its rate of production and rate of excretion. If rate of excretion (GFR) is ZERO, then its rate of rise will equal rate of production
  – In any infant, rate of production is about 0.5 mEq/L per day; in a young child, 1.0 mEq/L per day; in an adult 1.5-2.0 mEq/L per day
Case Three

- Five year old male presents with periorbital edema, abdominal distension, and ankle swelling
- He has a weight gain of 5 lb over the past 4 days
- Notable in his history are a recent URI, and decreased urine output only 1-2 times per day.
- His HR is borderline tachycardia, Blood Pressure 92/54
Case Three Labs**

- Na 128
- K 4.9
- Cl 90
- HCO3 26
- BUN 12
- Cr 0.5
Questions Case Three

• What do you think the child’s diagnosis is?**
• What do you suspect the FENa and Urine Osmolality are?**
• Why is hyponatremia associated with his condition?**
• How do you fix the hyponatremia?**
Answers Case Three

• He has nephrotic syndrome, likely minimal change disease. This can be confirmed by checking a urine protein level, and diagnostically with a serum albumin and total cholesterol**

• Circulating volume is low in hypoalbuminemia,** so his urine sodium came back as expected, <20 mEq/L and FENA <1%; urine osms 560 mosm/L
Answers Case Three

- In nephrotic syndrome (or any condition with hypoalbuminemia), circulating volume is decreased as there is less oncotic pressure to maintain volume in the plasma volume and it moves instead to the interstitial volume.**
  - This low circulating volume is a physiologic stimulus for ADH**
  - ADH causes free water retention and a concentrated urine. So children with nephrotic syndrome can retain free water and develop hyponatremia**
Answers Case Three

• Giving saline as crystalloid will result in worsening edema and minimal improvement in serum sodium concentration**
  – Instead, treatment must be to correct the hypoalbuminemia**
  – Ultimately this will correct with treatment of the underlying condition, childhood nephrotic syndrome, with corticosteroids
  – If there is a pressing need for correction before the corticosteroids take effect, this can be done with IV Albumin infusion (often done in coordination with furosemide as the albumin will only have a transient effect if not excreted promptly may worsen fluid retention)
Case Four

• 12 month old male with neuroblastoma receiving chemotherapy including cyclophosphamide
• He is prescribed 1 and ½ Maintenance fluid rate with ½ NS for 3 days
• He has no edema but a slight weight gain over this time, normal heart rate, blood pressure
Case Four Labs**

- Na 128
- K 3.6
- Cl 96
- HCO3 22
- BUN 5
- Cr 0.3
Questions Case Four

- What do you suspect the FENa and Urine Osmolality are?
Case Four Urine Labs**

- Urine Na 95 mEq/L
- FENa 2.1 %
- Urine Osm 780 mosm/L
Questions Case Four

• What is the child’s diagnosis?**
• What will your management be?**
Answers Case Four

• This child has SIADH**
• He has no physiologic stimuli for ADH secretion**
  – He has normal circulating volume and no increase in serum osmolality
  – Yet he has a concentrated urine, which means ADH is present and active
  – With no physiologic stimuli, this indicates inappropriate ADH secretion.
Answers Case Four

- Treatment is restriction of free water intake**
- Giving extra isotonic sodium chloride may actually make matters worse
  - The kidney senses replete circulating volume so will excrete (not reabsorb) the sodium
  - Because of the inappropriate ADH, the kidney will retain the fluid (water) in the saline even so
  - Therefore giving fluids at a brisk rate (rather than a restricted rate), even isotonic fluids, will make matters worse
Conditions Associated with SIADH**

- CNS Disease—stroke, hemorrhage, infection, trauma
- Certain malignancies (mostly adult ones like lung cancer), but neuroblastoma can cause it
- Medications—carbamazepine, cyclophosphamide, SSRIs, and many others
- Surgery/Trauma
- Pulmonary Disease, in particular infection
- Pain, Vomiting, Stress Response
- Pregnancy
Case Five

• 6 year old female develops polyuria and polydipsia
• Her weight is decreased and she has an increased respiratory rate
Case Five Labs**

- Na 128
- K 5.8
- Cl 94
- HCO3 10
- BUN 20
- Cr 0.7
- Glucose 450
Questions Case Five

