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- Measurement of Tubular Function
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- Chronic Tubulointerstitial Nephritis

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- Toxins

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- Toxins

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- Vasculitides
- Rheumatoid Arthritis (RA)
- Cancer
- Infections
- HIV-Associated Renal Disease

# Diuretics

- References
NORMAL RENAL FUNCTION

RENAL STRUCTURE AND FUNCTION

Nephron
- the individual renal tubule and its glomerulus
- glomerulus
  - Bowman’s capsule - blind end of the renal tubule
  - glomerular capillaries - filtering membrane which consists of
    A) fenestrated endothelial cells
    B) basement membrane
    C) podocytes of visceral epithelial cells
- mesangium - consists of scattered cells with contractile and phagocytic function which are capable of laying down both matrix and collagen and of secreting biologically active mediators
- proximal convoluted tubule (PCT)
  - reabsorbs 65% of glomerular filtrate, including glucose, amino acids, proteins, vitamins via active transport (water follows passively)
  - reabsorbs ~2/3 of filtered Na⁺ mostly via electroneutral Na⁺ – H⁺ exchange
  - important site of ammoniagenesis
- loop of Henle
  - 25% of filtered Na⁺ is absorbed at the thick ascending limb mostly via channel mediated (Na⁺-K⁺-2Cl⁻) reabsorption of Na⁺, K⁺, and Cl⁻
  - 15% of filtered water is removed in loop of Henle
- distal convoluted tubule (DCT)
  - reabsorbs 5-10% filtered Na⁺ probably via directly coupled NaCl pathway (without K⁺)
  - relatively impermeable to water (5% of filtered water is removed in this segment)
  - late distal segment is a site of ADH and aldosterone action
- juxtaglomerular (J-G) apparatus
  - adjacent to glomerulus where afferent arteriole enters
  - consists of
    - myoeptithelial cells - modified granulated smooth muscle cells in the media of the afferent arteriole that contain renin
    - macula densa - specialized region of the distal tubule which controls renin release
- collecting duct system
  - final regulation of fluid and electrolyte balance
  - along with late distal segment, responds to ADH and aldosterone

RENAL HEMODYNAMICS

- Renal Blood Flow (RBF) = 20–25% of cardiac output = 1200 mL/minute
- Renal Plasma Flow (RPF) = RBF x (1 - hematocrit) = 600 mL/minute
- Glomerular Filtration Rate (GFR)
  - plasma volume filtered across glomeruli to Bowman’s capsule per unit time
  - 20% of RPF = 120 mL/min
  - maximal in young adulthood and decreases thereafter
- Filtration Fraction (FF)
  - volume of plasma filtered across glomeruli, relative to the volume of plasma flowing to the kidneys per unit time
  - FF = GFR/RPF
  - as RBF and RPF decrease, FF must increase to preserve GFR; this is done by Angiotensin II (All)

CONTROL OF RENAL HEMODYNAMICS

- goal is maintenance of GFR in the face of varying RBF (autoregulation)
- mechanism
  - decreased RBF —> renin released from juxtaglomerular apparatus
  - renin activates angiotensinogen —> Angiotensin I
  - Angiotensin Converting Enzyme (ACE) activates AI —> All
  - All constricts efferent renal arterioles, leading to an increase in filtration fraction, maintaining GFR in the face of decreased RBF
NORMAL RENAL FUNCTION . . . CONT.

TUBULAR REABSORPTION AND SECRETION
- the ultrafiltrate which crosses the glomerular capillaries into Bowman’s space starts its journey along the tubular system
- in the tubule, it is further modified by reabsorption (tubular lumen to bloodstream) or secretion (bloodstream to tubular lumen)

<table>
<thead>
<tr>
<th>Table 1. Processes Occurring Along the Nephron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>PCT</td>
</tr>
<tr>
<td>Thick Ascending Limb of Loop of Henle</td>
</tr>
<tr>
<td>DCT</td>
</tr>
</tbody>
</table>

ENDOCRINE FUNCTION OF THE KIDNEY

**Erythropoietin**
- hormone produced by kidneys (and liver to a lesser degree) in response to hypoxia
- stimulates erythrocyte production and maturation
- produced in kidneys by fibroblast-like cells in cortical interstitium
- responds in 1.5 to 2 hours
- in renal disease anemia results from decreased renal capacity for Epo production and release, as well as decreased red blood cell life span (toxic hemolysis)

**Vitamin D**
- vitamin D is converted to the 25-hydroxy-vitamin D form in the liver
- the kidney converts 25-hydroxy-vitamin D to 1,25-dihydroxy-vitamin D
- in renal disease this capacity becomes impaired and contributes to the tendency towards hypocalcemia and subsequent secondary hyperparathyroidism (since 1,25-dihydroxy-vitamin D is necessary for intestinal calcium absorption)

MEASUREMENT OF RENAL FUNCTION

**Serum Creatinine**
- an indirect estimate of renal function using a product of creatinine metabolism
- value is dependent on muscle mass as well as renal function (e.g. an elderly woman with chronic renal failure may have the same creatinine concentration as a 30 year old weightlifter)
- changes in creatinine concentration may reflect pathology better than absolute values of creatinine (true GFR overestimated since secreted by tubules)
- creatinine values may not be reflective of degree of renal disease as creatinine concentration does not start to rise significantly until GFR is quite diminished

![Figure 4. Serum Creatinine Concentration as a Function of GFR](image)

**Creatinine Clearance**
- estimate of GFR
- should be full 24 hour collection

![Figure 3. Vitamin D Activation](image)
NORMAL RENAL FUNCTION . . . CONT.

- Creatinine clearance as a reflection of GFR can be estimated by the following formula:
  \[
  \text{GFR} = \frac{\text{UCr} \times \text{Vu}}{\text{PCr}}
  \]
  - UCr is urine creatinine concentration
  - Vu is urine flow rate
  - PCr is plasma creatinine concentration

- Alternatively, GFR can be estimated using the formula:
  \[
  \frac{(140 \text{ - age})(\text{weight}) \times 1.2 \text{ (men)} \text{ or } 0.85 \text{ (women)}}{\text{PCr}}
  \]
  - age in years, weight in kg, PCr in umol/L
  - Normal value ranges from 75-120 ml/min

**Clinical Pearl**
- There is an inverse relationship between serum creatinine concentration and creatinine clearance (e.g., if serum creatinine doubles in a given person, creatinine clearance has been halved).

**Blood Urea Nitrogen (BUN)**
- Less accurate and should not be used alone as a test of renal function
- Modified by ECF volume, protein intake, catabolism, renal blood flow
- Secreted and reabsorbed in nephron

**MEASUREMENT OF TUBULAR FUNCTION**
- Urinary concentration
  - A.m. urine osmolality or specific gravity (s.g.)
- Acidification (i.e., appropriate urine pH given serum pH)
  - If urinary pH is > 5.3 when patient is acidic consider RTA (exceptions exist)
- Potassium excretion
  - Can calculate the Trans-Tubular K⁺ Gradient (TTKG)
  - The value assesses distal tubular K⁺ secretion and can be helpful in the setting of hypokalemia or hyperkalemia (see below)
  \[
  \text{TTKG} = \frac{\text{UK}}{\text{PK}} \times \frac{\text{Uosm}}{\text{Posm}}
  \]
  - UK is urinary K⁺ concentration
  - PK is plasma K⁺ concentration
  - Uosm is urinary osmolarity
  - Posm is plasma osmolarity

- Fractional Excretion (FE) of various solutes (X)
  \[
  \text{FEX} = \frac{\text{UX}}{\text{PX}} \times 100\%
  \]
  \[
  \text{Ucr/Pcr}
  \]

**The Kidney in Pregnancy**
- Increased kidney size and dilatation of renal pelvis and ureters (increased UTI risk) due to increased progesterone levels leading to increased smooth muscle relaxation of the collecting system
- 50% increase in GFR along with decreased creatinine and BUN
- 25-50% increase in renal blood flow
- Blood pressure falls in 1st trimester (100/60), rises slowly toward normal in 2nd and 3rd trimesters
- Glucosuria, slight proteinuria (< 200 mg/24 hours) often occur

**Renal Risk Factors for Adverse Pregnancy Outcome**
- Pre-existing hypertension
- Creatinine ≥ 180 umol/L
- Nephrotic-range proteinuria
- Active UTI
- Collagen-vascular disease, especially if not in remission or if associated with antiphospholipid antibodies
URINE STUDIES

GENERAL
- freshly voided specimen
- use dipstick for urinalysis (specific gravity, pH, glucose, protein, hemoglobin, nitrites, leukocytes)
- centrifuge for 3-5 minutes
- resuspend sediment and perform microscopy to look for cells, casts, crystals, and bacteria

URINALYSIS

Specific Gravity
- the ratio of weights of equal volumes of urine and H₂O (measures weight of solutes in urine)
- an estimate of urine osmolality (and if kidneys are working, of the patient's state of hydration)
- values < 1.010 reflect dilute urine, values > 1.020 reflect concentrated urine
- may get falsely high values if losing glucose or proteins in urine

pH
- urine pH is normally between 4.5-7.0
- if persistently alkaline, consider:
  - renal tubular acidosis
  - UTI with urease producing bacteria (e.g. Proteus)

Glucose
- freely filtered at glomerulus and reabsorbed in proximal tubule
- may indicate hyperglycemia (once blood glucose levels exceed 9-11 mmol/L, renal tubular capacity for reabsorption of glucose is overwhelmed)
- in the absence of hyperglycemia, may indicate proximal tubule dysfunction (e.g. Fanconi syndrome - pan PCT transport dysfunction with glucosuria, aminoaciduria, phosphaturia, uricosuria, hypocalcemia, hypomagnesemia and proximal RTA) or increased GFR (e.g. pregnancy)

Protein
- detection by dipstick only measures albumin levels in urine
- therefore, other protein such as Bence-Jones may be missed on dip but will be detected by other means such as acid precipitation
- false +ve on dip: pH > 7, concentrated urine, blood contamination
- false -ve: dilute urine dipsticks are available to detect microalbuminuria (i.e. very small amounts of albumin) in order to monitor the onset/progress of diabetic renal disease
- gold standard is the 24 hour urine collection for total protein (see Proteinuria section)

Clinical Pearl
- If a patient has clinically (dipstick) detectable proteinuria it is unnecessary to send urine for microalbumin levels!

Nitrites
- nitrates in urine are converted by bacteria to nitrites
- positive result suggests but does not make the diagnosis of UTI
- false +ve: contamination
- false -ve: inadequate bladder retention time (takes 4 hrs to convert nitrates to nitrites), prolonged storage of urine (leads to degradation of nitrites), certain pathogens (S. faecalis, other gram-positive organisms, N. gonorrhoea, and Mycobacterium tuberculosis) do not convert nitrates to nitrites

Ketones
- positive result can occur with: prolonged starvation, fasting, alcoholic or diabetic ketoacidosis
- false +ve: high urine ascorbic acid, very acidic urine of high specific gravity, abnormal-coloured urine; urine containing levodopa metabolites

Hemoglobin/RBCs
- high urine ascorbic acid can give false -ve dipstick result
- if urine dip positive for blood but no RBC on microscopy, may indicate hemoglobinuria (e.g. hemolysis) or myoglobinuria (e.g. rhabdomyolysis)

MICROSCOPY (see Hematuria section) (see Colour Atlas NP1-10)

Erythrocytes
- normal is up to 2-3 RBCs per high power field (HPF)
- spiculated, polymorphic RBCs suggest glomerular bleeding
- non-spiculated, uniform RBCs suggest extraglomerular bleeding
Leukocytes
- up to 3 per HPF is acceptable
- detection of leukocytes by dipstick leukoesterase method indicates at least 4 per HPF
- indicates inflammatory process in the urinary system (e.g. UTI)
- if persistent sterile pyuria consider chronic urethritis, prostatitis, interstitial nephritis (especially if WBC casts), renal TB, viral infections, calculi, papillary necrosis
- eosinophiluria suggests allergic interstitial nephritis, cholesterol emboli syndrome

Casts
- protein matrix formed by gelation of Tamm-Horsfall mucoprotein (glycoprotein excreted by renal tubule) trapping cellular debris in tubular lumen and moulding it in the shape of the tubules

Table 2. Interpretation of Casts

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaline</td>
<td>Not indicative of disease</td>
</tr>
<tr>
<td>RBC</td>
<td>Glomerular bleeding (e.g. glomerulonephritis)</td>
</tr>
<tr>
<td>Leukocyte</td>
<td>Pyelonephritis, Interstitial nephritis</td>
</tr>
<tr>
<td>Heme-granular</td>
<td>ATN, Proliferative GN</td>
</tr>
<tr>
<td>Fatty casts/oval fat bodies</td>
<td>Nephrotic syndrome</td>
</tr>
</tbody>
</table>

