Some things you should know about laboratory tests…*But maybe you don't*

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When lab tests are useful

1. Managing patients during critical care transports
2. While transporting patient to medical facilities for evaluation of laboratory abnormalities

Objectives

1. Review some basic laboratory tests.
2. Appreciate how patterns of laboratory test results can offer insight into etiology.
3. Learn how laboratory test calculations can add additional clinical information.
4. Review some limitations of laboratory tests.

Treat the patient, not the laboratory values.

ELECTROLYTES & RENAL FUNCTION TESTS

A case of "bad labs"

Hypernatremia & Renal Failure

- 89 year old white female
- Coming from nursing home due to abnormal labs
- Sodium 172 mmol/L
- Potassium 4.2 mmol/L
- Chloride 137 mmol/L
- Carbon dioxide 21 mmol/L
- What are some causes of hypernatremia?

Hypernatremia

- Hyperaldosteronism
- Cushing's disease or syndrome
- Diabetes insipidus (deficiency of ADH)
- Dehydration

- BP 122/66, SBP 99 later
- HR 64/min
- RR 21/min
- $SpCO_2$ 98% on 4 L oxygen per min
- Tongue dry, skin turgor poor
- What is the cause of the hypernatremia in this patient? Treatment?

- BUN 212 mg N/dL
- Creatinine 6.10 mg/dL
- What do these values indicate?
- Does this change your therapy?

Acute Renal Failure

- Intrinsic renal disease
  - Acute tubular necrosis: ischemia, toxins
  - Acute glomerulonephritis
  - CKD with missed dialysis
- Post-renal
  - Obstruction: stone, tumor, enlarged prostate
- Pre-renal
  - Dehydration, shock, heart failure

Use of the BUN/creatinine ratio

- In intrinsic causes of acute renal failure, the BUN/creatinine ratio is typically 10-15.
- In pre-renal causes of acute renal failure, the BUN/creatinine ratio is typically >20.
- In this case, the BUN/creatinine ratio was 34.8.
- Do you want to stick with the same treatment?

Creatinine Clearance

- About 50% of the nephrons must be destroyed before the serum creatinine rises *above the reference range*
- Creatinine Clearance is a more accurate test of renal function
- Clearance is defined as the mL of plasma cleared of a substance per minute

Creatinine Clearance

- Calculated from the 24-hr urine creatinine, urine volume, and the serum creatinine
- Should be corrected for body surface area
- Decreases naturally with age
- Reference Ranges:
  - Males >85 mL/min/1.73 m^2
  - Females >75 mL/min/1.73 m^2

Creatinine Clearance

- Problems in collecting 24-hr urine
- Various calculations used to estimate Creatinine Clearance
- Current is the MDRD equation:
  - http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx
  - Corrected for African-American race & sex
  - Normals are reported as "≥60 mL/min/1.73 m^2"

Anion Gap

- The purpose of the anion gap is to determine the etiology of a metabolic acidosis.
- The anion gap is a measurement of unmeasured anions. These unmeasured anions are the conjugate bases of organic acids.
  - Lactate, ketone bodies from DKA, salicylate…

Anion Gap

- Based on the principle of electroneutrality
- Anion Gap = $[Na^+] - [Cl^-] - [HCO_3^-]$
- Normal range = 12 ± 4 mmol/L
  - Normal range varies with methodology.

EMERGENCY MEDICINE www.emedmag.com

CASE #1

A 72 year-old woman is admitted after being found unwell in her home by family members. She has a decreased level of consciousness and cannot give any history, but her daughter states that the dosage of one of her diabetes medications was increased 2 weeks ago, and earlier in the week she seemed to be suffering from a "stomach flu." On examination, she is hypotensive, tachycardic, and tachypneic. She responds only to painful stimuli but has no other remarkable findings. You order basic laboratory studies and find a [high] anion gap metabolic acidosis.

Anion Gap

High Anion Gap Metabolic Acidosis	Normal Anion Gap Metabolic Acidosis
Lactic acidosis ***(metformin)*** Ketoacidosis (diabetic, alcoholic, starvation) End-stage renal failure Methanol intoxication Ethylene glycol intoxication Salicylate intoxication	Diarrhea (most common)

MUDPILES

Toxin	Organic acid that accumulates (Unmeasured anion)
Methanol	Formic acid
Uremia	Uremic toxins
Diabetic ketoacidosis	Acetoacetate, β-hydroxybutyrate
Paraldehyde	
Iron or isoniazid	Lactic acid from iron toxicity
Ethylene glycol	Oxalic acid (binds calcium)
Lactic acidosis	Lactic acid
Salicylates (aspirin)	Salicylic acid

CASE STUDY 2

- Na 129, Cl 78, tCO_2 12
- Anion Gap = 129 – (78 + 12) = 39
- Blood glucose = 1,890 mg/dL
- Diagnosis is diabetic ketoacidosis

HYPERKALEMIA

- Is the sample hemolyzed?
  - Hemolysis raises potassium
- How old is the sample?

