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Clinical Presentations of Kidney Disease (other than Renal Failure)

1. **Glomerular syndromes**
    a. Proteinuria and nephrotic syndrome
    b. Hematuria and acute nephritis
2. **Tubular syndromes**
    a. Fanconi syndrome
    b. Renal tubular acidosis (RTA)
    c. Loss of concentrating ability (polyuria)
3. **Vascular diseases of the kidney**
    a. Hypertension
    b. Hemolytic uremic syndrome

The study and classification of renal parenchymal disease is traditionally based on identifying the primary target of injury. The targets of injury in the kidney include the glomeruli, the blood vessels and the tubulointerstitial compartment. The clinical presentations are somewhat distinctive for each target of injury, at least in the early phases. Injury beginning in any of these compartments eventually affect the other compartments and thus the clinical picture tends to converge toward nonspecific renal failure with scarring in all compartments (**end stage renal disease** = ESRD).

1. Glomerular syndromes

The intact glomerulus filters the blood to form tubular fluid by restricting passage of protein and cells. When there is injury to the filtration barrier, proteins and RBC pass into the tubular fluid and urine. Glomerular injury is thus characterized by proteinuria and hematuria. Proteinuria or hematuria may be asymptomatic and thus the first sign of glomerular disease may be an abnormal urinalysis (sometimes listed as the syndrome of "**asymptomatic urinary abnormalities**"). Neither proteinuria nor hematuria are specific for glomerular disease and therefore some refinement in the analysis of these finding is necessary for proper diagnosis of the problem.

a. Proteinuria and nephrotic syndrome

The glomerulus restricts passage of protein into the urine on the basis of size and charge. A reasonable model of the filtration barrier is that it contains pores restricting molecules with effective molecular radius above 40-45 A and contains widely distributed polyanionic molecules which limit passage of negatively charged proteins (like **albumin** which is 66 kD with effective molecular radius of approximately 36 A but with a strong net negative charge). Small, neutral or cationic proteins are filtered and mostly reabsorbed in the proximal tubule where they are recycled or metabolized.

In the thick ascending limb of the loop of Henle, Tamm-Horsfall protein is secreted into the tubule. The normal function of this protein is not known though it is suspected that it is antibacterial. Because of its tendency to form into a gel, it appears to form the matrix of cellular casts in the urine in pathologic conditions.

Normal urinary protein excretion is less than 150 mg/day, two-thirds of which is Tamm-Horsfall protein.

Screening for abnormal urinary protein excretion is usually done by **Dipstick** which gives a color reaction as follows: Negative; 1+ at 30mg/dl urine; 2+ 100 mg/dl urine; 3+ at 300 mg/dl urine; 4+ at over 1000 mg/dl urine. The dipstick primarily detects albumin.

Urinary protein/creatinine ratio ($U_{P/Cr}$) estimates the 24-hour protein excretion from a spot urine collection. Normal creatinine excretion is approximately 1-1.5 g/day so $U_{P/Cr}$ (when protein and creatinine are expressed in the same units) gives a reasonable estimation of daily protein excretion in grams.

More precise quantitation of protein excretion is often attempted with a **24 hr urine collection** (though this technique is prone to error in collection and the total excretion of creatinine should be measured simultaneously to assure collection adequacy)

Abnormal protein excretion has 3 patterns:

Glomerular pattern – primarily albumin

Tubular pattern – primarily small molecular weight proteins (especially β2-microglobulin MW=11.8 kD) from failure of injured tubules to reabsorb and process normally filtered proteins

Over production pattern (Bence-Jones proteinuria) – monoclonal light chains in plasma cell dyscrasia; an important point is that the dipstick will not reliably detect Bence-Jones proteins

Proteinuria is therefore not specific for glomerular injury. In addition to tubular injury, it may result from inflammation anywhere in the urinary tract. Transient proteinuria (with a mixed glomerular and tubular pattern) can result from exercise or fever by unclear mechanisms (perhaps stress hormone mediated hemodynamic changes). Orthostatic proteinuria is a benign condition seen in up to 5 % of adolescents. In all of these non-specific conditions the proteinuria is generally low grade (usually less than 1 g/day). Persistent, "high grade" proteinuria (> 2 g/day) usually signifies significant injury to the glomerular capillary loop. Isolated proteinuria (up to approximately 3.5 g/day in an adult) may likely be asymptomatic. Urinary protein excretion greater than 3.5 g/day/1.73 m^2 is often termed "nephrotic range proteinuria" and will likely present with the full blown nephrotic syndrome.

Nephrotic syndrome = Proteinuria > 3.5g/day/1.73 m^2 + Hypoalbuminemia + Edema + Hypercholesterolemia

Glomerular proteinuria can be characterized as selective or non-selective based on the ratio of the clearance of IgG to that of albumin or transferrin in the urine (IgG is a γ globulin with MW 150 kD; transferrin is in the β1 band on protein electrophoresis and has MW 88 kD).

