Laboratory test interoperation focus on drug related issues

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Introduction

- Generally, laboratory tests should be ordered **only if the results of the test will guide decisions** about the care of the patient.
- Serum, urine, and other bodily fluids can be analyzed routinely; however, the economic cost and impact on the quality of life related to obtaining these data must always be balanced by benefit to patient-specific outcomes.
- What pharmacist should know?
    - Medication management
    - Monitoring (Efficacy, safety)
    - Contraindications

Ordering, Monitoring and Interpreting Laboratory Tests to Optimize Medication Management

LAB TESTS

A Canadian Pharmacists Association continuing professional development program

Normal range?

Normal values may vary from laboratory to laboratory, depending on techniques and reagents used.

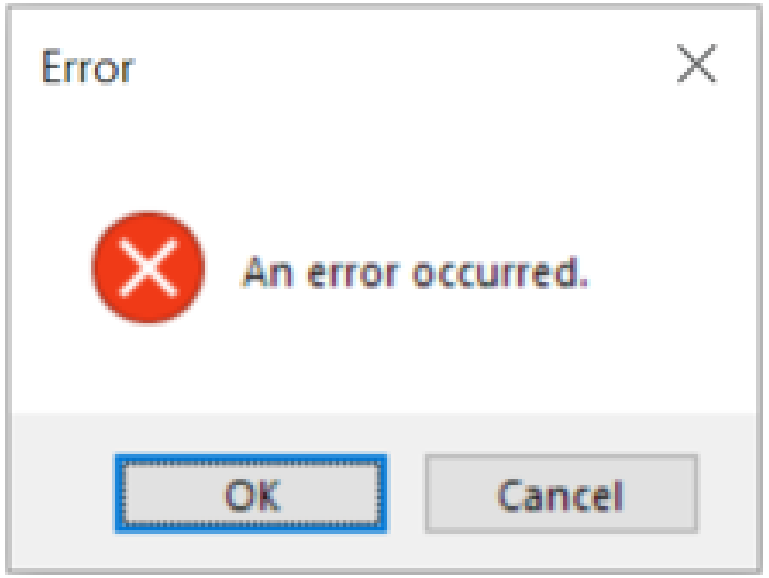
Normal values may also vary depending on the patient's age, gender, weight, height, and other factors.

Reference range

Remember:
Always treat the patient, not the laboratory values!

Error!

- Sex, Age, Pregnancy
- Incorrect test ordered (Albumin)
- Sample incorrectly labeled
- Improper preparation for test (fasting)
- Medication
- Improper timing of test(Vancomycin)
- Collection incomplete or improper(24-hour urine)
- Improper handling or storage (Hyperkalemia)
- Poor accuracy or precision
- Exercise



		Disease Status	
		Subjects with disease	Subjects without disease
Test	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)

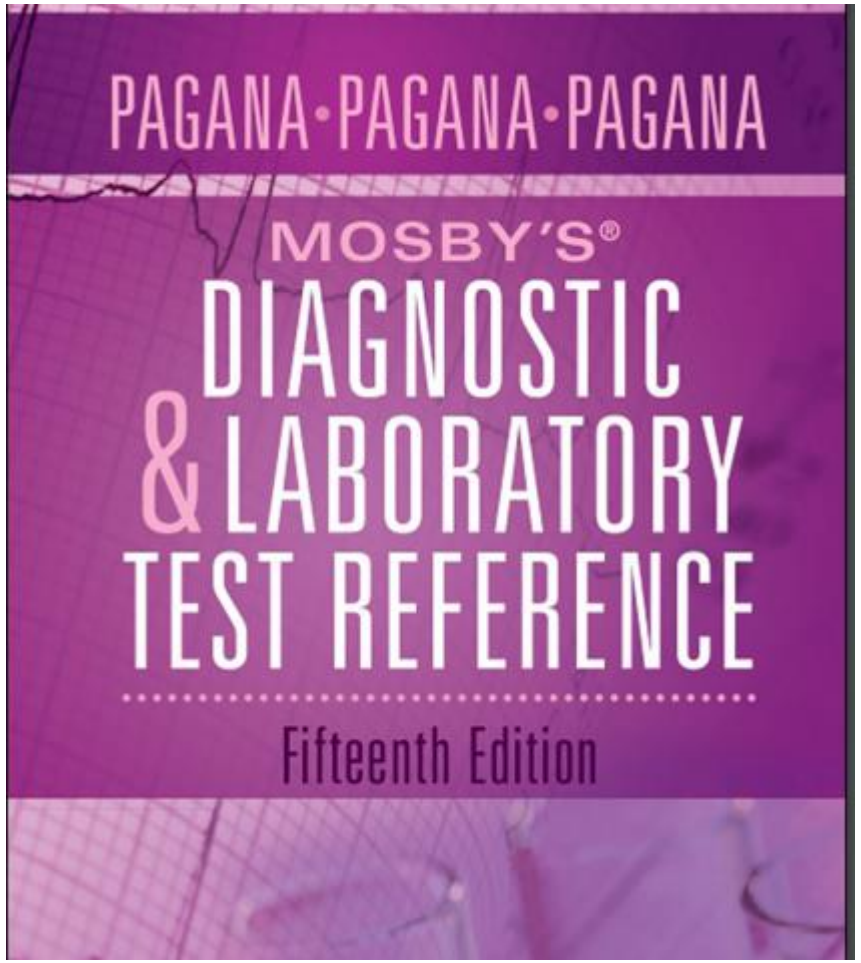
Sensitivity (Se) $\frac{TP}{TP + FN}$

Specificity (Sp) $\frac{TN}{FP + TN}$

- **Precision**: repeatability of a laboratory test
- **Accuracy** : result that is reflective of the "true" value
- **Sensitivity:** correctly identify the disease or condition.
- **Specificity:** rule out individuals who do not have the disease or condition.

Drug-Lab interactions

- Nature of effect
- Route of administration
- Direction and strength of effect
- Level of documentation
- Sex of patient
- Age of patient
- Onset of effect after starting the medication
- Duration of effect after stopping the medication
- Clinical significance of effect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TEST REFERENCE
Fifteenth Edition

sodium (Na), blood

Type of test
Blood

Normal findings
Adult/elderly: 136-145 mEq/L or 136-145 mmol/L (SI units)
Child: 136-145 mEq/L
Infant: 134-150 mEq/L
Newborn: 134-144 mEq/L

Possible critical values
< 120 or > 160 mEq/L

Test explanation and related physiology
Sodium is the major cation in the extracellular space, in which serum levels of approximately 140 mEq/L exist. Therefore sodium salts are the major determinants of extracellular osmolality. The sodium content of the blood is a result of a balance between dietary sodium intake and renal excretion.

Many factors regulate homeostatic sodium balance. Aldosterone causes conservation of sodium by decreasing renal losses. Natriuretic hormone, or third factor, increases renal losses of sodium. Antidiuretic hormone (ADH), which controls the resorption of water at the distal tubules of the kidney, also affects serum sodium levels.

Physiologically, water and sodium are very closely interrelated. As free body water is increased, serum sodium is diluted, and the concentration may decrease. The kidney compensates by conserving sodium and excreting water. If free body water were to decrease, the serum sodium concentration would rise; the kidney would then respond by conserving free water.

Interfering factors

- Recent trauma, surgery, or shock may cause increased levels.
- Drugs that may cause *increased* levels include anabolic steroids, antibiotics, carbenicillin, clonidine, corticosteroids, cough medicines, estrogens, laxatives, methyldopa, and oral contraceptives.
- Drugs that may cause *decreased* levels include angiotensin-converting enzyme inhibitors, captopril, carbamazepine, diuretics, haloperidol, heparin, nonsteroidal antiinflammatory drugs, intravenous (IV) fluids, sulfonylureas, triamterene, tricyclic antidepressants, and vasopressin.

