Renal Pathology

Assignment Page

Kidney, Big Robbins, Chapter 20, Compact Robbins, Chapter 13
Lower Urinary tract, Big Robbins, Chapter 21, Compact Robbins, Chapter 17
Male reproductive, Big Robbins Chapter 21, Compact Robbins, Chapter 17

Clinical Lab Source:

Urea nitrogen (BUN and UUN)
Creatinine (serum, urine and clearances)
Acute renal failure panel
Urinalysis (Know how to interpret a “urinary sediment”)
PSA
Alkaline phosphatase
Acid phosphatase
HCG

Wheater: Kidney, lower urinary tract and male reproductive

Slides to be concerned with:

Renal: 23, 79, 80, 91, 95, 112, 113, 133, 145, 164, 175

Male reproductive: 85, 162, 177, 178, 200.

Lab exercise: You will be asked to calculate a clearance of some sort, so know how to do it.

There are paper cases at the end of the renal section, but some deal with male reproductive and so we may wait to do them until both units are completed.

Online: There are three online modules for this unit,
   - Number 8, the case of Mr. Potter’s angina,
   - The urinalysis review module, number 22 and
   - Number 26, the acid-base review unit.
Renal Disease

I) Introduction

A) Anatomy, microanatomy and physiology

B) Function: Waste control; RBC; PB; Electro

C) Specialized local functions, properties and problems:
   i) glomerulus
   ii) medulla

II) Classes of diseases: all the biggies

III) Embryology:

A) Mesoderm

B) Mesonephros: early; cloaca connection; goes

C) Mesonephric duct and metanephric “bud”

D) Problems: migration; failure to regress; failure of fusion; U/G diaphragm

E) No amniotic fluid

IV) Assessment of renal function

A) H&P
B) X-ray; IVP; Cat; MRI

C) Lab: U/A; CBC; Enzymes: Serum Creatinine; BUN; CREATININE CLEARANCE; Ammonia; Complement; Bx

Clearance of anything = \[
\frac{[\text{Urine of x} \text{ (vol in ml/min)}]}{[\text{Plasma of x}]}\]

D) Urinalysis

1. Dipstick:
   - protein: should be under 150mg in 24 hr
   - esterase: your WBC’s
   - nitrite: the bug, at least indirectly (bug converts nitrate -> nitrite)
   - bilirubin: most are sensitive to about 0.2-0.4 mg/%
   - blood (actually hemoglobin and myoglobin, actually detects the “heme” portion)
   - albumin: some detect this separately
   - pH: most urine is acidic, about pH 6. Alkaline urine may mean bug or renal tubular acidosis.
   - specific gravity: range from 1.003-1.030. If 1.023 or more = can concentrate.
   - glucose: should be none. Renal threshold for most about 180mg/%. Strip measures from 75-300mg/%. Specific but vitamin C inhibits test.
   - ketones: actually acetone and acetoacetic acid. Detects at about 5-10mg/%

2. Sediment analysis:

   A. Casts
      - Hyaline casts: Orange of pale blue: Protein for the most part: nephrotic
      - RBC: dark red orange : intact RBC’s : nephritic
      - Blood: red orange but no identifiable RBC’s: Hgb. or myoglobin
- WBC: pale blue to orange with intact WBC’s: pyelonephritis

- Epithelial: blue grey with tubular epithelial cells: epithelial cell damage

- Granular: blue grey with fine granules: probably broken down WBC’s

- Waxy: pale blue to orange with refractile quality and “cracked” borders giving a “waxy” appearance

- Fatty: blue orange to grey with vacuoles: nephrotic

- Mixed: any combination of above

- Broad casts: may have any of above appearance but most often like a waxy cast. These are 2-6 times as large as any others. These come from the collecting ducts. Means a lot of protein: nephrotic or myeloma.

B. Crystals:

- Ph of urine is very important:

- Acidic urine

- Basic urine

- Medication hx

C. Cells

- RBC’s

- WBC’s

- tubular epi

- transitional

- sperm

- benign or malignant

- cytopathologic effect

D. Bacteria

- is the urine ever sterile?

- how many bugs and WBC’s
E. Foreign matter

- fibers
- crystals

F. Culture results
- was it clean catch?
- number of colonies?
- organism?

V) Clinical syndromes:

Azotemia (what’s this?)
- pre-renal
- renal
- post renal

A) Nephritic

B) Nephrotic

C) Acute Kidney Injury

D) Chronic renal failure; azotemia vs uremia

E) Infections; upper and lower pattern

F) Stones
G) Asymptomatic blood and protein, what does it mean?

