NEPHROLOGY

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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 thin layer of fenestrated endothelial cells, a basement membrane and visceral epithelial cells of Bowman's capsule (i.e. podocytes)
  - 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)
  - reasborbs ~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
    - myoepithelial 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

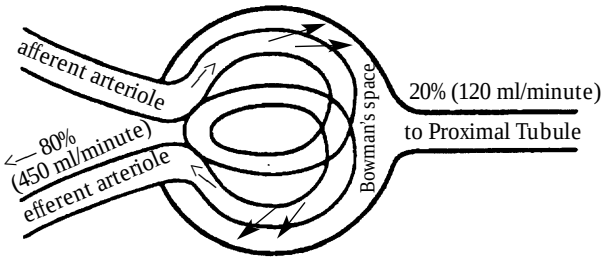


Figure 1. Glomerular Filtration

- ❑ 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 (AII)

CONTROL OF RENAL HEMODYNAMICS

- goal is maintenance of GFR in the face of varying RBF (autoregulation)
- mechanism: decreased RBF causes renin release from J-G apparatus. Renin activates AI to angiotensinogen to Angiotensin I (AI); Angiotensin Coverting Enzyme (ACE) activates AI to AII; AII constricts the efferent renal arterioles, rising filtration fraction and maintaining GFR
- as RBF and RPF decrease, FF must increase to preserve GFR; this is done by Angiotensin II (AII)

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 1. Processes Occurring Along the Nephron

Site	Absorption	Secretion
PCT	Na^+, HCO_3^- glucose, amino acids, phosphates, vitamins	organic acids
Thick Ascending Limb of Loop of Henle		Na^+, K^+, $C1^-$
DCT	Na^+, $C1^-$	H^+, K^+

ERYTHROPOIETIN

- hormone produced by kidneys (and liver to a lesser degree) in response to hypoxia
- produced in kidneys by fibroblast-like cells in cortical interstitium
- the amount of oxygen available not oxygen saturation or hemoglobin concentration determine erythropoietin (Epo) release
- responds in 1.5 to 2 hours, to hypoxia as brief as 15 minutes
- in renal disease anemia results from decreased renal capacity for Epo production and release, as well as decreased red blood cells life span (toxic hemolysis, hypersplenism)

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 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 be more reflective of pathology than absolute values
- 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

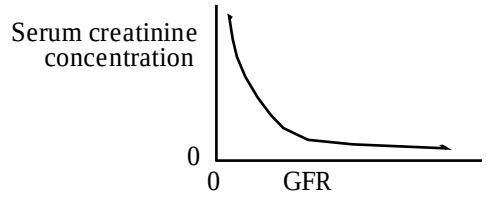


Figure 2. Serum Creatinine Concentration as a Function of GFR

Creatinine Clearance
- ❏ estimate of GFR (actually an overestimate as some creatinine is secreted)
- ❏ should be full 24 hour collection
- ❏ creatinine clearance as a reflection of GFR can be estimated by the following formula

GFR = [U]Cr x Vu/PCr
where [U]Cr is urine creatinine concentration, Vu is urine flow rate and PCr is plasma creatinine concentration

alternatively, GFR can be estimated using the formula:

$$\frac{(140 - age)(weight) \times 1.2 \text{ (men) or } 0.85 \text{ (women)}}{PCr}$$

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 doubles in a given person, 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 acidotic 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)

$$TTKG = \frac{UK/PK}{Uosm/Posm}$$

Where UK is urinary K^+ concentration, PK is plasma K^+ concentration, Uosm is urinary osmolarity and Posm is plasma osmolarity

- ❏ Fractional Excretion (FE) of various solutes (X)

$$FeX = \frac{UX/PX}{Ucr/Pcr} \times 100\%$$

THE KIDNEY IN PREGNANCY

- ❏ increased kidney size and dilatation of renal pelvis and ureters (increased UTI risk)
- ❏ 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 per 24 hours) often occur

Notes

Renal Risk Factors for Adverse Pregnancy Outcome
- ❑ pre-existing hypertension
- ❑ collagen-vascular disease, especially if not in remission or if associated with antiphospholipid antibodies
- ❑ creatinine ≥ 180 umol/L
- ❑ nephrotic-range proteinuria
- ❑ active UTI

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 H_2O (measures weight of solutes in urine)
- ❑ an estimate of urine osmolality (and if kidneys are working, of the patient's state of hydration)
- ❑ values below 1.010 reflect dilute urine, values above 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 renal tubular acidosis) or increased GFR (e.g. pregnancy)

Protein
- ❑ detection by dipstick really 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 patient has clinically (dipstick) detectable proteinuria it is unnessary to send urine for microalbumin levels!

Hemoglobin
- ❑ 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

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
- ❑ see Hematuria section

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

hyaline	• not indicative of disease • concentrated urine • fever • exercise
RBC	• glomerular bleeding (e.g. glomerulonephritis) = active sediment
leukocyte	• pyelonephritis • interstitial nephritis
hemegranular	• ATN • proliferative GN
fatty casts/oval fat bodies	• nephrotic syndrome

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

Index	Pre-Renal	Intra-Renal (e.g. ATN)
Urine Osmolality	> 500	< 350
Urine Sodium (mmol/L)	< 20	> 40
$FENa^+$	< 1%	> 3%
Plasma BUN/Cr (SI Units)	> 80:1	< 40:1

- ❑ high urine Na^+ in the setting of acute renal failure indicates intra-renal disease or the presence of non-reabsorbable anions (e.g. ketones)
- ❑ high urine Na^+ in the setting of hyponatremia: diuretics, tubular disease (Bartter's syndrome, see below), SIADH
- ❑ a high $FENa^+$ but low $FEC1^-$ 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) in contrast to 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

Table 4. Quantitative Proteinuria

Daily Protein Excretion	Meaning
< 150 mg	normal
150 mg - 2 g	glomerular disease tubular disease orthostatic overflow
2 g - 3 g	usually glomerular may be tubular
> 3 g	almost always glomerular unless light chains (multiple myeloma)

