

APPROACH TO A CASE OF PROTEINURIA

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Disclaimer: Only for educational purpose and not for commercial activity



Content

- Case scenario
- Introduction to proteinuria
- Methods of urinary protein measurement
- Causes of proteinuria
- Evaluation & Management

Case scenario

A 15 years old boy has presented to you with chief complaints of:

1.Frothy urine for one month

2.Facial puffiness for 20 days

How will you approach?

Differential Diagnosis?

Introduction

Urine analysis is an important investigation to diagnose kidney diseases.

Proteinuria is one of the earliest & most important finding of urine examination

Proteinuria can be **transient** due to benign renal causes or **persistent** due to organic renal causes.

DEFINITION

- Healthy individuals can excrete less than 150mg /d of total protein and less than 30mg/d of total albumin
- **Proteinuria** –Urinary protein excretion > 150mg/ day
- **Albuminuria**- Urinary albumin excretion > 30mg/day

COMPOSITION OF NORMAL URINARY PROTEIN (150 mg/day)

- Tamm-horsfall protein(Maximum) (40%)
- Albumin (20%)
- Immunoglobulins
- Hormones, Enzymes
- Mucopolysaccharides

MEASUREMENT OF URINARY PROTEIN

Qualitative

- Urine dipstick
- Sulfosalicylic acid test
- Heat coagulation test

Quantitative

- 24-hour urinary protein
- Spot urinary Albumin/creatinine ratio(ACR)

MEASUREMENT OF URINARY PROTEIN

□ Urine dipstick

- Primarily detect albuminuria
- less sensitive for other forms of proteinuria (low molecular weight proteins, Bence Jones protein, gamma globulins).

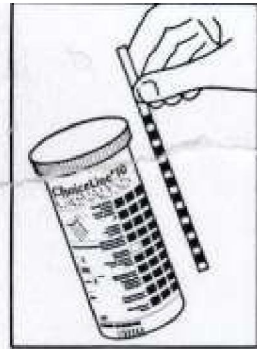


MEASUREMENT OF URINARY PROTEIN

Urine dipstick

- Measures albumin concentration via a colorimetric reaction between albumin and tetrabromophenol blue producing different shades of green according to the concentration of albumin in the sample
- Negative
- Trace — between 15 and 30 mg/dL
- 1+ — between 30 and 100 mg/dL
- 2+ — between 100 and 300 mg/dL
- 3+ — between 300 and 1000 mg/dL
- 4+ — >1000 mg/dL

MEASUREMENT OF URINARY PROTEIN



IVD



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LOT

Specific Gravity Densidad Densidade 60 sec/seg.								
	1.000	1.005	1.010	1.015	1.020	1.025	1.030	
pH 60 sec/seg.								
	5.0	6.0	6.5	7.0	8.0	9.0		
Leukocytes Leucocitos 60-120 sec/seg.								
	neg.	ca. 15	ca. 75	ca. 125	ca. 500	Leuko/µL		
Blood/Hemoglobin/ Sang(re)(ue)/Hemoglobina 60 sec/seg.								
	neg.	ca. 5-10	ca. 10	ca. 25	ca. 25	ca. 50	ca. 50	ca. 250
Ery/µL								
Nitrite/Nitrito/Nitritos 60 sec/seg.								
	neg.	+	++					
Ketones/ C.Cetónicos 60 sec/seg.								
	neg.	5 (0.5)	15 (1.5)	50 (5)	150 (15)	mg/dL (mmol/L)		
Bilirubin/Bilirrubina/ 60 sec/seg.								
	neg.	+	++	+++				
Urobilinogen(o)/ Urobilinogênio 60 sec/seg.								
	normal	1 (17)	4 (70)	8 (140)	12 (200)	mg/dL (µmol/L)		
Protein/Proteínas/ Proteínas 60 sec/seg.								
	neg.	15 (0.15)	30 (0.3)	100 (1)	300 (3)	1000 (10)	mg/dL (g/L)	
Glucose/Glucosa/ Glucose 60 sec/seg.								
	normal	100 (5.5)	300 (17)	1000 (55)	mg/dL (mmol/L)			



Pitfalls of Dipstick method

❑ False positive –

- Very Alkaline sample pH >7.0
- contaminated by antiseptic agents
 - Chlorhexidine or Benzalkonium chloride
- Iodinated radiocontrast agents.
- Gross hematuria