VI) Glomerular Disease, Overview; lots of stuff, but biggies are IMMUNE AND DM

A) nephritic: acute; massive; RBC casts!!; protein; dec urine output; incr B/P

B) nephrotic: chronic or later phase; >3.5 gm protein/day; lipids in urine; low albumin

C) chronic renal failure; azotemia; uremia; “frost”; pericarditis etc; bleeding; anemia

D) general features (review prostaglandins and dec clot formation)

  i) mesangial proliferation

  ii) leukocytes infiltrate

  iii) BM thickening; regular vs irregular

  iv) scarring

  v) segmental pattern
vi) thrombi in small vessels and endothelial damage

vii) antibody; where are they; specific vs Ag-Ab complex passive injury; foreign vs. domestic; complement fixation without Ag-Ab; diffuse vs clumps; CHARGE

viii) RPGN; crescents, what do they mean?

ix) tubular changes and interstitial fibrosis
   - TNF
   - Ag/Ab complex

tax) Heymann nephritis, Ag from brush border used to trigger response in rats
   - Ab binds in glomerulus

xi) planted antigens, many sources, sticks in BM
   Meds, DNA, host and foreign proteins
   Haptens
   AB follows
   - Ag/Ab complex vs. anti-basement membrane specific Ab
     - Goodpasture syndrome, anti-collagen IV (not Heymann factor)
- The specific actors
  - neutrophils and monocytes, C’5a
  - T-lymphs and NK cells
  - platelet adherence and thrombosis
  - Mesangial cells produce cytokines chemokines, NO, growth factors

- Alternate complement pathway

- Progressive loss of renal function once you reach 30-50%
  - Focal segmental glomerulosclerosis
  - Tubulointerstitial fibrosis
Table 21-3. GLOMERULAR DISEASES

Primary Glomerulopathies
- Acute diffuse proliferative glomerulonephritis
- Poststreptococcal
- Non-poststreptococcal
- Rapidly progressive (crescentic) glomerulonephritis
- Membranous glomerulopathy
- Lipoid nephrosis (minimal change disease)
- Focal segmental glomerulosclerosis
- Membranoproliferative glomerulonephritis
- IgA nephropathy
- Focal proliferative glomerulonephritis
- Chronic glomerulonephritis

Systemic Diseases
- Systemic lupus erythematosus
- Diabetes mellitus
- Amyloidosis
- Goodpasture syndrome
- Polyarteritis nodosa
- Wegener granulomatosis
- Henoch-Schönlein purpura
- Bacterial endocarditis

Hereditary Disorders
- Alport syndrome
- Thin membrane disease
- Fabry disease

Table 21-5. IMMUNE-MECHANISMS OF GLOMERULAR INJURY

Antibody-Mediated Injury

In situ immune complex deposition
- Fixed intrinsic tissue antigens
  - Goodpasture antigen (anti-GBM nephritis)
  - Heymann antigen (membranous glomerulonephritis)
  - Mesangial antigens
  - Others
- Planted antigens
  - Exogenous (infectious agents, drugs)
  - Endogenous (DNA, immunoglobulins, immune complexes, IgA)

Circulating immune complex deposition
- Endogenous antigens (e.g., DNA, tumor antigens)
- Exogenous antigens (e.g., infectious products)

Cytotoxic antibodies

Cell-Mediated Immune Injury

Activation of Alternative Complement Pathway
E) Acute (proliferative) GN

- strep types, 12, 4, 1 and Red Lake (49)
  - ASO titer
- nephritic syndrome, RBC CASTS
- what’s proliferating?
- membrane thick

F) RPGN Rapidly progressive (crescentic) GN

- Many different disease may lead to this
- Anti-BM, Ag/Ab complex, no antibodies
- Fibrin deposits in layers of crescents

G) membranous GN, nephrotic syndrome, (protein, lipids......)