CALCIUM

Chemical form	Percentage
Free (ionized)	47%
Protein-bound (mostly albumin)	43%
Complexed (phosphate, carbonate, citrate, etc.)	10%

pH incr.->

Ca^{2+} + albumin-H ⟷ Ca-albumin complex + H^+

<-pH decr.

- If the albumin is significantly decreased (malnutrition, liver disease), the total calcium will be low but the ionized calcium may be normal.

HEMOGLOBIN A_{1c} Glycosylated Hemoglobin

- Glucose reacts non-enzymatically with hemoglobin to form HbA_{1c}
- The extent of glycosylation increases with increasing glucose concentration
- The HbA_{1c} level is an indication of the average glucose level for the past 3 months
- Reference Range: 4-6%

HEMOGLOBIN A_{1c}

Usage	Cutoff
Goal for diabetic control	<7.0%
Screening for diabetes	>6.5%

Point-of-care Glucose Tests

- Fasting whole blood glucose is 12-15% ***lower*** than plasma.
- Fasting capillary glucose is 2-5 mg/dL ***higher*** than venous.
- **But** post-prandial capillary glucose averages 30 mg/dL ***higher*** than venous.
- Capillary glucose may be ***depressed*** with poor perfusion: cold, hypotension or shock, Raynaud's, vasopressors, dehydration.

LIVER FUNCTION TESTS

Liver Function Tests

- Enzymes released from liver cells when injured
  - Aspartate Transaminase (AST)
  - Alanine Transaminase (ALT)
  - Alkaline Phosphatase
  - Gamma-glutamyl transferase (GGT)
- Bilirubin, total and direct
- Why are there so many LFTs?

Classifying acute liver disease

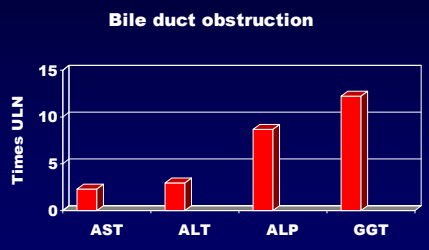
Acute hepatocellular necrosis

- Viral hepatitis
- Alcoholic hepatitis
- Wilson's disease
- α-1 Anti-trypsin deficiency
- Autoimmune hepatitis
- Hemochromatosis
- Infectious mononucleosis
- Non-alcoholic fatty liver disease

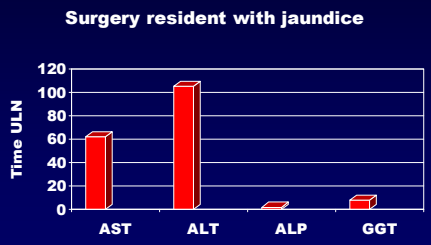
Obstructive jaundice

- Gallstone
- Stricture
- Granuloma
- Abscess
- Tumor or metastasis
- Drug-induced
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Carcinoma of Pancreas



Acute Hepatitis B



Non-hepatic cause of jaundice

- Dispatched for an 11-year old male who is "not acting right" and has been vomiting.
- Arrived to find AA patient lying in bed, eyes open and staring ahead but otherwise unresponsive.

Non-hepatic causes of jaundice

- Mother states patient developed a headache 2 days ago and has been vomiting since yesterday night.
- Denies diarrhea, negative PMH
- Treating with Aleve and Pedialyte *but no aspirin*.
- Mother Haitian, father African-American

Non-hepatic causes of jaundice

- Despite dark complexion, patient appears jaundiced, especially on palms.
- Skin warm, not excessively dry
- RR 24, HR 135, BP 100/60, SpO_2 100%
- Glucose 150 mg/dL
- ECG sinus rhythm
- Abdomen soft & non-tender, not distended

Non-hepatic causes of jaundice

- Hemolytic anemia
  - Transfusion-related
  - Autoimmune
  - DIC, hemolytic uremic syndrome
  - Hemoglobinopathies, e.g., sickle cell anemia
  - Glucose-6-phosphate dehydrogenase deficiency

