Proteinuria and Nephrotic Syndrome
Speaker Disclosures

- Relevant Financial Relationships: No disclosure.
- Relevant Nonfinancial Relationships: No disclosure.
- I have no actual or potential conflict of interest in relation to this program/presentation.
Urine Dip Positive for Protein

Non-Significant Levels of Urine Protein

Orthostatic Proteinuria

Transient Proteinuria

Asymptomatic

Urine Positive for Protein AND Blood

Concern for Glomerulonephritis (GN)
...PIGN, MPGN, IgA, HSP, Lupus, ANCA vasculitis, Anti-GBM

Urine Positive for Protein AND Concerning Symptoms

Ex. Nephrotic Syndrome

Persistent Asymptomatic Proteinuria

Consider Further Evaluation and Referral to Pediatric Nephrology

False Positive

NORMAL
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Transient Proteinuria
Objectives

• Asymptomatic Proteinuria without Hematuria
  • Identification of transient and orthostatic proteinuria
  • Initial workup and referral or persistent proteinuria

• Nephrotic syndrome
  • Early recognition of nephrotic syndrome
  • Initiation of management
  • Review of complications
Proteinuria???
Urine Dipstick Screening

- Only detect urine albumin
  - Will see glomerular but not tubular (low molecular weight) proteinuria
- False positive:
  - Very alkaline urine
  - Antiseptic agents (chlorhexidine)
  - Radiocontrast agents
  - Very concentrated urine
# Classification of Proteinuria

<table>
<thead>
<tr>
<th>Type</th>
<th>Urine Protein to Creatinine Ratio</th>
<th>24-hour Urine Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 0.2 mg/mg (&gt; 2 yo)</td>
<td>&lt; 100 mg/m2/day</td>
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<tr>
<td></td>
<td>&lt; 0.5 mg/mg (6 mo-2 yo)</td>
<td>can be up to 300 mg/m2/day in neonates</td>
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<tr>
<td>Non-Nephrotic Elevated Proteinuria</td>
<td>0.2-2 mg/mg (&gt; 2yo)</td>
<td>100-1000 mg/m2/day</td>
</tr>
<tr>
<td></td>
<td>0.5-2 mg/mg (6 mo-2 yo)</td>
<td></td>
</tr>
<tr>
<td>Nephrotic Range Proteinuria</td>
<td>&gt; 2 mg/mg</td>
<td>≥ 1000 mg/m2/day</td>
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Asymptomatic Proteinuria

*without Hematuria*
Case 1

4-year-old little girl with 1+ protein on screening dipstick urinalysis
Asymptomatic Proteinuria
without Hematuria

• Insignificant protein elevation
• False positive test
• Transient
  • Most common cause
  • Many causes ex. fever, exercise, stress, seizures and hypovolemia
  • Will not be present on repeat
• Orthostatic
  • Increased protein in the upright position, returns to normal when recumbent
  • Will not be present on a first morning urine specimen
• Persistent
  • Needs full evaluation for underlying kidney disease with referral to Nephrology

Positive test in 5-10% of school age children, 0.1% will have persistent proteinuria
Asymptomatic Proteinuria without Hematuria

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First Morning Urinalysis

**First Morning Urinalysis for Urine Protein to Creatinine Ratio**

- Empty their bladder before lying down to sleep
- Collect the urine from the first urination in the morning.
- Keep the urine specimen cold (refrigerated, and then on ice while transporting)
- Bring to laboratory the same day
Asymptomatic Proteinuria without Hematuria

**History**
- Febrile illness or exercise, seizure
- Recent throat or skin infection (concerning for post infectious glomerulonephritis (GN))
- Gross hematuria, symptoms of increased blood pressure (concerns for GN)
- Edema (concerns for nephrotic syndrome or GN)
- Symptoms of systemic illness (joint pains, rashes, bleeding, weight loss, fever)
- Symptoms of UTI, history of UTIs
- Exposure to or concern for HIV or hepatitis