- planted Ag
- Ag-Ab complex
- SLE; tumors
- Hep B or C, Tb, drugs (chronic Ag/Ab load)
- DM, not really Ab; most are unknown

- Goodpasture’s syndrome
  Membranous pattern
  Pulmonary infection
  Ab to BM

H) minimal change; **foot process disease**

- nephrotic; children 2-6;
- steroids very helpful
- lymphokine?; T-cell mediated; “lipoid”

I) membranoproliferative; serum complement levels dn; “train track” splitting of BM

  i) Type I; C-3 and IgG,
    - subendothelial
ii) Type II; “dense deposit disease”

- IgG absent
- alternate pathway
- bad outcome
J) focal/segmental GN, **epithelial damage**

- HIV
- heroine user
- not all glomeruli
- rarely “reflux nephropathy

K) chronic GN

- end stage of many things
- cause often never discovered
- peri-capsular fibrosis
- uremia & anemia

L) DM !!! hits it all, every part of kidney

  i) glomerulus; K/W disease, diffuse and regular; NODULAR

  ii) vascular; large, small and everything !!

  iii) tubules

  vi) interstitium
M) amyloid

N) Berger Disease

- IgA, polymeric form, mesangial deposits
- common disease
- mesangial deposits
- Recurrent hematuria, young people.
VII) Tubular disease

A) ATN: ischemia and toxic are biggies; total urine shutdown; nothing gets out

i) vascular

ii) severe glomular injury

iii) local inflammation

iv) DIC

v) urinary obstruction

vi) toxic

vii) Hbg and myoglobin damage

viii) common observation

- death of epithelial cells
- clogged tubules = casts
- proximal mostly
- LOSS OF CONCENTRATING GRADIENT
- recovery marked by lots of urine and decreased serum K

B) tubulointerstitial
i) toxic

ii) infections, do bugs have Ab coating?

iii) uric acid; leukemia trx

iv) immuno

v) analgesic nephropathy

C) pyelonephritis

i) acute

- blood and pus in urine, wbc casts
- common bugs
- instrumentation

ii) chronic

- DM
- vascular
- “thyroidization”
- papillary necrosis with DM
iii) factors common to many situations

- UTI; instrumentation
- REFLUX; ureter implant angle !!; obstruction

iv) Urate nephropathy
   - Acute
   - Chronic

D) myeloma kidney - clogged up, NOT replaced with plasma cells

VIII) Vascular
A) atherosclerosis; **DM is a SMALL VESSEL DISEASE !!**;

B) B/P; hyaline vascular; hyperplastic; malignant - necrotizing

C) Renal artery stenosis

D) clotting
   
   i) DIC
   
   ii) TTP
   
   iii) hemolytic uremic syndrome
   
   - childhood
   
   - adult
   
   iv) renal cortical necrosis of pregnancy and eclampsia
   
   v) vascular injury associated with gram neg sepsis

E) emboli
F) SS Hbg disease

G) Cortical Necrosis

IX) Congenital; common, about 10%

A) vascular

B) location

C) cystic disease

D) agenesis

E) ureter

X) Cystic disease, other than “single simple cyst”

A) pathophysiology

i) obstruction with increase pressure

ii) membrane compliance, ie weakened walls

iii) hyperplasia of lining with bulging
B) polycystic disease  global distribution in kidney, bilateral

i) adult = auto dominant; 1 in 1000
   - Adult presentation, accounts for ~5%-10% of all renal failure
   - PKD 1 & 2 (polycystin) trans-membrane
     - cell/cell and cell/matrix interaction

ii) juvenile = auto rec; rare; several types; compound herterzygotes
   - presents with failure as children (hence juvenile)
   - PKHD1

C) medullary cysts, 4 varieties, 2 very rare

1. Medullary sponge
   - presents as adult, incidental finding, X-Ray or autopsy.
   - hematuria, infections, little calcifications. Lacks scarring.

2. Medullary cystic disease complex (nephronophthisis)
   - progressive
   - cortex-medullary junction cysts
   - tubulointerstitial damage leads to failure
     - kids have polyuria and polydypsia, Na wasting
     - multiple genes, some leading to dominant, others recessive

D) dialysis
E) following infection with scar formation

F) renal cystic dysplasia is something different; bilateral or unilateral; cartilage; obstruction