• Why is the serum sodium low?**
• This is a case of dilutional hyponatremia**
• In the setting sodium-independent hyperosmolality (e.g. from hyperglycemia) the serum sodium will be “diluted” by water as it moves out of cells to the extracellular volume**
• This differs from actual total body sodium depletion**
  – In dilutional hyponatremia, as the cause of the hyperosmolality is corrected, the serum sodium concentration will also normalize
• In diabetic ketoacidosis, there can also be total body sodium depletion
  – The osmotic diuresis (from the glycosuria) induces higher renal excretion of sodium
Various Etiologies of Hyponatremia**:
Clinical Utilization of U\textsubscript{Na} and U\textsubscript{osm}

<table>
<thead>
<tr>
<th>Increased Weight</th>
<th>U\textsubscript{Na}</th>
<th>U\textsubscript{OSM}</th>
<th>Decreased Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoalbuminemia</td>
<td>&lt;10</td>
<td>&gt;500</td>
<td>Dehydration/Volume Depletion</td>
</tr>
<tr>
<td>Nephrosis/Cirrhosis</td>
<td></td>
<td></td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>AGN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Volume expansion</td>
<td>&gt;10</td>
<td>&lt;300</td>
<td></td>
</tr>
<tr>
<td>Water intoxication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excess IV Fluids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>&gt;50</td>
<td>&lt;=300</td>
<td>Adrenal Insufficiency</td>
</tr>
<tr>
<td>Sepsis, Shock, Nephrotoxin</td>
<td></td>
<td></td>
<td>Salt losing Nephropathy</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Interstitial Nephritis/ Cystic Disease/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urinary Tract Obstruction</td>
</tr>
<tr>
<td>Non-Physiologic ADH</td>
<td>&gt;50</td>
<td>&gt;500</td>
<td>DKA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Osmotic Diuretics</td>
</tr>
</tbody>
</table>
Take Home Points for Practice

• The etiology of hyponatremia can be determined through assessment of clinical volume status, urine sodium excretion (FENa), & urine osmolality

• If the renal response to a suggested clinical volume state appears inappropriate, consider renal tubular pathology—tubular injury, tubular dysfunction, or inappropriate hormone secretion (e.g. SIADH)

• Treatment of low volume states respond well to volume and electrolyte repletion; treatment of excess volume states respond to management of underlying disorder (e.g. nephrotic syndrome) and thoughtful supportive restrictions (e.g. SIADH)
Case 1

- 7 year old male presents with tea colored urine
- Otherwise well, no known trauma, URI symptoms 1 month ago, now better. +Headache, otherwise ROS negative
- PMHx—well managed Type 1 DM dx’d 4 years prior
- On Insulin, acetaminophen as needed
- Soc Hx, Fam Hx: non-contributory
- Exam
  - BP 150/80, vitals otherwise normal for age
  - 95% ht, 97% wt (mom noted weight is up 5 pounds from a week ago)
  - exam otherwise normal, fundi wnl, no edema, normal abdomen and lungs
What is the next step?
What is the next step?

- First, confirm true hematuria**--
  - Is U/A + for blood?
    - If U/A neg blood—ingestion (beets, med)
- Next confirm RBC in urine**
  - Is Microscopy + for RBCs?
  - If Microscopy neg for RBCs then think:
    - Myoglobinuria
    - Hemoglobinuria
    - Old specimen or other false positive
### DDx Gross Hematuria in Children**

<table>
<thead>
<tr>
<th>Glomerular (Kidney)</th>
<th>Non-Glomerular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic signs/sx</td>
<td>Localized signs/sx</td>
</tr>
<tr>
<td>Brown or black color</td>
<td>Pink/red urine +/- clots</td>
</tr>
<tr>
<td>RBC casts, dysmorphic RBCs</td>
<td>eumorphic RBCs</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>Tumors, Trauma</td>
</tr>
<tr>
<td>Post-Infectious</td>
<td>Infection, Inflammation</td>
</tr>
<tr>
<td>MPGN, SLE</td>
<td>Cystic disease, Congenital anomaly, Crystalluria</td>
</tr>
<tr>
<td>IgA Nephropathy, HSP</td>
<td>(Calciuria)</td>
</tr>
<tr>
<td>HUS</td>
<td>Stones, Sickle cell</td>
</tr>
<tr>
<td>Alport’s, Thin BM Dz</td>
<td></td>
</tr>
</tbody>
</table>
Patient’s Urinalysis
Acute Glomerulonephritis

- What next?
Answer

• Should include evaluation of Severity**
  – Lytes, BUN, Cr
  – Quantitate proteinuria
  – Blood Pressure

• Should include evaluation of Etiology**
  – CBC, Strep titers, ANA, C3, C4, ANCA, and/or anti-GBM titers, etc...each should be considered based on clinical context
  • In this case, perhaps CBC, Strep titers, C3, C4
  – Renal Ultrasound if not straightforward and you still need to consider non-glomerular etiologies
What are clinical indicators of a severe glomerulonephritis?