Procedure and patient care

- See inside front cover for Routine Blood Testing.
- Fasting: no
- Blood tube commonly used: red or green

Abnormal findings

▲ Increased levels (hypernatremia)

Increased sodium intake
Excessive dietary intake
Excessive sodium in IV fluids

Decreased sodium loss
Cushing syndrome
Hyperaldosteronism

Excessive free body water loss
Excessive sweating
Extensive thermal burns
Diabetes insipidus
Osmotic diuresis
GI loss

▼ Decreased levels (hyponatremia)

Decreased sodium intake
Deficient dietary intake
Deficient sodium in IV fluids

Increased sodium loss
Addison disease
Diarrhea
Vomiting or nasogastric aspiration
Diuretic administration
Chronic renal insufficiency

Increased free body water
Excessive oral water intake
Excessive IV water intake
Congestive heart failure
Syndrome of inappropriate ADH (SIADH) secretion
Osmotic dilution

Third-space losses of sodium
Ascites
Peripheral edema
Pleural effusion
Intraluminal bowel loss (ileus or mechanical obstruction)

S

notes

What is Drug-related laboratory test interference?

- Both prescription and over-the-counter (OTC) drugs can cause laboratory test results to be incorrect (false increase or decrease).
  Note: The amount of result increase or decrease may be dose dependent.
- Incorrect results can lead to diagnosis and treatment errors that could harm the patient. Prior to laboratory testing, it is important to identify if your patients are taking any OTC supplements or prescription drugs.
- This guide identifies some of the more common laboratory test results which may be impacted by drug interferences.

Test Abbreviations

ACE: angiotensin-converting enzyme
AST: aspartate aminotransferase
ALT: alanine aminotransferase
CEA: carcinoembryonic antigen
CGM: continuous glucose monitors
DHEA-S: dehydroepiandrosterone sulfate
Free T3: free triiodothyronine
Free T4: free thyroxine
FSH: follicle-stimulating hormone
HBcAb: hepatitis B core antibody
HBsAb: hepatitis B surface antibody
HBsAg: hepatitis B surface antigen
HCV Ab: hepatitis C antibody
HCG: human chorionic gonadotropin
IgE: immunoglobulin E
IgM: immunoglobulin M
INR: international normalized ratio
LH: luteinizing hormone
PAM: pralidoxime
PSA: prostate-specific antigen
PT : prothrombin time
PTH: parathyroid hormone
SAT: stool antigen test
TIBC: total iron-binding capacity
TSH: thyroid stimulating hormone
UBT: C-urea breath test

For additional test information visit Lab Tests Online:
https://labtestsonline.org/

For herbal supplement information visit the National Institutes of Health (NIH) 'Herbs at a Glance' website:
https://nccih.nih.gov/health/herbsataglance.htm

Visit the FDA MedWatch website to view clinically important safety information:
https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program

OVER-THE-COUNTER (OTC) DRUGS

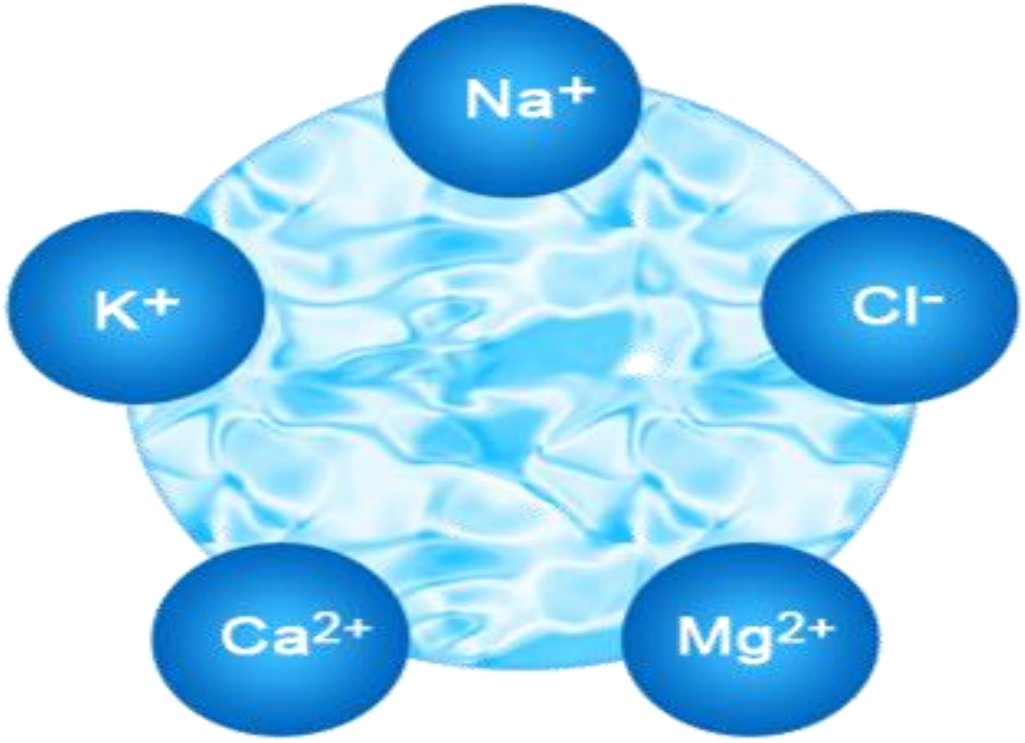
OTC Drug	Laboratory Test Potentially Affected
Biotin (Vitamin B7) *Sources of biotin naturally occur in foods and can be found in multi-vitamin, B-complex, and biotin only supplements.* Note: Interference and the level of result interference may be method dependent; contact the performing laboratory with test result questions and interpretation concerns)	False Mild Increase: Free T4, FreeT3, Testosterone, Estradiol, Cortisol, IgE False Moderate Decrease: TSH, FSH, LH, Insulin, Autoantibodies, Vitamin B12, Folate, Vitamin D, PSA, CEA, HCG, PTH, Thyroglobulin, Ferritin, DHEA-S, Hepatitis A IgM, HBsAg, HBsAb, HBcAb, HCV Ab False Decrease: Troponin (method dependent)
Acetaminophen Red Wine	False Increase: CGM Interference
Herbal Supplements	
Chan Su Lu-Shen-Wan Dan Shen Asian and Siberian Ginseng "Cleansing" Herbal Supplements	False Mild Increase: Digoxin
Kava-Kava	False Mild Increase: AST, ALT, Bilirubin
St. John's Wort	False Mild Decrease: Theophylline, Digoxin
Caffeine	False Mild Increase: Metanephrines
Others	
Nicotine	False Mild Increase: Fatty Acids, Aldosterone, Cortisol, Tumor Markers, ACE

ASCLS
The American Society for Clinical Laboratory Science

PRESCRIPTION DRUGS

Prescription Drug	Laboratory Test Potentially Affected
Amiodarone Cotrimoxazole Daptomycin Erythromycin Omeprazole NSAIDS Propranolol Telavancin	False Mild Increase: PT and INR
High-dose glucocorticoids Dopamine/ Dobutamine Octretide	False Mild Decrease: TSH
Imipenem/ Cilastatin (Primaxin)	False Positive: Galactomannan
IV administered Vitamin C	False Mild Increase: Glucometer Results
Ciprofloxacin Chloroquinine Quinine	False Mild Increase: Urine Protein
PAM salts for organophosphorus poisoning	False Severe Increase: Glucose
Cephalosporin	False Positive: Urine Glucose Urine Ketone Direct Coombs Test
Psychotropic Drugs	False Positive: Pregnancy Tests Drug Screening
Contrast Media *Prior to having laboratory specimens collected it is recommended to wait at least 4 hours after contrast media is administered.*	ACE Protein levels (blood) Calcium Creatinine TIBC Zinc Magnesium Selenium
Proton Pump Inhibitors (PPI) omeprazole, lansoprazole, dexlansoprazole, rabeprazole, pantoprazole, esomeprazole, esomeprazole	False Negative: UBT SAT False Positive: UBT (long-term use)
Spironolactone	False Increase: Digoxin
Labetalol Ranitidine	False Positive: Amphetamines
Rifampin	False Positive: Opioids
Lisinopril Albuterol Atenolol	False Increase: CGM Interference

Fluids and electrolytes



Na	Cl	BUN	Glucose
K	CO_2	SCr	

BMP

Sodium

- *Reference Range: 135-145 mEq/L or mmol/L*
  - predominant cation of extracellular fluid
  - Sodium is important in establishing serum osmolarity and osmotic pressure relationships between ICF and ECF

Hypernatremia
Relative water deficiency

Hyponatremia
Dilutional hyponatremia

Table 1. Mechanisms of Drug-Induced Hyponatremia

Class	Drug	Mechanism
Diuretics	*Thiazide:* indapamide, chlorthalidone, amiloride/hydrochlorothiazide *Loop:* furosemide	Hypovolemic/euvolemic (decreases total body sodium)
Antidepressants (SSRIs)	Sertraline, fluoxetine, paroxetine, citalopram, venlafaxine	SIADH
Antipsychotics	Amisulpride, aripiprazole, chlorpromazine, clozapine, fluphenazine, haloperidol, pimozide, risperidone, thioridazine, thiothixene, trifluoperazine	SIADH
Anticonvulsants	Carbamazepine, oxcarbazepine	SIADH
COX-2 inhibitor	Celecoxib	SIADH
Chemotherapeutic agents	Vincristine, vinblastine, carboplatin, cisplatin, cyclophosphamide	SIADH

COX-2: cyclooxygenase-2; SIADH: syndrome of inappropriate antidiuretic hormone secretion; SSRI: selective serotonin reuptake inhibitor.
Source: References 14-17.