G) Simple cyst - space occupying lesion

H) Prune belly syndrome, is this for real?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Pathologic Features</th>
<th>Clinical Features or Complications</th>
<th>Typical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult polycystic kidney disease</td>
<td>Autosomal dominant</td>
<td>Large multicystic kidneys, liver cysts, berry aneurysms</td>
<td>Hematuria, flank pain, urinary tract infection, renal stones, hypertension</td>
<td>Chronic renal failure beginning at age 40–60 yr</td>
</tr>
<tr>
<td>Childhood polycystic kidney disease</td>
<td>Autosomal recessive</td>
<td>Enlarged, cystic kidneys at birth</td>
<td>Hepatic fibrosis</td>
<td>Variable, death in infancy or childhood</td>
</tr>
<tr>
<td>Medullary sponge kidney</td>
<td>None</td>
<td>Medullary cysts on excretory urography</td>
<td>Hematuria, urinary tract infection, recurrent renal stones</td>
<td>Benign</td>
</tr>
<tr>
<td>Familial juvenile nephronophthisis</td>
<td>Autosomal recessive</td>
<td>Cricomedullary cysts, shrunken kidneys</td>
<td>Salt wasting, polyuria, growth retardation, anemia</td>
<td>Progressive renal failure beginning in childhood</td>
</tr>
<tr>
<td>Adult-onset medullary cystic disease</td>
<td>Autosomal dominant</td>
<td>Cricomedullary cysts, shrunken kidneys</td>
<td>Salt wasting, polyuria</td>
<td>Chronic renal failure beginning in adulthood</td>
</tr>
<tr>
<td>Simple cysts</td>
<td>None</td>
<td>Single or multiple cysts in normal-sized kidneys</td>
<td>Microscopic hematuria</td>
<td>Benign</td>
</tr>
<tr>
<td>Acquired renal cystic disease</td>
<td>None</td>
<td>Cystic degeneration in end-stage kidney disease</td>
<td>Hemorrhage, erythrocytosis, neoplasia</td>
<td>Dependence on dialysis</td>
</tr>
</tbody>
</table>
XI) Urinary tract obstruction and stones; leads to infection and hydronephrosis; permanent loss

A) congenital; ureteral implant angle; anomalous vessel

B) BPH

C) Tumors

D) Inflammation; radiation

E) renal pap necrosis

F) pregnancy; pressure; smooth muscle dysfunction

G) neural dysfunction “functional”

H) stones; know types, most frequent three
   - dehydration
   - calcium oxalate
   - Struvite, magnesium ammonium, what bug?
   - Uric acid
   - Congenital problems
   - Consequences

XII) Tumors
A) Cortical adenoma
- < 2 cm
- no mets
- no anaplasia
- clear cells

B) Renal cell ca
- clear cell
  - necrosis and hemorrhage
  - vascular margins
  - mets widely, very unpredictable
  - B/P and RBC’s
- Papillary renal cell ca
  - papillary formations with
  - fibrovascular cores

C) Childhood = Wilm’s
- myxomatous
- unilateral
- embryonal- two cell types - little tubules

D) Transition cell - pelvis
XIII) Lower Urinary tract

A) Congenital
- UPJ
- UVJ
- vessels

A) congenital
- exstrophy

B) Infections
- ascending
- instrumentation
C) Interstitial cystitis (Hunner ulcer)
   - chronic with fibrosis
   - ulceration late, mast cells

D) External compression - pregnancy, tumors, retroperitoneal fibrosis

E) Neurological
   - cord injuries
   - MS

F) Bladder stones, drug injury, toxins, radiation, surgical damage, indwelling catheters

G) Malcoplakia
   - raised yellow mucosal plaques
   - large foamy histiocytes
   - Michaelis-Gutmann bodies
   - chronic E. Coli or proteus infection
G) tumors

- papillary transitional ca
- grades and stages
- smoking
- industrial exposure

- Rhabdomyosarcoma

- Muscular hypertrophy

H) Urethra

- congenital,
  - hypospadias
  - epispadias
- inflammation: viral, bacterial, mycoplasma, uroplasma, abscess, reflux in male

- tumors, condyloma, squamous cell ca
Renal and Male Reproductive Diseases Case Studies

Case 1

HISTORY: This 79-year-old woman was first admitted 14 months before death with recurrent hematuria. Intravenous pyelogram showed a dilated right ureter and a large mass in the urinary bladder. Transurethral resection showed transitional cell carcinoma. She was readmitted 6 months later for treatment of a suprapubic fistula. She was last admitted because of cough, fever and chest pain.

PHYSICAL FINDINGS: Dyspneic woman with breath sounds which were decreased bilaterally. A large suprapubic mass was present.