• Acute kidney injury/elevated creatinine
• Hypertension
• Severe proteinuria, nephrotic range proteinuria, in particular nephrotic syndrome
• Why and how can glomerulonephritis cause nephrotic syndrome?
Recap on Podocytes and Glomerular Basement Membrane

• Podocytes
  – Help create the negatively charged slit diaphragm that prevents many serum proteins (e.g. albumin) from filtering across the glomerulus
• Minimal Change Disease is a result of podocytes that are no longer functioning (they are “effaced”)
  – Negative charge slit diaphragm is gone
  – Serum proteins (e.g. albumin) filter into the Bowman’s Space
Severe Glomerulonephritis

- When there is severe involvement of the basement membrane, then one might think of the podocytes as innocent bystanders.
- Therefore, Nephrotic Syndrome is a manifestation of severe proteinuria and a marker for a severe glomerulonephritis (GN).
- If such a GN goes untreated, or does not resolve spontaneously (e.g. post-infectious), then this results in a poor long-term prognosis.
Serology Interpretation

• Let’s say you get C3 and C4 and ASLO titer
• Results show a + ASLO titer, but C3 and C4 are normal

• What is your diagnostic interpretation?**
Answer

• Should state that the normal C3 and C4 makes this less likely to be post-strep or post-infectious GN.
• The positive strep titers likely represents past strep associated illness (anytime over prior 6-12 months), but not necessarily resulting in post-infectious GN.
• More likely another cause, like IgA Nephropathy, for example...
Back to Patient

- CBC normal
- ANA Neg, C3 very low, C4 normal, Post-strep titers positive
- Pr/Cr ratio 7.2!
What is your presumptive diagnosis?**

A. IgA Nephropathy
B. Alport Syndrome
C. Membranoproliferative GN
D. Post-Infectious GN
What is your presumptive diagnosis?

D. Post-Infectious GN (PIGN/PSGN)**
• Low C3, + Post-Strep titers, and acute presentation are all consistent with PIGN**
• As this is also a common etiology, based on the above, can make a presumptive diagnosis of Post-Infectious GN
• IgA Nephropathy and Alport Syndrome are not associated with a low C3**
• IgA Nephropathy occurs concurrent with a resp infection, not afterwards**
• MPGN is associated with a low C3, but is significantly less common than PIGN
How could you confirm this?**

A. Monitoring for spontaneous resolution and return of C3 to normal over next 2-3 months
B. Response to empiric treatment with Corticosteroids
C. Renal Biopsy
How could you confirm this?

A. Monitoring for spontaneous resolution and return of C3 to normal over next 2-3 months**

- Should expect full resolution of PIGN over coming months
- Often gross hematuria resolves over 1-2 weeks, and hypertension and proteinuria gradually resolve over a few weeks to months as well
- If no resolution after 2-3 months, then may need to consider alternate etiologies
How could you confirm this?

- PIGN is treated with supportive measures**; corticosteroids have not been shown to help it resolve faster or prevent complications
- Most PIGN resolves completely, but longitudinal follow-up may illustrate higher risks for hypertension and proteinuria again as adults
  - Not from recurrence, rather from chronic impacts on glomeruli number and filtration pressures
  - Even so, these effects are uncommon, generally not during childhood, and prognosis is generally excellent
How could you confirm this?

• If no improvement over 2-3 months,** then may have to consider alternative etiologies (like MPGN) and would confirm this via renal biopsy
• At present time, given likelihood of PIGN, a renal biopsy is not necessary
• However, in the setting of AKI, and risk for a rapidly progressive course, a renal biopsy would be done to confirm a PIGN etiology (rather than MPGN, which would require different treatment)
But what about his Hypertension?**

A. Provide reassurance. If this is post-strep GN, it will get better on its own so it does not require treatment

B. It is severely elevated for a 7 yo so warrants treatment with a low sodium diet and an ACE Inhibitor until the GN resolves

C. It is severely elevated for a 7 yo, so warrants treatment with a low sodium diet and thiazide diuretic until the GN resolves
But what about his Hypertension?