Crystals
- most have no pathologic significance, resulting from urinary concentration, acidification and cooling of urine
- calcium oxalate: double pyramids appearing as a square containing a cross; might indicate ethylene glycol toxicity
- calcium phosphate: narrow rectangle needles, clumped in a radiating pattern
- uric acid: red/brown, rhomboid shaped
- calcium magnesium ammonium pyrophosphate (triple phosphate): coffin lids; associated with recurrent UTI by urea-splitting organisms (Proteus, Klebsiella)

URINE ELECTROLYTES
- can be used to evaluate the source of an electrolyte abnormality or to grossly assess tubular function
- Na⁺, K⁺, Cl⁻, osmolality and pH are commonly measured
- there are no 'normal' values; output is based on intake in properly functioning kidneys and in disease states, the values are interpreted in light of the pathology

Examples of Common Urine Electrolyte Abnormalities

Table 3. Distinguishing Pre-Renal from Intra-Renal Disease in Acute Renal Failure

<table>
<thead>
<tr>
<th>Index</th>
<th>Pre-Renal</th>
<th>Intra-Renal (e.g. ATN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Osmolality</td>
<td>&gt; 500</td>
<td>&lt; 350</td>
</tr>
<tr>
<td>Urine Sodium (mmol/L)</td>
<td>&lt; 20</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>FENa⁺</td>
<td>&lt; 1%</td>
<td>&gt; 3%</td>
</tr>
<tr>
<td>Plasma BUN/Cr (SI Units)</td>
<td>&gt; 80:1</td>
<td>&lt; 40:1</td>
</tr>
</tbody>
</table>

- high urine Na⁺ in the setting of acute renal failure indicates intrarenal disease or the presence of non-reabsorbable anions (e.g. ketones)
- high urine Na⁺ in the setting of hyponatremia: diuretics, tubular disease (eg. Bartter's syndrome), SIADH
- a high FENa⁺ but low PECI⁺ is seen in metabolic alkalosis secondary to vomiting
- osmolality is useful to estimate the kidney's concentrating ability
- the value for (Na⁺ + K⁺)-Cl⁻, also known as the urine net charge, is useful in discerning the cause of metabolic acidosis:
  - a negative value indicates the presence of unmeasured positive ions (i.e. ammonium) which is seen in metabolic acidosis 2º to non-renal causes (e.g. diarrhea)
  - a positive value suggests RTA, where ammonium excretion is not elevated and the urine net negative charge is positive
- urine pH is useful to grossly assess renal acidification
  - 'low' pH (< 5.5) in the presence of low serum pH is an appropriate renal response
  - a high pH in this setting might indicate a renal acidification defect (RTA which is a collection of low ammonium excretion diseases)
**ABNORMAL RENAL FUNCTION**

**PROTEINURIA**

Proteinuria
(determine using dipstick and/or 24 hour urine collection)

Physiological
young healthy persons

Orthostatic
• proteinuria occurs with standing
• 5% of adolescents
• generally resolves spontaneously

Pathological
(determine with urine protein electrophoresis and 24 hour urine collection)

Constant
• rule-out underlying disease and follow-up
• may develop renal disease in the future

Tubulointerstitial
• usually < 2g/24 hour
• mixed LMW proteins

Glomerular
• usually > 2g/24 hour
• primarily albumin

Overflow
• < 2g/24 hour
• primarily light chains and LMW proteins
• occurs with increased GFR, increased plasma light chain concentration

Primary
Proliferative
Nonproliferative

Secondary
Proliferative
Nonproliferative

**Figure 5. An Approach to Proteinuria**

**Table 4. Quantitative Proteinuria**

<table>
<thead>
<tr>
<th>Daily Protein Excretion</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150 mg</td>
<td>Normal</td>
</tr>
<tr>
<td>150 mg - 2 g</td>
<td>Glomerular disease</td>
</tr>
<tr>
<td></td>
<td>Tubular disease</td>
</tr>
<tr>
<td></td>
<td>Orthostatic</td>
</tr>
<tr>
<td></td>
<td>Overflow</td>
</tr>
<tr>
<td>2 g - 3 g</td>
<td><strong>Usually glomerular</strong></td>
</tr>
<tr>
<td></td>
<td>May be tubular</td>
</tr>
<tr>
<td>&gt; 3 g</td>
<td><strong>Almost always glomerular</strong></td>
</tr>
<tr>
<td></td>
<td>Unless light chains (multiple myeloma)</td>
</tr>
</tbody>
</table>

- normally < 150 mg protein/day is lost in the urine
  - 40% albumin
  - 40% Tamm-Horsfall mucoprotein (from cells of the ascending limb of the Loop of Henle (i.e. does not arise from the plasma and forms the matrix for casts)
  - 15% immunoglobulin
  - 5% other plasma proteins
- filtration of plasma proteins at the glomerular capillary interface is based on
  - size
    - fenestration in the basement membrane excludes protein with a MW > albumin (60,000)
    - proteins of MW less than albumin may filter through glomerular barrier but are normally reabsorbed and catabolized by renal tubular cells
  - charge
- glomerular dysfunction produces proteinuria, usually > 2 g/day consisting of higher MW proteins (especially albumin) resulting in decreased oncotic pressure causing:
  - hyperlipidemia due to hepatic lipoprotein synthesis stimulated by the decreased plasma oncotic pressure
  - tissue edema
ABNORMAL RENAL FUNCTION . . . CONT.

- with tubular dysfunction there is no hyperlipidemia because albumin is not lost, although modest excretion of LMW proteins (up to 2g/day) may occur (there may be associated edema but this is due to decreased GFR and therefore salt and water retention, not to hypoalbuminemia)
- rarely, "overflow" proteinuria occurs where the filtered load of proteins (usually LMW) overwhelms tubular capacity for reabsorption
  - filtered load = GFR x plasma protein concentration
  - "overflow" proteinuria occurs secondary to:
    - increased GFR (e.g. in pregnancy)
    - increased plasma protein concentration (e.g. immunoglobulin light chains - multiple myeloma)

HEMATURIA
- gross hematuria: pink, red, or tea-coloured urine
- microscopic hematuria: appears normal, may be detected by dipstick
- age-related causes:
  - glomerular causes predominate in children and young adults
  - fewer than 5% of cases of hematuria in patients age > 40 result from glomerular lesions

<table>
<thead>
<tr>
<th>Hematuria but NO RBCs on microscopy</th>
<th>True Hematuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudohematuria</td>
<td>Hematological</td>
</tr>
<tr>
<td>• coloured urine but negative dipstick</td>
<td>• coagulopathy</td>
</tr>
<tr>
<td>• differential diagnosis</td>
<td>• sickle hemoglobinopathies</td>
</tr>
<tr>
<td>• food (e.g. beets)</td>
<td>•</td>
</tr>
<tr>
<td>• dyes</td>
<td></td>
</tr>
<tr>
<td>• medication (e.g. rifampin)</td>
<td></td>
</tr>
</tbody>
</table>

Hematological
- coagulopathy
- sickle hemoglobinopathies

Nephrological
- (casts and/or protein)

Urological
- (no casts or protein)
  • think anatomically:
    - ureter
    - bladder
    - urethra
    - miscellaneous (e.g. TB)

Hematological
- coagulopathy
- sickle hemoglobinopathies

Figure 6. An Approach to Hematuria

Investigations for Hematuria
- guided by history and physical findings
- standard initial workup
  - urine R&M, C&S
  - BUN, Cr
- if find casts and/or protein in urine: think nephrologic problem
  - further investigations
    - CBC, glucose, lytes
    - 24 hr urine protein and creatinine
- if find RBCs only (no casts, no protein), gross hematuria in only part of the urine stream and/or pain on urination: think urologic problem
  - further investigations
    - CBC
    - KUB, abdo/pelvic U/S
    - ± urology consult
- other possible investigations: complement, ASOT, ANA, ANCA, anti-GBM Abx, cryoglobulins, Hep B and C screening, HIV
ELECTROLYTE DISORDERS

HYPONATREMIA/HYPERNATREMIA

Introduction
- Hyponatremia/hypernatremia are disorders of water balance
- Hyponatremia suggests too much and hypernatremia is too little water in the extracellular fluid relative to Na+
- Hyponatremia and hypernatremia can each be associated with normal, decreased or increased total body Na+
- ECF volume is determined by Na+ content, not Na+ concentration (Na+ deficiency or excess leads to ECF volume depletion or expansion, respectively)
- Water moves out of cells in response to increased osmolality and into cells in response to decreased osmolality of ECF (as long as the osmoles do not freely traverse the plasma membrane, as does urea)
- Clinical signs and symptoms of hyponatremia/hypernatremia are secondary to cells (especially in brain) shrinking (hypernatremia) or swelling (hyponatremia)

Table 5. Clinical Assessment of ECF Volume (Total Body Na+)

<table>
<thead>
<tr>
<th></th>
<th>Hypovolemic</th>
<th>Hypervolemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JVP</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Orthostatic drop</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Auscultation of heart</td>
<td>Tachycardia</td>
<td>S3</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td>Inspiratory crackles</td>
</tr>
<tr>
<td>Interstitial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin turgor</td>
<td>Decreased</td>
<td>Normal/increased</td>
</tr>
<tr>
<td>Absent</td>
<td></td>
<td>Present</td>
</tr>
<tr>
<td>Edema</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output</td>
<td>Decreased</td>
<td>Variable</td>
</tr>
<tr>
<td>Decreased</td>
<td></td>
<td>Increased</td>
</tr>
<tr>
<td>Body weight</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Hct, serum protein</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hyponatremia

<table>
<thead>
<tr>
<th>Na+</th>
<th>H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>hypovolemic hyponatremia (e.g. diuretics, gastroenteritis)</td>
</tr>
<tr>
<td>Na+</td>
<td>H2O</td>
</tr>
<tr>
<td>normal</td>
<td>euvolemic hyponatremia (e.g. SIADH)</td>
</tr>
<tr>
<td>Na+</td>
<td>H2O</td>
</tr>
<tr>
<td>normal</td>
<td>hypervolemic hyponatremia (e.g. CHF, cirrhosis + ascites, nephrosis + edema)</td>
</tr>
</tbody>
</table>

Hypernatremia

<table>
<thead>
<tr>
<th>Na+</th>
<th>H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>hypovolemic hypernatremia (e.g. no access to water: coma, babies)</td>
</tr>
<tr>
<td>Na+</td>
<td>H2O</td>
</tr>
<tr>
<td>normal</td>
<td>euvolemic hypernatremia (e.g. diabetes insipidus)</td>
</tr>
<tr>
<td>Na+</td>
<td>H2O</td>
</tr>
<tr>
<td>normal</td>
<td>hypervolemic hypernatremia (rare, e.g. Na+ ingestion, hypertonic saline)</td>
</tr>
</tbody>
</table>

Figure 7. Classification of Hyponatremia/Hypernatremia

HYPONATREMIA
- Hyponatremia is defined as a decrease in serum [Na+] to < 136 mmol/L

Clinical Features
- Depend on degree of hyponatremia and more importantly, rapidity of onset
- Neurologic symptoms prexunate - secondary to cerebral edema
- Early: nausea, anorexia, malaise, lethargy, weakness, somnolence
- Late: headache, decreased level of consciousness (LOC), seizures, death
- Work-up includes ECF volume status assessment, serum osmolality, serum electrolytes, glucose, creatinine, urine osmolality, urine Na+ concentration, and urine R & M
### ELECTROLYTE DISORDERS . . . CONT.