Drug induced hypernatremia

Drug	Main mechanism (s)
Lithium	i) Hypercalcemia leading to nephrogenic diabetes insipidus and causing water loss ii) Central diabetes insipidus
Hypervitaminosis A and D	Hypercalcemia leading to nephrogenic diabetes insipidus
Cisplatin	Hypokalemia leading to nephrogenic diabetes insipidus
Aminoglycosides	Hypokalemia leading to nephrogenic diabetes insipidus
Demeclocycline	Nephrogenic diabetes insipidus
Amphotericin B	Nephrogenic diabetes insipidus
Phenytoin	Central diabetes insipidus
Ethanol	Central diabetes insipidus
Loop diuretics	Water loss
Manitol	Osmotic diuresis
Corticosteroids	Urea increase
Vasopressin receptor inhibitors (vaptans)	Water diuresis
Lactulose/sorbitol	Hypotonic gastrointestinal losses
Hypertonic $NaHCO_3$ or NaCl solution	Increased Na^+ administration

Potassium

- *Reference Range: 3.5-5.0 mEq/L or mmol/L*
- major intracellular cation in the body
- filtered freely at the glomerulus of the kidney, reabsorbed in the proximal tubule, and secreted into the distal segments of the nephron.

Hyperkalemia
- AKI/CKD
- Hemolysis, burn
- Acidosis

Hypokalemia
- Severe diarrhea
- Hypomagnesemia

Hypokalemia and mechanisms for its occurrence	Drugs involved
Prokinetic effect	Cisapride (Prepulsid®)
Digestive loss	Laxatives, Kayexalate
Urinary loss	Glucocorticoids
	Mineralocorticoids
	High ceiling diuretics and thiazides
	Glycyrrhizinic acid
	β-Lactamines at high doses
	Aminosides
	Amphotericin B (by acute tubular necrosis)
Transfer of intracellular K^+	β_2 Mimetics (IV): salbutamol, adrenalin
	Insulin at high doses (IV)
	Blood alkalinizing drugs

Drugs Known to Induce Hyperkalemia

Method of Induction	Examples
Drug-inducing transmembrane potassium movement	Non-selective beta blockers Digoxin intoxication Intravenous cationic amino acids Mannitol Suxamethonium
Drugs that affect aldosterone secretion	ACE inhibitors ARBs Direct renin inhibitors NSAIDs and COX-2 inhibitors Calcineurin inhibitors
Drugs that cause tubular resistance to the action of aldosterone	Aldosterone antagonists Potassium-sparing diuretics Trimethoprim, pentamidine
Potassium-containing agents	Salt substitutes and alternatives Penicillin G, stored blood products

Calcium

- *Reference Range: 8.5-10.5 mg/ dL or 2.1-2.6 mmol/L*
- The total calcium content resides primarily in the bone, with only about 1% freely exchangeable with that in the ECF
- About 40% of the calcium in the ECF is bound to plasma proteins (especially albumin), 5% to 15% is complexed with phosphate and citrate, and about 45% to 55% is in the unbound, ionized form

Hypercalcemia
- Malignancy
- Hyperparathyroidism
- Vit D toxicity

Hypocalcemia
- Deficiency in production or the response to PTH or vitamin D

Drug induced hypocalcemia

- Inhibitors of bone resorption (Bisphosphonates, calcitonin), especially in vitamin D deficiency
- Cinacalcet
- Calcium chelators (EDTA, citrate, phosphate)
- Foscarnet (complexing with calcium)
- Phenytoin (Conversion of vitamin D to inactive form)
- Fluoride poisoning
- Chemotherapy (cisplatin)

Approx. 80% of all cases are caused by Malignancy or Primary Hyperpathyroidism

- V Vitamins
- I Immobilization
- T Thyrotoxicosis
- A Addison's disease
- M Milk-alkali syndrome
- I Inflammatory disorders
- N Neoplastic related disease
- S Sarcoidosis

- **T Thiazide, other drugs - Lithium**
- **R Rabdomyolysis**
- **A AIDS**
- **P Paget's disease, Parental nutrition, Pheochromocytoma, Parathyroid disease**

Correction

- Because calcium in the serum is partially bound to plasma proteins (mostly albumin), the serum calcium concentration is affected by the concentration of these plasma proteins.
- The total serum calcium will decrease by 0.8 mg/dL for each decrease of 1.0 g/dL in serum albumin concentration.
- (4 – albumin patient) x 0.8 + calcium = corrected calcium.

Magnesium

- *Reference Range: 1.5-2.4 mEq/L or 0.75-1.2 mmol/L*
- An intracellular electrolyte
- An important metabolic role in the phosphorylation of adenosine triphosphate
- Hypomagnesemia
  - Malnourishment
- Hypermagnesemia
  - Excessive ingestion of magnesium-containing antacids
  - Patients with reduced renal function
  - Can slow conduction in the heart, prolong PT intervals, and widen the QRS complex

Drug Group (Drug Substance)	Mechanism/Effect
Aminoglycosides (e.g., gentamicin, tobramycin, amikacin)	increased renal magnesium loss, secondary hyperaldosteronism
Antimicrobial medication (Pentamidine)	increased renal magnesium loss
Antiviral medication (foscarnet)	nephrotoxicity, increased renal magnesium loss
Beta adrenergic agonists (e.g., Fenoterol, salbutamol, theophylline)	increased renal magnesium excretion, metabolic abnormalities (magnesium shift into cells)
Bisphosphonates (pamidronate)	renal impairment, magnesium excretion
Chemotherapeutic agents (e.g., amsacrine, cisplatin)	nephrotoxicity, cisplatin accumulates in renal cortex, increased renal magnesium loss
Immunosuppressants (cyclosporine, sirolimus)	2- to 3-fold increased urinary magnesium excretion (→ magnesium wasting)
Loop diuretics, esp. long-term use (e.g., furosemide)	increased renal magnesium loss, secondary hyperaldosteronism
Monoclonal antibody (e.g. cetuximab, panitumumab)	EGFR blockade in the nephron impairs the active transport of magnesium (→ magnesium wasting)
Polyene antifungals (amphotericin B)	nephrotoxicity
Proton pump inhibitors	loss of active magnesium absorption via transient receptor potential melastatin-6 and -7 (TRPM6/7)
Thiazide diuretics, esp. long-term use (e.g., hydrochlorothiazide)	increased renal magnesium loss, secondary hyperaldosteronism

Phosphate

- *Reference Range: 2.5-4.5 mg/ dL or 0.80-1.45 mmol/L*

- The extracellular concentration of phosphate as inorganic phosphorus is the prime determinant of the intracellular concentration
- The source of phosphate for ATP and phospholipid synthesis
- Is influenced by parathyroid hormone, intestinal phosphate absorption, renal function, bone metabolism, and nutrition