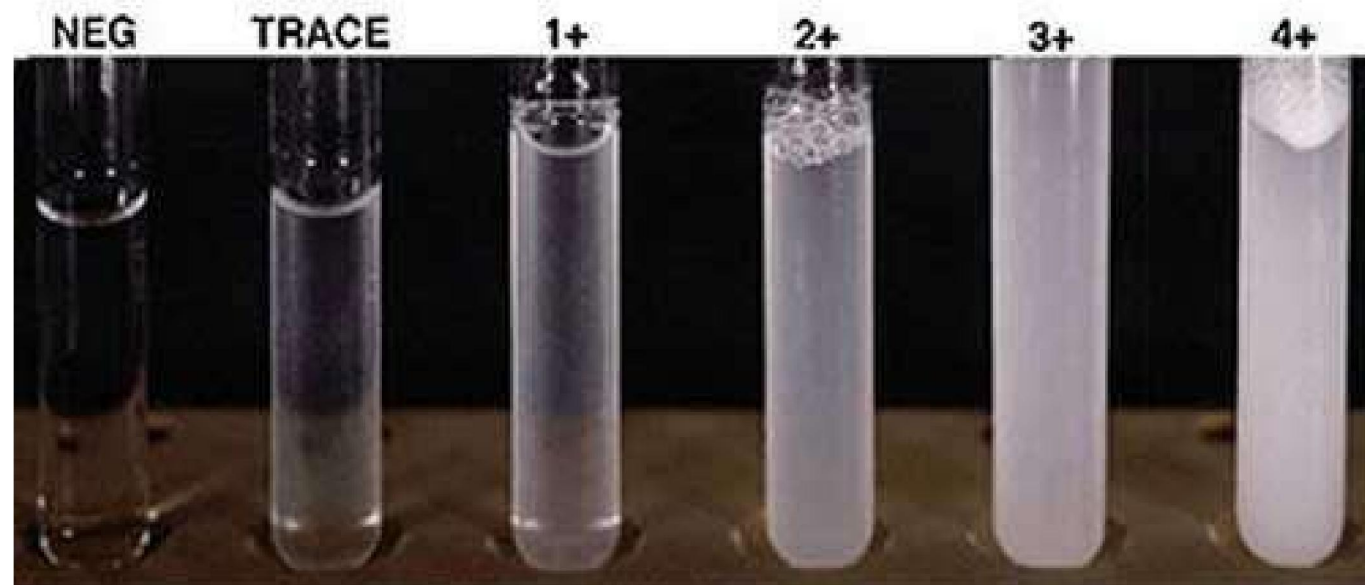
❑ False Negative –

- dilute urine (specific gravity <1.005)
- In which the predominant urinary protein is not albumin

MEASUREMENT OF URINARY PROTEIN

- Sulfosalicylic acid test

- Detects all proteins in the urine including the low molecular weight proteins that are not detected by the dipstick method
- Performed by mixing one part urine with three parts 3 percent sulfosalicylic acid, followed by assessment of the degree of turbidity



Heat and Acetic Acid Test

- ▶ If turbidity develops add 1-2 drops of glacial acetic acid
- ▶ If turbidity is due to phosphate or carbonate precipitation, it will disappear with acetic acid

Negative : No cloudiness

Trace: Barely visible cloudiness.

1+ : Definite cloud without granular flocculation

2+ : Heavy and granular cloud without granular flocculation

3+ : Dense cloud with marked flocculation.

4+ : Thick curdy precipitation and coagulation

Grading based on 24 hour proteinuria

< 150mg/24 hours- Normal

150-500 mg/24 hours-Functional(<1mg/24 hr)

>500mg/24 hours- Significant

>3.5gm/24 hours-Nephrotic range

>4gm/24 hours- Massive

Grading based on 24 hour albuminuria

<30mg/24 hours- **Normal**

30-300 mg/24 hours- **Microalbuminuria**

>300 mg/24 hours-**Albuminuria**

>2200 mg/24 hours- **Nephrotic range**

Grading based on Spot urinary ACR

<30mg/gram- **Normal**

30-300 mg/gram - **Microalbuminuria**

>300 mg/gram- **Albuminuria**

>2200 mg/gram- **Nephrotic range**

MECHANISMS OF PROTEIN HANDLING BY KIDNEY



- Glomerular capillary wall permits passage of small molecules while restricting macromolecules