LABORATORY FINDINGS:
- Hct: 39%
- WBC: 17,100/cu mm
  - Differential: PMN-81%, bond-5%, monos-2%, lymphs-10%, Eos-1%, baso-1%
- CLINICAL COURSE: Antibiotic therapy was instituted but she died on the second hospital day.

Which clinical feature is least typical of this patient's bladder tumor?

Based on the data presented, the immediate cause of death was most likely?

A biopsy of the suprapubic fistula would probably have shown what?

Case 2

HISTORY: This 72-year-old man was transferred from a local hospital because of intractable heart failure, pneumonia and oliguria. One year before he had been treated with physical therapy for severe right back pain. The pain persisted, however, and he also developed severe right scapular pain.

PHYSICAL FINDINGS: Confused, cachectic elderly man with ankle edema, bilateral moist bubbling rales, hepatomegaly and enlarged, firm, nodular prostate.

LABORATORY FINDINGS:
- Hematocrit: 37%
- Hemoglobin: 11.5 g/dl
- WBC: 14,000/cu mm
- Urea nitrogen: 196 mg/dl (nl:8-25 mg/dl)
- Creatinine: 2.2 mg/dl (nl:0.6-1.5 mg/dl)
- Calcium: 12.1 mg/dl (nl:8.5-10.5 mg/dl)
- Phosphorus: 3.5 mg/dl (nl:3.0-4.5 mg/dl)
- Alkaline phosphatase: 230 mU/ml (nl:13-39 mU/ml)
- Acid phosphatase: 5.1 U/ml (nl:0.13-0.63 U/ml)
- Albumin: 3.6 g/dl (nl:3.5-5.0 g/dl)
- PSA 8 mcg/L
- Chest x-ray: multiple bilateral 1-2 cm. densities in the lungs, bilateral effusions, a right lower lobe
infiltrate, and lytic lesions in the right scapula and vertebral bodies.

The etiology of the bone pain was most probably due to? Why are both alkaline and acid phosphatase high?

The hepatomegaly may be attributed to what?

What histological pattern would you expect to see with this tumor, and what stage does this man’s case represent?

**Case 3**

HISTORY: This 12-year-old male elementary school student was admitted to the hospital complaining of swelling of the face, pallor and lethargy of four days duration. One month prior to admission he had experienced painful swelling of his cervical lymph nodes associated with an erythematous rash and fever. He was treated at home with ointment and aspirin. Several of his close friends had complained of severe sore throats at about this same time.

PHYSICAL FINDINGS: BP-140/90 mm Hg; slight pitting edema of ankles and puffiness of face.

LABORATORY RESULTS:
- WBC-12,000/mm³ (nl: 4,000-11,000/cu mm) with 83% neutrophils
- urinalysis-reddish brown with 1+ protein, more than 100 RBC/hpf, RBC casts, 25 WBC/hpf
- BUN-75 mg/dl (nl: 8-25 mg/dl); serum creatinine-5 mg/dl (nl: 0.5-1.2 mg/dl)

What is the MOST LIKELY cause of this boy’s disease?

The lymphadenopathy reported in this patient's history is MOST LIKELY do to what?

Which of the following is the most probable long term outlook for this patient?

Which laboratory test(s) would be most helpful in confirming your suspicions?

**Case 4**

HISTORY: This 50-year-old female office manager was admitted to the hospital complaining of an abrupt weight gain and sudden swelling of the legs. Both signs had been present for one day at the time of admission.

PHYSICAL FINDINGS: No abnormalities except those reported as chief complaint

LABORATORY RESULTS:
- urine-4+ protein with no red cells and rare white cells,
  24-hour protein excretion 8.5 grams
- serum cholesterol-450 mg/dl (normal-150-300 mg/dl)
- serum albumin-2.1 g/dl (normal-3.5-5.0 g/dl)
- BUN-17 mg/dl
- serum creatinine-1.3 mg/dl
What best explains the pronounced proteinuria without hematuria?
Swelling of the legs is most probably due to what?
What are some of the conditions in which we see this symptom complex and what other laboratory tests would help you with the diagnosis?
Acid-Base Balance and the Anion Gap

1. The body strives for electrical neutrality.
   a. Cations = Anions
   b. One of the cations is very special, H\(^+\), and its concentration is monitored and regulated very closely.
   c. Volatile acid (CO\(_2\)) and non-volatile acids, lactate, H\(_2\)PO\(_4\)^-, H\(_2\)CO\(_3\)