Hypophosphatemia

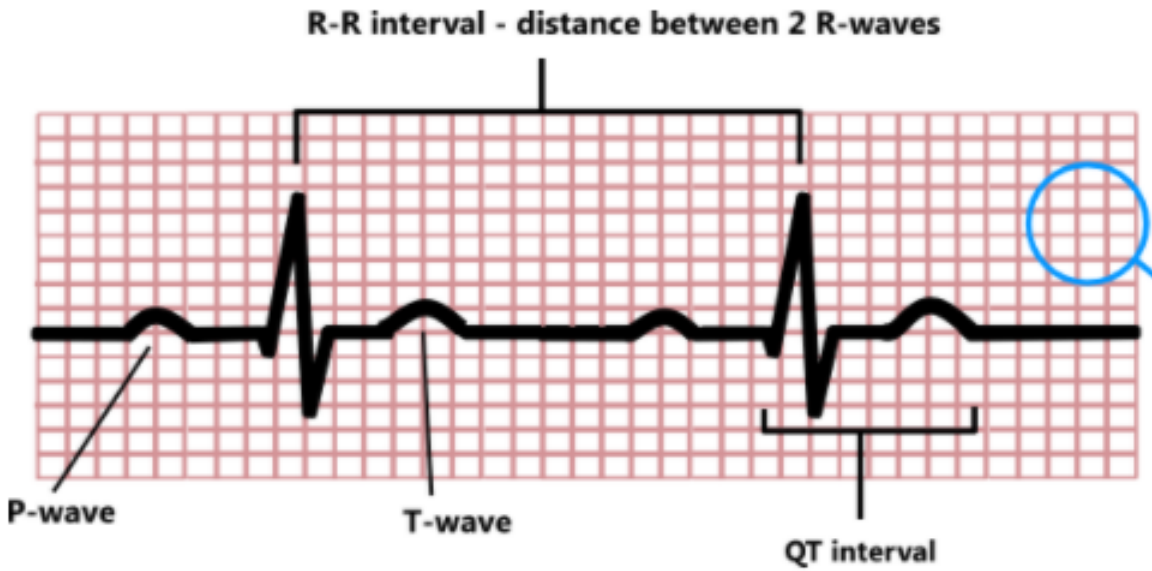
- Malnourished patients
- Antacids
- Chronic alcoholics, and septic patients
- involve nervous system dysfunction, muscle weakness, rhabdomyolysis, cardiac irregularities, and dysfunction of leukocytes and erythrocytes.

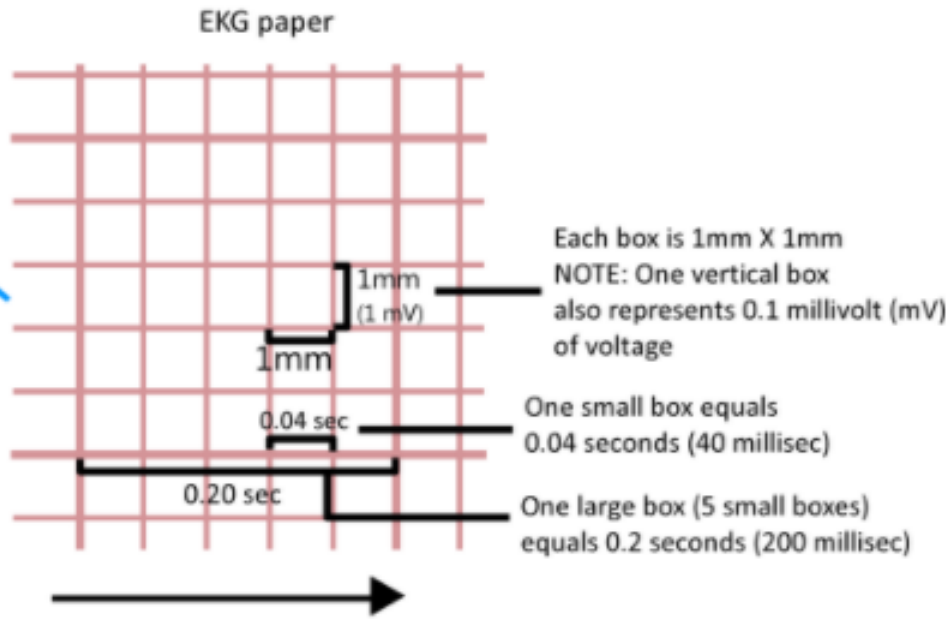
Hyperphosphatemia

- Renal insufficiency
- Increased vitamin D
- Hypo-parathyroidism
- Advanced malignancies
- Several drugs, such as penicillin, corticosteroids, some diuretics, furosemide, and thiazides, can induce hyperphosphatemia as an adverse reaction.

1. Pseudohypophoshatemia
   - Mannitol
2. Shifts of extracellular phosphate into cells
   - Acute respiratory alkalosis (salicylate poisoning, mechanical ventilation)
   - Administration of glucose, fructose, insulin therapy, parenteral nutrition
   - Catecholamine action: epinephrine, dopamine, salbutamol, xanthine derivatives, hypothermia
   - Rapid cellular proliferation (erythropoetin, GM-CSF therapy)
3. Decreased intestinal phosphate absorption
   - Phosphate–binding antacids
4. Increased urinary phosphate excretion
   - Carbonic anhydrase inhibitors
   - Diuretics (hydrochlorthiazide, indapamide, furosemide)
   - Theophylline, bronchodilators, corticosteroids
   - Drug-induced FS
   - Volume expansion (drug-induced SIADH, administration of saline)
   - Bisphosphonates
   - Estrogens, mestranol
   - Acyclovir
   - Imatimib mesylate
5. Hypophosphatemia resulting from more than one mechanism
   - Drug-induced metabolic acidosis (alcohol, toluene)
   - Alcohol
   - Drugs that cause vitamin D deficiency or resistance: phenytoin, phenobarbital
   - Acetaminophen poisoning
   - Intravenous iron administration

PROLONGED QT INTERVAL





Bazett Formula

$$QT_c = \frac{QT}{\sqrt{RR}}$$

Normal QT_c interval ≤ 440 ms
Prolonged QT_c interval > 500 ms

Normal QT interval

- In general, a normal QT_c interval is considered ≤ 440 ms
- A prolonged QT_c interval is > 500 ms

- Hypokalemia
- Hypomagnesemia
- Hypocalcemia

Blood Urea Nitrogen

- *Reference Range: 8-20 mgldL or 2.8-7.1 mmol/L*
- Urea nitrogen is an end product of protein metabolism
- Produced solely by the liver, transported in the blood, and excreted by the kidneys
- Acute or chronic renal failure is the most common cause of an elevated BUN
- High protein intake and conditions that increase protein catabolism (or upper GI bleeding) can increase the BUN concentration.
- A water deficit tends to concentrate the urea nitrogen, and a water excess dilutes the urea nitrogen

Ratio of BUN to SCr

- A normal ratio is roughly 15:1
- Greater than 20:1 :decreased blood flow to the kidney
  - Prerenal disease
    - Dehydration
    - Conditions involving reduced cardiac output
  - Increased protein in the blood
    - Dietary intake
    - An upper CI bleed

Less than 15:1

- Renal failure
- significant malnourishment (decreased intake of protein)
- Severe liver disease in which the liver is no longer able to form urea.

Dose adjustment

Creatinine

- *Reference Range: 0.6-1.2 mg/dL or 53-106 µmol/L*
- Is derived from creatine and phosphocreatine, major constituents of muscle
- Is remarkably constant and is determined primarily by an individual's muscle mass or lean body weight
- Excreted renally almost exclusively by glomerular filtration
- A decrease in the GFR results in an increase in the SCr

$$\text{Measured 24 hr } CrCl_{(mL/min)} = \frac{[\text{Urine conc}_{(mg/dL)}] \times [\text{Total urine volume}_{(mL/min)}]}{SCr_{(mg/dL)}}$$

(Eq. 2-3)

Calculation of estimated clearance according to the Cockcroft-Gault formula*:

$$\frac{[140 - \text{age (years)}] \times \text{ideal weight (kg)}}{([\text{creatinine (mg/dl)}] \times 72)}$$

* For women, multiply by 0.85

An 85 years old female (weight: 40 kg) with dementia need to be treated for a symptomatic UTI with ciprofloxacin, as her urine culture E.coli was resistant to all other safer! Classes.Can you calculate the appropriate dose for her?
Her serum creatinine is 0.8 mg/dL

Calculation of estimated clearance according to the Cockcroft-Gault formula*:

$$\frac{[140 - \text{age (years)}] \times \text{ideal weight (kg)}}{([\text{creatinine (mg/dl)}] \times 72)}$$

* For women, multiply by 0.85

$$\left(\frac{(140-85)\times 40}{1*72}\right)\times 0.85 = 26\ mL/min$$

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Back **Ciprofloxacin (systemic): Drug information**

