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PROTEINURIA IN CHILDREN:
FROM DIPSTIK TO DIAGNOSIS

SPEAKER

Dr Swati Bhardwaj

CHAIRPERSONS

Dr Vinay Aggarwal, Dr Dinesh Laroia, Dr BB Aggarwal, Dr Dinesh Kaul

8:13:22 AM

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Dr Swati Bhardwaj

8:13:22 AM

DESIGNATION	Principal Consultant Pediatric Nephrology
CURRENT AFFILIATION	BLK MAX Super Speciality Hospital
ACHIEVEMENTS	Publications in National and International Journals Reviewer for Indian Journal of Pediatrics and BMC Pediatrics Secretary IAP Central Delhi, 2020

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Dr Vinay Agarwal

8:13:22 AM

DESIGNATION	**Associate Director Pediatric Nephrology** **Max Super speciality, Saket**
AFFILIATIONS	Indian Society of Paediatric Nephrology (ISPN) British Association for Paediatric Nephrology (BAPN) International Paediatric Nephrology Association (IPNA),

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Dr Dinesh Laroia

8:13:22 AM

DESIGNATION	Consultant Pediatrician
CURRENT AFFILIATION	Saraswati Memorial Hospital
ACHIEVEMENTS	Former Member: - National commission for Protection of Child Rights - Central adoption Resource Authority - Central Social welfare board - EB member Central IAP 2012/& 2013 - President IMA KBB

Dr B B Aggarwal

- Director, Centre for Child Health, BLK-MAX Super Specialty Hospital
- Secretary, IAP Delhi State Branch (2014)
- President IAP Central Delhi Branch 2010 & 2025

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NAME	Dr. Dinesh Kaul
DESIGNATION	Senior Consultant Division of Pediatric Infectious Disease
CURRENT AFFILIATION	Sir Ganga Ram Hospital, New Delhi
ACHIEVEMENTS	• Worked as a clinical investigator in various vaccine related clinical research trials. • Has published in various indexed and non indexed journals. • Authored few chapters in different text books of HIV infection, pediatrics and hemoglobinopathies/thalassemia. • Membership for various pediatric societies (IAP). • (Ex-offico) Central Delhi IAP Branch. • On editorial working group/board for Current Medical Research & Practice Journal (published by SGRH & Wolters Kluwer).

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Approach to Proteinuria: from Dipstick to Diagnosis

Dr Swati Bhardwaj
Principal Consultant Pediatric Nephrology
BLK MAX Centre for Child Health

Proteinuria

- Hippocrates
  - bubbles in urine → kidney problem
- Early sign of kidney disease
- Important predictor of progression of kidney disease
- Could be transient/persistent;

  physiological/pathological

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Objectives

How to

- Define
- Quantify
- Types of proteinuria
- Evaluation & Management

- Case studies

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Proteinuria: How much is normal?

- A small amount of protein normally excreted in urine
  - 50% Tamm-Horsfall protein
  - 15% albumin
  - Lysosomes, Immunoglobulins, hormones (insulin, vasopressin, GH, PTH), micro globulins, RBP
- Normal daily protein excretion
  - Protein <150 mg/day
  - Albumin <30 mg/day
- Transient proteinuria in 10% of routine urine examinations in children
  - Persistent < 1 %

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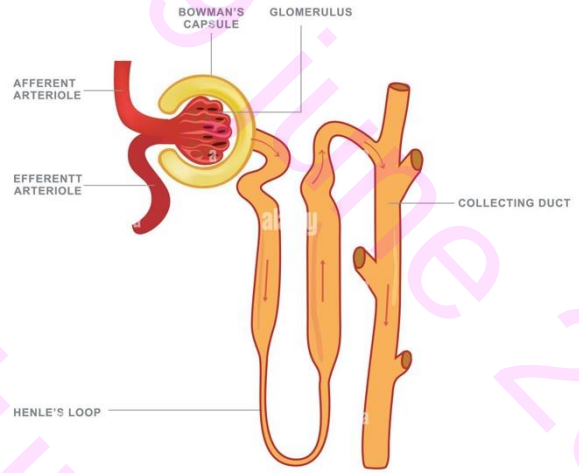
Proteinuria: Pathophysiology

Glomerular Proteinuria

- Leaky filter → marker of glomerular disease
- E.g. nephrotic syndrome, glomerulonephritis

Tubulointerstitial Proteinuria

- Damage to tubules leads to impaired reabsorption or increased excretion
- AIN, ATN, Fanconi syndrome, toxins/medications, CAKUT