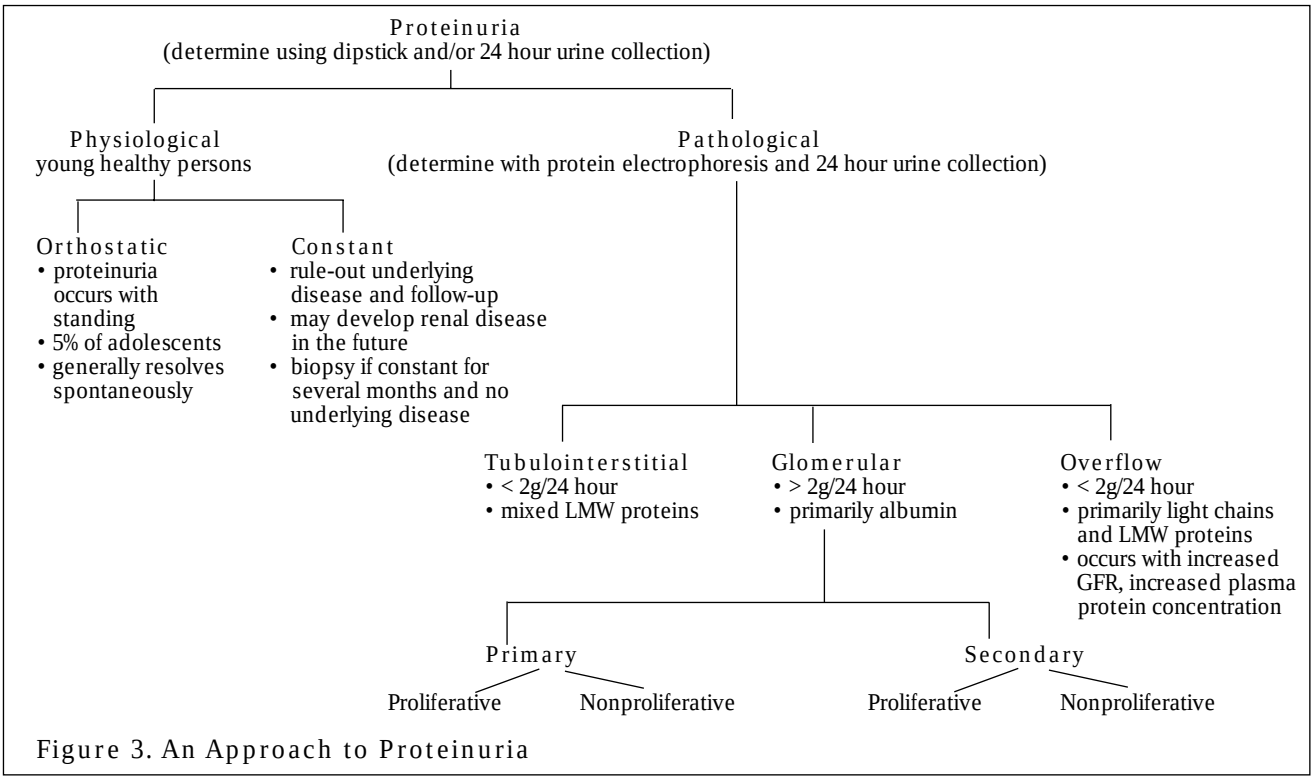


Figure 3. An Approach to Proteinuria

- ❑ 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
- ❑ plasma proteins are filtered at the glomerular capillary interface based on charge and size
- ❑ fenestrations in the glomerular basement membrane exclude proteins of molecular weight (MW) greater than and equal to albumin (MW 60 000)
- ❑ proteins of MW less than albumin may filter through the glomerular barrier but are normally reabsorbed and catabolized by renal tubular cells
- ❑ therefore, tubular dysfunction can give modest excretion of LMW proteins up to 2 g/day
- ❑ glomerular dysfunction produces proteinuria, usually > 2 g/day consisting of higher MW proteins (especially albumin)
- ❑ albumin loss causes decreased oncotic pressure with resulting tissue edema and hyperlipidemia
- ❑ hyperlipidemia results from hepatic lipoprotein synthesis stimulated by the decreased plasma oncotic pressure
- ❑ with tubular dysfunction there is no associated edema or hyperlipidemia because albumin is not lost
- ❑ 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
- ❑ isolated hematuria: no significant proteinuria, cells or urinary casts
  - likely secondary to a UROLOGICAL problem
- ❑ hematuria associated with proteinuria, cells or casts
  - likely secondary to a NEPHROLOGICAL problem
- ❑ causes are also age-related
  - glomerular causes predominate in children and young adults
  - fewer than 5% of cases of hematuria in patients age > 40 result from glomerular lesions

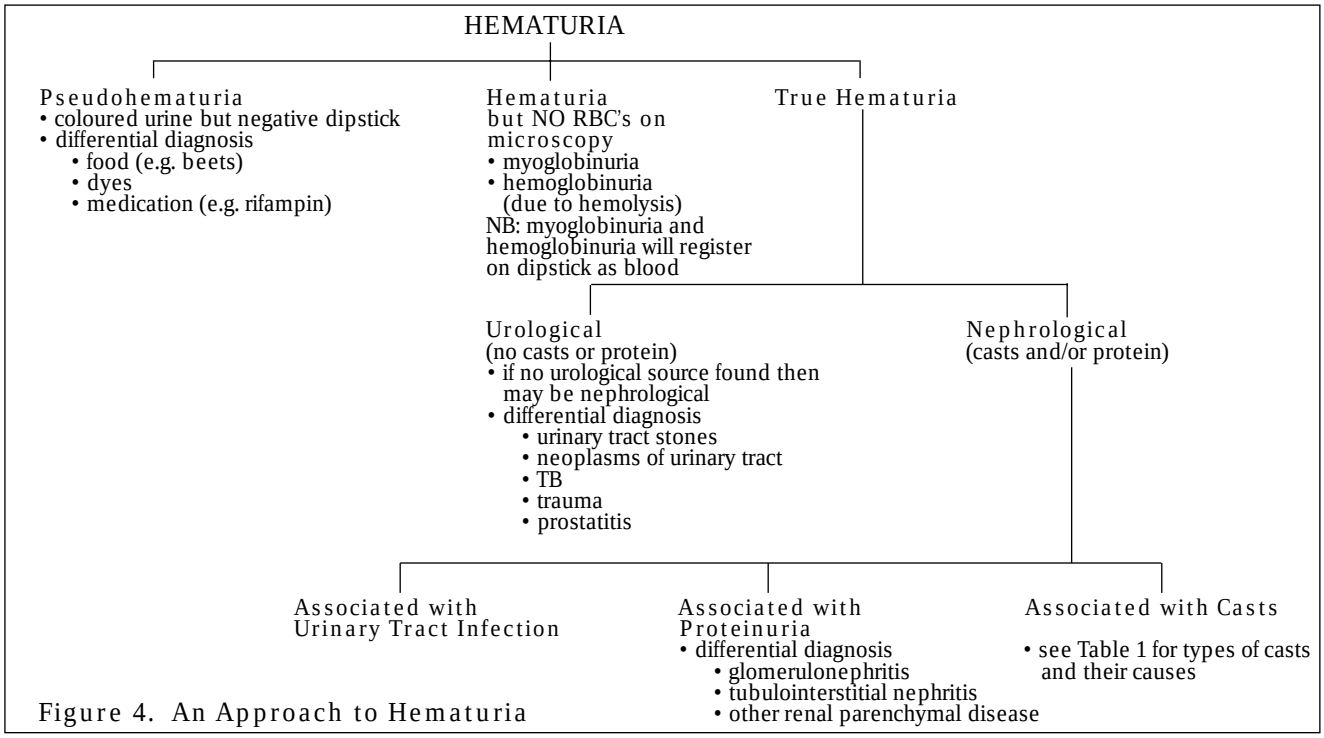


Figure 4. An Approach to Hematuria

Table 5. An Approach to Hematuria

	Nephrologic	Urologic
Symptoms	• constitutional (if 2º to systemic disease) • arthralgia • rash • deafness (Alport's syndrome)	• pain • gross blood • prostatism
Signs	increased blood pressure (occasionally)	
Urine	• protein • casts	RBC's only
Labs	increased Cr (occasionally)	normal Cr (unless obstructed)

Possible investigations (depending on setting)
serum complement, ASO, ANA, ANCA, anti-GBM antibodies, cryoglobulins, hep B and C, 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 for example)
- ❏ clinical signs and symptoms of hyponatremia/hypernatremia are secondary to cells (especially in brain) shrinking (hypernatremia) or swelling (hyponatremia)

Table 6. Clinical Assessment of ECF Volume (Total Body Na^+)

	Hypovolemic	Hypervolemic
Intravascular		
JVP	decreased	increased
blood pressure	orthostatic drop	normal to increased
auscultation of heart	tachycardia	S_3
auscultation of lungs	normal	pulmonary edema
Interstitial		
skin turgor	decreased	edema
Other		
body weight	decreased	increased
Hct, serum protein	increased	decreased

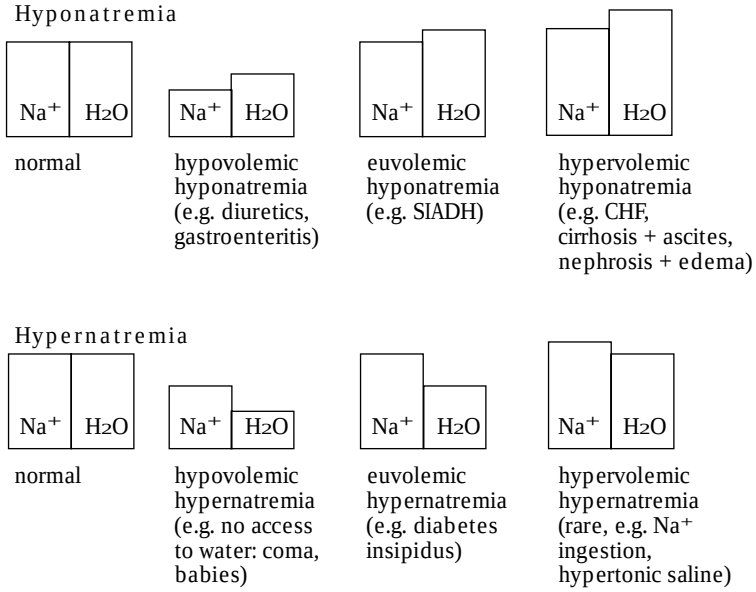


Figure 5. Classification of Hyponatremia/Hypernatremia

HYPONATREMIA

Clinical Features

- ❑ depend on degree of hyponatremia and more importantly rapidity of onset
- ❑ neurologic symptoms predominate, 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, urine osmolality, urine Na^+ concentration, serum electrolytes, glucose, creatinine, and urine R & M