Highly selective proteinuria

- $C_{IgG}:C_{Albumin}$ or $C_{IgG}:C_{Transferin}$ is < 0.1
- Indicates proteinuria is primarily due to defective charge selectivity with intact size selectivity
- Characteristic of childhood minimal change disease

Non-selective proteinuria

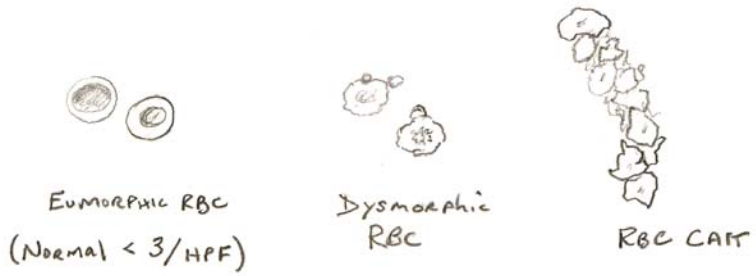
- $C_{IgG}:C_{Albumin}$ or $C_{IgG}:C_{Transferin}$ is > 0.2
- Indicates a significant component of abnormal size selectivity
- Mixed size and charge selectivity defect with non-selective proteinuria is usual with most diseases causing glomerular proteinuria other than minimal change disease

b. Hematuria and acute nephritis

Normal urine averages 120,000 RBC/day with a normal range said to be up to 1,000,000 RBC/day.

Hematuria (blood in the urine) may be obvious to the naked eye ("macroscopic") or may be detected only on urinalysis ("microscopic"). Dipstick screening detects hemoglobin with a sensitivity corresponding to 5-20 RBC/microliter of urine (5 RBC/μL X 10^6 μL /L X 1.5 L urine production/day = 7,500,000 RBC/day). Finding 4 RBC/HPF (high power field) on microscopic examination of the spun urine (which most would agree is significant microhematuria) corresponds to 2-8 RBC/microliter urine. A positive dipstick without RBC on microscopic analysis suggests free hemoglobinuria or myoglobinuria.

Hematuria may have its source anywhere in the urinary tract (or contamination from the genital tract) and may result from an extended list of pathologic processes (e.g., infections, stones or neoplasia). Tubulointerstitial nephritis causes hematuria and may be difficult to distinguish from glomerular disease in the differential diagnosis of acute nephritis. **"Glomerular hematuria"** is indicated by the presence of "dysmorphic" RBC, RBC casts or associated significant proteinuria.



There are several definable clinical patterns of glomerular hematuria:

- **Chronic asymptomatic microscopic hematuria**
- **Gross (macroscopic) hematuria (acute or recurrent)**

- **Acute nephritis** =
  Acute onset of glomerular hematuria with variable proteinuria, azotemia, oliguria, hypertension and edema
- **Rapidly progressive glomerulonephritis (RPGN)** =
  Acute nephritis with progression to severe renal failure in days to weeks

2. Tubular syndromes

Tubular injury is characterized by abnormalities of solute transport.

Tubulointerstitial diseases may present as **acute renal failure (ARF)** and acute tubular necrosis (ATN) is, in fact, the most common cause of intrinsic ARF in adults. Tubulointerstitial disease may also progress insidiously and present in the late stages as **chronic renal failure**. During chronic progression to renal failure, the patient may manifest findings (sometimes subtle) indicative of renal tubular damage ("tubular" syndromes).

a. Fanconi syndrome=
Generalized loss of proximal tubule function (glycosuria without diabetes mellitus, aminoaciduria, phosphaturia, uricosuria and proximal RTA)

b. Renal tubular acidosis (RTA) = Metabolic acidosis due to failure of renal acid excretion

Three types:
1) Type 1: inadequate proton secretion in the distal nephron
2) Type 2: defective bicarbonate reabsorption in the proximal tubule
3) Type 4: impaired aldosterone effect with hyperkalemia and acidosis

c. Defective urinary concentrating ability usually manifested as **polyuria, nocturia and isosthenuria**

3. Vascular disease in the kidney

Vascular injury causes hypoperfusion and ischemic renal damage.

The onset of vascular damage may be sudden (as with **renal involvement in a systemic vasculitis**) but is more commonly chronic and progressive and clinically silent for most of its course. Chronic injury is often associated with **hypertension** and atherosclerosis. Hypertension is both a cause and effect of vascular injury in the kidney.

Renovascular hypertension is the syndrome of elevation of blood pressure due to conditions interfering with arterial perfusion of the kidney (such as renal artery stenosis) and is caused by stimulation of the renin-angiotensin-aldosterone system.

Arterionephrosclerosis is the pattern of vascular and parenchymal kidney damage resulting from systemic hypertension from any cause.

One distinctive form of microvascular injury, thrombotic microangiopathy, is associated with the **hemolytic uremic syndrome (HUS =** Hemolytic anemia + renal failure + thrombocytopenia**)**.