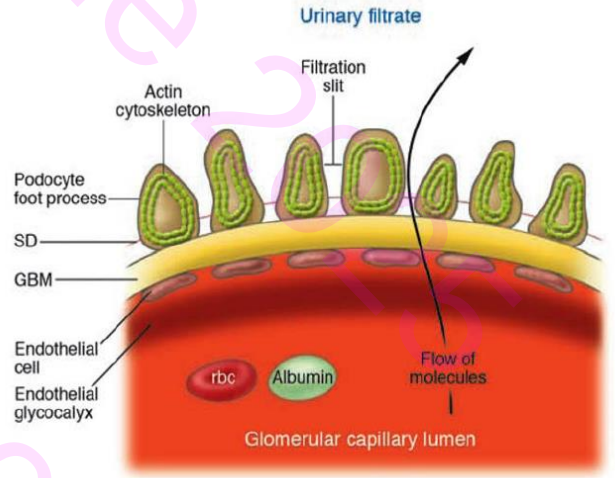


Overflow Proteinuria

- Filtered protein load > resorptive capacity of tubules
- E.g. myoglobinuria, hemoglobinuria, Light chains in Multiple myeloma

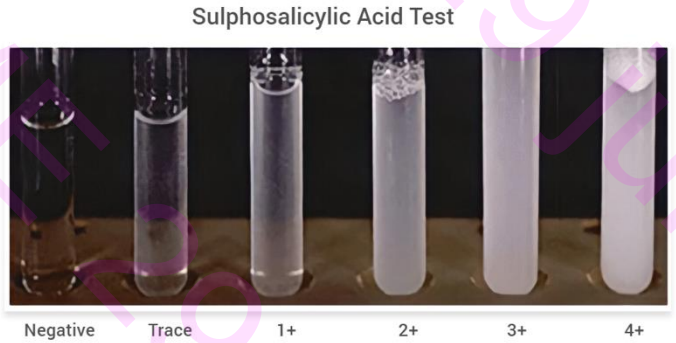
Others

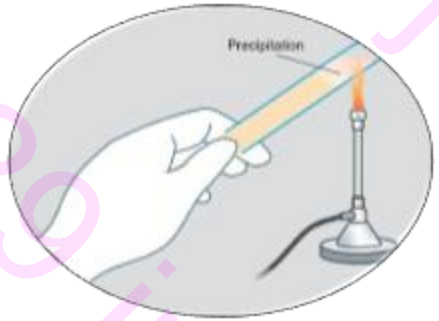
- Transient exercise, fever, CHF, HTN, UTIs
- Orthostatic proteinuria



Measurement of Proteinuria

- Qualitative
  - Heat coagulation
  - Sulfosalicylic acid turbidometry
  - Dipstick
  - Automated Dipstick testing
- Quantitative
  - 24 hr urine protein estimation
  - spot urine protein/creatinine ratio





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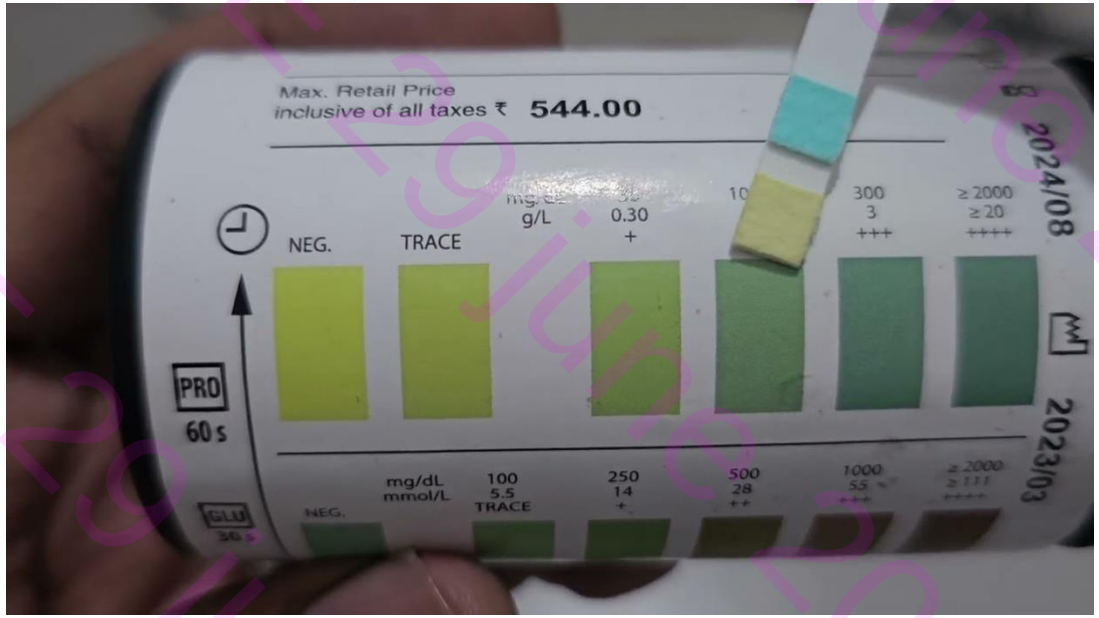
Dipstick Method