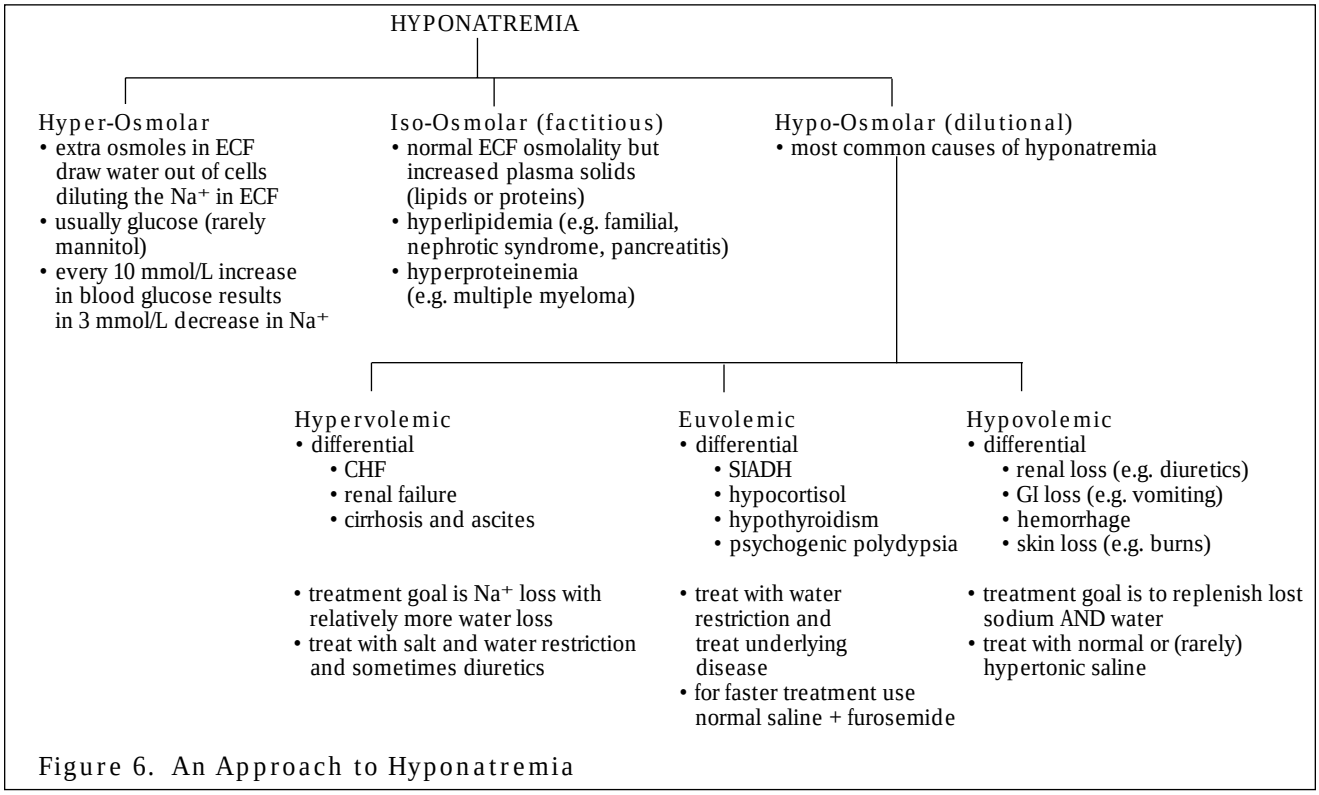


Figure 6. An Approach to Hyponatremia

- ❑ it is dangerous to correct hyponatremia too quickly
- ❑ hyponatremia with CNS symptoms is an emergency
- ❑ can consider treatment in two steps: acute correction of symptomatic hypoNa^+ and longer term correction of asymptomatic or residual hypoNa^+
- ❑ acute correction: use normal saline or hypertonic (3% or 5%) saline
- ❑ aim for raising the Na^+ concentration by 1-2 mEq/L/hr over 4-6 hours (to values between 120 and 125 mEq/L but no more than 8 mEq/L in first day)
- ❑ can estimate the sodium requirement as: [desired Na^+ concentration change x 0.6 x body weight]
- ❑ rapid correction of hyponatremia can lead to osmotic demyelination most commonly of the central pons (called Central Pontine Myelinosis - dysarthria, dysphagia, lethargy, coma, paralysis, ataxia, pseudobulbar palsy - which can take weeks to recover and usually incurs permanent sequelae)

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

- ❑ characterized by a hyperosmolar urine out of proportion to serum osmolality, and a non-low urine sodium (e.g. > 30 meq/L) and $FENa^+$
- ❑ in addition to SIADH, drugs which cause nausea (narcotics, antineoplastic agents) NSAIDs, barbiturates, carbamazepine, TCA's, oxytocin may also cause increased ADH as can trauma and surgery

Table 7. Disorders Associated with SIADH

Tumour	Pulmonary	CNS
oat cell CA bronchogenic CA adenoCA of pancreas Hodgkin's disease thymoma	pneumonia lung abscess TB	brain tumour encephalitis subarachnoid hemorrhage acute intermittent porphyria head trauma

HYPERNATREMIA

- ❑ too little water relative to total body Na^+; always a hyperosmolar state
- ❑ much less common than hyponatremia because protected by thirst and the increased release of ADH

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 subarachnoid or intracerebral hemorrhage
- ❑ acute increases are more dangerous since in chronic increase there is compensation by intracellular retention of potassium, sodium, amino acids, myoinositol

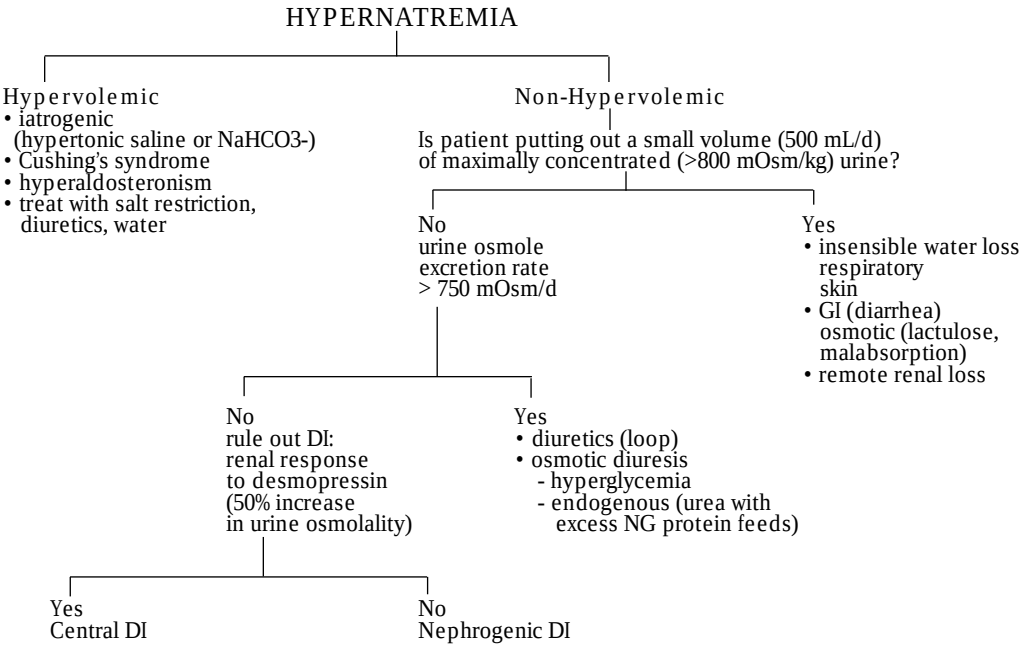


Figure 7. An Approach to Hypernatremia

Treatment of Hypernatremia

- ❑ give normal saline first to boost ECF and achieve hemodynamic stability
- ❑ then PO or NG tube water or IV 1/2 NS or D5W while monitoring Na^+
- ❑ can estimate free water deficit by the formula ($[Na^+] – 140)/140$ x total body water where total body water is (weight x 0.5) for men and (weight x 0.4) for women
- ❑ aim to replenish this deficit over 48-72 hours, lowering serum Na^+ by no more than 0.5 mEq/L/h (12 mEq/L/d)
- ❑ 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)

- ❑ may be central or nephrogenic
- ❑ central DI etiology: neurosurgery, granulomatous diseases, trauma, vascular events, CA
- ❑ nephrogenic DI etiology: lithium (most common), hypoK^+, hyperCa^+
- ❑ diagnosis of Diabetes Insipidus
  - the urine 24 hour osmole excretion is not elevated
  - H_2O 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: PO_4^{3-}, HCO_3^-, penicillin
- ❑ K^+ excretion is reflected by the following formula

$$K^+ \text{ Excretion} = (\text{Urine flow rate})(\text{Urine } K^+ \text{ concentration})$$