- His BP elevation is severe (Stage 2 hypertension) and his symptoms of headache may suggest it is symptomatic.
- Even though PIGN is self-limited, associated hypertension can be severe and result in acute complications like hypertensive encephalopathy**
- Therefore BP elevation is typically treated**
  - Either an ACE-Inhibitor or a diuretic may be good first line choice
  - However if there is an elevated creatinine an ACE-Inhibitor would be contra-indicated
  - ACE-Inhibitors through their effect on glomerular hemodynamics may increase the creatinine even further
Why did he gain weight?**

A. With his acute GN and HTN he was more sedentary, so this is increased body fat
B. With his acute GN, his GFR may be decreased so this is likely fluid weight from renal failure
C. With his acute GN, renin is stimulated and his nephrons are likely reabsorbing salt and water so this is fluid weight
D. With his acute GN and being sick, he probably actually lost weight, so this is measurement error
Why did he gain weight?

A. With his acute GN, renin is stimulated and his nephrons are likely reabsorbing salt and water so this is fluid weight**

• Choice B is not correct in this case because his creatinine and GFR are normal

• However, this is another plausible option for someone with an impaired GFR
Case 2

- 6 yo male presents with pinkish-red colored urine
- Otherwise well, no known trauma, no recent medications, in school but no obvious illness, ROS completely negative
- PMHx, Soc Hx, Fam Hx all Non-Contributory
- Exam
  - normal BP and vitals, 50% ht and wt
  - Exam otherwise completely normal
Next Step

Urine dip and microscopy to confirm whether this is hematuria? Glomerular vs. Non-glomerular?**

Patient’s results: U/A + blood, trace protein Many eumorphic RBC, no casts
How would you evaluate at this point?
How would you evaluate at this point?**

• DDx of non-glomerular hematuria**
  – Urine Ca/Cr and Renal U/S
    • If either positive for stones, consider 24 hour urine for stone chemistries
  – Any symptoms/signs of infection? If so, Urine Cx
  – Could consider Lytes BUN, Cr, CBC, Pr/Cr—if still need to be certain to exclude a GN etiology
Results

• Ca/Cr 0.47 (Nml <0.2)
• Renal U/S neg, other screens normal

• 3 months later—presents with flank pain and passes stone!
Hypercalciuria

• Why care?
  – Presence of hematuria worrisome to parents
  – Risk for stones**—VERY PAINFUL!!!
  – Can be associated with nephrocalcinosis**
    • deposits of calcium within tubulointerstitial parenchyma
    • can cause progressive scarring and loss of function

• Who develops?
  – Idiopathic (probably multifactorial—genetics, diet, etc...)
  – Certain ‘tubulopathies’ (e.g. Dent’s disease, Bartter’s syndrome)
  – Medication induced
Childhood Kidney Stones**

• When Infants and children develop stones
  – Stone is not the disease. It’s a sign of the disease

• Every child with kidney stones or nephrocalcinosis should have a thorough evaluation as to the cause**
  – H&P into systemic disorders
    • Growth and development, blood pressure, bone related signs/symptoms
    • Dietary history (attention to excess or deficiency), fluid intake, meds including vitamins and supplements
  – Fam Hx of stones, hematuria, renal failure
  – Urinalysis, urine and serum chemistries, imaging
  – STONE analysis (send the stone for chemical analysis)
Clinical Constellation of Childhood Kidney Stones**

- Acute Flank Pain not the rule, though is the presenting finding in majority
- Often difficult to diagnose in infants and young children**
  - nonspecific discomfort, may be in abdomen or hip
- Hematuria-microscopic or macroscopic
  - Stones or crystalluria (eg hypercalciuria) or nephrocalcinosis
- Dysuria and frequency (bladder irritation)
Causes/Risks of Stones in Children**

- **Calcium Oxalate**—radioopaque—50-70%
  - Risks are hypercalciuria, hyperoxaluria, and/or hypocitraturia
- **Calcium Phosphate**—radioopaque –15-30%
  - Form in alkaline urine, common in children with metabolic bone disease or immobilization
- **Struvite**—radioopaque –15%
  - Form in alkaline urine, associated with urinary tract infection with urease producing organisms
- **Cystine**—radioopaque—5%
  - Form in acidic urine, hereditary proximal tubule transporter defect
- **Uric Acid**—5%
  - Radiolucent and form in acidic urine
- **Other**—5%
How do you treat idiopathic (most common form) hypercalciuria (and prevent nephrolithiasis)?