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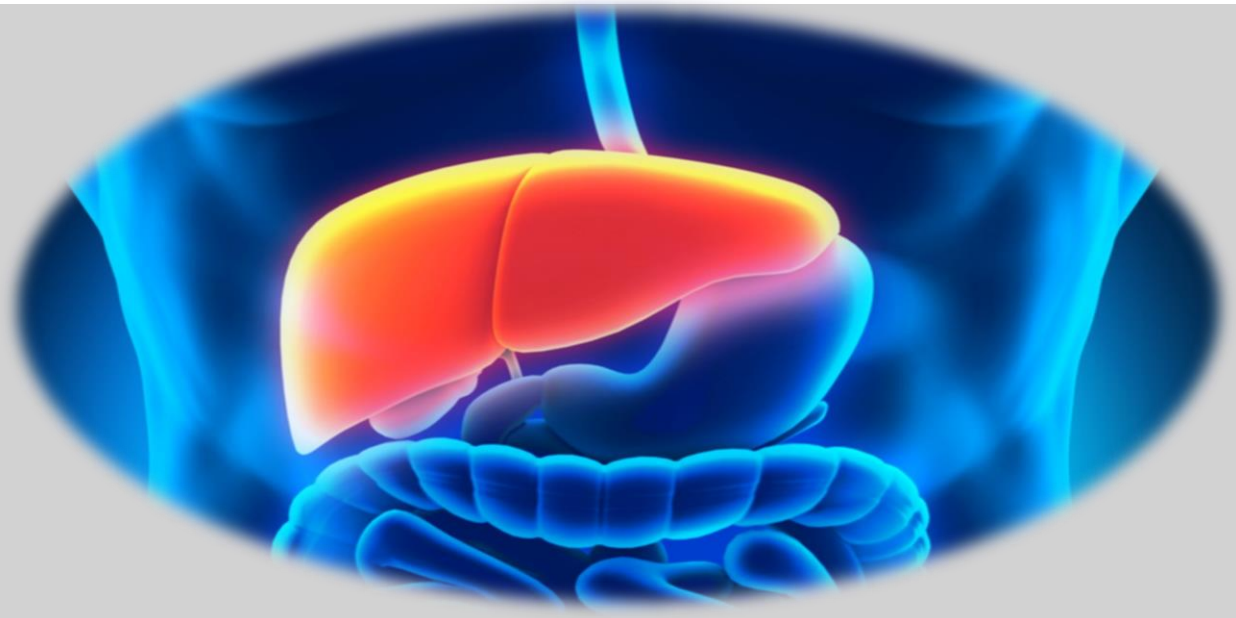
Topic Outline

- ALERT: US Boxed Warning
- Brand Names: US
- Brand Names: Canada
- Pharmacologic Category
- Dosing: Adult
- Dosing: Renal Impairment: Adult
- Dosing: Hepatic Impairment: Adult
- Dosing: Pediatric
- Dosing: Renal Impairment: Pediatric
- Dosing: Hepatic Impairment: Pediatric

Ciprofloxacin Dosage Adjustments in Altered Kidney Function[a]

CrCl (mL/minute)	Oral, immediate release	Oral, extended release	IV
CrCl >50 to <130	500 to 750 mg every 12 hours	1 g every 24 hours	400 mg every 8 to 12 hours
CrCl 30 to 50	250 to 500 mg every 12 hours[b]	1 g every 24 hours	400 mg every 8 to 12 hours
CrCl <30	500 mg every 24 hours[b]	500 mg every 24 hours	200[c] to 400 mg every 12 to 24 hours
Hemodialysis, intermittent (thrice weekly)[e]	250[d] to 500 mg every 24 hours[b]	500 mg every 24 hours	200[c] to 400 mg every 24 hours
Peritoneal dialysis	250[d] to 500 mg every 24 hours[b]	500 mg every 24 hours	200[c] to 400 mg every 24 hours

LIVER FUNCTION TESTS



Aspartate Aminotransferase

- *Reference Range: 0-35 units/L or 0-0.58 µkat/L*
- AST is abundant in heart and liver tissue and moderately present in skeletal muscle, the kidney, and the pancreas.

- AST determinations have been used to evaluate myocardial injury and to diagnose and assess the prognosis of liver disease resulting from hepatocellular injury.

Alanine Aminotransferase

- *Reference Range: 0-35 units/L or0-0.58 µkat/L*
- elevations in serum ALT are more specific for liver-related injuries or diseases.

- Although ALT is relatively more abundant in hepatic tissue versus cardiac tissue than AST, the liver still contains 3.5 times more AST than ALT.

Alkaline Phosphatase

- *Reference Range: 30-120 units/L or 0.5-2.0 µkat/L*
- A large group of isoenzymes that play important roles in the transport of sugar and phosphate.
- ALP is derived primarily from liver and bone
- This enzyme is secreted into the bile, and substantially elevated ALP serum concentrations can be seen with mild intrahepatic or extrahepatic biliary obstruction
- Drug-induced cholestatic jaundice (e.g., chlorpromazine or sulfonamides) can increase serum ALP concentrations

Classification of liver test abnormalities

Hepatitis (hepatocellular)	ALT ≥3 x ULN	R ≥5
Cholestasis	ALP ≥2 x ULN	R ≤2
Mixed	ALT ≥3 x ULN ALP ≥2 x ULN	R >2 to <5

ALT: alanine aminotransferase; ALP: alkaline phosphatase; ULN: upper limit normal; R: ALT/ULN divided by ALP/ULN.

$$R = \frac{ALT/_{ULN}}{ALP/_{ULN}}$$

Intrinsic	Idiosyncratic	
Acetaminophen	Allopurinol	Lapatinib
Amiodarone[§]	Amiodarone[§]	Methyldopa
Anabolic steroids	Amoxicillin-clavulanate	Minocycline
Antimetabolites	Bosentan	Nitrofurantoin
Cholestyramine[**]	Dantrolene	Pazopanib
Cyclosporine	Diclofenac	Phenytoin
Valproic acid	Disulfiram	Pyrazinamide
HAART drugs	Felbamate	Propylthiouracil
Heparins[**]	Fenofibrate	Statins[§]
Nicotinic acid	Flucloxacillin	Sulfonamides
Statins[§]	Flutamide	Terbinafine
Tacrine[**]	Halothane	Ticlopidine
	Isoniazid	Tolvaptan
	Ketoconazole	Tolcapone
	Leflunomide	Trovafloxacin
	Lisinopril	

Bilirubin

- *Total Bilirubin-Reference Range: 0.1-1.0 mg/dL or 1.7-17.1 µmol/L*
- *Direct (Conjugated) Bilirubin-Reference Range: 0-0.2 mg/dL or 0-3.4/-µmoI/L*

Assess severity of liver disease (Child-Pugh score)			
	1 point	2 points	3 points
Bilirubin (Total)	<2 mg/dL	2-3 mg/dL	>3 mg/dL
Albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
INR	<1.7	1.7-2.2	>2.2
Ascites	Absent	Mild to Moderate	Severe
Encephalopathy	No	Grade 1-2	Grade 3-4

Total score
A (5–6 points)
B (7–9 points)
C (10–15points)

Assess severity of liver disease (Child-pugh score)			
	1 point	2 points	3 points
Bilirubin (Total)	<2 mg/dL	2-3 mg/dL	>3 mg/dL
Albumin	>3.5 g/dL	2.8-3.5 g/dL	<2.8 g/dL
INR	<1.7	1.7-2.2	>2.2
Ascites	Absent	Mild to Moderate	Severe
Encephalopathy	No	Grade 1-2	Grade 3-4

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban	Warfarin
A (5–6 points)	No dose reduction				INR (2-3)
B (7–9 points)	Use with caution	Use with caution	Use with caution	Do not use	INR (2-3)
C (10–15points)	Do not use	Do not use	Do not use	Do not use	INR (2-3)

Monitoring of pharmacotherapy

Monitoring of efficacy examples

Drug	Test	Drug	Test	Drug	Test
Heparin	PTT	Anti-DM	Glycemic profile	Vancomycin, AG	Level
Warfarin	INR	Statins	Lipid profile	Anti-epileptics	Level
Enoxaparin	Anti-Xa	Anti-gout	Uric acid	Digoxin	Level
DOAC	?	Levothyroxin	TFT	CNI	Level
Iron, B12, folic acid	Retic, Hgb, iron profile	Antibiotics	CRP. PCT, cultures	Lithium	Level