#### HYponatremia

**Hyper-Osmolar**
- Extra osmoles in ECF draw water out of cells diluting the Na⁺ in ECF
- Usually glucose (rarely mannitol)
- Every 10 mmol/L increase in blood glucose results in 3 mmol/L decrease in Na⁺

**Iso-Osmolar (factitious)**
- Normal ECF osmolality but increased plasma solids (lipids or proteins)
- Hyperlipidemia (e.g., familial, nephrotic syndrome, pancreatitis)
- Hyperproteinemia (e.g., multiple myeloma)

**Hypo-Osmolar (dilutional)**
- Most common causes of hyponatremia
- Draw water out of cells increased plasma solids diluting the Na⁺ in ECF

### Hypervolemic
- CHF
- ARF, CRF
- Cirrhosis and ascites
- Pregnancy

### Euvolemic
- SIADH
- Adrenal insufficiency
- Psychogenic polydipsia

### Hypovolemic
- Diuretics
- Salt-wasting nephropathy
- Diarrhea
- Excessive sweating
- Third spacing (e.g., peritonitis, pancreatitis, burns)

#### Treatment of Hyponatremia

**A. Definitely Acute** (known to have developed over < 24-48 hours)
- Most commonly occurs in hospital (dilute IV fluid and reason for ADH excess: e.g., post-operative)
- Less risk to rapid correction since adaptation has not fully occurred
- If symptomatic
  - Correct rapidly with 3% NaCl at 1-2 cc/kg/h up to PNa = 125-130 mmol/L
  - May need furosemide to deal with volume overload

**B. Chronic or Unsure**

1. **If Symptomatic** (seizures or decreased level of consciousness)
   - Must partially correct acutely
   - Aim for 1 of PNa by 1-2 mmol/L/hr for 4-6 hrs, but limit total rise to 8 mmol/L in 24 hrs
   - Use 3% NaCl at 1-2 cc/kg/hr
   - May need furosemide

2. **If Asymptomatic**
   - Water restrict (start with 1 L/day)
   - Correct underlying cause, e.g.
     - Treat CHF
     - Stop offending drug
     - Treat hypothyroidism
   - Consider IV 0.9% NaCl (normal saline) plus furosemide (causes urine excretion that is somewhat hypotonic)
   - Refractory: demeclocycline 300-600 mg PO bid
     - Causes renal resistance to ADH
   - Monitor electrolytes frequently to avoid over-rapid correction

---

**Figure 8. An Approach to Hyponatremia**

**Pathophysiology**
- Acute hyponatremia (< 24-48 hours)
  - More likely to be symptomatic
- Chronic hyponatremia (> 24-48 hours)
  - May still be symptomatic but less likely at any given degree of hyponatremia since adaptation occurs
  - Adaptation: mainly is an export of intracellular particles
  - Brain cell size returns towards normal
  - Risk of excessive brain cell shrinkage when hyponatremia corrected: may develop osmotic demyelination
  - Example of osmotic demyelination is central pontine myelinolysis:
    - Quadriplegia, cranial nerve palsies, decreased level of consciousness
    - May be irreversible

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- Most commonly occurs in hospital (dilute IV fluid and reason for ADH excess: e.g., post-operative)
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   - Monitor electrolytes frequently to avoid over-rapid correction
ELECTROLYTE DISORDERS . . . CONT.

C. **Patients at Particular Risk of Osmotic Demyelination**
   - those with associated
     - rise in PNa > 8 mmol/L/d if chronic hyponatremia
     - hypokalemia
     - malnutrition
     - hypovolemic hyponatremia after correction (stimulation for volume-mediated ADH rapidly disappears)
     - psychogenic polydipsia, deprived of water

**Impact of IV Solution on Plasma Na+**
- after selecting the appropriate infusate (e.g. 0.9% NaCl in water), can apply following formula to estimate the change in the serum Na⁺ caused by retention of 1 L of any infusate; TBW = 0.6 x wt(kg) for men, 0.5 x wt(kg) for women

\[
\text{change in serum Na}^+ = \frac{\text{infusate [Na}^+] - \text{serum [Na}^+]}{\text{TBW (L)} + 1 \text{ L}}
\]

**Syndrome of Inappropriate AntiDiuretic Hormone Secretion (SIADH)**
1. urine that is inappropriately concentrated for the serum
2. high urine sodium (> 10 meq/l)
3. high FENA⁺ because no ECFV depletion

**Table 6. Disorders Associated with SIADH**

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Pulmonary</th>
<th>CNS</th>
<th>Miscellaneous</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell CA</td>
<td>Pneumonia</td>
<td>Mass lesion</td>
<td>Post-op state</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Bronchogenic CA</td>
<td>Lung abscess</td>
<td>Encephalitis</td>
<td>Pain</td>
<td>TCAs</td>
</tr>
<tr>
<td>AdenoCA of pancreas</td>
<td>TB</td>
<td>Subarachnoid hemorrhage</td>
<td>Severe nausea</td>
<td>SSRIs</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>Acute respiratory failure</td>
<td>Stroke</td>
<td>HIV infection</td>
<td>Antineoplastics</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Positive pressure ventilation</td>
<td>Head trauma</td>
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<td>Vincristine</td>
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<td></td>
<td></td>
<td>Acute psychosis</td>
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<td>Cyclophosphamide</td>
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<tr>
<td></td>
<td></td>
<td>Acute intermittent porphyria</td>
<td></td>
<td>Other</td>
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<td></td>
<td></td>
<td>DDAVP</td>
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<td>Oxytocin</td>
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<td>Nicotine</td>
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<td>Carbamazepine</td>
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<td>Barbiturates</td>
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<td>Chlorpropamide</td>
</tr>
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<td></td>
<td>Barbiturates</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Chlorpropamide</td>
</tr>
</tbody>
</table>

**HYPERNATREMIA**
- hypernatremia is defined as an increase in serum [Na⁺] to > 145 mmol/L
- too little water relative to total body Na⁺; always a hyperosmolar state
- less common than hyponatremia because protected by thirst and the increased release of ADH
- almost always implies a problem with water intake

**HYPERNATREMIA**

**Hypervolemic (rare)**
- iatrogenic
  (hypertonic saline or NaHCO₃)
- Cushing's syndrome
- hyperaldosteronism
- treat with salt restriction, diuretics, water

**Non-Hypervolemic**
- Is patient putting out a small volume (500 mL/d) of maximally concentrated (> 800 mOsm/kg) urine?
  - No
    - urine osmole excretion rate > 750 mOsm/d
    - likely DI: renal response to DDAVP (50% increase in urine osmolality)
    - Nephrogenic DI
  - Yes
    - diuretics (loop)
    - osmotic diuresis
    - endogenous (urea with excess NG protein feeds)

**Figure 9. An Approach to Hypernatremia**
Clinical Features
- due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, coma, seizures, death ± polyuria, thirst, ± evidence of volume depletion
- increased risk of intracranial hemorrhage
- with chronic hypernatremia cells import and generate new osmotically active particles → cell size returns toward normal
- with acute hypernatremia - no time for such an adaptation → more likely to be symptomatic

Treatment of Hypovolemic Hypernatremia
- hypernatremia with ECF volume depletion implies a sodium AND water deficit. Give 1-2 L NS first to boost ECF volume and achieve hemodynamic stability then PO or NG tube water or IV 1/2 NS or D5W while monitoring (Na+) every 3-5 hrs
- hypernatremia with ECF volume excess should be treated with diuresis or with dialysis if renal failure present to remove excess total body Na+; water replacement can then be done using D5W
- in those patients with a water deficit and presumed normal total body sodium content, an approximation of water replacement needed to correct serum Na+ to normal is
  \[
  \text{H}_2\text{O deficit} = \frac{\text{TBW} \times (\text{serum Na}^+ - 140)}{140}
  \]
  - TBW = 0.6 x wt (Kg) for men, 0.5 x wt (Kg) for women
  - Correct H2O deficit with hypotonic IV solution (D5W or 1/2 NS)
- for example, consider a 70 kg male with serum Na+ = 168 mmol/L
  \[
  \text{H}_2\text{O deficit} = \frac{70 \times 0.6 (168 -140)}{140} = 8.4 \text{ L}
  \]
  - water content of hypotonic IV solutions varies; e.g. 1L D5W approximately equals 1L free water. 1L 1/2 NS approximately equals 500 ml free water
  - after selecting the appropriate infusate, can apply formula (see Hyponatremia section) to estimate the change in the serum [Na+] caused by retention of 1 L of any infusate
  - aim to replenish water deficit over 48-72 hours, lowering serum Na+ by no more than 0.5 mmol/L/h (12 mmol/L/d) except those in whom the disorder has developed over a period of hours; i.e. give 1/2 calculated H2O deficit in 24 hrs; correct remaining deficit in next 1-2 days
  - rapid correction may lead to cerebral edema; the brain creates additional intracellular osmoles in the setting of hypernatremia in order to retain water; if volume is then quickly restored fluid is drawn into the brain causing edema
  - besides correcting deficit, need to give fluids for maintenance and ongoing losses (e.g. 1/2 normal saline); this is helped by monitoring urine/stool losses and composition

Diabetes Insipidus (DI)
- central or nephrogenic
- central DI etiology: neurosurgery, granulomatous diseases, trauma, vascular events, CA
- nephrogenic DI etiology: lithium (most common), hypoK+, hyperCa+, congenital
- diagnosis of Diabetes Insipidus
  - urine 24 hour osmole excretion is not elevated
  - H2O deprivation for 12-18 hours; if fails to concentrate urine, DI probably present
  - if then responds to exogenous ADH (10 micrograms intranasally), central DI present and treat with DDAVP (ADH analogue)
  - if still fails to concentrate urine, nephrogenic DI present; must treat with water (D5W or PO), as kidneys do not respond to ADH; thiazides may help as well

HYPOKALEMIA
Factors which Increase Renal K+ Loss
- increased distal tubular flow rate and Na+ delivery
- increased aldosterone
- increased unreabsorbable anions in tubule lumen: HCO₃⁻, penicillin, salicylate
- hypomagnesemia
- K⁺ Excretion = (Urine flow rate)(Urine K⁺ concentration)
### Table 7. Causes of Hypokalemia

<table>
<thead>
<tr>
<th>Decreased Intake</th>
<th>Increased Loss</th>
<th>Redistribution into Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited dietary intake</td>
<td><strong>Non-renal</strong> (urine K⁺ loss &lt; 25 mmol/d)</td>
<td>Metabolic alkalosis</td>
</tr>
<tr>
<td>Clay ingestion</td>
<td>(a) Skin - unusual</td>
<td>Insulin (especially in total body K⁺ depletion)</td>
</tr>
<tr>
<td></td>
<td>(b) Diarrhea</td>
<td>β-2 agonists (ventolin), theophylline</td>
</tr>
<tr>
<td></td>
<td><strong>Renal</strong> (urine K⁺ loss usually &gt; 25 mmol/d, unless loss occurred previously)</td>
<td>Tocolytic agents</td>
</tr>
<tr>
<td></td>
<td>(a) Diuretics</td>
<td>Uptake into newly forming cells</td>
</tr>
<tr>
<td></td>
<td>• Furosemide</td>
<td>• Vitamin B₁₂ injections in pernicious anemia</td>
</tr>
<tr>
<td></td>
<td>• hydrochlorothiazide</td>
<td>• Colony stimulating factors ′WBC production</td>
</tr>
<tr>
<td></td>
<td>(b) Primary hyperaldosteronism or secondarily due to RAS</td>
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</tr>
<tr>
<td></td>
<td>(c) Vomiting (mainly due to bicarbonaturia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(d) Other rare causes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Renal tubular acidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inherited renal tubular lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>e.g. Bartter’s syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Amphotericin B</td>
<td></td>
</tr>
</tbody>
</table>

### Clinical Features

- Often have no symptoms, particularly when mild (3.0 – 3.5 mmol/L)
- With more severe hypokalemia, may see fatigue, generalized weakness, myalgia, constipation
- As hypokalemia becomes more severe, muscle necrosis, arrhythmias can occur and rarely paralysis can develop with eventual respiratory impairment
- Arrhythmias occur at variable level of [K⁺] – more likely if
  - Digoxin used
  - Hypomagnesemia present
  - Coronary artery disease
- ECG changes are more predictive of clinical picture than K⁺ levels
- ECG changes
  - Flattened or inverted T waves
  - U waves
  - Depressed ST segment
  - Prolongation of Q-T interval
  - With severe hypoK⁺ see P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity
- Can also assess plasma renin and aldosterone, as well as acid-base status, urinary electrolytes, and serum Mg²⁺ for causes of hypokalemia

### Treatment

- Serum levels do not correlate well with deficit (can have from 200-600 mmol or more deficit)
- Risk of hyperkalemia secondary to K⁺ supplements is especially high in elderly, diabetics, and patients with decreased renal function
- If urine output and renal function are impaired, correct with extreme caution
- Oral sources - food, tablets, KCl liquid solutions
- IV - usually KCl
  - Initially use saline solutions to mix, not dextrose, since this may exacerbate hypoK⁺ via insulin release
  - Maximum 40 mmol/L via peripheral vein, 60 mmol/L via central vein
  - Maximum infusion 20 mmol/hr
- K⁺-sparing diuretics (triamterene, spironolactone, amiloride) can prevent renal K⁺ loss
HYPERKALEMIA

Table 8. Causes of Hyperkalemia

<table>
<thead>
<tr>
<th>Factitious</th>
<th>Increased Intake</th>
<th>Cellular Release</th>
<th>Decreased Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>KCl tablets</td>
<td>Intravasc. Haemolysis</td>
<td>Decreased excretion</td>
</tr>
<tr>
<td>Prolonged use of tourniquet</td>
<td>Diet</td>
<td>Tumour lysis syndrome</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Sample hemolysis</td>
<td>IV KCl</td>
<td>Rhabdomyolysis</td>
<td>Effective circulating volume depletion</td>
</tr>
<tr>
<td>Leukocytosis (extreme)</td>
<td></td>
<td>Insulin deficiency</td>
<td>Hypoaldosteronism (see Table 9)</td>
</tr>
<tr>
<td>Thrombocytosis (extreme)</td>
<td></td>
<td>Hyperosmolar states</td>
<td>NSAIDS in renal insufficiency</td>
</tr>
<tr>
<td>Sample taken from vein into which IV is running</td>
<td></td>
<td>(e.g. hyperglycemia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metabolic acidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(except for ketoacidosis and lactic acidosis)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beta blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digitalis overdose</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Succinylcholine</td>
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</tr>
</tbody>
</table>