A. Drink lots of fluids to make a dilute urine
B. Low Sodium Diet
C. High Citrate Diet
D. Thiazide Diuretic
Answer

• All of these can be effective measures to make urine calcium more soluble (dilute urine, calcium citrate is soluble) or reduce urine calcium (low sodium diet, thiazide diuretic**

• Typical management is to discuss these options with the patient and family
  – Most asymptomatic (apart from the hematuria) patients choose more conservative therapies (fluid intake, diet)
  – Most patients with recurrent stones choose pharmacotherapy (e.g. thiazide)
14 year old Caucasian boy presents with maroon urine
He is otherwise healthy, playing touch football with friends earlier that day. Denies obvious trauma or rough tackle.
ROS otherwise NEG
Soc Hx — Athlete, starting 9th grade, doing well, no substance use, not sexually active
Fam Hx — Mother with hypertension
Exam — HR 60; BP 138/84; tall and thin, athletic build; otherwise completely normal, no abd masses or tenderness, no edema
Next step--Urinalysis

• 1.025, pH 6, trace protein, large blood, many dysmorphic RBCs/hpf, no casts
Discuss the top three diagnoses on your differential**
Discuss the top three diagnoses on your differential**

• Options to discuss might include:
  – Renal Trauma
  – Congenital GU Anomaly (aggravated by mild trauma)
  – Cystic Kidney Disease/Autosomal Dominant Polycystic Kidney Disease
  – Glomerulonephritis/Thin Basement Membrane Disease
What would your evaluation be?**
Evaluation**

- Urine Calcium/Cr normal
- Basic Metabolic Panel normal
- Renal Ultrasound reveals b/l enlarged kidneys with multiple cysts
- Diagnosis—Presumed Autosomal Dominant Polycystic Kidney Disease (ADPKD)
ADPKD in children**

- A significant minority of cases of ADPKD present in childhood**
  - Occasionally on prenatal imaging, especially with known family history
  - More commonly with acute onset gross hematuria (often in setting of trauma or exertion)
  - Hypertension is a common presentation
- Asymptomatic screening of children of parents with ADPKD is not currently recommended**
  - Screening of these children’s Blood Pressure and a urinalysis for protein at health maintenance is generally recommended
  - Presence of hypertension and/or proteinuria are associated with progression of chronic kidney disease, and can be treated to delay progression**
Name three things you might do as far as clinical management**
ADPKD Management**

- **Strict Blood Pressure Control using RAAS inhibition**—target <120/80 has illustrated slower decline of renal function
- **Control of proteinuria with RAAS inhibition**—similarly, this delays progression of CKD and may prevent future development of ESRD
- If kidneys >15cm— may need to restrict from high impact sports/activities (risk of trauma and cyst rupture—massive bleeding)
- **High Fluid intake**— ADH is associated with cyst growth, so suppressing ADH with super-hydration may slow progression
- **Patient Education and connections with resources/networks**
Case 4

- 16 yo female with diarrheal illness x 2 weeks presents with brown colored urine
- No recent travel or new foods, no emesis, but crampy abd pain results in decreased intake
- At first thought urine was just super-concentrated, but now dark brown
- Medications—took some Cipro after 1 week of illness, tylenol and motrin prn pain
- PMHx healthy, Soc Hx non-contrib, Fam Hx notable for Grave’s Disease
- Exam
  - BP normal, vitals normal, Ht 50%, Wt 10%
  - Otherwise completely normal, no edema, mild non-specific diffuse abd tenderness
Next step

• Real hematuria? Upper vs. Lower?**
  – U/A + blood, 2+ protein, MANY RBC Casts (very impressive)

• What is your DDx Acute GN** (of note—also w/diarrheal illness and abd pain!)
Differential Diagnosis**

• Should include:
  – Diarrhea associated Hemolytic Uremic Syndrome (HUS)
  – IgA Nephropathy
  – Henoch Schonlein Purpura
  – PIGN
  – Vasculitis-associated (Lupus, Polyarteritis)
Differential Diagnosis**