Diabetes

- FPG ≥126 mg/dL (7.0 mmol/L)*
  - Fasting is defined as no caloric intake for ≥8 hours
- 2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)*
  - Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water
- A1C ≥6.5% (48 mmol/mol)*
- In a patient with classic symptoms of hyperglycemia or hyperglycemia crisis, a random PG ≥200 mg/dL (11.1 mmol/L)

Pre-diabetes

- **FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG),** ***(WHO; the IFG cut off is 110 mg/dl)***

OR

- **2-h PG in the 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)**

OR

- **A1C 5.7–6.4% (39–46 mmol/ml)**

Glycemic goals

Time	Normal	Patients with DM	Pregnancy
Fasting	70-99	80-130	<99
1-2 hours after meal	<140	<180	<120
Hb1AC	5.7 %	7%	6.5%

TABLE 53-6
Factors Affecting A1C

Cause	Effect on A1C
Hemoglobinopathies (sickle cell trait, acetylated or carbamylated[a] hemoglobin)	Decreased or increased
Anemias	
Hemolytic	Decreased
Iron deficiency	Increased
Blood loss	Decreased
Blood transfusion	Decreased
Erythropoietin-stimulating agents	Decreased
Antioxidants	Decreased[b]

[a]Carbamylated hemoglobin equaling 0.063% of total hemoglobin is formed for every 1 mmol/L of serum urea.
[b]Reported with vitamins C (1 g/d) and E (1,200 mg/d). Possible mechanism is competitive inhibition of hemoglobin glycosylation.
A1C, glycosylated hemoglobin; RBC, red blood cell.
A detailed listing of factors that interfere with A1C test results is available at http://www.ngsp.org/factors.asp.

Monitoring Parameters

ACC/AHA Blood Cholesterol Guideline recommendations (ACC/AHA [Grundy 2019]; ACC/AHA [Stone 2014]):

Lipid panel (total cholesterol, HDL, LDL, triglycerides): Lipid profile (fasting or nonfasting) before initiating treatment. Fasting lipid profile should be rechecked 4 to 12 weeks after starting therapy and every 3 to 12 months thereafter. If 2 consecutive LDL levels are <40 mg/dL, consider decreasing the dose.

Hepatic transaminase levels: Baseline measurement of hepatic transaminase levels (AST and ALT); measure AST, ALT, total bilirubin, and alkaline phosphatase if symptoms suggest hepatotoxicity (eg, unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine or yellowing of skin or sclera) during therapy.

Monitor closely for myopathy/rhabdomyolysis. Instruct patients to report unexplained muscle pain, tenderness, weakness, or brown urine, particularly if accompanied by malaise or fever.

CPK: CPK should not be routinely measured. Baseline CPK measurement is reasonable for some individuals (eg, family history of statin intolerance or muscle disease, clinical presentation, concomitant drug therapy that may increase risk of myopathy). May measure CPK in any patient with symptoms suggestive of myopathy (pain, tenderness, stiffness, cramping, weakness, or generalized fatigue).

Evaluate for new-onset diabetes mellitus during therapy; if diabetes develops, continue statin therapy and encourage adherence to a heart-healthy diet, physical activity, a healthy body weight, and tobacco cessation.

If patient develops a confusional state or memory impairment, may evaluate patient for nonstatin causes (eg, exposure to other drugs), systemic and neuropsychiatric causes, and the possibility of adverse effects associated with statin therapy.

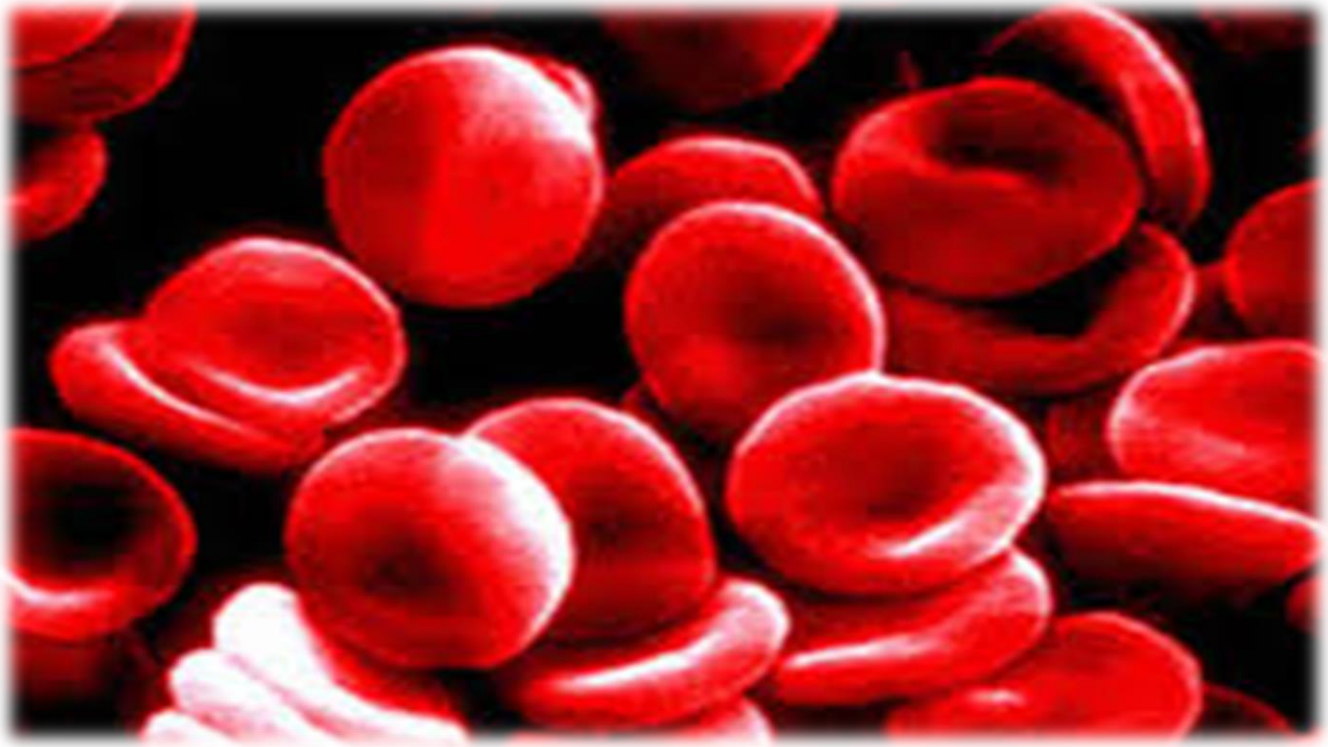
Manufacturer's labeling: Consider neuromuscular and serologic testing if immune-mediated necrotizing myopathy is suspected.

Reference Range

Treatment goals: May vary depending on clinical condition, different clinical practice guidelines and expert opinion. Refer to clinical practice guidelines for specific treatment goals.