Table 9. Causes of Hypoaldosteronism

<table>
<thead>
<tr>
<th>Lack of Stimulus of Aldosterone Release</th>
<th>Primary Adrenal Problem</th>
<th>Aldosterone Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hyporeninemic, hypoaldosteronism</td>
<td>• Adrenal insufficiency of any cause</td>
<td>• K⁺ - sparing diuretics</td>
</tr>
<tr>
<td>• Associated with DM-2, NSAIDs, chronic interstitial nephritis</td>
<td>[e.g. Addison's disease, AIDS (due to CMV or other causes)], metastatic cancer</td>
<td>• Spironolactone</td>
</tr>
<tr>
<td>• Angiotensin converting enzyme inhibitors</td>
<td>• Heparin</td>
<td>• Amiloride</td>
</tr>
<tr>
<td></td>
<td>• Congenital adrenal hyperplasia with 21-hydroxylase deficiency</td>
<td>• Triamterene</td>
</tr>
</tbody>
</table>

Clinical Features

- usually asymptomatic but may develop muscle weakness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniagenesis and metabolic acidosis
- if severe, ECG changes and cardiotoxicity (do not correlate well with K⁺ concentration)
  - peaked and narrow T waves
  - decreased amplitude and eventual loss of P waves
  - prolonged PR interval
  - widening of QRS and eventual merging with T wave (sine-wave pattern)
  - AV block
  - ventricular fibrillation, asystole

Treatment

- acute therapy is warranted if K⁺ high, symptoms present, ECG changes
- general measures
  - perform ECG, repeat blood test, r/o pseudohyperkalemia (i.e. hemolyzed specimen)
  - hold exogenous K⁺ and K⁺ - retaining meds

1. Protect Heart

- Ca²⁺ gluconate 1-2 amps ONLY (10 mL of 10% solution) IV (cardioprotectant); giving more can result in calcium toxicity and death!

2. Shift K⁺ into Cells

- regular insulin (Insulin R) 10-20 units IV, with 1/2 to 1 amp D50W; must monitor blood glucose q1h
- NaHCO₃ 1-3 amps (given as 3 amps of 7.5% or 8.4% NaHCO₃ in 1L D5W)
- β₂-agonist (ventolin) in nebulized form
3. Enhance K⁺ Removal from Body
   A. via urine - try furosemide, may need IV NS to avoid hyperkalemia
      • try fludrocortisone (synthetic mineral corticoid) if suspect aldosterone deficiency
   B. via gut
      • cation-exchange resins: Calcium Resonium or Kayexalate (less preferred because it binds Na⁺ in exchange for K⁺) plus sorbitol PO to avoid constipation
      • kayexalate enemas with tap water (not sorbitol)
   C. dialysis (renal failure, life threatening hyperK⁺ unresponsive to therapy)

Clinical Pearl
- In patients with diabetes, increased K⁺ and hyperglycemia, often just giving insulin to restore euglycemia is sufficient to correct hyperkalemia.

ACID-BASE DISORDERS
- an approach (see Figure 10)
- normal HCO₃⁻ = 25 mEq/L
- normal pCO₂ = 40 mmHg

Figure 10. An Approach to Acid-Base Disorders

RENAL CONTRIBUTION TO ACID-BASE BALANCE
- proximal tubule
  • reabsorbs filtered HCO₃⁻ (stimulated by All, hypovolemia)
  • generates ammonium and HCO₃⁻ (stimulated by hypokalemia, intracellular acidosis)
- distal tubule excretes H⁺ produced by the body (stimulated by intracellular acidosis, hypokalemia, aldosterone) → bound to NH₃ (made in proximal tubule) as NH₄⁺
- dysfunction of either of these tubular processes may cause systemic acidemia (hence RTA)
- Type I RTA (distal)
  • unable to fully excrete daily H⁺ load and accumulates in body because of decrease in NH₄⁺ in urine
- Type II RTA (proximal)
  • impaired HCO₃⁻ reabsorption: lost in urine and buffer is depleted
- Type IV RTA
  • decreased aldosterone activity or aldosterone responsiveness
  • distal tubule can't excrete K⁺ → hyperkalemia
  • hyperkalemia causes insufficient ammoniagenesis to generate HCO₃⁻ and to accept H⁺ distally
- in setting of metabolic or respiratory acidosis, expect enhanced renal excretion of NH₄⁺
ACID-BASE DISORDERS . . . CONT.

1° METABOLIC ACIDOSIS

- to determine cause, first calculate the AG in blood sample
  \[ \text{AG} = \text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-) \]
- increased AG metabolic acidosis (4 types)
  1. Lactic
     - usually due to hypoxia, most commonly hypoperfusion, also low PO_2 or severe anemia
     - liver disease or severe ethanol abuse can impair lactate clearance and cause lactic acidosis
  2. Ketoacidosis
     - diabetic
     - starvation
     - alcoholic
  3. Toxins
     - methanol
     - ethylene glycol
     - salicylate
  4. Renal Failure (advanced)
     - normal anion gap metabolic acidosis
     - diarrhea
     - proximal RTA
     - distal RTA
     - urine union gap = \((\text{Na}^+) + (\text{K}^+) - (\text{Cl}^-)\)
       - if > 0, suggests problem is lack of NH_4^+ in urine (i.e. distal RTA)
       - if < 0, suggests adequate NH_4^+ in urine (cause likely diarrhea)
     - pure anion gap acidosis = fall in HCO_3^- matches the rise in anion gap
     - mixed AG/non-AG metabolic acidosis = fall of HCO_3^- greater than rise in AG (i.e. renal failure, diarrhea)
     - concurrent metabolic alkalosis = if the rise in AG is greater than the fall of HCO_3^- (or vice versa)
     - Osmolar gap = measured osmolality – calculated osmolality
       - where calculated osmolality = \(2 \times [\text{Na}^+] + [\text{urea}] + [\text{glucose}]\)
       - normal osmolar gap < 10
       - if gap > 10, consider: ethanol, methanol, ethylene glycol

Respiratory Compensation in Metabolic Acidosis

- hyperventilation such that the decrease in pCO_2 = decrease HCO_3^-
  - expected: 1-1.3 mmHg decreased PCO_2 for every 1 mEq/L decreased HCO_3^-
  - if pCO_2 decreases more than expected, there is also a 1° respiratory alkalosis
  - if pCO_2 decreases less than expected, there is also a 1° respiratory acidosis
  - if HCO_3^- = 15 (decrease by 10), expected pCO_2 = 27-30 (40-10 to 13)
  - if instead pCO_2 = 35, a respiratory acidosis is also present or,
    - if measured pCO_2 = 20, a respiratory alkalosis is also present

Treatment of Metabolic Acidosis

- treat underlying cause
- correct coexisting disorders of [K^+]
- consider giving exogenous alkali (usually NaHCO_3) if
  - severe reduction [HCO_3^-] e.g. < 5 mmol/L
  - no metabolizable anion (e.g. can metabolize only lactate or ketoacid anions, leading to regeneration of HCO_3^-)
  - no hypokalemia (e.g. giving HCO_3^- can exacerbate hypokalemia, so correct K^+ deficit first)
  - no ECF volume overload exists (since give Na^+ load with NaHCO_3)

1° METABOLIC ALKALOSIS

- etiology
  - generation of new HCO_3^-
    - GI loss (vomiting, NG suction)
    - diuretics (contraction alkalosis)
    - milk alkali syndrome, exogenous NaHCO_3
    - hypokalemia
    - impaired HCO_3^- excretion
      - reduced GFR
      - primary or secondary hyperaldosteronism; aldosterone causes greater H^+ loss via DCT H^+ pump leading to HCO_3^- generation; aldosterone promotes hypokalemia which is a stimulus for ammoniagenesis and HCO_3^- generation
  - other
    - Bartter's syndrome
    - hypomagnesemia
ACID-BASE DISORDERS ... CONT.

Categories and Treatment
- saline (chloride) sensitive metabolic alkalosis (most common)
  - ECF volume depletion
  - treatment: NaCl (volume repletion); replace coexisting KCl deficit
- saline (chloride) insensitive metabolic alkalosis
  - ECF volume normal or high
  - usually aldosterone or glucocorticoid excess
  - treatment involves correction of underlying disease, replenishing K⁺ and Mg⁺ deficits, and possibly spironolactone

Respiratory Compensation in Metabolic Alkalosis
- hypoventilation (an upper limit to compensation exists - breathing cannot be stopped)
- pCO₂ increases 0.5-0.7 mmHg for every 1 mEq/L increase in HCO₃⁻

I° RESPIRATORY ACIDOSIS (HYPOVENTILATION)

Causes
- can’t breathe
  - severe COPD
  - airway obstruction
  - severe parenchymal disorders
  - neuromuscular disorders
- won’t breathe
  - sedatives
  - central sleep apnea
  - hypothyroidism

Renal Compensation in Respiratory Acidosis
- the kidney synthesizes additional HCO₃⁻ to combat the acidemia
- acutely, increase in HCO₃⁻ = 0.1 x increase in pCO₂ (no time for renal compensation)
- chronically, increase in HCO₃⁻ = 0.3 x increase in pCO₂ (kidneys are doing a better job of reducing acidemia)

I° RESPIRATORY ALKALOSIS (HYPERVENTILATION)

Causes
- sepsis, liver disease, pregnancy, salicylates, any lung disease
  (asthma, pulmonary emboli, pneumonia, CHF)

Renal Compensation in Respiratory Alkalosis
- the kidney excretes HCO₃⁻
- acutely, decrease in HCO₃⁻ = 0.2 x decrease in pCO₂
- chronically, decrease in HCO₃⁻ = 0.5 x decrease in pCO₂
- remember - a patient with decreased HCO₃⁻ may simply be hyperventilating (I° respiratory alkalosis) and not acidemic (don’t give HCO₃⁻ without checking systemic pH)

Expected Compensation in Acid Base Disorders

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidosis</td>
<td>↓ HCO₃⁻ = ↑ PCO₂</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkalosis</td>
<td>↑ 10 HCO₃⁻ = ↓ 5-7 PCO₂</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MIXED DISTURBANCES
- mixed acid-base disorder means there are at least 2 independent, primary disorders
  - identified by
    - neutral pH
    - or, inadequate compensation
    - or, “excessive” compensation
- treatment (with HCO₃⁻) is guided by arterial blood gas pH, not simply HCO₃⁻ level alone (a common mistake!)
# RENAL FAILURE

## Classification
- acute renal failure
- chronic renal failure
- acute on chronic renal failure
- end-stage renal disease (ESRD)

### Table 10. Classification of Renal Failure

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Abrupt onset of multisystem illness</td>
<td>History of kidney problems, hypertension</td>
</tr>
<tr>
<td></td>
<td>Previously known normal function</td>
<td>Previous problems in pregnancy might be a clue to chronicity</td>
</tr>
<tr>
<td>Physical</td>
<td>Depends on underlying disease (e.g. rash, joint effusion)</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>Marked edema</td>
<td>Retinopathy</td>
</tr>
<tr>
<td></td>
<td>Encephalopathy</td>
<td>LVH</td>
</tr>
<tr>
<td></td>
<td>Kidneys normal size or swollen</td>
<td>Less encephalopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidneys small except in PCKD, DM, amyloid</td>
</tr>
<tr>
<td>Lab</td>
<td>Normal to slight anemia</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Severe hyperkalemia</td>
<td>Modest hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>Normal to slight hypocalcemia</td>
<td>Marked hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>Normal to slight hyperphosphatemia</td>
<td>Marked hyperphosphatemia</td>
</tr>
<tr>
<td></td>
<td>Normal alkaline phosphatase</td>
<td>Increased alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(increased bone turnover from secondary hyperparathyroidism)</td>
</tr>
</tbody>
</table>

*Acute increase in creatinine* | *Previously elevated creatinine*  

## ACUTE RENAL FAILURE

![Figure 11. Acute Renal Failure](image)

**ARF**

- **Pre-Renal**
  - Hypovolemia
    - Absolute
      - Hemorrhage
      - GI loss
      - Skin loss
      - Renal loss
      - 3rd spacing
    - Effective
      - Low cardiac output
      - Cirrhosis
      - Sepsis
  - Art. occlusion

- **Renal**
  - Vascular
    - Vasculitis
    - malignant HTN
  - Glomerular
    - GN
  - Interstitial
    - AIN
  - Tubular
    - ATN

- **Postrenal**
  - (obstruction of collecting system)
    - Think anatomically
      - Ureter
      - Bladder
      - Urethra

- **Ischemic**
- **Toxin**
  - Endogenous
    - Pigments (Hgb, Mgb)
    - Proteins (Bence-Jones)
    - Crystals (uric acid)
  - Exogenous
    - Antibiotics
    - Contrast agents
ACUTE RENAL FAILURE . . . CONT.