Diagnosis

- Autoimmune hemolytic anemia
  - Incidence 1:80,000 in children
  - Many cases are idiopathic
  - Some cases may be triggered by:
    - Drugs, e.g., penicillin, α-methyldopa
    - Viral illness

Laboratory Studies

- CBC
  - Hemoglobin = 2.4 g/dL
  - MCV normal (normocytic)
  - MCHC normal (normochromic)
- Reticulocyte count increased
- Direct anti-globulin (Coombs test) positive
  - Sign that RBCs are coated with antibodies

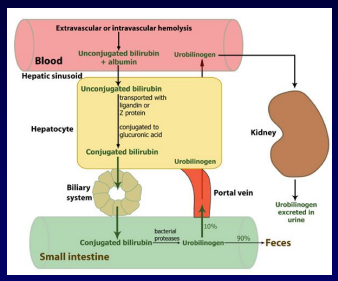
Laboratory Studies

- Chemistry tests
  - Bilirubin
    - Total bilirubin increased
    - Indirect bilirubin *increased*, more than direct
  - Ammonia *normal*
- Enzyme tests
  - AST & LDH increased
  - Alkaline phosphatase & GGT WNL

Laboratory Studies

- Urine tests
  - Urine bilirubin (bile) negative or weak pos.
  - Urine urobilinogen increased

Bilirubin Metabolism

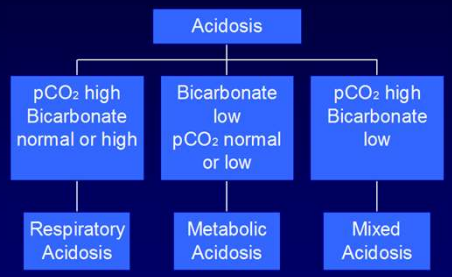


Acid-Base and Blood Gases

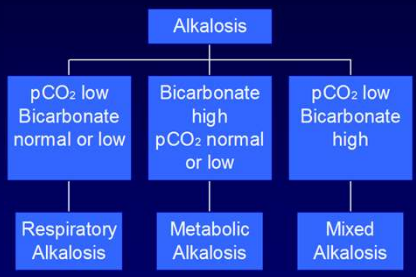
Diagnosing Acid-Base Disorders

- Look at the pH first
  - If pH<7.35 ⇒ Acidosis
  - If pH>7.45 ⇒ Alkalosis
- Look at the CO_2 and bicarbonate next to determine the primary cause.
- Once you have determined the primary cause, determine if there is compensation by the other component.

ACIDOSIS



ALKALOSIS



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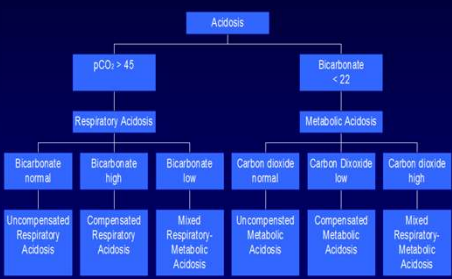

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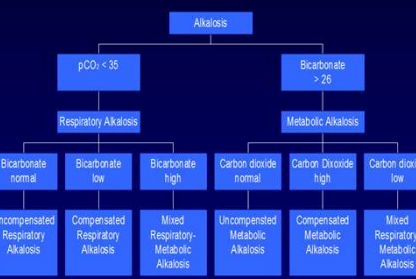


EXAMPLE 1

- pH 7.28, pCO_2 58, bicarbonate 33
- Diagnosis: Partially compensated Respiratory Acidosis
- Note that we determined the primary disorder is respiratory first, then we looked at the bicarbonate second to see if there was compensation.

EXAMPLE 2

- pH 7.28, pCO_2 23, bicarbonate 10.8
- Blood glucose 1,890 mg/dL
- Diagnosis: Partially compensated Metabolic Acidosis
  - DKA
- ***Tip for ventilator management:*** The low carbon dioxide here is compensatory and should not be fixed.

CARDIAC BIOMARKERS

What's new with Troponin?

- Original (conventional) troponin assays lacked sensitivity
  - Most normal patients were "Not detected"
  - Needed to monitor Tn levels for 6-9 hr until MI ruled out
- Newer (high-sensitivity) troponin assays are more sensitive

Troponin I

- iSTAT cTnI at Chippenham
- High sensitivity TnI with cutoff 0.8 ng/mL
- Order every two hours: 0 & 2 hr.
- Normal TnIs without upward trend at 2 hr rules out AMI

Non –MI causes of elevated troponin

- Defibrillation
- Myocarditis
- Myocardial contusion
- Acute and chronic congestive heart failure
- Cardiac surgery
- Renal failure
- Pulmonary embolism
- Sepsis, Shock
- Hypothyroidism

Third Universal Definition of MI

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.