Causes of Hypokalemia

- ❑ decreased intake (unusual as a sole cause but may exacerbate other causes)
  - limited dietary intake
  - clay ingestion
- ❑ redistribution into cells
  - metabolic alkalosis
  - hormones: insulin, beta-2 agonists, alpha-blockers
  - uptake into newly forming blood cells: vitamin B_{12} injections in pernicious anemia, colony stimulating factors increasing WBC production
- ❑ increased losses
  - GI: diarrhea (especially secretory: carbohydrate intolerance, lactulose)
  - skin: sweating
  - renal
    - increased distal flow: diuretics, osmotic diuresis (hyperglycemia, urea)
    - increased K^+ secretion: primary hyperaldosteronism, secondary hyperaldosteronism (renin secreting tumours, renal artery stenosis, hypovolemia), congenital adrenal hyperplasia, Bartter's syndrome, Cushing's syndrome, Liddle's syndrome, vomiting, excess NG suction, DKA, penicillins, proximal (Type 2) RTA

Clinical Features

- ❑ symptoms rare until $K^+ < 3.0$ mEq/L
- ❑ first see fatigue, muscle weakness, cramps, myalgia, and later can progress to hypoventilation, paralytic ileus, rhabdomyolysis, arrhythmias
- ❑ 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-U interval
  - with severe hypoK^+ see P-R prolongation, wide QRS, arrhythmias
- ❑ increases risk of digitalis toxicity
- ❑ can distinguish distal renal from other causes of hypoK^+ by looking at the TTKG:
  - TTKG > 4 suggests K^+ loss due to secretion at the level of the distal tubules
  - TTKG < 2 suggests non renal or proximal renal losses (osmotic diuresis, diuretics)
- ❑ can also assess serum renin and aldosterone, as well as acid-base status, urinary electrolytes, and serum Mg^{2+} for causes of hypokalemia

Treatment

- ❑ serum levels do not correlate well with deficit (can have from 200-600 or more mmol deficit)
- ❑ hypokalemia due to cellular shifts should be corrected with PO K^+ not IV
- ❑ risk of hyperkalemia secondary to hypoK^+ 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
- ❑ IV - usually KCl (may use $KHCO_3^-$ or Kcitrate in RTA or diarrhea)
  - 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

HYPERKALEMIA

Causes

- ❑ factitious (pseudohyperkalemia)
  - common
  - prolonged use of a tourniquet
  - sample hemolysis

- leukocytosis, thrombocytosis
- drawing blood out of vein into which IV is running

❑ increased intake (rarely solely responsible)
- may be iatrogenic (K^+ pills, IV KCl) especially in patients with other conditions (see below) predisposing to hyperkalemia

❑ cellular release
- intravascular hemolysis, tumour lysis syndrome, rhabdomyolysis
- insulin deficiency
- hyperosmolar states (e.g. hyperglycemia)
- metabolic acidosis (especially inorganic)
- beta-blockers (rarely a sole cause)
- digitalis overdose
- depolarizing muscle relaxants (succinylcholine)

❑ decreased output
- decreased distal solute delivery
  - ECF volume contraction
  - protein malnutrition
  - ARF, CRF
  - NSAIDs in renal insufficiency
- inadequate secretion of K^+ in distal nephron
  - hyporeninemic hypoaldosteronism (renal insufficiency diabetic nephropathy, chronic tubulointerstitial disease)
  - 1º hypoaldosteronism (adrenal insufficiency, adrenal enzyme deficiency)
  - 2º hypoaldosteronism (ACE inhibitors, NSAIDs, heparin)
  - resistance to aldosterone (pseudohypoaldosteronism, tubulointerstitial disease, K^+ sparing diuretics, trimethoprim, pentamidine)
  - enhanced Cl^- reabsorption (chloride shunt) in Gordon's syndrome, cyclosporin, hyperK^+, distal (Type 4) RTA

Clinical Features

❑ usually asymptomatic but may develop muscle weakness, paresthesias, areflexia, ascending paralysis, and hypoventilation

❑ impaired ammoniagenesis and metabolic acidosis

❑ if severe ECG changes and cardiotoxicity (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

❑ can measure TTKG: values less than 10 suggest inadequate K^+ secretion at the distal tubules (see above for potential causes)

Treatment

❑ acute therapy is warranted if K^+ high, symptoms present, ECG changes
- perform ECG, repeat blood test, r/o pseudohyperkalemia
- hold exogenous K^+ and K^+ – retaining meds
- Ca^{2+} gluconate 1-2 amps ONLY (10 mL of 10% solution) IV (cardioprotectant); giving more can result in calcium toxicity and death!
- regular insulin (Insulin R) 10-20 units IV, with 1/2 to 1 amp D50W
- $NaHCO_3^-$ 1-3 amps (given as 3 amps of 7.5% or 8.4% $NaHCO_3^-$ in 1L D5W)
- ß2-agonist (albuterol = ventolin) in nebulized form
- cation-exchange resins: Kayexalate or Calcium Resonium
- dialysis (renal failure, life threatening hyperK^+ unresponsive to therapy)

Clinical Pearl

❑ In diabetics with increased K^+ and hyperglycemia, simply give insulin to restore euglycemia and monitor K^+ rather than initiating K^+ lowering therapy

- ❑ an approach (see Figure 8)
  - look at arterial pH to establish acidemia vs. alkalemia
  - look at HCO_3^- and pCO_2 to establish major process (respiratory/metabolic)
  - determine expected and actual compensations to establish secondary process
  - determine anion gap (AG) and compare AG with HCO_3^- changes (increase in AG should equal decrease in HCO_3^- in pure AG acidosis)
  - if AG acidosis, calculate osmolar gap to detect non-ionic osmoles (alcohols)
- ❑ normal HCO_3^- = 25 mEq/L
- ❑ normal pCO_2 = 40 mmHg

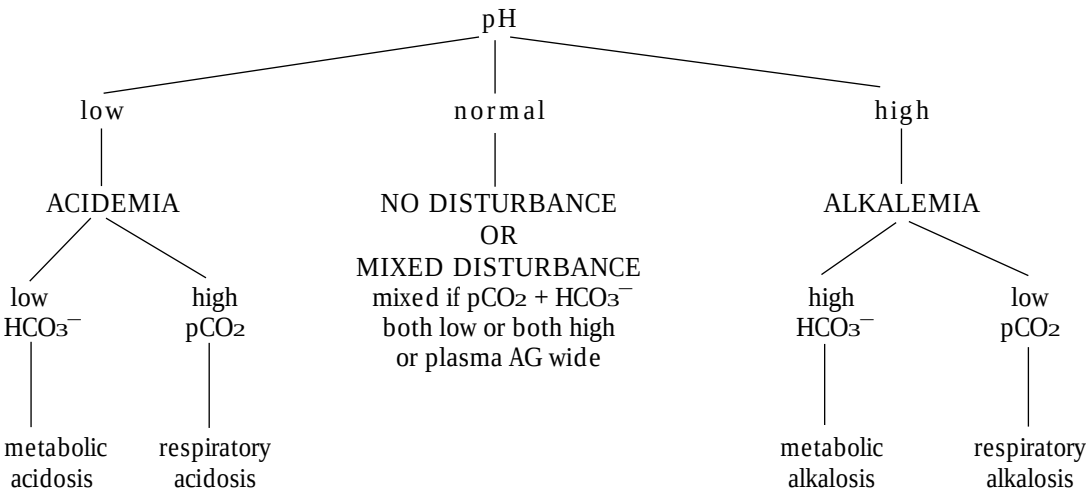


Figure 8. An Approach to Acid-Base Disorders

RENAL CONTRIBUTION TO ACID-BASE BALANCE

- ❑ proximal tubule reabsorbs filtered HCO_3^- (stimulated by AII, hypovolemia)
- ❑ proximal tubule generates ammonium and HCO_3^- (stimulated by AII, hypovolemia, hypokalemia, intracellular acidosis)
- ❑ distal tubule excretes H^+ produced by the body (stimulated by intracellular acidosis, hypokalemia, hypovolemia, aldosterone)
- ❑ 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
- ❑ Type II RTA (proximal)
  - impaired HCO_3^- reabsorption: lost in urine and buffer is depleted
- ❑ Type IV RTA
  - decreased aldosterone activity or aldosterone responsiveness
  - distal tubule can't excrete H^+, K^+
  - insufficient ammoniagenesis to generate HCO_3^- and to accept H^+ distally
  - associated with hyperkalemia (unlike proximal and distal RTA)