- definition: abrupt decline in renal function leading to increased nitrogenous waste products

**Diagnostic Approach**
1. acute vs. chronic: previous creatinines? kidney size?
2. Hx/physical exam: go through differential
3. Investigations
   - Blood: CBC, electrolytes, BUN, creatinine (if \( BUN > 1 \) creatinine, think prerenal failure), \( Ca^{2+} \), \( PO_4^{3-} \)
   - Urine R&M
   - Urinary indices (urine Na+, urine creat/plasma creat, urine osmolality, FENa+)
4. Foley catheterization (rule out bladder outlet obstruction)
5. fluid challenge (i.e. sive fluid bolus to rule out most prerenal causes)
6. abdo U/S (assess kidney size, post-renal obstruction)
7. ± renal biopsy

**TREATMENT**

**Pre-Renal**
- correct ECF volume depletion with normal saline (not D5W)
- improve cardiac output (if possible)

**Renal**
- remove toxic/ischemic insults
- attention to fluid status
- supportive treatment of
  - intravascular volume overload
  - hyperkalemia
  - hyperphosphatemia
  - metabolic acidosis
  - hypocalcemia

**Post-Renal**
- relieve obstruction (specific therapy is etiology-dependent)
- possible therapies include:
  - in-dwelling bladder catheter
  - nephrostomy
  - stenting

**Clinical Pearl**
- Post-renal failure is not necessarily associated with anuria or even oliguria.

**Supportive Therapy For All Causes of Renal Failure**
- drug modification: avoid nephrotoxic drugs, dosage modification of renally excreted drugs
- K+ restriction
- salt restriction

**INDICATIONS FOR DIALYSIS IN ARF (vs. IN CRF)**

- Hyperkalemia (refractory)
- Acidosis (refractory)
- Volume overload
- Elevated BUN (> 35 mM)
- Pericarditis
- Encephalopathy
- Edema (pulmonary)

**PROGNOSIS**
- high mortality with multiorgan failure
- renal prognosis related to severity of underlying disease and subsequent complications

**Clinical Pearl**
- The 2 most common causes of acute renal failure in hospitalized patients are prerenal azotemia and acute tubular necrosis.
CHRONIC RENAL FAILURE

many etiologies: continuum of progressive nephron loss and declining renal function
asymptomatic until severe insufficiency develops
regional variation in leading causes worldwide
  • in North America: diabetes (> 30%), hypertensive renal disease (23%), chronic
    GN (10%) (e.g. IgA nephropathy), polycystic kidney disease (5%)
  • frequently patients present at end-stage with small, contracted kidneys, unknown etiology

CLASSIFICATION
primary or secondary glomerulonephritis
tubulointerstitial disease (e.g. autoimmune interstitial nephritis)
vascular (e.g. DM, HTN)
hereditary (e.g. autosomal dominant polycystic kidney disease, Alport's)

CLINICAL FEATURES OF UREMIA
CNS: confusion, inability to concentrate, fatigue, asterixis, restless leg syndrome, sensory and
motor neuropathy
CVS: CHF, HTN with target organ damage (LVH, retinopathy), pericarditis, accelerated atherosclerosis
GI: nausea, vomiting, anorexia, upper GI hemorrhage, constipation
SKIN: pruritus, ecchymoses, hyperpigmentation, “sallow colour”, “uremic frost”
ENDOCRINE: hyperlipidemia, decreased sex hormone levels, decreased sex drive, menstrual irregularities,
secondary hyperparathyroidism
HEMATOLOGICAL: normocytic anemia, bleeding, impaired cellular immunity
MSK: nocturnal muscle cramping

COMPLICATIONS
uremia/azotemia: serum Cr may not obviously rise until GFR is < 50% normal
water: inability to concentrate or dilute urine; polyuria, nocturia
potassium imbalance: during advanced renal failure
anemia: due to decreased erythropoietin production (normocytic)
hyperphosphatemia, hypocalcemia, decreased vitamin D production and 2o hyperPTH
renal osteodystrophy (2o hyperPTH = osteitis fibrosa cystica, and osteomalacia)
acid-base: normal AG metabolic acidosis progressing to increased AG metabolic acidosis when GFR is
20% of normal

TREATMENT
restriction of Na+, K+ (40 mEq/day), H2O, PO43– (800-1000 mg/day), protein (modestly 0.9 g/kg/day)
adjust drug doses
treat HTN: drugs (especially ACE-inhibitors – beware of risk of hyperkalemia), sodium restriction
(target BP <125/75)
erthropoietin in anemia (hematocrit < 30%)
treat renal osteodystrophy
phosphate binders such as calcium carbonate if hyperphosphatemic
calcium supplements, activated vitamin D analogues (e.g. Rocaltrol)
correction of acidosis with oral NaHCO3 when serum HCO3– is < 20 mEq/L

INDICATIONS FOR DIALYSIS IN CRF
may be same as ARF
more commonly = “dwindles”
  • anorexia, nausea, vomiting, severe fatigue, pruritus, muscle cramps
dialyse when creatinine clearance < 10% of normal (< 10 mL/min)
diabetics less tolerant of uremia, dialyse when creatinine clearance < 15%
of normal (< 15 mL/min)
prognosis: all with progressive renal failure progress to dialysis/transplant
DIALYSIS AND RENAL TRANSPLANTATION

DIALYSIS

Goals
- ultrafiltration = fluid removal
  - in absence of renal function, daily fluid intake must be removed (less bowel and insensible losses)
  - the water removed is not pure water, it drags along other solutes ("solvent drag", “convection”)
- solute removal (by diffusion and ultrafiltration)
  - products of metabolism (urea, “uremic toxins”, etc.) and other solutes (K+, phosphates) normally excreted by kidneys are removed

<table>
<thead>
<tr>
<th>Table 11. Peritoneal Dialysis vs Hemodialysis</th>
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</thead>
<tbody>
<tr>
<td>Peritoneal Dialysis</td>
</tr>
<tr>
<td>Rate</td>
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<tr>
<td>Location</td>
</tr>
<tr>
<td>Ultrafiltration</td>
</tr>
<tr>
<td>Solute removal</td>
</tr>
<tr>
<td>Membrane</td>
</tr>
<tr>
<td>Method</td>
</tr>
<tr>
<td>Complications</td>
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</tbody>
</table>

Clinical Pearl
- The most common cause of morbidity and mortality in an end-stage renal disease patient is cardiovascular complications (CHF, CAD, CVD, PVD).

RENFAL TRANSPLANTATION
- best way to reverse uremic signs and symptoms
- 2 types: cadaver donor, living donor (related or unrelated)
- kidney transplanted into iliac fossa, renal artery anastomosed to internal iliac artery

Immunosuppression
- chronic therapy
  - corticosteroids
  - azathioprine
  - cyclosporine
  - Cellcept (MMF)
  - Tacrolimus (FK506)
- treatment of acute rejection
  - anti-T-cell monoclonal antibody (OKT3)
  - anti-thymocyte globulin (RATS)

Rejection
- types
  - hyperacute (within 0.5 hrs, in operating room)
  - acute: vascular, cellular
  - chronic

Problems
- immunosuppression: infections, neoplasms
- rejection
- cyclosporine nephropathy
**GLOMERULAR DISEASE**

**GENERAL CONSIDERATIONS**
- glomerular disease can be classified according to presentation or according to etiology

**CLASSIFICATION OF GLOMERULAR DISEASE ACCORDING TO SYNDROME/PRESENTATION**
- most cases of glomerular disease present somewhere on a spectrum between pure acute nephritic syndrome and pure nephrotic syndrome

<table>
<thead>
<tr>
<th>pure nephrotic</th>
<th>subnephrotic proteinuria, some RBC casts</th>
<th>asymptomatic proteinuria</th>
<th>asymptomatic hematuria (± RBC casts)</th>
<th>RBC casts, abnormal renal function</th>
<th>nephritic</th>
</tr>
</thead>
</table>

**Pure Acute Nephritic Syndrome**

**Clinical/Lab Features**
- abrupt onset of hematuria (microscopic or macroscopic)
- RBC casts
- proteinuria (usually < 3 g/day)
- acute renal failure
- oliguria
- HTN
- edema (salt and water retention 2° to poor GFR)

**Major Causes**
- 1°: postinfectious glomerulonephritis, crescentic glomerulonephritis
- 2°: SLE, Wegener's granulomatosis, Goodpasture's disease (anti-GBM disease)

**Pure Nephrotic Syndrome**

**Clinical/Lab Features**
- heavy proteinuria (> 3 g/day)
- hypoalbuminemia
- edema
- hyperlipidemia/lipiduria
- ± RBC casts (if mixed nephrotic/nephritic syndrome)

**Major Causes**
- 1°: minimal change disease, membranous glomerulopathy, focal glomerulosclerosis
- 2°: DM, amyloidosis, drugs (gold, penicillamine, heroin)

**Asymptomatic Urinary Abnormalities**

**Clinical/Lab Features**
- isolated proteinuria (usually < 2 g/day) and/or isolated hematuria

**Major Causes**
- proteinuria alone: isolated proteinuria, orthostatic proteinuria
- hematuria ± proteinuria: IgA nephropathy, hereditary nephritis (Alport's syndrome)
- hematuria alone: thin basement membrane disease

**Other Presentations of Glomerular Disease Rapidly Progressive GN (Crescentic GN)**

**Clinical/Lab Features**
- hematuria + RBC casts and/or dysmorphic RBCs
- proteinuria
- renal failure (occurring over weeks-months)
- diffuse glomerular “crescents” (proliferation of parietal epithelial cells and phagocytes within Bowman's capsule and perhaps from recruitment of fibroblasts) on renal biopsy

**Major Causes**
- 3 types based on presence/absence of immune deposits and IF (immunofluorescence)
  - type I: linear deposition of anti-GBM antibodies (that cross-react with pulmonary alveolar basement membrane – Goodpasture's disease)
  - type II: granular immune complex deposition
  - type III (most common): pauci-immune, no detectable immune deposits, usually ANCA-positive
- treat aggressively with glucocorticoids and cyclophosphamide (plasmapheresis for anti-GBM disease)
- poor prognosis if present with advanced renal insufficiency
Chronic GMN

Clinical/Lab Features
- proteinuria, hematuria, HTN, chronic glomerular inflammation (occurs over years), ± progressive renal insufficiency

Major Causes
- 1º: focal segmental glomerulosclerosis, membranoproliferative GN, nonspecific GN, membranous GN
- 2º: SLE, DM

CLASSIFICATION OF GLOMERULAR DISEASE ACCORDING TO ETIOLOGY

PRIMARY GLOMERULAR DISEASE
- glomerular disease which is not secondary to systemic disease, metabolic disease, drugs or hereditary causes
- classified according to histological lesions:
  - minimal change (most common cause of nephrotic syndrome (NS) in children, but also seen in adults)
    - inactive sediment, LM usually normal
    - EM shows fusion of foot processes of glomerular epithelial cells
      - most respond to prednisone but may relapse
      - cyclophosphamide or cyclosporine may be used for frequent relapers
    - natural history: eventual resolution although some progress to focal segmental sclerosis
  - membranous glomerulopathy (most common cause of idiopathic NS in adults)
    - diffuse thickening of glomerular capillary wall
    - IF shows granular IgG and C3 in capillary loops
    - EM shows epithelial deposits
    - no definitive therapy, trials with prednisone and other immunosuppressants give conflicting results
    - poor prognostic features: male sex, high creatinine at presentation, persistent high grade proteinuria > 6 months
  - focal segmental glomerulosclerosis
    - focal segmental areas of glomerular sclerosis
    - IF shows IgM in sclerotic areas
    - EM shows foot process fusion and sclerosis
    - presents as proteinuria and inactive sediment
    - HTN may or may not be present
    - renal function may be normal to reduced
    - natural history is of gradual decline in renal function in many
    - therapy: high dose long-term steroids will lead to remission in about 1/3 of patients
  - mesangial proliferative GN
    - IgA becomes trapped in mesangium and activates complement
    - IF shows granular mesangial deposits
    - presents as asymptomatic gross hematuria up to a few days after URTI or G1 infection or, more commonly, as microscopic hematuria on routine urinalysis
    - mixed nephritic-nephrotic picture
    - often seen in children and young adults
    - most often idiopathic, but also occurs with other diseases, including hepatic cirrhosis and gluten enteropathy
    - 15-20% progress to CRF
    - therapy: high-dose oral steroids may lead to remission, but frequent relapses occur

SECONDARY GLOMERULAR DISEASE

A. Systemic Diseases

Diabetes Mellitus (see Diabetes and the Kidney section)
- progressive glomerulosclerosis
- microalbuminuria progressing to clinically detectable proteinuria

Systemic Lupus Erythematosus
- Idiopathic autoimmune disease that involves multiple organs
- kidney is involved in 60-70%; usually presents as GN
- antinuclear antibodies and immune complex deposition
- WHO classification of glomerular involvement
  - Class 1: normal LM, may have deposits by IF or EM
  - Class 2: mesangial deposits
  - Class 3: focal proliferative GN
  - Class 4: diffuse proliferative GN
  - Class 5: membranous GN
  - Class 6: advanced sclerosing GN
- prognosis depends on class (e.g. class 4 has the worst outcome)
- responsive to immunosuppressive therapy
- rarely can present as thrombotic microangiopathy, especially if anticardiolipin antibodies are present
GLOMERULAR DISEASE ... CONT.