Ultra-sensitive Troponin Assays

- Will be able to measure troponin levels within the normal range.
- Will be able to follow patients as they progress through the normal range to abnormal.
- May permit ruling out MI in one hour.

B-Natreuretic Peptide (BNP)

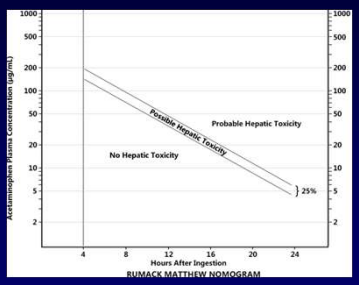
- A test for CHF
- BNP is released by the left ventricle when it is stretched
- False-positives in pulmonary HTN, pulmonary embolus

TOXICOLOGY TESTS

Drugs Not Detected on Routine Urine Drug Screens

- "Bath Salts"
  - Synthetic cathinones
- Ecstasy (XTC, MDMA, Molly)
- Gamma-hydroxybutyrate (GHB)
- K-2 or Spice
  - Synthetic cannabinoids
- Jimson weed
- Salvia
- Rohypnol (flunitrazepam)
- Metcathinone (Cat)
- 25I-NBMD (25I)
- LSD
- Fentanyl

Acetaminophen overdose



CEREBROSPINAL FLUID TESTS

CSF TESTS

- Normal color and clarity of CSF are colorless and clear (like water)
  - Xanthochromia is a pink, yellow or orange color in centrifuged CSF indicative of CNS bleeding, especially subarachnoid hemorrhage.
    - Most useful if patient presentation is delayed >6h.
  - Pleocytosis is an increased number of RBC or WBC in CSF which causes a cloudy specimen

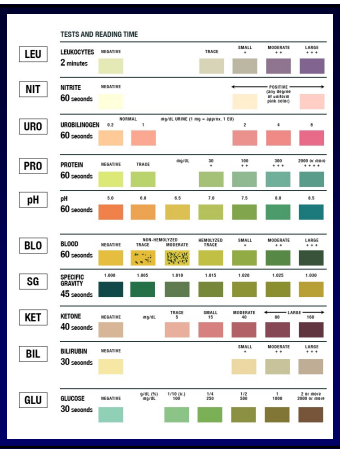
CSF TESTS

- ***Tip***: In bacterial meningitis, look for a cloudy specimen with elevated WBC, protein and lactate, decreased glucose, and presence of bacteria on the Gram stain.

Bacterial Meningitis

- Normal CSF glucose is ≈ 2/3 of serum
- CSF glucose <1/2 of serum is suggestive of bacterial meningitis
- CSF WBC >1,000/µL usually caused by bacterial meningitis

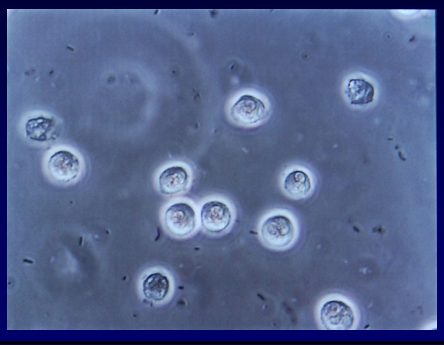
URINALYSIS



Urinalysis Patterns

- Urinary tract infections
  - Dysuria, cloudy, odor, RBC (chem & micro), WBC (chem & micro), protein, bacteria (chem [nitrite] & micro)
- "Nephritic" urine
  - Acute glomerulonephritis
    - RBC, WBC, protein, RBC & WBC casts
- Hyperglycemia
  - Glucose + ketones
- ***Tip:*** Berra's Rule: "You can see a lot by looking."

Urinary tract infection



HEMATOLOGY TESTS

- CBC
  - RBC and Red Cell Indices
  - Hemoglobin and Hematocrit
  - WBC
  - Differential cell count
  - Platelet count
- Coagulation tests
  - PT and PTT

RED BLOOD CELL TESTS: RBC, Hemoglobin & Hematocrit

- ***Tip:*** Generally, the same factors control RBC, Hct and Hb.
- ***Tip:*** Remember the average RBC is 5, the average Hb is 15 and the average Hct is 45.
- ***Tip:*** The ratio of Hct to Hb in normal red cells is 3:1.
- ***Tip:*** The transfusion trigger is a Hb < 7.