1° METABOLIC ACIDOSIS

- ❑ to determine cause, first calculate the AG in blood sample = $Na^+ – (HCO_3^- + Cl^-)$
- ❑ increased AG metabolic acidosis
  - ketoacidosis
  - lactic acidosis, D-lactic acidosis
  - renal failure with GFR < 20% of normal
  - drugs: salicylates, ethylene glycol, methanol
    - osmolar gap = measured plasma osmolality minus calculated plasma osmolality ($2Na^+$ + BUN + glucose)
    - normal osmolar gap < 10 mosm/kg
    - if gap > 10, consider unmeasured osmoles (e.g. alcohols)
- ❑ normal AG metabolic acidosis
  - loss of HCO_3^- in urine (proximal RTA) or GI tract (diarrhea)
  - failure of kidney to make new HCO_3^- (distal RTA)
- ❑ for metabolic acidosis, if the fall in HCO_3^- matches the rise in AG, it is a pure AG acidosis

- ❑ if the fall in HCO_3^- > rise in anion gap, consider mixed AG/non-AG metabolic acidosis (i.e. renal failure and diarrhea)
- ❑ if AG rise is > HCO_3^- fall, consider a concurrent metabolic or respiratory alkalosis

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 primary respiratory alkalosis
  - if pCO_2 decreases less than expected, there is also a primary respiratory acidosis
    example:
    - 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

1º METABOLIC ALKALOSIS

- ❑ etiology
  - generation of new HCO_3^-
    - GI loss (vomiting, NG suction)
    - diuretics
    - milk alkali syndrome, exogenous $NaHCO_3$
    - hypokalemia
  - impaired HCO_3^- excretion
    - reduced GFR
    - volume contraction alkalosis
    - 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

Categories and Treatment

- ❑ saline (chloride) sensitive metabolic alkalosis (most common)
  - ECF volume depletion
  - treatment: NaCl (volume repletion)
- ❑ 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)
- ❑ pCO_2 increases 0.5-0.7 mmHg for every 1 mEq/L increase in HCO_3^-

1º RESPIRATORY ACIDOSIS (HYPOVENTILATION)

Causes

- ❑ severe COPD, drugs (sedatives), altered level of consciousness, sleep apnea, neuromuscular disorders

Renal Compensation in Respiratory Acidosis

- ❑ the kidney retains HCO_3^- to combat the acidemia
- ❑ acutely, increase in HCO_3^- = 0.1 x increase in pCO_2 (no time for renal compensation)
- ❑ chronically, increase in HCO_3^- = 0.3 x increase in pCO_2 (kidneys are doing a better job of reducing acidemia)

1º RESPIRATORY ALKALOSIS (HYPERVENTILATION)

Causes
- ❑ pneumonia, sepsis, pulmonary embolism, liver disease, pregnancy, salicylates, heart failure

Renal Compensation in Respiratory Alkalosis
- ❑ the kidney excretes HCO_3^-
- ❑ acutely, decrease in HCO_3^- = 0.2 x decrease in pCO_2
- ❑ chronically, decrease in HCO_3^- = 0.5 x decrease in pCO_2
- ❑ remember - a patient with decreased HCO_3^- may simply be hyperventilating (1º respiratory alkalosis) and not acidemic (don't give HCO_3^- without checking systemic pH)

MIXED DISTURBANCES
- ❑ mixed acid-base disorders identified by neutral pH with pCO_2 and HCO_3^- that are both low or both high or wide plasma AG
- ❑ treatment (with HCO_3^-) is guided by arterial blood gas pH, not simply HCO_3^- level alone (a common mistake!)
    - example: patient with liver disease on spironolactone
        - acidemia due to spironolactone (aldosterone inhibition)
        - alkalemia due to hyperventilation of liver disease
        - balance: pH = 7.40, HCO_3^- = 12 mEq/L (respiratory alkalosis and metabolic acidosis both lower HCO_3^-)
        - this patient has a neutral pH and does not require HCO_3^-

RENAL FAILURE

Table 8. Classification of Renal Failure

	Acute	Chronic
history	• abrupt onset of multisystem illness • previously known normal function	• history of kidney problems, hypertension • previous problems in pregnancy
physical	• depends on underlying disease • rash • joint effusion • marked edema • encephalopathy • kidneys normal size or swollen	• peripheral neuropathy • retinopathy • LVH • less encephalopathy • kidneys small except in PCKD, DM, amyloid
lab	• normal to slight anemia • severe hyperkalemia • normal to slight hypocalcemia • normal to slight hyperphosphatemia • normal alkaline phosphate	• anemia • modest hyperkalemia • marked hypocalcemia • marked hyperphosphatemia • increased alkaline phosphate

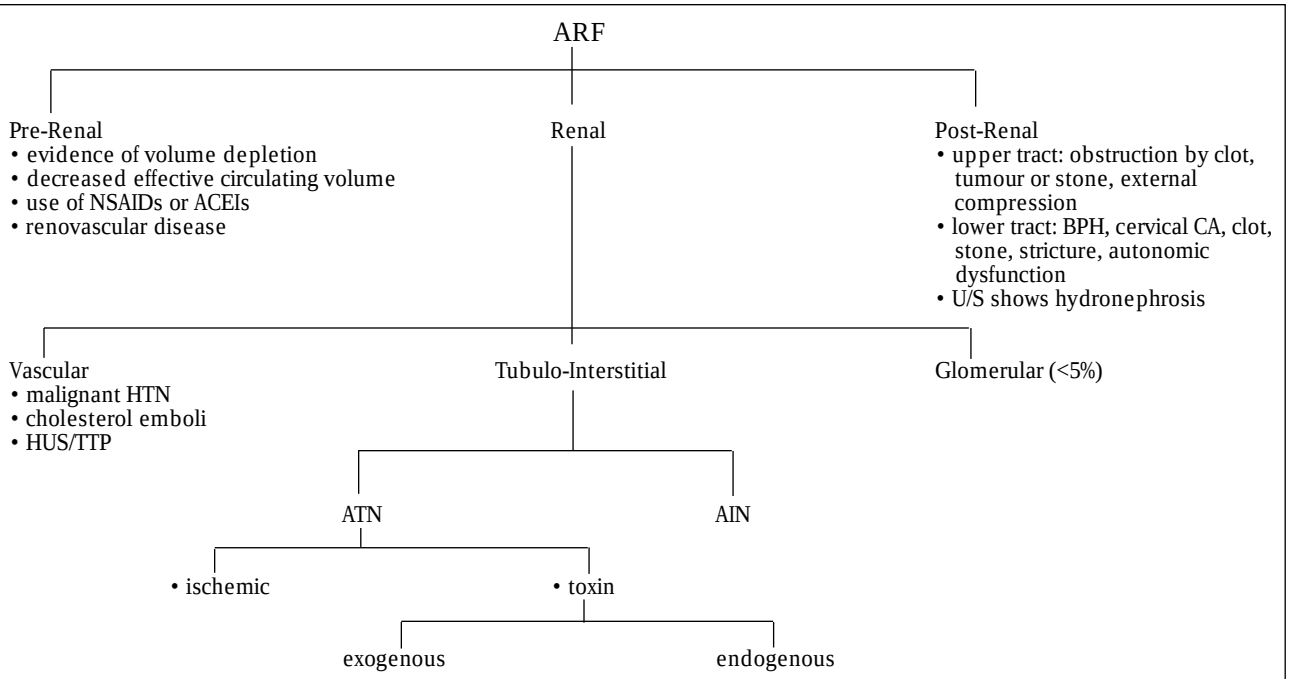


Figure 9. Acute Renal Failure

- ❑ definition: abrupt decline in renal function leading to increased urea and increased serum creatinine
- ❑ plasma creatinine rises 50-175 µM/24 hrs - if rise is greater, may be rhabdomyolysis, catabolic patient, or total renal shutdown

TREATMENT

- ❑ always look for and correct pre-renal and post-renal causes first
  - always look for evidence of chronic renal failure
  - always place Foley catheter in patient while investigating the cause of ARF
  - always get an abdominal U/S unless cause is very obvious
    - 2 reasons
      - rule out post-renal causes of renal failure
      - assess size of the kidneys (if kidneys small; indicates an underlying chronic condition)

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
  - hypermagnesemia

Post-Renal

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

Clinical Pearl
- ❑ Post-renal failure not necessarily associated with anuria or even oliguria