Other Systemic Diseases to Consider
- Henoch-Schönlein Purpura
  - non-thrombocytopenic purpura, arthralgia, abdominal pain
  - and GN (proteinuria, hematuria)
- "shunt" nephritis (immune complex GN 2° to chronic indolent infection, also seen with infective endocarditis)
- vasculitic: PAN, Wegener's Granulomatosis
- thrombotic microangiopathy, TTP, HUS, DIC

B. Metabolic Diseases

Amyloidosis
- initially see nodular deposits of amyloid in mesangium
- eventually, see progressive depositions of amyloid everywhere
- deposits are birefringent with Congo Red (apple green colour)
- presents as nephrotic syndrome with progressive renal insufficiency
- can be 1° or 2° amyloidosis

Dysproteinemias
- cryoglobulinemia
  - circulating cold precipitable Ig
  - purpura, necrotizing skin lesions, arthralgias, fever, hepatosplenomegaly

C. Hereditary Nephropathies

Alport's Syndrome
- hereditary nephritis sometimes associated with sensorineural deafness
- there are other less well-defined hereditary nephropathies

D. Drug Induced
- e.g. NSAIDs, gold, penicillamine

E. Neoplasms - can lead to “paraneoplastic” GNs
- lymphoma, leukemia
- adenocarcinoma of lung, colon, stomach or breast
- usually membranous or minimal lesion

F. Infections
- hepatitis B, hepatitis C, HIV
- syphilis
- malaria
- schistosomiasis

G. Post-Infectious GN
- abrupt onset of macroscopic hematuria, oliguria, ARF (sudden decrease in GFR), fluid retention (edema, HTN) – i.e. a nephritic syndrome
- urinary protein excretion generally < 3 g/day
  - presents with acute GN
  - typically, poststreptococcal (Group A), 7-12 days after infection
  - planted antigen or immune complex deposition
  - LM shows diffuse proliferative changes (increased number of cells in glomerulus)
  - IF shows granular pattern of IgG and C3 deposits
  - EM shows subepithelial “humps”
  - spontaneous resolution, manage fluid overload and HTN as needed
  - most completely recover but some reports of chronic renal insufficiency in adults (unclear)

General Laboratory Investigations
- urinalysis
- blood tests
- 1° glomerular disease: creatinine, albumin, cholesterol
- 2° glomerular disease: CBC, ESR, immunoelectrophoresis, complements, ANA, ANCA, cryoglobulins, hepatitis B serology, hepatitis C serology, VDRL, HIV
- 24 hr urine creatinine and protein
- radiology
  - CXR (infiltrates, CHF, pleural effusion)
  - renal ultrasound
- renal biopsy indications:
  - medication non-responsive nephrotic syndrome
  - progressive renal impairment of unknown etiology

General Principles of Management of 1° and 2° Glomerular Disease
- remove offending cause
- salt restriction
- diuretics
- antihypertensives
- anticoagulation in selected cases (nephrotic proteinuria and/or serum albumin < 20g/L)
- immunosuppressants in selected cases
- SLE/PAN: steroids (immunosuppressants)
- Wegener's Granulomatosis: cyclophosphamide
### Table 12. Nephritic vs. Nephrotic Syndrome

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Pure Nephritic Syndrome</th>
<th>Pure Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Neutrophil/eosinophil infiltration followed by mononuclear cell infiltration</td>
<td>• Structural and/or charge changes occur in glomerular capillary wall —&gt; ↑ permeability —&gt; ↑ proteinuria</td>
</tr>
<tr>
<td></td>
<td>• Often have glomerular cell proliferation (epithelial cell, and/or endothelial and/or mesangial cell)</td>
<td>• Severe proteinuria leads to hypoalbuminemia, ↓ intravascular oncotic pressure, and thus ↓ edema and renal sodium and water retention</td>
</tr>
<tr>
<td></td>
<td>• Glomerular capillary obstruction —&gt; capillary rupture —&gt; RBC leakage into tubules —&gt; hematuria with RBC casts, mild proteinuria</td>
<td>• Liver increases lipoprotein synthesis and secretion due to lipoprotein loss in urine —&gt; hyperlipidemia and lipiduria</td>
</tr>
<tr>
<td></td>
<td>• Retention of fluid which remains primarily intravascular —&gt; HTN</td>
<td>• Retention of fluid which becomes primarily interstitial —&gt; EDEMA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pure Nephritic Syndrome</th>
<th>Pure Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• ± gross hematuria (coke-coloured urine)</td>
<td>• Frothy urine</td>
</tr>
<tr>
<td></td>
<td>• Mild edema</td>
<td>• Generalized edema (esp. periorbital)</td>
</tr>
<tr>
<td></td>
<td>• Malaise</td>
<td>• ± symptoms of ↓ tissue fluid (eg. SOB, swollen abdomen, swollen scrotum, etc.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs</th>
<th>Pure Nephritic Syndrome</th>
<th>Pure Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• HTN</td>
<td>• BP variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ± signs of ↓ tissue fluid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Findings</th>
<th>Pure Nephritic Syndrome</th>
<th>Pure Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Micro/macrophematuria with RBC casts</td>
<td>• Hypoalbuminemia</td>
</tr>
<tr>
<td></td>
<td>• Proteinuria usually &lt; 2 g/day</td>
<td>• Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Proteinuria &gt; 3 g/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ± RBC casts in urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(if mixed nephritic/nephrotic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ± oval fat bodies in urine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1º causes (intrinsic to kidney)</th>
<th>Pure Nephritic Syndrome</th>
<th>Pure Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranoproliferative GN</td>
<td></td>
<td>Minimal change disease</td>
</tr>
<tr>
<td>Mesangial proliferative GN</td>
<td></td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td></td>
<td>Membranous GN</td>
</tr>
<tr>
<td>Idiopathic rapidly progressive GN</td>
<td></td>
<td>Membranoproliferative GN</td>
</tr>
<tr>
<td>Anti-GBM disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2º causes</th>
<th>Pure Nephritic Syndrome</th>
<th>Pure Nephrotic Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-infectious GN</td>
<td></td>
<td>DM</td>
</tr>
<tr>
<td>Collagen vascular disease (SLE, polyarteritis nodosa, Wegener's granulomatosis)</td>
<td></td>
<td>SLE</td>
</tr>
<tr>
<td>SBE</td>
<td></td>
<td>Amyloid</td>
</tr>
<tr>
<td>Misc: Goodpasture's syndrome, Henoch-Schönlein purpura, Cryoglobulinemia</td>
<td></td>
<td>Infections (SBE, Hep B, Hep C, HIV, post-strep)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoplastic (lymphoma, leukemia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs (gold, penicillamine, heroin)</td>
</tr>
</tbody>
</table>
### Table 13. Glomerulonephritis Summary Chart

<table>
<thead>
<tr>
<th>NON-PROLIFERATIVE</th>
<th>Presentation</th>
<th>LM</th>
<th>IF</th>
<th>EM</th>
<th>Management</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change</td>
<td>nephrotic</td>
<td>normal</td>
<td>negative</td>
<td>fusion of foot processes</td>
<td>prednisone</td>
<td>excellent</td>
</tr>
<tr>
<td>Membranous</td>
<td>nephrotic</td>
<td>capillary wall thickening</td>
<td>granular IgG, C₃ in capillary loops</td>
<td>subepithelial electron dense deposits (EDD)</td>
<td>controversial</td>
<td>rule of thirds</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>nephrotic</td>
<td>focal and segmental sclerosis +/- hyalinosis</td>
<td>negative or segmental IgM, C₃ in necrotic areas</td>
<td>focal sclerosis, foot processes fusion, subendothelial EDD</td>
<td>high-dose corticosteroids</td>
<td>variable</td>
</tr>
</tbody>
</table>

### PROLIFERATIVE

<table>
<thead>
<tr>
<th>Mesangial Proliferative GN (usually IgA nephropathy)</th>
<th>asymptomatic urinary abnormalities to nephrotic</th>
<th>mesangial proliferation</th>
<th>negative or mesangial IgA &amp; C₃</th>
<th>mesangial deposits</th>
<th>supportive +/- ACE inhibitors? +/- Fish oil?</th>
<th>usually good</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Infectious GN diffuse proliferative</td>
<td>nephritic syndrome</td>
<td>diffuse proliferation</td>
<td>granular diffuse IgG &amp; C₃</td>
<td>subepithelial “humps”</td>
<td>supportive</td>
<td>good, especially in kids</td>
</tr>
</tbody>
</table>

| Crescentic GN type I                              | rapidly progressive | epithelial crescents | linear antiGBM, Ig | no deposits | steroids, cytotoxic plasmapheresis | poor |
| type II                                           | —                   | —                     | granular Ig, C₃ in capillary loops | EDD in capillary walls | steroids, cytotoxic | poor |
| type III                                          | —                   | —                     | negative | no deposits | steroids, cytotoxic | poor |
TUBULOINTERSTITIAL NEPHRITIS

Definition
- inflammatory cell infiltrate affecting primarily the renal interstitium and tubule cells, with no primary glomerular damage
- functional tubule defects are disproportionately greater than the decrease in GFR

Manifestations
- If proximal tubule mainly affected:
  - Fanconi syndrome (decreased reabsorption in the proximal tubule such that glucose, amino acids, and increased phosphates are found in the urine)
  - proximal RTA
- If distal tubule mainly affected:
  - distal RTA
  - Na+-wasting nephropathy
  - +/- hyperkalemia, type IV RTA
  - +/- nephrogenic DI
- anemia (low Epo)
- signs and symptoms of renal failure may occur (see above)
- radiographic, ultrasonographic, and radionuclide studies only show evidence of acute or chronic renal disease, although etiology may be seen (e.g. polycystic kidney disease, urinary tract obstruction)
- classified as acute vs. chronic (can also be classified as 1º vs. 2º)

ACUTE TUBULOINTERSTITIAL NEPHRITIS

Etiology
- acute allergic drug reactions
  - antibiotics: beta-lactams, sulfonamides, rifampin, quinolones
  - NSAIDs
- other drugs: sulfonamide diuretics (furosemide), phenytoin
- infections
  - systemic: Brucellosis, CMV, infectious mononucleosis, Legionnaire's disease, leptospirosis, streptococcal infections, Rocky Mountain spotted fever, syphilis, toxoplasmosis, M. pneumoniae
  - renal: bacterial pyelonephritis, renal TB, fungal nephritis
  - immune-mediated: SLE, necrotizing vasculitis (especially with Wegener's), acute graft rejection, associated with some acute glomerulonephritides
- idiopathic

Clinical Features
- signs and symptoms associated with electrolyte and acid-base abnormalities described above
- other manifestations depend on underlying etiology (e.g. in SLE, systemic infection)
- may see abrupt GFR decline and oliguria
- fever, rash, eosinophilia in the setting of drug-induced TIN
- flank pain, CVA tenderness in renal infection
- ongoing acute TIN can progress to chronic renal failure and uremia

Laboratory Investigations
- urine
  - WBCs, WBC casts, protein (< 3.5 g/day), hematuria, glycosuria, aminoaciduria
  - eosinophils if allergic interstitial nephritis
  - electrolyte abnormalities: phosphaturia, bicarbonaturia, uricosuria, increased FENa+, dilute urine
- blood
  - eosinophilia if drug reaction
  - non-AG metabolic acidosis
  - hypophosphatemia, hyperkalemia
  - increased BUN and creatinine if renal failure developing

Treatment
- treat underlying cause (e.g. stop offending meds, give antibiotics if bacterial pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)
- supportive measures: treat metabolic abnormalities, treat acute renal failure if develops

CHRONIC TUBULOINTERSTITIAL NEPHRITIS
- characterized by interstitial fibrosis with atrophy and loss of tubules

Etiology
- persistence or progression of acute TIN
- nephrotoxins
  - analgesics (NSAIDs, phenacetin, acetaminophen)
  - endogenous (hypercalcemia, hypokalemia, oxalate nephropathy, uric acid nephropathy)
  - metals (copper, lead, lithium, mercury, cisplatin)
  - radiation
TUBULOINTERSTITIAL Nephritis . . . CONT.