2. Blood pH is described by the Henderson-Hasselbalch equation

\[
pH = 6.1 + \log \frac{\text{HCO}_3^-}{\text{PaCO}_2 \times 0.0301}
\]

3. Note the importance of
   a. Arterial CO\(_2\), indicated as PaCO\(_2\),
   b. Bicarbonate, HCO\(_3\)^-
   c. Carbonic anhydrase

4. We measure the pH of **arterial** blood.
   a. Arterial blood has been through the lungs and should be at optimal pH.
   b. This is not the case for venous blood.
   c. 7.35-7.45
   d. Central nervous system control of respirations and therefore PaCO\(_2\)
   e. The control of bicarbonate, HCO\(_3\)^-, by the kidneys
      i. Retention or
      ii. Excretion
5. So how does it all work under normal circumstances to keep our pH about 7.4?

a. Normally, CO₂ production and loss are matched

b. PaCO₂ is maintained at about 40 mmHg

c. PaCO₂ is regulated by respiration rate, either slowing down or speeding up respirations, to either blow off or retain CO₂.

   a. Control comes from the CNS by regulating respiration rate.

b. Production rate of CO₂ is not subject to regulation,

d. The kidney regulates plasma [HCO₃⁻] (by extension [H⁺] and pH) by three mechanisms

   a. Reabsorption of filtered HCO₃⁻, this is a recovery operation

b. Formation of titratable acid, H₂PO₄⁻ distal tubule

c. Excretion of NH₄⁺ distal tubule
Get this. The kidney glomerulus passively filters on the order of 4000 mmol of HCO₃⁻ each day. This has to be reabsorbed. To lose it would be a disaster. In order to reabsorb this filtered load of HCO₃⁻, the tubular cells must therefore secret 4000 mmol of hydrogen ions. This allows the conversion of carbonic acid to CO₂ and water, which will passively come back into the proximal tubular cell. The secretion of titratable acid by the kidney, used to actually modify the blood pH, goes on in the distal tubule.

6. Basically, the regulation of arterial pH includes
   
   a. Regulation of PaCO₂ by the respiratory system.
   
   b. Regulation of HCO₃⁻ by the kidneys
   
   c. Chemical buffering in the form of NH₄⁺ and H₂PO₄⁻ secretion by the distal convoluted tubule cells.

7. Simple acid/base disorders, adjustments and compensation for running a road race.
   
   a. Primary respiratory and/or metabolic disturbances invoke predictable compensatory changes to restore the PaCO₂ and pH to normal.

   If uncomplicated by other factors, a high PaCO₂ means a lowered pH. Respiration picks up because of the elevated PaCO₂. The increased respiration rate results in the blowing off CO₂, which pulls the pH back up into the healthy range.

   Buffering capacity comes thanks to the miracle of carbonic anhydrase.

   ![Diagram of carbonic anhydrase reaction]

   Metabolic acidosis means extra H⁺ ions are coming from a metabolic derangement, such as lactic acidosis in a diabetic, which will result in excessive respiration rate, lowering the PaCO₂, while at the same time raising the PaO₂.
Predict the degree of respiratory compensation with a **metabolic acidosis**.

\[ \text{PaCO}_2 = (1.5 \times [\text{HCO}_3^-]) + 8 \]

\( \text{PaCO}_2 \) decreases 12 mmol/L for each mmol/L of \( \text{HCO}_3^- \)

Thus a patient with a metabolic acidosis and 12 mmol/L of \( \text{HCO}_3^- \) would be expected to have a \( \text{PaCO}_2 \) between 24 and 28. If it’s higher or lower, there is something else going on, in other words a **mixed acid/base disorder**.

For simple acid/base disturbances, the diagram below can be quite helpful.