Supportive Therapy For All Causes of Renal Failure
- ❑ drug modification: avoid nephrotoxic drugs, dosage modification
- ❑ potassium restriction
- ❑ salt restriction

INDICATIONS FOR DIALYSIS IN ARF (vs. IN CRF)
- ❑ ECF volume overload unresponsive to diuretics
- ❑ hyperkalemia unresponsive to treatment
- ❑ severe acidosis
- ❑ uremic pericarditis
- ❑ uremic encephalopathy - alteration of mental status, asterixis, seizures, coma
- ❑ uremic polyneuropathy - myoclonus, twitchiness
- ❑ "evil humours" - even in absence of above indications, a very high urea or creatinine, or even a not-so-high urea or creatinine in an oliguric/catabolic (e.g. post-op) patient

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

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
- ❑ glomerular: 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 creatinine 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 secondary hyperparathyroidism
- ❑ renal osteodystrophy (2º hyperparathyroidism = 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), H_2O, PO_4^{3-} (800-1000 mg/day), protein (modestly 0.9 g/kg/day)

- ❑ adjust drug doses
- ❑ treat HTN: drugs (especially ACE-inhibitors), sodium restriction (target BP <125/75)
- ❑ 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 $NaHCO_3^-$ when serum HCO_3^- is < 20 mEq/L
- ❑ erythropoietin in anemia (hematocrit < 30%)

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 (< 0.15 ml/second)
- ❑ diabetics less tolerant of uremia, dialyse when creatinine clearance < 15% of normal
- ❑ 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

Peritoneal Dialysis

- ❑ slower than hemodialysis but less stressful and can be done at home
- ❑ in-dwelling catheter inserted through abdominal wall into peritoneal cavity
- ❑ high dextrose fluid infused into cavity, dwells for a variable period, then drained
- ❑ ultrafiltration occurs across peritoneum via osmotic pressure of dextrose in dialysate (water moves from plasma to hyper-osmolar dialysate), e.g. 2 L into blood and 2.5 L out of blood means 0.5 L ultrafiltered
- ❑ solute removal via diffusion down concentration gradient (i.e. urea from 30 mmol/L in plasma to 0 mmol/L in dialysate) and also by convection along with ultrafiltrate
- ❑ problems: infection at catheter exit site, bacterial peritonitis, long term metabolic effects of glucose loading

Hemodialysis

- ❑ blood travels along tubing from vessel to artificial kidney where it is in contact with fluid on other side of semi-permeable artificial membrane
- ❑ ultrafiltration via hydraulic pressure imposed across membrane of artificial kidney
- ❑ solute removal via concentration gradient and by convection with ultrafiltered volume
- ❑ problems: vascular access (veins clot, give out), bleeding due to heparinization, hemodynamic stress of "extracorporeal" blood circuit, disequilibrium syndrome

Clinical Pearl

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

RENAL 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 rejections
  - 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

GLOMERULONEPHRITIS

GENERAL CONSIDERATIONS

Clinical Features
- ❑ depends if 1º or 2º
- ❑ 1º GN
  - edema, HTN, fatigue, uremia, decreased urine volume, hematuria or cola-coloured urine, flank discomfort
  - presents with nephrotic syndrome, nephritic syndrome, or a mixture of both
- ❑ 2º GN
  - all of above, plus symptoms and signs of underlying disease
  - collagen vascular: rash, Raynaud's, photosensitivity, polyarthralgia, otitis, and sinusitis
  - vasculitis: rash, abdominal pain, mononeuritis multiplex
  - SLE: rash, joint effusion, pleuritis, pericarditis
  - Wegener's Granulomatosis: nasal deformity, middle ear effusion
  - Goodpasture's syndrome: hemoptysis, SOB, fleeting pulmonary infiltrates

Nephrotic Syndrome
- ❑ proteinuria of >3.5 g/24 hr
- ❑ hypoalbuminemia
- ❑ edema
- ❑ hyperlipidemia
- ❑ hypercoaguability

Differential Diagnosis of Nephrotic Syndrome
- ❑ 1º
  - minimal change disease (most common cause in children)
  - membranous glomerulopathy (most common cause of idiopathic nephrotic syndrome in adults)
  - focal sclerosis
- ❑ 2º
  - diabetic nephropathy
  - amyloidosis
  - drugs (gold, penicillamine)

Laboratory
- ❑ urinalysis
- ❑ blood tests
- ❑ 1º GN: creatinine, albumin, cholesterol

- ❑ 2º GN: 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:
  - nephrotic syndrome, unless young patient (assume minimal change disease)
  - progressive renal impairment of unknown etiology

Management of 1º and 2º GN
- ❑ remove offending cause
- ❑ salt restriction
- ❑ diuretics
- ❑ antihypertensives
- ❑ immunosuppressives in selected cases
- ❑ 1º GN
  - minimal lesion: corticosteroids, cyclophosphamide as steroid sparing agent
  - membranous
  - focal sclerosis
  - mesangial proliferative
  - membrano-proliferative

  } corticosteroids, other immunosuppressives, all controversial
  - crescentic: corticosteroids, +/– other immunosuppressives, +/– plasmapheresis (for antiGBM disease)
- ❑ 2º GN
  - SLE/PAN: steroids ± immunosuppressives
  - Wegener's Granulomatosis: cyclophosphamide

Prognosis
see below for specific disease entities

PRIMARY GLOMERULONEPHRITIS
- ❑ glomerular disease which is not secondary to systemic disease, metabolic disease, drugs or hereditary causes

I. Nonproliferative GN
- ❑ no extra cells in glomerulus
- ❑ inactive sediment
- ❑ may see oval fat bodies and fatty casts which reflect the lipiduria and do not imply an "active sediment"

Minimal Change
- ❑ most common cause of nephrotic syndrome in children, but not rare in adults either
- ❑ presents as nephrotic syndrome
- ❑ inactive sediment
- ❑ LM usually normal
- ❑ EM shows fusion of foot processes of glomerular epithelial cells
- ❑ most respond to prednisone but may relapse
- ❑ cyclophosphamide may be useful in inducing remission or relapse
- ❑ natural history is of eventual resolution although some progress to focal segmental sclerosis

Membranous
- ❑ most common cause of idiopathic nephrotic syndrome 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 immunosuppressive agents give conflicting results
- ❑ poor prognostic features: male sex, high creatinine at presentation, persistent high grade proteinuria > 6 months

Focal Segmental Sclerosis
- ❑ 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
- ❑ renal function may be normal to reduced
- ❑ HTN may or may not be present
- ❑ natural history is of gradual decline in renal function
- ❑ therapy: high dose long-term steroids

II. Proliferative GN
- ❑ extra cells in the glomerulus
- ❑ usually presents as nephritic syndrome
- ❑ active sediment = RBC, RBC casts, heme-granular casts
- ❑ variable proteinuria

Mesangial Proliferative (i.e. Berger's Disease)
- ❑ IgA nephropathy or Berger's disease
- ❑ IgA becomes trapped in mesangium and activates complement
- ❑ IF shows granular mesangial deposits (Christmas tree-like)
- ❑ presents as asymptomatic gross hematuria a few days after URTI or GI infection or as microscopic hematuria on routine urinalysis
- ❑ 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

Diffuse Proliferative (Post-lnfectious)
- ❑ i.e. post-Strep infection
- ❑ immune response to Group A (beta-hemolytic) *Strep*
- ❑ planted antigen or deposition of circulating Ag/Ab complex
- ❑ LM shows large glomerulus and decreased Bowman's space
- ❑ EM shows subepithelial "humps"
- ❑ presents as acute nephritic syndrome 10-12 days after bacterial infection
- ❑ no treatment is of proven benefit
- ❑ 95% of kids recover
- ❑ in adults the prognosis is not as good

Crescentic (Epithelial Proliferative)
- ❑ 3 types
    - type I: linear deposition of antiglomerular BM antibodies i.e. antiglomerular BM antibody that cross-reacts with pulmonary BM (Goodpasture's disease)
        - smoking plays a permissive role in hemoptysis
        - IF shows a linear deposition along the glomerular BM
        - EM: GBM disruption but no electron dense deposits
    - type II: granular immune complex deposits
    - type III: Pauci-immune (may be associated with ANCA-positivity)
- ❑ prognosis: if diagnosed early and treated aggressively (steroids, cyclophosphamide, +/– plasmapheresis) may stabilize
- ❑ if advanced, prognosis poor