Uric Acid

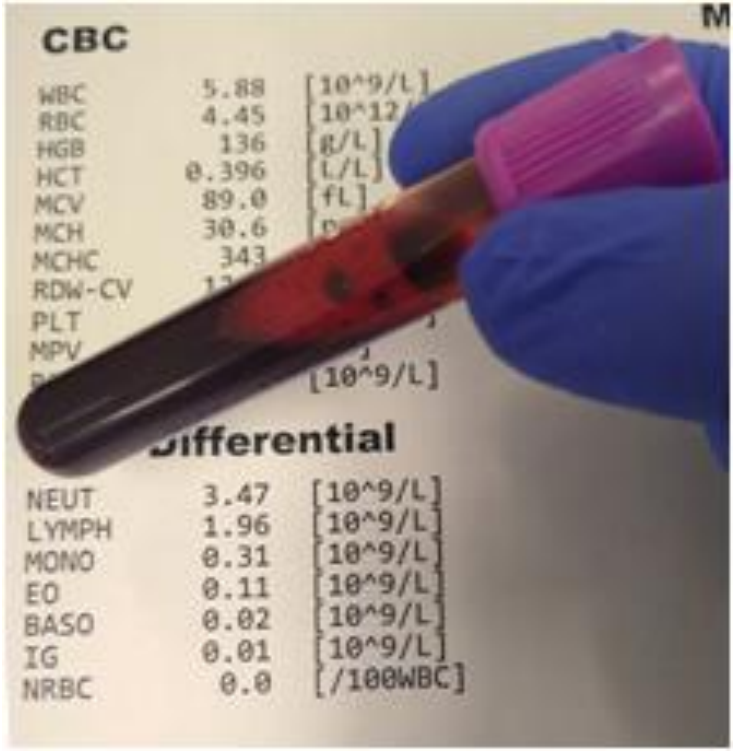
- *Reference Range: <7.0 mg/ dL or 0.42 mmol/L*
- End product of purine metabolism
- No biological function
- Gout
- Increased serum uric acid concentrations
  - Renal dysfunction
  - increased purine metabolism resulting from cytotoxic therapy



HEMATOLOGY

Complete blood count/ hemopgram

- The CBC is an extremely common laboratory test
  - Hemoglobin (Hgb)
  - Hematocrit (Hct)
  - White blood cells (WBCs)
  - Red blood cells (RBCs)
  - Mean corpuscular volume (MCV)
  - Mean corpuscular hemoglobin (MCH)
  - Mean corpuscular hemoglobin Mconcentration (MCHC)
- **Platelet** count and **WBC differential**.



Hemoglobin

Increased Hemoglobin
- Polycythemia vera
- COPD
- Chronic smokers
- Regular vigorous exercise
- Live at high altitude

Decreased Hemoglobin
- Anemia of all types (IDA)
- Blood loss
- Hemolysis
- Pregnancy,
- Fluid replacement

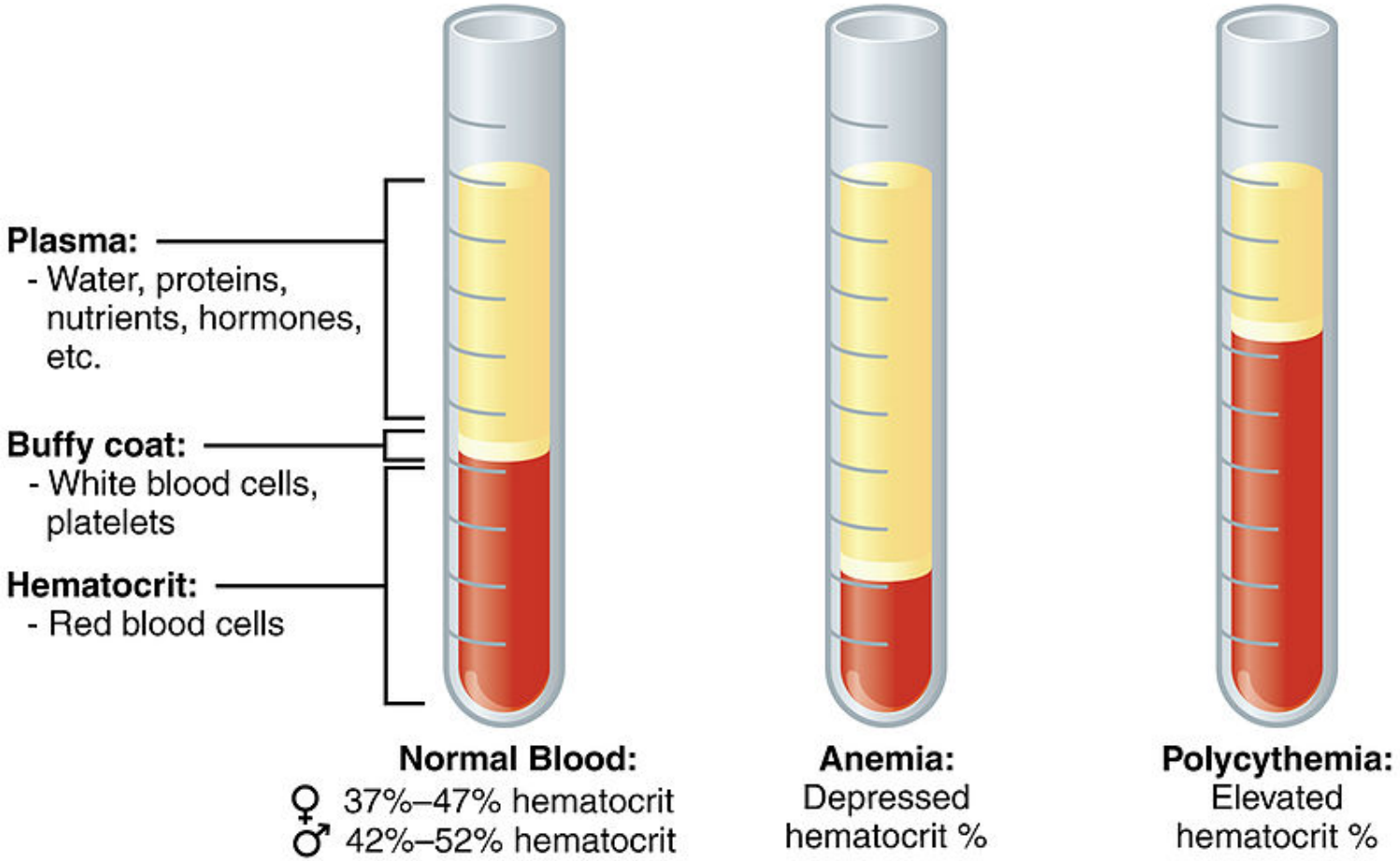
Reference Range
Male: 14-18 g/dL
Female: 12-16 g/dL

Hematocrit

Increased
- Polycythemia vera
- COPD
- Chronic smokers
- Regular vigorous exercise
- Live at high altitude
- Dehydration and shock

Decreased
- Anemia of all types (IDA)
- Blood loss
- Hemolysis
- Pregnancy
- Cirrhosis
- Hyperthyroidism
- Leukemia

Reference Range
Male: 39-50 %
Female: 33-45 %


Plasma:
- Water, proteins, nutrients, hormones, etc.
Buffy coat:
- White blood cells, platelets
Hematocrit:
- Red blood cells
Normal Blood:
♀ 37%–47% hematocrit
♂ 42%–52% hematocrit
Anemia:
Depressed hematocrit %
Polycythemia:
Elevated hematocrit %

Red blood cell count

Increased

- Polycythemia vera
- High altitudes
- Strenuous exercise

Decreased

- Anemia
- Lymphomas Leukemia
- Drug induced hemolytic anemia

Reference Range
Male: 4.2-5.9 × 10^6
Female: 3.5-5.5 × 10^6

MCV (Mean Corpuscular Volume)

Increased
Folate deficiency
Vitamin B12 deficiency
Alcoholism
Chronic liver disease
Hypothyroidism
Anorexia

Decreased
- Iron deficiency anemia
- Hemolytic anemia,
- Lead poisoning
- Thalassemia

Medications
- Valproic acid
- Zidovudine, stavudine,
- Antimetabolites

Reference Range
76-100 µm3/cell

Mean cell hemoglobin

- MCHC measures the concentration of Hgb
- MCH measures the weight of Hgb in the average RBC
- Changes in the Hgb content of RBCs alter the color of these cells.
- Normochromic anemias
  - Changes in the size of RBCs (MCV) are associated with corresponding changes in the weight of Hgb (MCH), but the concentration of Hgb (MCHC) remains normal.
- Hypochromic
  - A decrease in RBC Hgb, reflected by reduced MCHC, and may indicate iron-deficiency anemia.

Mentzer index = MCV/RBC count in millions

If, >13 – iron deficiency anemia is more likely

<13 – beta thalassemia is more likely

White Blood Cells

- *Reference Range: 4-11 x 10^3 /µL*

- WBCs comprise five different types of cells.
- All WBCs contribute to host defense mechanisms.
- Neutrophils are the most abundant followed in order of frequency by lymphocytes, monocytes, eosinophils, and basophils.

Neutrophils

Reference Range: 40%-70% of WBC

The number of neutrophils is commonly increased during bacterial or fungal infections
Production of new leukocytes, an increase in the number of circulating immature neutrophils (e.g., bands), this phenomenon is commonly referred to as a "left shift," which suggests bacterial infection.