**Family History**
- Alport’s disease, progressive kidney disease, hematuria, early hearing loss, rheumatologic illness
Asymptomatic Proteinuria without Hematuria

- **Physical Exam**
  - Rashes
  - Joint swelling or redness
  - Edema
  - Hypertension
General Approach

Algorithm for evaluation of asymptomatic proteinuria in children

- Abnormal urine dipstick protein in an afebrile child
  - ≥1+
    - Obtain first AM void for urine total protein/creatinine ratio
    - Urinalysis (U/A) with microscopic exam
  - <0.2 mg protein per mg creatinine and normal U/A
  - Repeat dipstick on first AM void in one year

- Trace
  - >0.2 mg protein per mg creatinine or abnormal U/A (hematuria, pyuria)
  - Further evaluation:
    - History (drugs, family history)
    - Physical examination (blood pressure)
    - Laboratory evaluations: Creatinine, BUN, electrolytes, cholesterol, and albumin
    - Also consider (when appropriate):
      - Renal ultrasonography, serum C3/C4, antinuclear antibody testing (ANA), hepatitis B and C serology, HIV testing
    - Evaluation abnormal
      - Repeat urine dipstick on at least two additional samples
      - Refer to pediatric nephrologist
    - Evaluation normal
      - Proteinuria persistent
      - Negative

Refer to UpToDate topics on the evaluation of proteinuria in children for further details.

BUN: blood urea nitrogen; C3: complement component 3; C4: complement component 4.
* For children between 6 and 24 months, the threshold value is 0.5 mg protein to mg creatinine.
† Persistent proteinuria, elevated blood pressure, and impaired renal function (elevated serum creatinine) are suggestive of renal parenchymal damage. Such patients should be referred to a pediatric nephrologist (or a clinician with expertise in the care of children with renal disease).

Boyer, Olivia. “Evaluation of Proteinuria in Children.” In: UpToDate, Naudet P, Drutz J (Ed), UpToDate, Waltham, MA (accessed 6/7/2021.)
Asymptomatic Proteinuria without Hematuria

No Need for Follow Up
  • Transient or orthostatic

Referral to Nephrology
  • Persistent proteinuria

Clinical Judgement Critical
  - Careful history and examination
  - Set the pace of evaluation
  - When to call Nephrology
  - **Concern if there is hypertension or elevated creatinine
Nephrotic Syndrome
Case 2

3-year-old boy with runny nose who has developed progressive facial swelling especially around the eyes. The family tried giving Loratadine but it did not help.
Considerations

- Nephrotic Syndrome (*edema and proteinuria*)
- Glomerulonephritis (*proteinuria and hematuria, can have edema*)
- Seasonal Allergies
- Heart failure
- Liver failure
- Protein malnutrition
Case 2

3-year-old boy with runny nose who has developed progressive facial swelling especially around the eyes. The family tried giving Loratadine but it did not help.

Urine dip: negative for blood, 3+ protein

- **Nephrotic Syndrome** *(edema and proteinuria)*
- **Glomerulonephritis** *(proteinuria and hematuria, can have edema)*
- **Seasonal Allergies**
- **Heart failure**
- **Liver failure**
- **Protein malnutrition**
Nephrotic Syndrome

- Edema
- Nephrotic range proteinuria
  - 3+ urine dipstick or urine protein to creatinine ratio (UPC) > 2
- Hypoalbuminemia
- Hyperlipidemia

… and must not be concerned for glomerulonephritis (proteinuria with hematuria)
Nephrotic Syndrome

- 2-4 new cases per 100,000 children per year
- Peak incidence in pre-school children; 80% are less than 6 years of age at presentation, with a median age of 2.5 yrs for minimal change disease
- In young children, boys are more commonly affected than girls (3:2), but in teenagers and adults the ratio is equal
Causes of Nephrotic Syndrome in Children