Membrano-Proliferative
("Cross-Over" GN: Proliferative and Nonproliferative)
- ❑ presents as a nephritic-nephrotic mixture
- ❑ proteinuria and active sediment
- ❑ glomerular mesangium is expanded and hypercellular
- ❑ capillary walls are thickened
- ❑ treatment is controversial: interferon for hepatitis B-associated

SECONDARY GLOMERULONEPHRITIS

A. Systemic Diseases

Diabetes Mellitus (see Diabetes and the Kidney Section)
- ❑ progressive glomerulosclerosis
- ❑ presents as proteinuria initially (microalbuminuria progressing to clinically detectable proteinuria)

Systemic Lupus Erythematosus
- ❑ idiopathic autoimmune disease that involves multiple organs
- ❑ kidney is involved in 60-70%
- ❑ antinuclear antibodies and immune complex deposition
- ❑ WHO classification
    - 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

Other Systemic Diseases to Consider

- ❑ Henoch-Schonlein Purpura
  - non-thrombocytopenic purpura, arthralgia, abdominal pain and GN (proteinuria, hematuria)
- ❑ "shunt" nephritis (SBE)
- ❑ syphilis
  - congenital and 2º
- ❑ vasculitic: PAN, Wegener's Granulomatosis
- ❑ thrombotic microangiopathy, TTP, HUS, DIC
- ❑ scleroderma
- ❑ HIV-associated nephropathy

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

Dysproteinemias

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

C. Hereditary Nephropathies

Alport's Syndrome

- ❑ hereditary nephritis sometimes associates with sensorineural deafness
- ❑ three modes of inheritance have been described: X-linked dominant, autosomal dominant, and less often autosomal recessive

D. Drug Induces

- ❑ e.g. NSAIDs, gold, penicillamine

E. Neoplasms

- ❑ lymphoma, leukemia
- ❑ adenocarcinoma of lung, colon, stomach or breast
- ❑ membranous or minimal lesion

F. Infections

- ❑ hepatitis B, hepatitis C, HIV
- ❑ syphilis
- ❑ malaria
- ❑ schistosomiasis

Table 9. Glomerulonephritis Summary Chart

	Presentation	LM	IF	EM	Management	Prognosis
NON-PROLIFERATIVE						
minimal change	nephrotic	normal	negative	fusion of foot processes	prednisone	excellent
membranous	nephrotic	capillary wall thickening	granular IgG, C3 in capillary loops	subepithelial electron dense deposits (EDD)	controversial	rule of thirds
focal segmental	nephrotic	focal and segmental sclerosis +/– hyalinosis	negative or segmental IgM, C3 in necrotic areas	focal sclerosis, foot processes fusion, subendotheilial EDD	controversial	poor
PROLIFERATIVE						
mesangial (focal) proliferative	asymptomatic urinary abnormalities to nephrotic	mesangial proliferation	negative or mesangial IgA & C3	mesangial deposits	supportive	usually good
diffuse proliferative	nephritic syndrome	diffuse proliferation	granular diffuse IgA & C3	subepithelial “humps”	supportive	good, especially in kids
crescentic 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
membrano-proliferative	nephrotic	wide capillary wall, mesangial proliferation	C3, variable IgG	subendothelial EDD (type I) membranous EDD (type II)	controversial	poor

TUBULOINTERSTITIAL NEPHRITIS

Notes

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
- ❑ acquired nephrogenic diabetes insipidus 2º to tubular damage, decreased ADH responsiveness
- ❑ non-AG metabolic acidosis (proximal RTA from impaired HCO_3^- reabsorption) and hypophosphatemia
- ❑ hyperkalemia and Na^+-wasting (from decreased renin production and hypoaldosteronism)
- ❑ partial or complete Fanconi's syndrome
- ❑ 1,25-dihydroxy-vitamin D deficiency with hypocalcemia and 2º hyperparathyroidism
- ❑ 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 TIN

Etiology
- ❑ acute allergic drug reactions
  - beta-lactam antibiotics, sulfonamides, rifampin, quinolones, NSAIDs sulfonamide diuretics (furosemide), phenytoin, cimetidine, allopurinol
- ❑ renal infections: bacterial pyelonephritis, renal TB, fungal nephritis
- ❑ associated with systemic infection
  - Brucellosis, CMV, infectious mononucleosis, Legionnaire's disease, leptospirosis, streptococcal infections, Rocky Mountain spotted fever, syphilis, toxoplasmosis, *M. pneumoniae*
- ❑ 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
  - WBC, 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, 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 TIN
- ❑ characterized by interstitial fibrosis with atrophy and loss of tubules

Notes

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
- ❑ 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
  - sarcoidosis
  - idiopathic
  - chronic rejection
- ❑ neoplastic/paraproteinemic
  - multiple myeloma
  - light chain nephropathy
  - lymphoma/leukemia
  - amyloidosis
  - Waldenstrom's macrogobulinemia
  - cryoglobulinemia
- ❑ miscellaneous
  - DM
  - 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, hypercalcemia, metabolic acidosis

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

- ❑ one of two most common causes of ARF; pre-renal disease being the other
- ❑ usually results from ischemia or toxins

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

ISCHEMIA
- ❑ shock
- ❑ trauma +/– rhabdomyolysis
- ❑ sepsis or severe hypovolemia
- ❑ post-operative patients are at increased risk because of pre-operative fluid depletion, anesthesia and intra-operative fluid losses
- ❑ NSAIDs in volume depletion

TOXINS

Exogenous
- ❑ antibiotics
  - aminoglycosides (remember that 80 mg q8h is not a universal dose!)
  - cephalosporins
  - amphotericin B
- ❑ antiviral (cidofovir)
- ❑ chemotherapeutic drugs (cisplatin, methotrexate)
- ❑ contrast media
- ❑ heavy metals
- ❑ miscellaneous
  - fluorinated anesthetic agents
  - ethylene glycol
  - organic solvents
  - acetaminophen overdose
  - paraquat

Endogenous
- endotoxins (bacterial)
- myoglobin
- hemoglobin
- Bence-Jones protein, if combined with radiocontrast dye or volume depletion

Prognosis of ATN
- ❑ other than correcting the underlying problem, therapy for ATN is largely supportive
- ❑ kidneys usually get better if insult is removed
- ❑ prognostic factors include
  - age
  - severity of underlying disease
  - complications
  - previous episode of ARF

NSAID NEPHROPATHY

Notes

- ❑ NSAIDs act by blocking the cyclooxygenase enzyme needed in 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
    - perhaps the most common cause of drug-induced 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 with low $FENa^+$
    - treatment: discontinue NSAID, dialysis rarely needed
  - AIN
    - majority due to fenoprofen (60%), ibuprofen, naproxen; can be any NSAID
    - distinguish from other drug-induced AIN by rarity 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 ARF, requires NSAIDs 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
- ❑ papillary necrosis
- ❑ glomerulonephritis associated with diffuse vasculitis
- ❑ sodium retention
- ❑ hyperkalemia, metabolic acidosis (2^o to hyporeninemic hypoaldosteronism)
- ❑ excess water retention and hyponateremia exacerbation (due to elimination of ADH antagonistic effect of PG's)

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

- ❑ 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
  4) papillary necrosis
- ❑ DM is one of the causes of ESRD that does not result in small kidneys

Progressive Glomerulosclerosis

- ❑ stage I
  - 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 reflux nephropathy (see below)

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

Screening

- ❑ all patients over 15 years of age with a 5 year history of Type I 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)

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, aminoglycoside antibiotics, avoiding dye studies if possible, etc...)
- ❑ aggressive BP control: slows rate of decline in renal function and improves patient survival
- ❑ strict glycemic control: in DCCT shown to reduce microalbuminuria in Type 1 DM (primary and secondary prevention)
- ❑ 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 CrCl necessitates a referral to a nephrologist

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, $HgbA_{1C}$
- ❑ urinalysis
- ❑ ECG

Clues to 2º Causes
- ❑ onset < 20 or > 50 years
- ❑ bruits (renal artery stenosis)
- ❑ abnormal renal function, abnormal urinalysis (GN or TIN)
- ❑ 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 AII 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 inhibitor therapy or NSAIDs
  - when there is decreased RBF, GFR is dependent on angiotensin II-induced efferent arteriolar constriction and raising of filtration fraction

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!
- ❑ perhaps the only thing everyone agrees on is 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, U/S, 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, diabetes mellitus, 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

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: > 10^5 colony forming units (CFU)/mL in clean catch midstream urine or > 10^2/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 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)
  - start broad spectrum IV antibiotics until cultures return (imipenem or emropenem or piperacillin/tazobactam or ampicillin+gentamycin) and treat 2-3 weeks
  - follow-up cultures 24 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)