- Measures albumin

- False positive
  - Alkaline pH >7.0
  - hematuria, pyuria, bacteriuria,
  - Concentrated urine (Sp gravity >1.025)
  - Presence of pyridium, chlorhexidine, cephalosporins, radiographic contrast

- False negative
  - dilute urine sp gravity <1.010
  - Acidic urine pH <4.5



Automated Dipstick testing has comparable efficacy

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Quantitative Estimation of Proteinuria

- 24 hr urinary protein
  - Gold standard
  - All types of protein
- Urine protein to creatinine ratio (UPCR)
- Urine albumin to creatinine ratio (UACR)
  - first morning sample
  - UACR more sensitive for glomerular injury
  - Dependent on muscle mass of patient

Protein excretion

- highest in newborn up to 300 mg/m^2/day
- Reaches <150mg/day by adolescence
- 24 hr urinary protein <8 mg/m^2/hr can be normal in less than 6 months
- **UPCR can be extended up to 0.5 in 6 months to 2 years old.**

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Comparison

Test	***Pros***	***Cons***
Urine Dipstick	Cheap, easy Other abnormalities-multistix	***Detects albumin*** Semi-quantitative False positives /negatives
Urine ACR	Sensitive	Doesn't detect non-albumin protein Discrepancy in ACR and UPCR can be useful
UPCR	Detects ***all proteins*** Validated in pediatric population	Less validated for diabetic nephropathy Caution not to overinterpret small changes
24 hr urine protein	***Gold standard*** Useful for making treatment decisions in GN	Tedious Missed collection may alter results 24 hr creatinine estimation helps validate collection

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Definition

	Dipstick	*24-hr urine protein excretion mg/m²/h (g/m²/day)*	*First morning spot urine protein to creatinine ratio, mg/mg* *UPCR*	*24 hr urine albumin to creatinine ratio, mg/g (albuminuria category)* *ACR*
Physiologic	Nil, trace	<4 (0.1)	< 2 y: <0.5 ≥ 2 y: <0.2	< 30 (A1)
Pathologic				
Non-nephrotic proteinuria	1+, 2+	4-40 (0.1-1)	0.2-2	30—300 (A2) *Microalbuminuria*
Nephrotic range proteinuria	3+, 4+	>40 (>1)	> 2	> 300 (A3) *Macroalbuminuria*

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Etiology of Proteinuria

Transient Proteinuria

Persistent Proteinuria

- Proteinuria ≥ 1+
- Multiple occasions
- Over > 4 weeks

Glomerular Proteinuria

Albuminuria
Heavy proteinuria

Tubular Proteinuria

Low molecular weight proteinuria

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Intermittent Proteinuria

Spot assays vulnerable to diurnal variation, day to day variation, postural changes, muscle mass: First morning void samples are useful

Intermittent proteinuria

- Proteinuria detected in only few samples
- Exercise, fever, dehydration, cold exposure

Orthostatic proteinuria

- Elevated protein excretion in upright position
- Prevalence 0.65-5%, correlates with low BMI
- Benign; requires no treatment
- Rare after age of 30

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Case 1

- 4 year old girl with anasarca
- Investigations:
  - Urine protein 4+ by dipstick
  - Serum creatinine 0.44 mg/dL
  - Serum albumin 1.79 gm/dL
  - Serum Cholesterol 358 mg/dL
  - UPCR 12.5 mg/mg
- Type of Proteinuria?

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Glomerular Proteinuria: Causes

Primary glomerular disease

Idiopathic childhood nephrotic syndrome
Focal segmental glomerulosclerosis
Congenital nephrotic syndrome
Membranous nephropathy

Secondary glomerular disease

Post-infectious glomerulonephritis
IgA vasculitis
Lupus nephritis
Alport syndrome
Hepatitis B and C
Human immunodeficiency virus Amyloidosis

Others

Hemolytic uremic syndrome
Diabetes mellitus
Hypertension
Hyperfiltration, CAKUT, Reflux Nephropathy

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Evaluation

Urine dipstick

↓

≥1+ protein

↓

Repeat urine dipstick (in 1-2 weeks)

↓

≥1+ protein

↓

First morning urine PCR

↓

0.21 to 2 mg/mg

↓

Pathological proteinuria

← **< 0.2mg/mg**

Non-pathological proteinuria

Febrile

Exercise

Orthostatic

↓

Reassure and discharge

→ **> 2 mg/mg**

Investigate as per nephrotic syndrome

Pathological proteinuria

History and examination

Investigations to consider:

Urinalysis

Serum creatinine

Complement C3 & C4

Liver function tests

Hepatitis B &C, HIV serology

ANA, anti-dsDNA, ANCA, anti-GBM antibodies

Urine low molecular weight proteins if indicated

Ultrasound of kidneys and urinary tract

Gene mutation panel if indicated

Indications for renal biopsy:

Persistent proteinuria

>1g/m^2/day

Persistent proteinuria with any of the following features:

A) Microscopic haematuria

B) Reduced eGFR

C) Persistently low C3 >12 weeks

D) Hypertension

E) Clinical or serological evidence of collagen vascular disease or vasculitis

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Case 2

P-12 year girl

- Fever 3 days
- Vitals stable
- Normal General/systemic examination
- Urine R/M 2+ urine protein
- UPCR 1.88 mg/mg

- Managed symptomatically
- Proteinuria normalised in 2 weeks
- Recurrence with acute febrile illness 6 months later
- subsided within a week
- No hematuria/hypertension

Transient Proteinuria

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Case 4

7 year old Girl

- Fever 3 days
- Cough, throat pain
- Red urine 1 day

- Clinical Examination : throat congested, no edema, BP WNL

- Urine R/M ->50 RBC/hpf, Protein 2+
- Supportive treatment; afebrile in 48 hrs

At Discharge

- Red urine subsided

- Urine R/M 8-10 RBC/hpf UPCR 1.8 at discharge

- Blood and urine culture sterile

- Follow up 1 week : Urine R/M RBC 1-2/hpf, UP nil, UPCR 0.18

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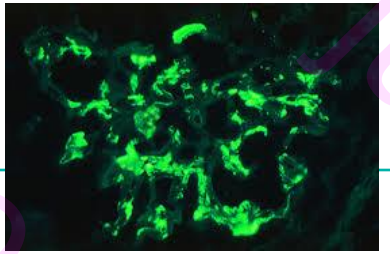
Case 4....



5 months later

- Fever high grade 2 days
- Cough 2 days
- Red/cola color urine 1 day

- Urine R/M RBC 100/hpf , protein 1+
- Urine promptly cleared in 48 hrs
- Urine protein Nil, UPCR 0.24

Kidney Biopsy : IgA Nephropathy

IgA Nephropathy

- Dominant immunoglobulin A glomerular deposits
- ***Syn-pharyngitic hematuria*** –classic
- Commonest glomerular disease in children presenting persistent microscopic hematuria-10-40%
- Treatment guided by proteinuria
  - ACEi
  - Corticosteroids
  - Additional immunosuppressive agents

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Case 5

P 13 year old body

- Recurrent UTI, Bilateral grade 5 VUR with DMSA showing scarring in both kidneys
- Bilateral ureteric reimplantation @ 4.5 years of age.

- Now headache, palpitations, High home BP up to 160/100 mmHg
- On evaluation Hypertension confirmed

- Serum creatinine 0.91 eGFR 72
- Urine protein 3+ by dipstick, UPCR 2.5
- Serum albumin 3.9, Cholesterol 152
- 24 hr urine protein 2.3 gms/day

Reflux Nephropathy

- Proteinuria
- Hypertension

↓

Predictor of progression of renal disease

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General Management

Persistent non-nephrotic range proteinuria

- Monitor BP, urinalysis, creatinine
- Avoid excess salt & protein intake
- ACEi and ARB
  - for albuminuria; no evidence of benefit in tubular proteinuria
  - antiproteinuric & nephroprotective action

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Tubular proteinuria

- Defective tubular reabsorption of low molecular weight proteins
  - Injury to tubular epithelium/ inherited disorders
  - Loss of LMW proteins: beta 2 or alpha 1 microglobulin, RBP, hormones
- Urine protein <1+, < 1 gm/day or 40 mg/m^2/day
- No edema, hypoalbuminemia
- Features of proximal tubular dysfunction

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Case 7

A 3 year male child

- Incidentally detected 1+ proteinuria during acute febrile illness
- Persistent on follow up
- UPCR 0.8 mg/mg
- 24 hrs urine protein 456 mg

Type of Proteinuria?

Urine ACR <30

- Received ACEi for 6 months
- Sub-nephrotic Proteinuria persisted
- Role of Kidney biopsy ??

- Urine beta 2 microglobulin > 50,000 mcg

- Clinical exome sequencing
  - Dent's disease type 1
  - X-linked recessive inheritance

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Summary

- Proteinuria could be a sign of potential renal disease & important risk factor for progression
- Symptomatic proteinuria calls for immediate investigation and treatment
- Asymptomatic, non-orthostatic, non-nephrotic proteinuria warrants careful evaluation & follow up
- All patients with structural abnormalities of kidneys and urinary tract should be monitored for proteinuria & Hypertension.
- Early initiation of treatment retards progression of renal disease

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