- infectious
  - renal TB
  - chronic bacterial pyelonephritis (in the setting of obstruction)
- chronic urinary tract obstruction (most common)
- vesicoureteric reflux
- cystic disease
  - polycystic kidney disease
  - medullary cystic disease
- immune
  - SLE
  - Sjögren's syndrome
  - sarcoidosis
  - idiopathic
  - chronic rejection
- neoplastic/paraproteinemic
  - multiple myeloma
  - light chain nephropathy
  - lymphoma/leukemia
  - Waldenstrom's macrogobulinemia
- miscellaneous
  - sickle-cell hemoglobinopathies

Clinical Features
- may be those of tubular dysfunction (see above)
- may be those of progressive renal failure and uremia
- dependent on underlying disease as well

Laboratory Investigations
- WBC, WBC casts, protein, glycosuria, aminoaciduria
- no eosinophilia or eosinophiluria
- electrolyte abnormalities: phosphaturia, bicarbonaturia, uricosuria, increased FENa+, dilute urine
- increased BUN, creatinine
- hyperkalemia, hypocalcemia, metabolic acidosis

Treatment
- stop offending agent (if applicable)
- supportive measures: correct metabolic disorders, treat CRF

NSAID Nephropathy

- NSAIDs act by blocking the cyclooxygenase enzyme thereby blocking prostaglandin synthesis
- prostaglandins (PG) have various actions on the kidney
  - vasodilation of renal arteries and arterioles to maintain renal blood flow
  - natriuresis
  - stimulation of renin release
  - antagonism of the effects of ADH
- NSAID-mediated renal disease can take the following forms:
  - vasomotor ARF
    - more common in the elderly and in patients with antecedent renal disease, or blood volume contraction (diuretics, CHF, cirrhosis, nephrotic syndrome)
    - ARF is precipitated by renal hypoperfusion secondary to PG synthesis inhibition leading to renal arterial and arteriolar vasoconstriction
    - clinically: oliguric within a few days of beginning NSAID
    - treatment: discontinue NSAID, dialysis rarely needed
  - AIN
    - majority due to fenoprofen (60%), ibuprofen, naproxen
    - distinguish from other drug-induced AIN by lack of eosinophilia and eosinophiluria, the presence of skin rashes, and the presence of nephrotic range proteinuria (can get regular AIN but in addition there is a unique NSAID AIN where both tubular and glomerular damage occur and significant proteinuria results)
    - unlike NSAID-induced vasomotor ARF, NSAID-induced AIN requires that NSAIDs be taken from days to months
    - resolves with discontinuation of NSAID but may take a long time necessitating interval dialysis
    - short term high dose steroids (1 mg/kg/day of prednisone) may hasten recovery
- NSAID nephropathy may also include:
  - papillary necrosis
  - sodium retention
  - hyperkalemia, metabolic acidosis (2˚ to hyporeninemic hypoaldosteronism)
  - excess water retention and hyponateremia exacerbation (due to elimination of ADH antagonistic effect of PGs)
**ACUTE TUBULAR NECROSIS**

**Clinical Presentation**
- typically presents abruptly after a hypotensive episode, rhabdomyolysis, or the administration of radiocontrast media
- in contrast, when aminoglycoside nephrotoxicity occurs, the onset is more insidious, with the plasma Cr rising slowly within 7 or more days of therapy
- urinary sediment: high FENa⁺, pigmented granular and epithelial casts in the urine

**Figure 12. Acute Tubular Necrosis**

- **Toxins**
  - **Exogenous**
    - Antibiotics
    - Aminoglycosides
    - Cephalosporins
    - Amphotericin B
    - Proteins
    - Antiviral (cidofovir)
    - Antineoplastics
    - Cisplatin
    - Methotrexate
    - Contrast media
    - Heavy metals
    - Other
      - Fluorinated anaesthetic
      - Ethylene glycol
  - **Endogenous**
    - Endotoxins (bacterial)
    - Myoglobin
    - Hemoglobin
    - Bence-Jones protein

- **Ischemia**
  - Shock
  - Trauma +/- rhabdomyolysis
  - Sepsis
  - Severe hypovolemia
  - Post-operative patients
  - NSAIDS in volume depletion

**Prognosis of ATN**
- therapy for ATN is largely supportive once underlying problem is corrected
- kidneys usually get better if insult is removed
- prognostic factors include
  - age
  - severity of underlying disease
  - complications
  - previous episode of ARF

**VASCULAR DISEASES OF THE KIDNEY**

**“Large” Vessel Disease**
- renal artery stenosis
- renal artery thrombosis
- renal artery emboli
- cholesterol embolic disease
- renal vein thrombosis

**“Small” Vessel Disease**
- hypertensive nephrosclerosis
- “malignant” nephrosclerosis
- cyclosporine nephropathy
- thrombotic microangiopathy
  - HUS, TTP, DIC, post-partum renal failure
**DIABETES AND THE KIDNEY**

- number one cause of end-stage renal failure in North America
- 35-50% of Type 1 will develop nephropathy, unknown percentage of Type 2
- classic proteinuria (> 150 mg/day) develops after 15-20 years of Type 1 (begins as microalbuminuria)
- once proteinuria is established, renal function declines with 50% of patients reaching ESRD 7 to 10 years after the onset of proteinuria
- associated with HTN and diabetic retinal microaneurysms
- not all diabetics with abnormal renal function have diabetic nephropathy; should have:
  - proteinuria
  - HTN
  - inactive urinary sediment
  - appropriate time course
  - retinopathy if Type 1
- four basic diabetic renal complications:
  1. progressive glomerulosclerosis
  2. atherosclerosis
  3. autonomic neuropathy leading to functional obstruction
  4. papillary necrosis
- DM is one of the causes of ESRD that does not result in small kidneys at presentation of ESRD

**Progressive Glomerulosclerosis**

- **stage 1**
  - INCREASED GFR (120-150%) (due to compensatory hyperfiltration of remaining nephrons)
  - +/- slight increased mesangial matrix
- **stage 2**
  - DETECTABLE MICROALBUMINURIA (> 30 mg/24hr)
  - increased GFR
  - increased mesangial matrix
- **stage 3**
  - increased microalbuminuria
  - CLINICALLY DETECTABLE PROTEINURIA (300 mg/24hr)
  - normal GFR
  - very expanded mesangial matrix
- **stage 4**
  - increased proteinuria (> 500 mg/24hr)
  - DECREASED GFR
  - < 20% glomerular filtration surface area present
  - sclerosed glomeruli

**Accelerated Atherosclerosis**

- common finding
- decreased GFR
- may increase AII production: results in increased BP
- increased risk of ATN secondary to contrast media

**Autonomic Neuropathy**

- affects bladder
- results in urinary retention
- residual urine promotes infection
- obstructive nephropathy

**Papillary Necrosis**

- Type 1 DM susceptible to ischemic necrosis of medullary papilla
- sloughed papilla may obstruct ureter: presents as renal colic or with obstructive features +/- hydronephrosis

**Treatment**

- must evaluate the patient for other causes of proteinuria besides diabetic nephropathy (e.g. hyperglycemia, UTI, essential HTN, CHF)
- also must ensure that the patient is not exposed to unnecessary insults to their kidneys (e.g. NSAIDs, aminoglycosides, avoiding dye studies if possible, etc.)
- strict glycemic control: in Diabetes Control and Complications Trial (DCCT) (1993), shown to reduce microalbuminuria in Type 1 DM (primary and secondary prevention)
- aggressive BP control: more significant than glycemic control in slowing rate of decline in renal function and improves renal survival
- protein restriction: decreases intraglomerular HTN, studies ongoing, worry of malnutrition
- ACE inhibitors
  - kidney protection independent of BP control, may preserve GFR (controversial)
  - reduced proteinuria, slowed renal deterioration
  - improved glucose use and insulin sensitivity a greater then 50% decrease in creatinine clearance necessitates a referral to a nephrologist
DIABETES AND THE KIDNEY . . . CONT.

CMAJ Guidelines for Kidney Disease in Diabetics (CMAJ Oct. 98)
- achieve best possible glucose control for type 1 diabetics to prevent renal complications
- screening
  - all patients over 15 years of age with a 5 year history of Type 1 diabetes should have annual screens for microalbuminuria
  - patients with Type 2 diabetes should be screened at the time of diagnosis and yearly thereafter must send specifically for microalbuminuria if no detectable protein on dipstick
- treat elevated microalbuminuria (> 30 mg/24 hr) in Type 1 diabetics with ACEi even in the absence of HTN
- Type 2 diabetics with elevated microalbuminuria may also benefit from ACEi
- refer any diabetic to a nephrologist or internist for long term management if there is 50% decrease in creatinine clearance

Clinical Pearl
- ACE inhibitors can cause hyperkalemia. Therefore, be sure to watch serum K+ - especially if patient with DM and renal insufficiency is put on ACE inhibitor.

HYPERTENSION

- hypertension occurs in 10-20% of population
- 95% of hypertension is “essential” (primary)
- 5% due to secondary causes including renal (renal parenchymal or renovascular) and non-renal

Initial Investigations
- history, physical (target organ damage: cardiac, neurologic, renal, ocular)
- serum Cr, K+, uric acid, cholesterol, triglycerides
- fasting blood sugar, HbAIC
- urinalysis
- ECG

Clues to 2˚ Causes
- onset < 20 or > 50 years
- abnormal renal function, abnormal urinalysis (GN or TIN)
- bruits (renal artery stenosis)
- hypokalemia in absence of diuretics (increased mineralocorticoids)
- unusual history (flank trauma, pheochromocytoma-like symptoms)
- poor response to therapy (high BP despite 2 or 3 antihypertensives)
- grade III or IV hypertensive retinopathy

RENOVASCULAR HYPERTENSION
- 1-2% of all hypertensives, 30-40% of malignant hypertensives
- suspect if
  - negative family history
  - epigastric or flank bruit
  - spontaneous hypokalemia
  - sudden onset or exacerbation
  - young female
  - history of atherosclerosis
  - difficult to control with antihypertensive therapy

Clinical Pearl
- Flash pulmonary edema can be associated with bilateral renal artery stenosis.

Etiology
- decreased renal perfusion of one or both kidneys leads to increased renin release, and subsequent
  - All production causing generalized arterioconstriction, raising systemic BP as well as hyperaldosteronemia leading to Na+ and water retention
  - the elevated BP can in turn lead to further damage of kidneys and worsening HTN
- 2 types
  - atherosclerotic plaques (proximal 1/3 renal artery), usually males > 55 years
  - fibromuscular hyperplasia (distal 2/3 renal artery or segmental branches), usually females between 35-50 years
- patients with single kidney and renal artery stenosis, or 2 kidneys and bilateral renal artery stenosis are at risk of ARF with ACE inhibitors or NSAIDs
  - when there is decreased renal blood flow, GFR is dependent on angiotensin II-induced efferent arteriolar constriction and raising of filtration fraction
**HYPERTENSION . . . CONT.**

**Investigations**
- renal U/S and dopplers
- digital subtraction angiography (venous puncture, complications related to dye)
- renal scan with ACE inhibitor (accentuates difference in GFR)
- arterial angiography

**Treatment**
- BP lowering medications (ACE-inhibitor drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- surgical, angioplasty +/- stent very controversial!
- angioplasty for simple fibromuscular dysplasia lesion in young patients

**HYPERTENSION CAUSED BY RENAL PARENCHYMAL DISEASE**
- any chronic renal disease can lead to HTN (GN, TIN, diabetic nephropathy)
- most common cause of secondary HTN
- mechanism of HTN not fully understood but may include:
  - excess renin-angiotensin-aldosterone system activation due to inflammation and fibrosis in multiple small intra-renal vessels (see Renovascular HTN Section)
  - production of unknown vasopressors or lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  - ineffective disposal of sodium with fluid overload

**Investigations**
- as well as above investigations, additional tests may include:
  - 24 hour urinary estimations of Cr clearance and protein excretion
  - imaging (IVP, US, CT, radionuclide scan)
  - immunologic testing
  - bacteriology and renal biopsy

**Treatment**
- most chronic renal disease cannot be reversed but treatment of the HTN can slow the progression of renal insufficiency
- control ECF volume: Na+ restriction (980 mmol/day intake), diuretic, dialysis with end-stage disease

**PYELONEPHRITIS**

**ACUTE PYELONEPHRITIS**
- Infection of the renal parenchyma with local and systemic manifestations of infection
- may be classified as uncomplicated or complicated
  - uncomplicated: in the absence of conditions predisposing to anatomic or functional impairment of urine flow
  - complicated: occurring in the setting of renal or ureteric stones, strictures, prostatic obstruction (hypertrophy or malignancy), vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell hemoglobinopathies, polycystic kidney disease, immunosuppression, and post-renal transplant

**Etiology**
- usually ascending microorganisms, most often bacteria
- in females with uncomplicated pyelonephritis usually E. coli
- causative microorganisms are usually E. coli, Klebsiella, Proteus, Serratia, Pseudomonas, Enterococcus, and S. aureus
- if S. aureus is found, suspect bacteremic spread from a distant focus (e.g. septic emboli in infective endocarditis) and suspect (possible multiple intra-renal microabscesses or perinephric abscess)

**Clinical Presentation**
- rapid onset (hours to a day)
- lethargic and unwell, fever, tachycardia, shaking, chills, nausea and vomiting, myalgias
- marked CVA or flank tenderness; possible abdominal pain on deep palpation
- symptoms of lower UTI may be absent (urgency, frequency, dysuria)
- may have symptoms of Gram negative sepsis

**Clinical Pearl**
- Patients (especially the elderly) with acute pyelonephritis +/- sepsis may present initially with only back pain, abdominal pain, symptoms of disturbed Gi function, or mental status changes.
PYELONEPHRITIS . . . CONT.