- ❑ 1:1000 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 predispose 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 anytime from early childhood to as late as 80 years of age
- ❑ the kidneys are normal at birth, symptoms are rare before 20
- ❑ very common in older adults, elderly
- ❑ kidneys may enlarge to 10 times normal volume
- ❑ symptoms and signs
  - often asymptomatic; discovered incidently on imaging
  - abdominal pain/lumbar pain
  - hematuria
  - HTN (up to 75% of adults)
  - progressive renal failure
  - rarely extra-renal presentation (e.g. rupture Berry aneurysm)

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 Notes)

Diagnosis

- ❑ positive family history
- ❑ ultrasound: cysts are usually detectable by age 20
- ❑ other modalities: CT scan with contrast (for equivocal cases)
- ❑ differential diagnosis: multiple simple cysts (not progressive like APCKD)
- ❑ must provide genetic counselling: 50% chance of transmission by affected parent

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

MEDULLARY CYSTIC DISEASE

- ❑ rare autosomal recessive disorder
- ❑ often results in end-stage renal failure during adolescence/childhood
- ❑ cysts difficult to image

MEDULLARY SPONGE KIDNEY

- ❑ nonfamilial disease
- ❑ presents in the fourth to sixth decades
- ❑ 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

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 intra-renal 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
- ❑ myeloma kidney: tubular deposits of light chains with surrounding inflammation
- ❑ light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine
- ❑ light chains may also precipitate in the tubules and form dense eosinophilic casts (can get Fanconi syndrome - a Type II RTA cast nephropathy with global dysfunction of proximal tubules)
- ❑ hypercalcemia may cause renal failure
- ❑ secondary amyloidosis may occur, presents with nephrotic syndrome
- ❑ plasma cells may infiltrate kidney
- ❑ Bence-Jones proteins are not detected on a urine dipstick

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
  - eg. 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

- ❑ 1º involvement rare
- ❑ 2º amyloidosis
- ❑ gold, penicillamine, NSAID nephropathy
- ❑ if Sjögren's, interstitial nephritis

CANCER

- ❑ 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, 2º amyloidosis, hypercalcemia
- ❑ infectious endocarditis: proliferative GN, cryoglobulinemic GN
- ❑ diphtheria, Legionnaire's, toxoplasmosis: interstitial nephritis
- ❑ syphilis: membranous GN
- ❑ malaria: variable glomerular involvement

HIV-ASSOCIATED RENAL DISEASE

- ❑ specific glomerular syndromes; HIV-associated nephropathy
  - focal and segmental glomerulosclerosis-like syndrome
  - IgA nephropathy
  - thrombotic microangiopathy (TTP)
  - other forms of glomerulopathy
- ❑ high predilection for young black males
- ❑ ARF secondary to sepsis, ECFV depletion etc...
- ❑ fluid-electrolyte and acid-base disturbances

DIURETICS

Loop Diuretics

- ❑ examples
  - furosemide (Lasix), bumetanide (Bumex), ethacrynate (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
- ❑ adverse effects
  - allergy in sulfa-sensitive individuals, electrolyte abnormalities (hypokalemia, hyponatremia, hypocalcemia, hypercalciuria/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 $Na^+/Cl^-/H_2O$ by inhibiting the Na^+/Cl^- transporter in the distal tubule and cortical loop of Henle
- ❑ clinical use
  - first line therapy for essential HTN (often in combination with other antihypertensives or loop diuretics), idiopathic hypercalciuria and recurrent renal stones, diabetes insipidus
- ❑ adverse effects
  - hypokalemia, increased serum urate levels, hypercalcemia, adversely affects lipid profiles, 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
  - the 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)
- ❑ adverse effects
  - hyperkalemia (caution with ACEI), gynecomastia (estrogenic effect of spironolactone)

Combination Diuretics

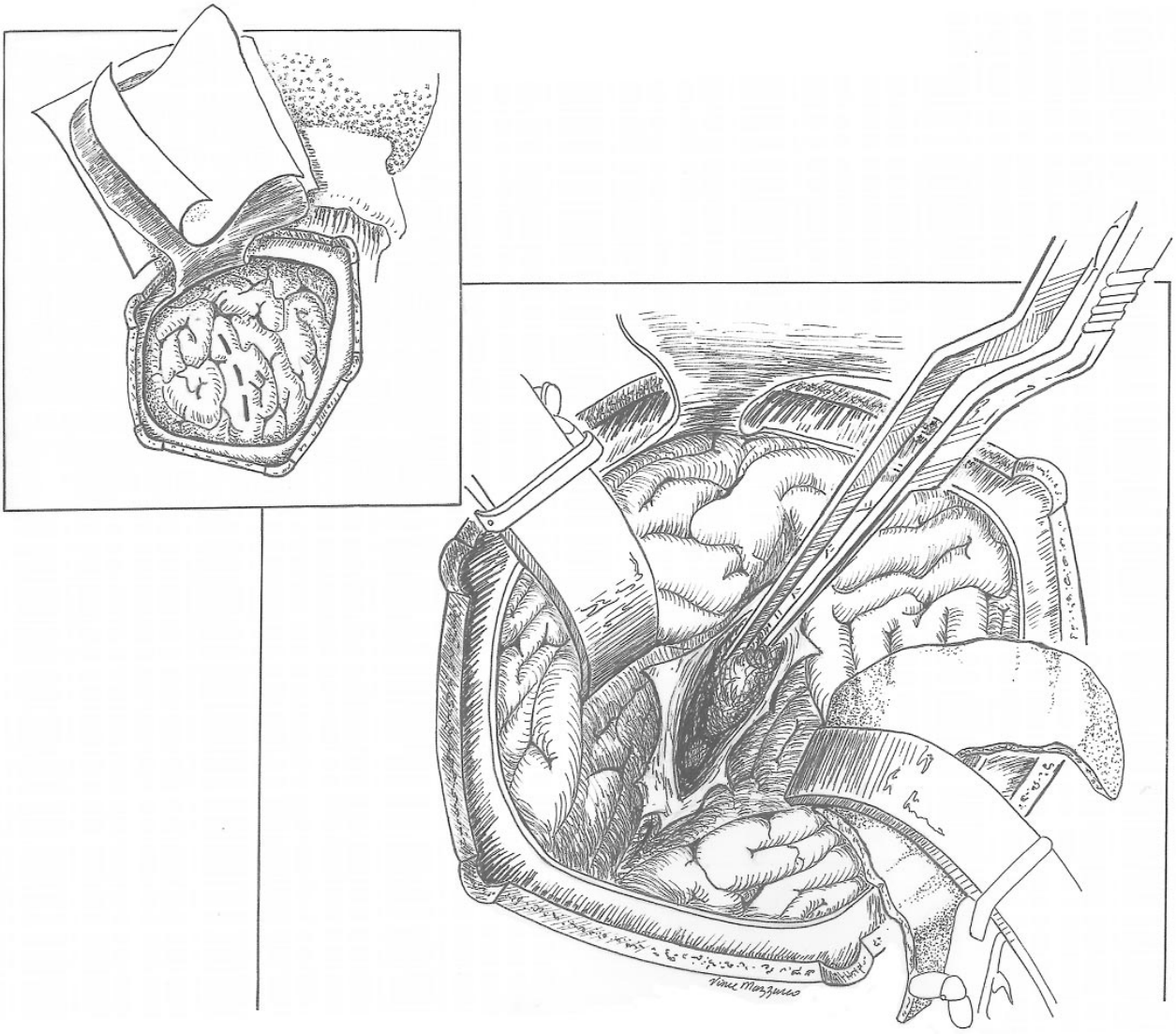
- ❑ examples
  - Dyazide, Maxide (triamterene and HCTZ), Aldactozide (spironolactone and HCTZ), Moduretic (amiloride and HCTZ), Vasoretic (enalapril and HCTZ), Zesteretic (lisinopril and HCTZ)
- ❑ clinical use
  - potassium-sparing drugs are combined with thiazide to reduce hypokalemia
  - ACEI are combined 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 $NaHCO_3$ by an indirect mechanism
- ❑ clinical use
  - glaucoma, to raise urine pH in cysteinuria
- ❑ 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
  - promote the excretion of body water (refractory edema, hyponatremia)
  - lower intracranial or intraocular pressure
  - prevention of ARF (by promoting diuresis and clearance of tubular debris)



Drawing by Vince Mazzurco