• Diarrhea associated Hemolytic Uremic Syndrome
  – Associated with E Coli strains (O157:H7) with Shiga-like Toxin**
  – Resultant endothelial injury causing thrombocytopenia and microangiopathic anemia particularly damages glomeruli causing acute kidney injury**
  – Treatment is supportive as it is generally spontaneously resolving as E Coli infection clears**
    • Even so, many children require dialysis and are at risk for other organ system involvement in particular CNS and pancreas**
Differential Diagnosis**

• Diarrhea associated Hemolytic Uremic Syndrome

• IgA Nephropathy**
  – Most common Acute GN in children after Post-Infectious GN
  – Usually occurs concurrently with Resp or GI muscosal infection
Differential Diagnosis**

- Henoch Schonlein Purpura (HSP)
  - The most common vasculitis in children; >50% of patients have renal involvement
  - Most are asymptomatic hematuria; small subset can present with hypertension, proteinuria, and renal insufficiency/failure and require treatment**
  - Treatment and pathology of kidney disease is similar to IgA Nephropathy
  - Prognosis** is similar to IgA Nephropathy
    - If BP and urine protein are normal or treated to within normal ranges, prognosis can be excellent
    - When presents with elevated creatinine or nephrotic syndrome, prognosis is not as good (similar to other GNs)
Results of evaluation...

- Chems WNL
- CBC WNL
  - No HUS
- Pr/Cr ratio 0.9
- ANA, Strep-titers, ANCA$s$ all NEG
  - No SLE, PAN
- C3 borderline, C4 WNL
  - Unlikely PIGN or MPGN
Hmm..

- Diagnosed with C. Diff Colitis
  - Treated with Flagyl and her diarrhea & abd pain resolved within 1-2 weeks
  - Never developed purpura or arthritis (no HSP)
  - Hematuria and proteinuria resolved
  - C3 completely normal 2 months later
- IgA Nephropathy? PIGN (can occur with chronic infections)
  - What to do?
  - What’s the treatment for IgA Nephropathy?
Answers

• Watchful waiting—she’s in spontaneous remission
  – If she relapses again with another GI illness or Resp illness, then likely IgA Nephropathy**
  – If never happens again, then likely PIGN**

• Only proven treatment for IgA Nephropathy is ACE-Inhibitor to relax glomerular capillary bed/decrease filtration pressure and prevent scarring
  – Fish Oil has a promising study, but not confirmed
  – For severe clinical presentations, steroids +/- other immunosuppressants
    • Some subjective experience, but no RCT yet to show benefit
Case 5

- 4 yo girl presents with eye swelling
- Pediatrician first thought allergies, tried anti-histamine, but it’s getting worse and now with abd distension and anasarca. She is active, has good appetite, no nausea/vomiting/diarrhea/fever, no hematuria or dysuria, +URI last week, now resolved
- PMHx eczema, Meds anti-histamine and topical moisturizer
- SocHx, FamHx Non-contributory
- Exam
  - Vitals Nml, Weight 90%, Height 50%, BP normal
  - Exam –Anasarca

- Can a Diagnosis of Nephrotic Syndrome be made?**
What’s missing?**

- **Urinalysis**
  - 1.030, moderate blood, 4+ Protein
  - Microscopy 10-20 RBCs, no RBC casts
- **Serum Albumin**—1.2
- **Cholesterol elevated**
- **Now – we can confirm diagnosis of nephrotic syndrome**
  - Edema, Nephrotic range proteinuria, hypoalbuminemia, elevated cholesterol
DDx Nephrotic Syndrome in Children**

- **Primary Nephropathy**
  - Minimal Change Disease**—by far the most common, especially in young children
  - Focal Segmental Glomerulosclerosis (FSGS)
  - Membranous Nephropathy

- **Secondary Nephropathy (systemic illness causing nephrotic syndrome)**
  - Systemic Lupus Erythematosus
  - Hepatitis associated nephropathy
  - HIV associated nephropathy

- **Glomerulonephritis (severe GN complicated by nephrotic syndrome)**

- Hereditary causes
Case 5—What Next?**

A. Renal Biopsy is needed to confirm Minimal Change before treating
B. Wait 2-4 weeks before treating to see if it spontaneously resolves
C. Begin empiric treatment with Corticosteroids and suspect Minimal Change if there is a good treatment response
Answer