MECHANISMS OF PROTEIN HANDLING BY KIDNEY

- Normal protein excretion affected by interplay of glomerular and tubular mechanisms
- Glomerular injury: abnormal losses of intermediate MW proteins like albumin
- Tubular damage: increased losses of low MW proteins

CLASSIFICATION OF PROTEINURIA

- Functional
- Glomerular
- Tubular
- Overflow

FUNCTIONAL PROTEINURIA

- Benign form of proteinuria
- Protein excretion is less than 500mg/day(may rise upto 1g/d)
- Includes 2 types
 1. Transient proteinuria
 2. Orthostatic proteinuria

Transient proteinuria

- If dipstick analysis shows 0 to +2 proteinuria, but subsequent dipstick tests are negative
- Potential triggers are acute illness, exercise, fever, heart failure and UTI.
- After potential trigger has been treated or resolved, repeat urine test is normal

ORTHOSTATIC PROTEINURIA

- ▶ This benign condition occurs in about 3 to 5 percent of adolescents and young adults which is characterized by increased protein excretion in the upright position but normal protein excretion when the patient is supine.
- ▶ To diagnose orthostatic proteinuria, split urine specimens are obtained for comparison.
- ▶ The daytime specimen typically has an increased concentration of protein, with the nighttime specimen having a normal concentration.

There should be no hematuria

Causes of proteinuria

► Benign

1. Fever
2. Strenuous exercise
3. Acute illness
4. Emotional stress
5. Orthostatic proteinuria

Due to increased renal blood flow

Pathological proteinuria

- ▶ Glomerular - Due to increased capillary permeability of glomerulus
Glomerulonephritis - Primary or secondary
- ▶ Tubular - Due to decreased tubular reabsorption of filtered proteins Tubulo-interstitial diseases
- ▶ Overflow - Due to increased production of low molecular weight proteins Monoclonal gammopathies, Leukaemias, Lymphomas

GLOMERULAR PROTEINURIA

- Occurs due to effacement of epithelial foot process and disruption of glomerular basement membrane
- Urinary protein electrophoresis shows large albumin spike indicative of increased permeability of albumin across damaged GBM

Presence of RBC cast/Dysmorphic RBCs

- Only proteinuria that can cause >2 g protein/24 hours with albumin:beta 2 macroglobulin ratio $>1000:1$

Glomerular proteinuria

Minimal change disease

Primary

Idiopathic membranous GN

FSGS

Membranoproliferative GN

IgA nephropathy

Secondary

Diabetes

Connective tissue disorders - Lupus nephritis

Amyloidosis

Preeclampsia

Infection - Post streptococcal, Hep B,C,HIV

Malignancy - Lymphoma, Lung & GI cancer

TUBULAR PROTEINURIA

- Occurs due to faulty reabsorption of normally filtered proteins by the proximal tubule
- Characterised by the presence of large amounts of small proteins in urine, with normal serum protein
- Rarely exceeds 1.5-2g/day

OVERFLOW PROTEINURIA

- Excessive production of an abnormal filterable plasma protein(monoclonal gammopathies) that exceeds the tubular capacity for reabsorption
- Usually less than nephrotic range
- Examples:Multiple myeloma(Bence Jones protein),Myoglobinuria in rhabdomyolysis and hemoglobinuria in hemolysis.

Pathological proteinuria

▶ Tubular

Hypertensive nephrosclerosis

Uric acid nephropathy

Interstitial nephritis

Heavy metals

Sickle cell disease

Drugs(eg.NSAIDS,Cyclosporin,Contrast)

Hypersensitive interstitial nephritis

▶ Overflow

Haemoglobinuria/Myoglobinuria

Myeloma Amyloidosis

Selective proteinuria

Only albumin and transferrin lost in urine

It is seen in Minimal Change GN

EVALUATION OF PROTEINURIA

PROTEINURIA ON URINE DIPSTICK

Quantify by 24-h urinary excretion of protein and albumin or first morning spot albumin-to-creatinine ratio

***Moderately increased albuminuria**
30–300 mg/d or
30–300 mg/g

***Severely increased albuminuria**
300–3500 mg/d or
300–3500 mg/g

Nephrotic range
>3500 mg/d or
>3500 mg/g

RBCs or RBC casts on urinalysis

Consider
Early diabetes
Essential hypertension
Early stages of glomerulonephritis (especially with RBCs, RBC casts)

*In addition to disorders listed under *moderately increased albuminuria consider*
Myeloma-associated kidney disease (check UPEP)
Intermittent proteinuria
Postural proteinuria
Congestive heart failure
Fever
Exercise

Nephrotic syndrome
Diabetes
Amyloidosis
Minimal change disease
FSGS
Membranous glomerulopathy
IgA nephropathy

* Moderately and severely increased albuminuria were previously termed “microalbuminuria” and “macroalbuminuria,” respectively.