Increased during:

Metabolic toxic states (e.g., diabetic ketoacidosis, uremia, eclampsia)
Physiological response to stress (e.g., physical exercise, childbirth)
Drugs (e.g., epinephrine, corticosteroids)
demargination from blood vessel walls

Agranulocytosis and absolute neutrophil count

- Neutropenia, is defined as a neutrophil count of less than 2,000 cells/ µL
  - Mild neutropenia (1000 ≤ ANC < 1500)
  - Moderate neutropenia (500 ≤ ANC < 1000)
  - Severe neutropenia (ANC < 500)
  - Profound neutropenia (ANC < 100)
  - Agranulocytosis refers to severe neutropenia

- The risk of infection increases significantly when the ANC is less than 500/µL
- The most common causes of neutropenia are metastatic carcinoma, lymphoma, and chemotherapeutic agents

Lymophocytes

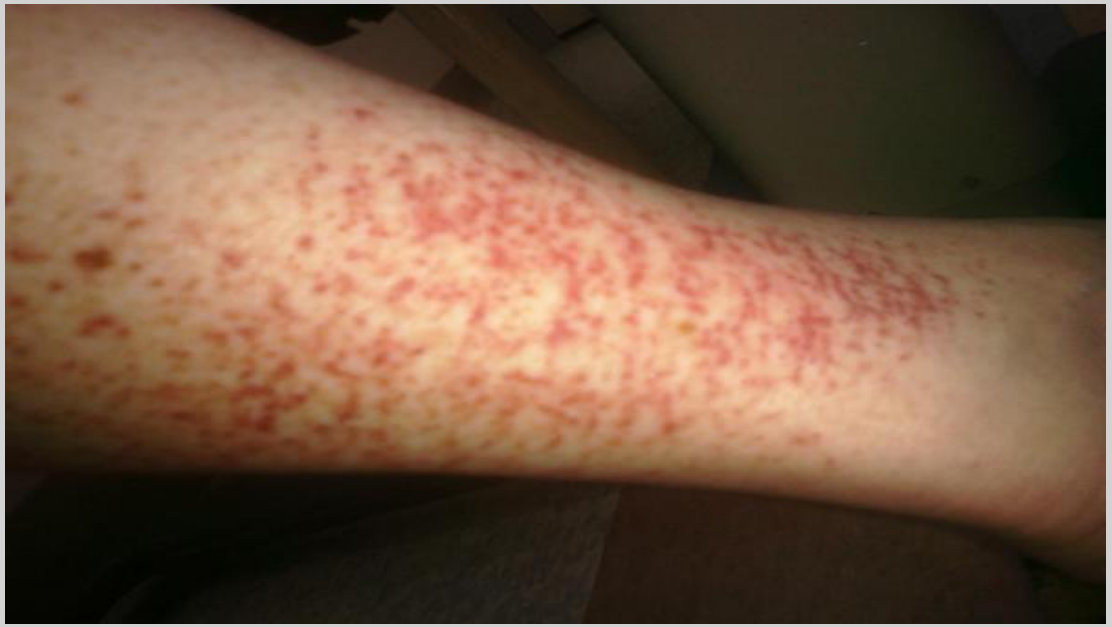
- *Reference Range: 20%-40% of WBC*
- The second most common WBC in circulating blood.
- Respond to foreign antigens by initiating the immune defense system.
- T lymphocytes (thymic dependent) participate in cell-mediated immune responses, and B lymphocytes (bone marrow derived) are responsible for humoral antibody responses.
- Immune deficiency disorders
- Lymphoma and viral infections such as infectious mononucleosis, mumps, and rubella.

Thrombocytes

- *Reference Range: 150- 450 x $10^3/\mu l$*

- Decreased platelet counts or thrombocytopenia may lead to petechiae, ecchymosis, and spontaneous hemorrhage.

- Causes include decreased platelet production, accelerated destruction, loss from excessive bleeding or trauma, dilution of blood samples secondary to blood transfusion, sequestration secondary to hypersplenism, disseminated intravascular coagulation, infection, or systemic lupus erythematosus



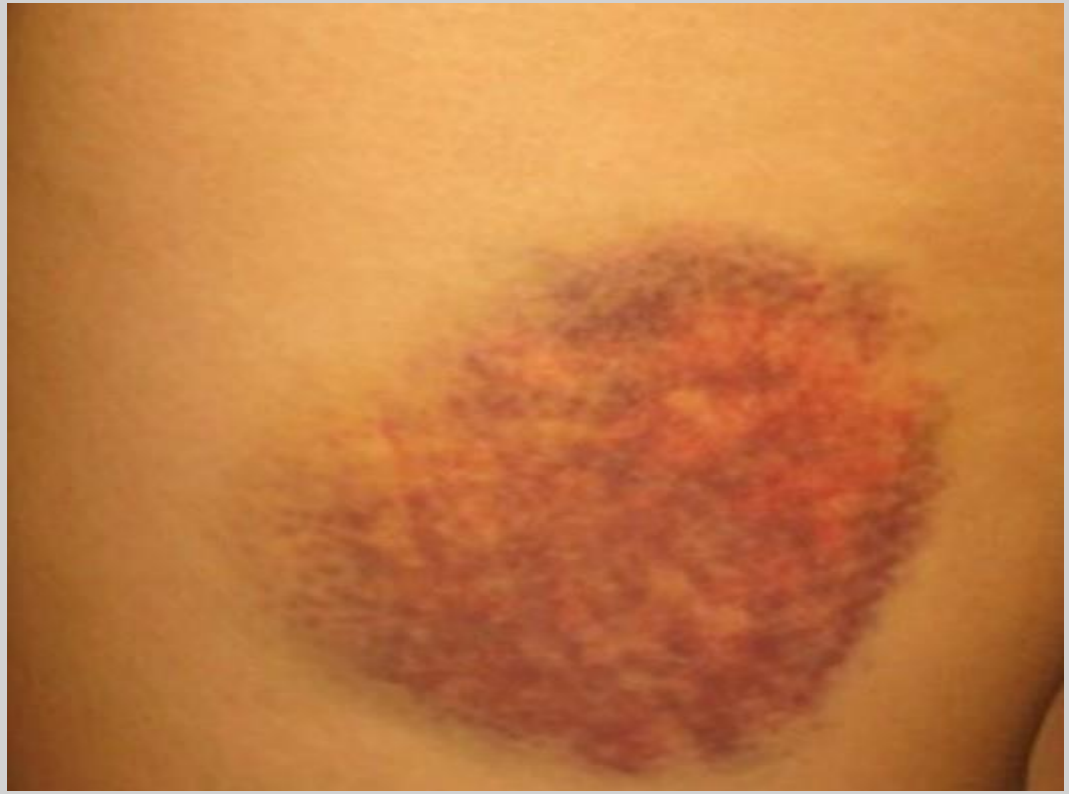


Table 1. Drugs Commonly Implicated as Triggers of Drug-Induced Thrombocytopenia.*

Drug Category	Drugs Implicated in Five or More Reports	Other Drugs
Heparins	Unfractionated heparin, low-molecular-weight heparin	
Cinchona alkaloids	Quinine, quinidine	
Platelet inhibitors	Abciximab, eptifibatide, tirofiban	
Antirheumatic agents	Gold salts	D-penicillamine
Antimicrobial agents	Linezolid, rifampin, sulfonamides, vancomycin	
Sedatives and anticonvulsant agents	Carbamazepine, phenytoin, valproic acid	Diazepam
Histamine-receptor antagonists	Cimetidine	Ranitidine
Analgesic agents	Acetaminophen, diclofenac, naproxen	Ibuprofen
Diuretic agents	Chlorothiazide	Hydrochlorothiazide
Chemotherapeutic and immunosuppressant agents	Fludarabine, oxaliplatin	Cyclosporine, rituximab

* For a more extensive list, see Aster,[2] Warkentin,[12] and George et al.[13] and the University of Oklahoma Web site (http://moon.ouhsc.edu/jgeorge/DITP.html).

- Causes of elevated platelet counts or thrombocytosis
  - Malignancy
  - Rheumatoid arthritis
  - Iron-deficiency anemia
  - Polycythemia vera
  - Postsplenectomy syndromes


Thanks for your attention