• Minimal Change Disease is the predominant cause
  – If everything consistent with minimal change (e.g. age, not a glomerulonephritis), can make presumptive diagnosis based on treatment response**
    • Age under 1 year suggests higher possibility of alternate causes (like hereditary causes)
    • Age above 10 years or so with broader differential (increasing likelihood for FSGS or in teenage years, Membranous Nephropathy)

• If anything presents atypically, or fails to respond to treatment, then further evaluation may be necessary, often including biopsy necessary
Minimal Change Disease

- Presumptive treatment, 2mg/kg or 60mg Prednisone Daily**
  - Usual response in 2-4 weeks, small number may take longer
  - Treat intercurrent infections/triggers
- Majority recur**
  - Significant minority one and done (up to 40%)
  - Others may develop frequent relapsing or steroid dependent
    nephrotic syndrome and require steroid-sparing therapy (e.g.
    cyclophosphamide)
  - If develops steroid resistance—reconsider other etiologies (e.g. FSGS)
- Consistent treatment response suggests an ultimately good
  prognosis, even if having recurrences**
Nephrotic Syndrome—Which of the follow are other considerations?**

A. Low Sodium Diet
B. Albumin—Furosemide Infusion
C. Infectious concerns
D. Hypercoagulopathy
Answer

- All of them!
- Low Sodium Diet is helpful—high sodium intake results in worsening edema (fills interstitial volume)**
- When fluid overload/edema is causing symptoms (resp distress) or complications, albumin-furosemide infusions can help mobilize edema**
Nephrotic syndrome is associated with an increased risk for infection**
- Loss of IgG in urine – hypogammaglobulinemia
- Fluid can get infected, in particular, cellulitis and Strep pneumo peritonitis or pneumonia

Nephrotic syndrome is associated with a hypercoaguable state and at increased risk for venous thrombosis** (especially with membranous nephropathy)
- Loss of pro-coagulants and anti-coagulants in urine but balance of these losses in a hypercoaguable state
Case 6

- 15 year old girl presents with asymptomatic proteinuria identified at sports physical (volleyball)
- PMHx negative, Meds/Supps/Drugs denies, SHx, FHx NC
- ROS completely neg
  - No hematuria, no dysuria, no abd pain, no cvat, no h/a, no fever
- Exam
  - Vitals Normal, normal BP, Ht 90%, Wt 50%
  - Otherwise 100% neg, no edema
  - U/A—1.025, 2+ Protein, otherwise negative
What to do next?
What to do next?**

• Quantitate proteinuria and assess positional pattern**
• If anything concerning then further evaluation needed
• The following would be concerning for more significant pathology:
  – >1gram/day (or Pr/Cr >1.0)
  – No orthostatic variation
  – Elevated blood pressure
  – Elevated serum creatinine (if measured)
DDx Proteinuria in Children**

• **Benign**
  – False positive (concentrated specimen)
  – Recent exercise, dehydration, physical stress
  – Orthostatic (benign positional) proteinuria
    • Classic is tall adolescent or 20-something

• **Pathologic**
  – FSGS, Membranous GN
  – SLE, Hepatitis Infection of HIV associated
  – Diabetic Nephropathy may start with asymptomatic proteinuria even in teens
  – Glomerulonephritis
  – Hereditary
Case 6 cont’d

• First morning Pr/Cr 0.16; afternoon Pr/Cr 0.76
  – Normal orthostatic pattern
• Treatment: Reassurance
• Cont to monitor for progression/worsening for a few years**
  – rarely asymptomatic proteinuria, even with reassuring initial eval, can be an early presentation of a pathologic lesion (e.g. FSGS)
Take Home Points for Practice

• Gross Hematuria may be a manifestation of
  – Glomerulonephritis, presenting with RBC casts, hypertension, and proteinuria or
  – Non-glomerular causes such as infection, hypercalciuria or congenital or acquired structural anomalies (stones, cysts, urinary tract dilation), presenting with urinary and/or abdominal/flank symptoms

• Elevated serum creatinine, hypertension, and nephrotic syndrome are clinical indicators of severity for an acute glomerulonephritis and warrant evaluation and treatment

• Nephrotic syndrome due to minimal change disease is most often responsive to steroids and has an excellent long-term prognosis, but is associated with serious complications requiring vigilence and support
Suggested Reading