• **Primary**
  • Congenital nephrotic syndrome (< 1 year old)
  • Minimal change disease
  • Focal Segmental Glomerulosclerosis
  • Membranous

• **Secondary**
  • Infections
  • Drugs
  • Cancer
  • Lupus
  • MPGN
  • IgA
  • Diabetes
Nephrotic Syndrome In Childhood

- 90% of cases of nephrotic syndrome between 1-10 years of age are
  - Likely to respond to steroids
  - Likely due to minimal change disease
  - Not secondary to other illnesses
  - No longer biopsied and so is termed idiopathic childhood onset nephrotic syndrome

In these patients we want to start treatment!
Nephrotic Syndrome in Childhood

- 80-90% will respond to their initial 8-week course of steroids, mostly within the first 3-4 weeks of treatment.
- About 92% of those that responded to initial steroid course would have minimal change disease on biopsy.

iskdc: Identification of patients with minimal change nephrotic syndrome from initial response to prednisone, 1981

<table>
<thead>
<tr>
<th>Relapse Pattern</th>
<th>n</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>471</td>
<td>100%</td>
</tr>
<tr>
<td>Steroid Responsive</td>
<td>368</td>
<td>78%</td>
</tr>
<tr>
<td>Steroid Resistant</td>
<td>103</td>
<td>22%</td>
</tr>
</tbody>
</table>

Identifying Who Can Start Treatment

Symptoms consistent with idiopathic childhood onset nephrotic syndrome

- Isolated edema with proteinuria (maybe recent triggering viral illness)
- Less than 6 years of age (1-12 years old if all other factors fit)
- No hypertension
- No hematuria
- Normal complements and creatinine for age
Identifying those at risk for other causes of nephrotic syndrome

1. Concerned for glomerulonephritis
   
   Hematuria, particularly those with gross hematuria, can have hypertension, elevated creatinine

2. Populations out of age range
   
   < 1 year old, greater than 10 years old

3. Concern for secondary disease
   
   Symptoms of vasculitis or lupus, concern for cancer or infections like hepatitis or HIV, drugs
What to do next?

• Appointment with Nephrology within 1 week

• **Laboratory Evaluation:**
  • Basic metabolic panel with albumin, C3, C4, triglycerides, CBC
  • ANA in those ≥ 10 yo or with symptoms
  • Urinalysis, urine protein to creatinine ratio
  • Varicella antibody titers (identify those at risk for severe varicella infection)
  • QuantiFERON gold (risk for TB reactivation with steroids)
Initiate Treatment

**Treatment:**
- Prednisone 60 mg/m2/day with maximum dose of 80 mg daily for 6 weeks
- Tums or ranitidine for gastric prophylaxis
- Low salt diet
- Low glycemic Index foods

**Infection Prevention:**
- Vaccinate: review pneumococcal vaccination, if over 2 years old plan to give PCV23

**Counseling**
- Risks from nephrotic syndrome
- Side effects of steroids
Counselling: Discuss Sequelae of Nephrotic Syndrome

- Fluid overload
- Intravascular volume depletion
- Thromboembolism
- Infection
Fluid Overload

- Shortness of breath
- Skin breakdown
- Immobility due to severe scrotal or labial edema
Intravascular Volume Depletion

- Tachycardia
- Reduced urine output
- Peripheral vasoconstriction
Thromboembolism

• Occurring in *2-3% of patients* with nephrotic syndrome

  o Common types of thrombosis
    o cerebral venous thrombosis (*sudden onset headache, neurologic symptoms*)
    o pulmonary embolism (*chest pain, shortness of breath*)
    o renal vein thrombosis (*thrombocytopenia, flank pain, hematuria*)

• Why??
  • Hemoconcentration
  • Immobility
  • Imbalance of clotting factors
Infection