CLINICAL EVALUATION- HISTORY

- Proteinuria is usually detected during a routine screen in asymptomatic patients
- Symptoms with duration (history of recent fever with sore throat, periorbital puffiness progressing to anasarca, frothy urine , high coloured urine, oliguria, nausea, vomiting , abdominal pain, joint pain etc)
- Past history- Diabetes, hypertension, renal disease, systemic illnesses
- Drug history- NSAIDS, Cyclosporin, exposure to heavy metals
- Family history of renal disease

PHYSICAL EXAMINATION

- Blood pressure, body weight
- Edema – particularly facial(around eyes), pedal edema, ascites
- Fundoscopic examination

Investigations

- Baseline investigations –

1. Complete blood count

2. Renal function test

3. Urine dipstick

4. Urine routine examination

5. 24 hour urinary protein

6. Spot urine ACR, PCR(albumin / protein to creatinine ratio)

7. Renal USG

Diagnostic Evaluation of Proteinuria

1. When proteinuria is found on a dipstick urinalysis, the urinary sediment should be examined microscopically

<i>MICROSCOPIC FINDING</i>	<i>PATHOLOGIC PROCESS</i>
Fatty casts, free fat or oval fat bodies	Nephrotic range proteinuria (> 3.5 g per 24 hours)
Leukocytes, leukocyte casts with bacteria	Urinary tract infection
Leukocytes, leukocyte casts without bacteria	Renal interstitial disease
Normal-shaped erythrocytes	Suggestive of lower urinary tract lesion
Dysmorphic erythrocytes	Suggestive of upper urinary tract lesion
Erythrocyte casts	Glomerular disease
Waxy, granular or cellular casts	Advanced chronic renal disease
Eosinophiluria*	Suggestive of drug-induced acute interstitial nephritis
Hyaline casts	No renal disease; present with dehydration and with diuretic therapy

* A Wright's stain of the urine specimen is necessary to detect eosinophiluria

Other tests

1. Fasting lipid profile
2. Hba1c
3. ANA
4. ANA
5. Serum C3/C4
6. Hepatitis B/C
7. Renal biopsy

SELECTED INVESTIGATIONS TO BE CONSIDERED IN PROTEINURIA

TEST	INTERPRETATION
Antinuclear Antibody	Elevated in SLE
Antistreptolysin O Titre	Elevated after streptococcal GN
Complement C3 & C4	Levels low in RPGN
ESR	If normal help to rule out infection or inflammation
Fasting Blood sugar	Elevated in Diabetes Mellitus
Hemoglobin, Hct	Low in CRF
HIV, VDRL & Hepatitis serology	All are associated with glomerular proteinuria
S. Electrolytes(Na ⁺ , K ⁺)	Screening for any abnormalities consequent to renal disease
Serum & Urine protein Electrophoresis	Abnormal in multiple myeloma
Serum Urate	Elevated urates can lead to tubulointerstitial disease and stones
USG KUB	For structural renal disease
Chest X Ray	Systemic diseases like sarcoidosis

MANAGEMENT

Treat the underlying cause -

- Blood pressure control, Glycemic control
- Edema- diuretics, sodium restriction
- ACE inhibitors, ARB's
- Lipid control
- Specific immunosuppressive therapies for primary glomerular diseases

MCQ

Most common cause of nephrotic range proteinuria in adults is

1. Minimal change GN
2. Amyloidosis
3. Diabetic nephropathy
4. PSGN

MCQ

Glomerular proteinuria can be differentiated from nonglomerular proteinuria by

1. Proteinuria < 1 g/day

2. RBC cast

3. Type of protein excreted is Tam-Horsfall protein

4. Albumin/Beta 2 macroglobulin ratio of 100:1

Thank you
for your
attention