Effects of Hemorrhage on RBC and H&H

- Immediate
  - Hypovolemia with normal RBC and H&H
- Acute
  - Dilution with decreases in RBC and H&H
    - Normocytic
  - Increased reticulocytes
- Chronic
  - Decreased RBC and H&H
    - Microcytic due to iron deficiency

Mean Cell Volume (MCV)

- Small red cells ("microcytosis") often due to iron-deficiency anemia
  - Dietary
  - Chronic (occult) bleeding, e.g., GI hemorrhage
- Large red cells ("macrocytosis") often due to vitamin B_{12} or folate deficiency
  - Dietary or pernicious anemia
  - Alcoholism

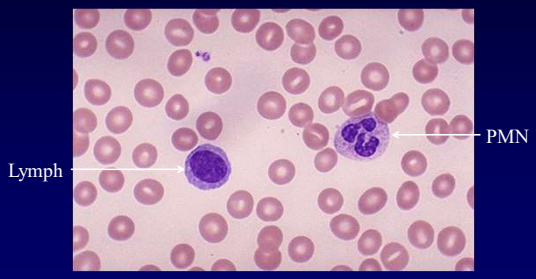
White Blood Cell Count

- ***Tip:*** Bacterial infections tend to give moderate increases (teens to 20's). With very high WBC, think about leukemia.

Differential Cell Count

- An enumeration of the different types of WBC in the blood
- Consists of neutrophils, lymphocytes, basophils, eosinophils and monocytes
- ***Tip:*** The absolute cell count (cells/μL) is often more useful than the percentage.

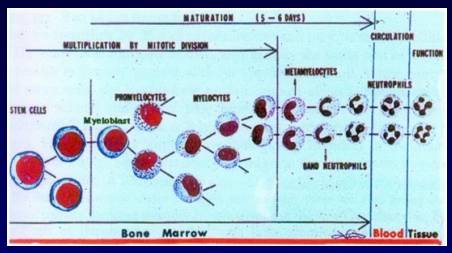
Wright-stained Blood Smear



Neutrophils

- Phagocytic cells that ingest bacteria, dead tissue, etc.
  - Increased in infections and inflammation
- Mature neutrophils have segmented nuclei ("segs")
  - Also called polymorphonuclear cells (PMNs, "polys")
- Less mature neutrophils have banded nuclei ("bands", "stabs")

Neutrophil maturation



Neutrophils

- ***Tip:*** In bacterial infections, look for fever, an elevated WBC and elevated neutrophils.
  - Look for a increase of less mature neutrophil forms in the blood (the bands, "bandemia") as the body recruits cells from the bone marrow to fight the infection.
    - This is called a ***"left-shift"*** for historical reasons.

A case of bacterial infection

- 36 year old female
- Infection of chest wall

CBC Results (partial)

Cell	Percentage	Normal Range
WBC	11,800/μL	$4.5\text{-}11\times10^3$
PMN (segmented)	64%	50-70%
Bands	21%	0-5%
Lymphocytes	5%	20-40%
Monocytes	7%	1-6%
Eosinophils	3%	1-5%
Basophils	0%	0-1%

Prothrombin Time (PT)

- Tests the *extrinsic* coagulation pathway
- Increased by DIC, liver disease
- Prolonged by warfarin (Comadin®)
- Difficult to standardize
- Reference ranges are variable

International Normalized Ratio (INR)

- Is the ratio of the patient's PT to the normal PT, corrected for the sensitivity of the reagents used to do the test
- Provides a universal yardstick to measure the effect of warfarin
- ***Tip:*** The target INR for most anti-coagulation is 2-3.

Activated Partial Thromboplastin Time

- Tests the *intrinsic* coagulation pathway
- Increased by DIC, liver disease, hemophilia A & B
- Prolonged by heparin
- Reference ranges often lab-specific
  - Lab often specifies a therapeutic range for heparin therapy (1.5-2 × normal value)
  - Heparin dosing is often weight-based

Other markers of coagulation activation

- D-dimer
  - Very sensitive but not specific test for deep vein thrombosis/pulmonary embolism
    - Use to rule out, not rule in DVT
    - Will be positive wherever there is bleeding & clot
- Fibrin degradation products (FDP, FSP)
  - Positive in disseminated intravascular coagulopathy (DIC)