Laboratory Investigations
- urine dipstick: +ve for leukocytes and nitrites, possible hematuria
- microscopy: > 5 WBC/HPF in unspun urine or > 10 WBC/HPF in spun urine, bacteria
- Gram stain: Gram negative rods, Gram positive cocci
- culture: > 10^3 colony forming units (CFU)/mL in clean catch midstream urine or > 10^2 CFU/mL in suprapubic aspirate or catheterized specimen
- CBC and differential: leukocytosis, high % neutrophils, left-shift (increase in band cells - immature neutrophils)
- blood cultures: may be positive in 20% of cases, especially in S. aureus infection
- consider investigation of complicated pyelonephritis: if fever, pain, leukocytosis not resolving with treatment within 72 hr, if male patient, or if there is history of urinary tract abnormalities (abdo/pelvis U/S, CT for renal abscess, spiral CT for stones, cystoscopy)

Treatment
- uncomplicated pyelonephritis with mild symptoms
  - 14 day course of TMP/SMX or fluoroquinolone or third generation cephalosporin
  - start with IV for several days and then switch to PO (can then be treated as outpatient)
- patient more than mildly symptomatic or complicated pyelonephritis in the setting of stone obstruction is a urologic emergency (placing patient at risk of kidney loss or septic shock)
  - start broad spectrum IV antibiotics until cultures return (imipenem or emropenem or piperacillin/tazobactam or ampicillin+gentamicin) and treat 2-3 weeks
  - follow-up cultures 2-4 weeks after stopping treatment
- if no improvement in 48-72 hr, need to continue on IV antibiotics, assess for complicated pyelonephritis or possible renal or perinephric abscess

Prognosis
- treated acute pyelonephritis rarely progresses to chronic renal disease
- recurrent infections often constitute relapse rather then re-infection

CHRONIC PYELONEPHRITIS
- a form of chronic tubulointerstitial nephritis of bacterial origin
- cortical scarring, tubulointerstitial damage, and calyceal deformities seen
- may be active (persistent infection) or inactive (persistent focal sterile scars post-infection)
- histologically indistinguishable from many other forms of TIN (severe vesicoureteric reflux, hypertensive disease, analgesic nephropathy)
- active chronic pyelonephritis may respond to antibiotics
- need to rule out TB

CYSTIC DISEASES OF THE KIDNEY

ADULT POLYCYSTIC KIDNEY DISEASE (APCKD)
- 1:1,000 people, accounts for about 10% of cases of renal failure
- more common than sickle-cell anemia, cystic fibrosis, hemophilia and muscular dystrophy
- autosomal dominant, linked to alpha-globin gene locus on chromosome 16p
- pathological defect thought to be due to:
  - abnormally weak basement membrane leading to segmental distention of tubule or vessel and cyst formation
  - proliferation of tubular epithelium
- abnormal basement membrane also predisposes to cyst formation in other organs
  - liver, - 33%
  - cerebral artery aneurysm - 10%
  - other associations: diverticulosis and mitral valve prolapse
  - less common: pancreas, spleen, thyroid, ovary, endothelium, seminal vesicles, and aorta

Clinical Course
- polycystic changes are bilateral and present any time from early childhood to as late as 80 years of age
- the kidneys are normal at birth, symptoms are rare before 20
- kidneys may enlarge to 10 times normal volume
- symptoms
  - often asymptomatic; discovered incidently on imaging
  - acute abdominal pain/lumbar pain
  - ± nocturia
  - rarely extra-renal presentation (e.g. ruptured berry aneurysm)
- signs
  - HTN (up to 75% of adults)
  - ± palpable kidneys
- investigations
  - BUN, Cr: to assess for progressive renal failure
  - urine R&M: to assess for hematuria
  - abdo U/S (best modality): enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, spaying of renal calyces
  - CT abdo with contrast (for equivocal cases)
Cystic Diseases of the Kidney...cont.

**Diagnosis**
- positive family history
- ultrasound: cysts are usually detectable by age 20
- differential diagnosis: multiple simple cysts (not progressive like APCKD)

**Complications**
- urinary tract infection
  - infected cysts most common in women due to ascending infection
  - treatment: TMP/SMX
- focal compression of intra-renal arteries by cysts → increased renin production → HTN
- if untreated will ACCELERATE progression to ESRD
- nephrolithiasis in 5-15% of APCKD (may form due to poor drainage from distorted calyceal system)
  - usually urate stones (see Urology Chapter)

**Management**
- goal: to preserve renal function
- must treat UTI early
- screen for HTN, treat aggressively with antihypertensives (e.g. ACE inhibitors)
- adequate hydration to prevent stone formation
- instrumentation of the GU tract should be avoided
- should avoid contact sports due to greater risk of injury if kidneys are large
- as ESRD develops, treat with peritoneal dialysis, hemodialysis or renal transplant
- screen for cerebral aneurysms only in patients with strong FHx of aneurysmal hemorrhages
- must provide genetic counselling: 50% chance of transmission by affected parent

**Medullary Cystic Disease**
- rare autosomal recessive disorder
- often results in end-stage renal failure during adolescence/childhood
- cysts difficult to image due to small size

**Medullary Sponge Kidney**
- nonfamilial disease
- presents in the fourth to sixth decades usually as passage of renal stones
- multiple cystic dilatations in the collecting ducts of the medulla
- benign with respect to the development of renal insufficiency
- increased incidence of renal calculi, infections, and HTN
- nephrocalcinosis may be seen on X-ray, medullary sponge defect seen on IVP

**Other Systemic Diseases and the Kidney**

**Hypertension Causing Renal Disease**
- HTN can cause renal disease - in this case, onset of HTN antedates impaired renal function
- results in nephrosclerosis
- both benign (slowly progressive) and malignant (necrotizing arteritis with accelerated HTN) nephrosclerosis can occur; this is due to intrarenal vascular sclerosis
- more common in blacks
- treatment: early control of BP

**Multiple Myeloma**
- a malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine
- kidney damage can occur for several reasons:
  - hypercalcemia
  - hyperuricemia
  - light chain deposition in tubules
  - 2° amyloidosis
- lab features: ↑ BUN, ↑ creatinine, urine protein electrophoresis positive for Bence Jones protein (not detected on urine dipstick), renal biopsy shows tubular deposits of light chains with surrounding inflammation (myeloma kidney)

**Scleroderma**
- interlobular arteries; intimal thickening and proliferation
- fibrinoid necrosis of afferent arterioles +/− glomeruli
- renal disease may present as "renal crisis" = malignant HTN, malignant nephrosclerosis

**Vasculitides**
- pathology characterized by focal necrotizing glomerulonephritis (inflammatory injury) +/− crescents
  - e.g. PAN, Wegener's Granulomatosis
- unusual to see actual vasculitis (vessel wall inflammation) in kidney biopsy
- similarly, unusual to see granulomas in kidney biopsy in Wegener’s Granulomatosis
RHEUMATOID ARTHRITIS
- 1° involvement rare
- 2° amyloidosis
- treatments for RA can also cause kidney damage: gold, penicillamine, NSAID nephropathy

CANCER
- cancer can have many different nephrological manifestations
- mild proteinuria is common in patients with solid tumours, but overt GN is rare
- minimal lesion or membranous GN with lymphoma
- membranous GN with solid tumours → nephrotic syndrome
- hypercalcemia
- hyperuricemia with tumour lysis
- chemotherapy (especially cisplatin) can lead to ATN
- obstruction with pelvic tumours or mets
- amyloidosis
- radiotherapy (radiation nephritis)

INFECTIONS
- hepatitis B: membranous GN, polyarteritis nodosa
- hepatitis C: membranoproliferative GN +/− cryoglobulins
- TB: “sterile” pyuria, granulomatous inflammation and caseous necrosis, abnormal IVP, 2° amyloidosis, hypercalcemia
- infective endocarditis: proliferative GN, cryoglobulinemic GN
- syphilis: membranous GN
- malaria: variable glomerular involvement

HIV-ASSOCIATED RENAL DISEASE
- specific glomerular syndromes; HIV-associated nephropathy
- focal and segmental glomerulosclerosis-like syndrome (“collapsing” nephropathy)
- thrombotic microangiopathy (TTP)
- IgA nephropathy
- other forms of glomerulopathy
- high predilection for young black males
- clinical features
  - heavy proteinuria, progressive renal failure, electrolyte and acid-base disturbances
- prognosis: without treatment, usually develop ESRD within months
- treatment: short-term, high dose steroids

DIURETICS

Loop Diuretics
- examples
  - furosemide (Lasix), bumetanide (Bumex), ethacrynic acid (Edecrin), torsemide (Demadex)
- mechanism
  - inhibition of Na+/K+/2Cl− channel in the thick ascending limb, venodilation
- clinical use
  - reduce ECF volume (e.g. heart failure, nephrotic syndrome, cirrhotic ascites), increase free water clearance (e.g. SIADH-induced hyponatremia), antihypertensive (but are poor antihypertensive agents)
- adverse effects
  - allergy in sulfa-sensitive individuals, electrolyte abnormalities (hypokalemia, hyponatremia, hypocalcemia, hypercalcuria/uricosuria (with stone formation), volume depletion with metabolic alkalosis

Thiazide Diuretics
- examples
  - hydrochlorothiazide (HCTZ), chlorothiazide (Diuril)
  - indapamide (Lozol, Lozide) and metolazone (Zaroxolyn) are related compounds
- mechanism
  - increases the excretion of Na+/Cl−/H2O by inhibiting the Na+/Cl− transporter in the distal tubule
- clinical use
  - first line therapy for essential HTN (often in combination with other antihypertensives), idiopathic hypercalcemia and recurrent renal stones, diabetes insipidus
- adverse effects
  - hypokalemia, increased serum urate levels, hypercalcemia, adversely affects lipid profiles in high doses, thiamine depletion
**Potassium-Sparing Diuretics**

- **examples**
  - spironolactone (Aldactone), triamterene (Dyrenium), amiloride (Midamor)
- **mechanism**
  - each acts at a different step in the DCT where Na⁺ is reabsorbed and K⁺ and H⁺ are excreted
  - net result is decreased Na⁺ reabsorption and H⁺ and K⁺ secretion: spironolactone is an aldosterone antagonist (aldosterone promotes normal functioning of the DCT Na⁺ channel); amiloride and triamterene directly close apical Na⁺ channels
- **clinical use**
  - ascites (spironolactone), reduces potassium excretion during therapy with thiazide or loop diuretics, cystic fibrosis (amiloride reduces viscosity of secretions), severe CHF
- **adverse effects**
  - hyperkalemia (caution with ACEi), gynecomastia (estrogenic effect of spironolactone)

**Combination Diuretics**

- **examples**
  - Dyazide, Maxide (triamterene and HCTZ), Aldactazide (spironolactone and HCTZ), Moduretic (amiloride and HCTZ), Vasoretic (enalapril and HCTZ), Zestoretic (lisinopril and HCTZ)
- **clinical use**
  - potassium-sparing drugs are combined with thiazide to reduce hypokalemia
  - ACEi are combined with thiazides to promote synergistic antihypertensive effect (ACEi reduces vasoconstriction and increased resistance which results secondarily from diuretic-induced volume contraction)

**Carbonic Anhydrase Inhibitors**

- **examples**
  - acetazolamide, methazolamide, and dichlorphenamide
- **mechanism**
  - inhibits carbonic anhydrase in proximal tubule, thereby inhibiting the reabsorption of NaHCO₃ by an indirect mechanism
- **clinical use**
  - glaucoma, to raise urine pH in cystinuria
- **adverse effects**
  - periodic paralysis (secondary to non-AG metabolic acidosis and hyperkalemia), adjunctive therapy in epilepsy

**Osmotic Diuretics**

- **examples**
  - mannitol, glycerol and urea
- **mechanism**
  - non-resorbable solutes that exert osmotic pressure in the renal tubules (proximal and collecting duct), promoting the excretion of water
- **clinical use**
  - lower intracranial or intraocular pressure
  - prevention of ARF (by promoting diuresis and clearance of tubular debris)

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