• Occurring in ~13% of patients with nephrotic syndrome

• Why?
  • Decreased immunoglobulins
  • Loss into the urine in addition and an impaired ability to make them
  • Alterations in complement pathway
  • Loss of factor B and D
  • Immunosuppressive therapy

• What types of Infections?
  • All kinds…
Infection – Specific Precautions

- Risk for encapsulated bacteria!
  - Sepsis
  - Meningitis
  - Cellulitis
  - Peritonitis (~3% of those with steroid responsive nephrotic syndrome)
    - Strep pneumoniae is the most common cause
    - to contact provider if they get fever and abdominal pain

- Recommend PCV23 vaccination!
Infection – Specific Precautions

• Risk for varicella!
  • Varicella antibody titers should be checked at diagnosis
  • Those who are not fully immune should receive prophylaxis if exposed
Counselling: Risks from Proteinuria

- **Fluid overload**
  - shortness of breath, skin breakdown, inability to walk
- **Intravascular volume depletion**
  - appearing unwell
- **Thromboembolism**
  - headache, shortness of breath, bloody urine, abdominal pain
- **Infection**
  - abdominal pain with fever, shortness of breath, exposure to varicella
Counseling: Side Effects of Steroids

- Decreased sleep - *make sure to give them in the morning*
- Increased moodiness
- Increased appetite and weight gain - *avoid foods with high glycemic index*
- Acne
- Increased body hair
- Swelling
- Increased bruising
- Roundness of face or buildup of fat between the shoulders
Counseling: Side Effects of Steroids

• Increased Risk for Infection
• Stomach irritation
  • Alert provider if you get a persistent stomachache
• Elevated blood pressure
  • Alert provider if you have nosebleeds, severe or persistent headaches, chest pain, shortness of breath
• Elevated intracranial pressure
  • Alert provider if you have headache, blurry vision
• Elevated blood glucose
  • Alert provider if you notice a dramatic increase in water intake and urination
**WHAT CAN WE EXPECT?**

- **93%** of children respond to steroids
- **85%** of children become disease-free during childhood
- **Relapses are common**
  - 74% of children who respond will relapse within 5 months
  - Infections are a common trigger for relapses

**Outcomes:**

- **22%** have no further active disease after initial treatment
- **30%** receive steroids only
  - On average, have 3 relapses in childhood
- **31%** receive steroids & another medication
  - On average, have 5 relapses in childhood
- **17%** receive steroids & 2 or more medications
  - On average, have 12 relapses in childhood
- **9%** receive ongoing care as an adult
- **1%** have progressive kidney disease

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PCV Vaccination

Routine vaccination with PCV13:
• For children ages 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

Vaccination of persons with high-risk conditions with PCV13 and PPSV23:
• All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.

For children 2 through 5 years of age with nephrotic syndrome:
• Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
• Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV (PCV7 and/or PCV13) were received previously.
• Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
• The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
• For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.

For children aged 6 through 18 years with nephrotic syndrome:
• If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
• If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
• If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.

A single revaccination with PPSV23 should be administered 5 years after the first dose.
Varicella

*If varicella immune status <1.0:*

**Vaccination**
- **Age 1 year to 13th birthday:** One dose of varicella vaccine 1 month after cessation of steroids but before the 13th birthday because of the potential increased severity of natural varicella after this age.
- **Healthy adolescents and young adults:** Administration of 2 doses of vaccine 4 weeks apart 1 month after cessation of steroids.

**Prophylaxis**
- **Types of Exposure to Varicella or Zoster for Which VariZIG or IVIG Is indicated in our patients on steroids** (Remember it must be given within 72 hours of exposure.)
  - **Household:** residing in the same household.
  - **Playmate:** face-to-face indoor play for > 5 minutes.
  - **Hospital:**
    - **Varicella:** In same 2- to 4-bed room or adjacent beds in a large ward, face-to-face contact with an infectious staff member or patient or visitor for > 5 minutes
    - **Zoster:** Intimate contact (eg, touching or hugging) with a person deemed contagious.