![Diagram of acid/base disturbances](image)
8. Mixed acid-base disorders. Here several problems of acid-base management are colliding at the same time. It’s definitely not just a matter of the body trying to compensate for one such disorder.

   a. An example would be a diabetic with ketoacidosis, who also happens to have emphysema, or develops a bad pneumonia (which is not all that unusual), and as a result develops a respiratory acidosis.

   b. You can even have a mixed condition consisting of an acidosis and alkalosis. Here the pH might even be in the reference range. How would know there is a actually a serious problem underlying things?

      i. Look at the anion gap.
      ii. Bicarb gap


   a. Get arterial blood gases and electrolytes at the same time.

   b. Compare the HCO₃⁻ value from the blood gases and lytes to verify accuracy.

   c. Calculate the anion gap (AG)

   d. Review the four common causes of high AG acidosis

      i. ketoacidosis
      ii. lactic acidosis
      iii. renal failure
      iv. toxin

   e. Review the two major causes of hyperchloremic, or non-gap, acidosis

      i. HCO₃⁻ loss from the GI tact
      ii. renal tubular acidosis

   f. Estimate compensatory response.

   g. Compare ΔAG and Δ HCO₃⁻

   h. Compare change in [Cl⁻] with change in [Na⁺]
i. **A good history and physical**

- Renal failure, chronic vomiting, sepsis, heart failure, pneumonia, COPD, drug use, especially sedatives and loop type diuretics (thiazides) and carbonic anhydrase inhibitors (acetazolamide)
- Better watch serum $[\text{K}^+]$, remember shifts with high $[\text{H}^+]$.

10. The **anion gap**, is really not a gap at all, it just represents the anions we don’t usually measure.

a. $\text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$, typically about 10 to 12 mmol

b. The AG represents anions such as proteins, phosphates, sulfates and organic anions.

c. **Increase in the AG**

i. Is most often due to increased serum lactate or acetoacetate.

ii. Rarely, an increased AG may be due to a decrease in cations such as $\text{Ca}^{2+}$, magnesium and/or $\text{K}^+$

d. **Decrease in the AG**

i. Increase in unmeasured cations

ii. Addition of something new to the blood such as $\text{Li}^+$

iii. Reduction in a major plasma protein such as albumin (renal loss).

iv. Hyperlipidemias and other less common causes.

11. Basic rules to keep in mind for simple, one cause, problems.

a. Is a pH disturbance metabolic or respiratory in origin?

- Respiratory acidosis, $\text{PaCO}_2$ is $> 44$
- Metabolic acidosis, $\text{HCO}_3^-$ is $< 22$
- Respiratory alkalosis, $\text{PaCO}_2$ is $< 36$
- Metabolic alkalosis, $\text{HCO}_3^-$ is $> 26$

b. If the primary change is

- $\text{HCO}_3^-$, then the underlying cause is most likely metabolic
- CO₂, the underlying cause is most likely respiratory

c. Metabolic acidosis with calculated ion gap

- increased endogenous acid production
  o lactate
  o ketoacidosis
  o accumulation of endogenous acids with renal failure
  o loss of HCO₃⁻, diarrhea
  o Toxic stuff like methanol and antifreeze

d. Metabolic acidosis with no ion gap

  o loss of HCO₃⁻, diarrhea
  o renal loss of HCO₃⁻, renal tubular acidosis
  o Carbonic anhydrase inhibition

e. Metabolic alkalosis

  - vomiting
  - milk-alkali syndrome
  - K⁺ wasting as with Conn’s syndrome
  - Loss of H⁺
  - Compensate is respiratory, retain CO₂

f. Respiratory acidosis

  - CNS
  - Airway obstruction
  - Neuromuscular and faulty respiration
  - CO₂ is high and the reason is poor ventilation
  - Compensation must be to increase HCO₃⁻

g. Respiratory alkalosis

  - CO₂ is low
  - Pregnancy
  - Sepsis
  - Anxiety and physical pain leading to increased resp rate
  - Salicylates
  - Liver disease
12. If only life could be this simple all the time. But, a person may have more than disease at a time that can cause an acid-base disturbance. So, how do you know?

a. With the coexistence of two metabolic acid-base disorders may be made apparent by calculating the difference between the change in the anion gap (\( \Delta AG \)), and the change in the serum CO\(_2\) \( (\Delta CO_2) \).

b. This value goes by several names, either the delta or bicarbonate gap.

\[
\text{Delta (bicarbonate) gap} = \Delta AG - \Delta HCO_3^-
\]

Where

\[
\Delta AG = \text{patient’s AG} - 12 \text{ mEq/L}
\]

\[
\Delta HCO_3^- = 27 \text{ mEq/L} - \text{patient’s HCO}_3^-
\]

If there is just one acid-base abnormality, there should be a 1:1 correlation between the rise in the anion gap and a corresponding drop in the bicarbonate.

Example: if the AG goes up by 10, then the HCO\(_3^-\) should drop by 10.

\[
\Delta AG - \Delta HCO_3^- = 10 - 10 = 0
\]

Just one acid-base problem here.

Variation of the bicarbonate gap from zero, either + or – means there is a mixed acid-base problem. However, it certainly doesn’t tell you the type.

13. Let’s see how this operates with two different mixed acid-base conditions.

**Case:** This 22 year-old man presents with several days of vomiting, nausea and abdominal pain. His blood pressure is low and he has tenting of the skin. His electrolytes are Na\(^+\) = 144, Cl\(^-\) = 95, K\(^+\) = 4.2, HCO\(_3^-\) = 14.

\[
\text{AG} = 35
\]

\[
\Delta AG = 23 (35 - 12)
\]

\[
\Delta HCO_3^- = 13 (27 - 14)
\]

HCO\(_3^-\) gap = +10

The high HCO\(_3^-\) gap indicates there are **two conditions** at work.
- **Metabolic acidosis** from dehydration and poor tissue perfusion (lactatic acid accumulation).

- **Metabolic alkalosis** from vomiting and loss of stomach acid.

14. Renal acidosis is in a league of its own.

   a. The renal tubules reabsorb HCO$_3^-$ and secretes acid

   b. Failure of either leads to renal tubular acidosis

   c. All forms of renal tubular acidosis are characterized by

      - minimally elevated to normal ion gap
      - hyperchlormia
      - net retention of HCl$^-$, generally
      - Three basic patterns
        o Distal type (type 1 RTA)
        o Proximal type (type 2 RTA)
        o Hypoaldosteronism (type 4 RTA)

<table>
<thead>
<tr>
<th></th>
<th>Type 1 RTA</th>
<th>Type 2 RTA</th>
<th>Type 4 RTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary defect</td>
<td>Impaired distal acidification</td>
<td>Reduced proximal bicarbonate reabsorption</td>
<td>Decreased aldosterone secretion or effect</td>
</tr>
<tr>
<td>Plasma bicarbonate</td>
<td>Variable, may be below 10 meq/L</td>
<td>Usually 12 to 20 meq/L</td>
<td>Greater than 17 meq/L</td>
</tr>
<tr>
<td>Urine pH</td>
<td>Greater than 5.3</td>
<td>Variable, greater than 5.3 if above bicarbonate reabsorptive threshold</td>
<td>Usually less than 5.3</td>
</tr>
<tr>
<td>Plasma potassium</td>
<td>Usually reduced but hyperkalemic forms exist; hypokalemia largely corrects with alkali therapy</td>
<td>Reduced, made worse by bicarbonaturia induced by alkali therapy</td>
<td>Increased</td>
</tr>
</tbody>
</table>

**A case of renal related acidosis:** Amy is a 24 year-old mother of one who develops acute renal failure after a perforated ulcer gave her peritonitis and shock. Her labs are Na$^+$ 140 mEq/L, K$^+$ 4 mEq/L, Cl$^-$ 115 mEq/L, CO$_2$ 5 mEq/L, pH = 7.12, PaCO$_2$ 13 mmHg, and HCO$_3^-$ 4 mEq/L.

\[ AG = 20 = (140 - (\text{Cl}^- + \text{HCO}_3^-)) \]
\[ \Delta AG = 9 = (21-12) \]

\[ \Delta HCO_3^- = 23 = (27-4) \]

\[ \Delta (HCO_3^-) \text{ gap} = 15 = \Delta AG - \Delta HCO_3^- \]

Her anion gap is up, but not off the chart. The bicarbonate gap is off. In other words, her HCO_3^- is significantly reduced at -14 mEq/L; that is 14 mEq/L lower than would be expected given her excess anion gap of 8 (above normal). Were this a simple ‘one cause’ acidosis, the acid causing her drop in pH should have lowered her CO_2 to only about 19 mEq/L. The fact that her CO_2 is actually 5 mEq/L means there must an additional reason for her acidosis.

- In this case a hyperchloremic metabolic acidosis, which is commonly seen with renal failure. Below are her two renal related problems.
  - Uremia from kidney failure causing the elevated AG.
  - The tubular related problem of HCO_3^- recovery and acid secretion, which leads to a non-ion gap acidosis with hyperchloremia.

Summing it up

Respiratory, metabolic and mixed problems
Compensation
Anion and bicarb gap
Renal contribution to normal pH and problems of renal acidosis
Hyperchoremia