

8. MEDCHEM 535 Diagnostic Medicinal Chemistry (2013)
Kidney Function, Urinalysis, Colorectal Cancer Screening

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A. Kidney Function

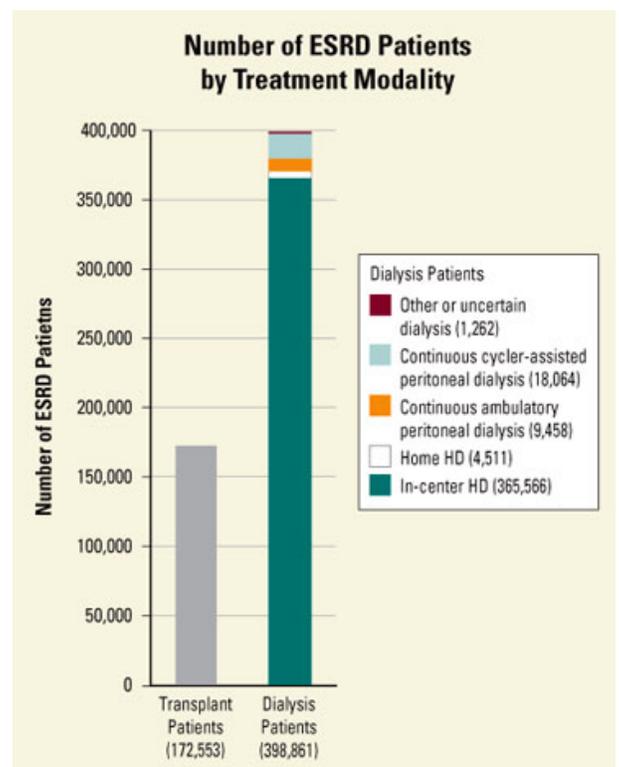
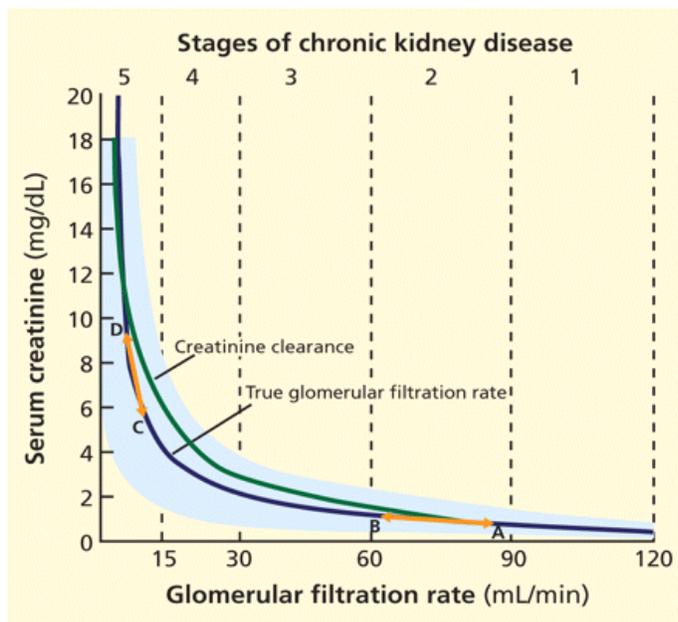
1. Kidney Disease Facts: (Kidney filters 180 L and produces 1.5 L of urine)

a. Approximately 26 million people in the US have chronic kidney disease. Estimated cost of treatment of Kidney Failure (ESRD) is \$42B. Cost of dialysis is \$80K/patient/yr. Prognosis: Mortality rate for ESRD is 200 deaths/1000 diagnosed.

b. Kidney disease severity is staged by estimates of glomerular filtration rates (GFR).

Disease Stage	GFR (ml/min/1.73 m ²)	Interpretation
1	>90	Normal (usually)
2	60-90	Diminished Function
3	30-60	Moderate (Chronic Kidney Disease; CKD) (10% of adults, 26% of adults over 60) (urinary ACR > 30 mg Alb/ gram creatinine)
4	15-30	Significant (nephrologist care; preparation for transpl. or dialysis; alter the dosing of some drugs)
5	<15	ESRD-Kidney Failure (dialysis or transplant)

ESRD requires transplant or dialysis



c. Initial indications of developing kidney disease are

- Elevated serum creatinine (SCr > 1.5 mg/dL)
- High protein/creatinine in urine (> 200 mg/gram)
- High ACR (mg albumin/gram creatinine)
 - ACR = 30-300 is micro-albuminuria
 - ACR > 300 is macro-albuminuria

d. Major causes of KD are

- Chronic hypertension
- Diabetes
- Glomerulonephritis
- Polycystic disease (heritable)
- Chronic kidney/bladder infections
- Chronic kidney stones

2. The Glomerular Filtration Rate (GFR) is the key marker of kidney disease. This value can be estimated from SCr alone, full Creatinine Clearance (CrCl) test (better) or determined (inulin and others). Another test is serum Cystatin C (a protein produced by all cells at a constant rate). Note from the figure above that CrCl and GFR are similar values but they are not the same thing.



a. The Cockcroft-Gault Equation: Creatinine clearance (CrCl) estimation from serum creatinine (SCr) alone:

Take value for serum creatinine and use equations to estimate CrCl. These equations can include terms for body weight, age and sex. It is important to know that SCr can also depend on race, diet and muscle mass. Also analysis of pediatric patients is treated differently. There are a number of online calculators of variable sophistication.

$$CrCl (mL/min) = \frac{(140 - age) \times Wt(kg)}{SCr(mg/dL) \times 72} \times 0.85 \text{ (if female)}$$

MDRD (modified diet in renal disease) estimates of GFR using SCr are also used and calculators exist for them.

b. Creatinine Clearance from serum and urine creatinine concentrations. Here 24 hour urine collections are the standard however 8 hours is often used. Creatinine is filtered and not absorbed however there is a slow secretion. Thus calculated CrCl will be higher than GFR.

$$CrCl (mL/min) = \frac{[Cr (urine)] \times Vol (urine)}{[SCr] \times Time (min \text{ urine collection})} \text{ standard}$$

$$CrCl (mL/min) = \frac{[Cr (urine)] \times (Vol (urine))}{[SCr] \times Time (min \text{ of urine collection})} \times \frac{1.73 m^2}{BSA}$$

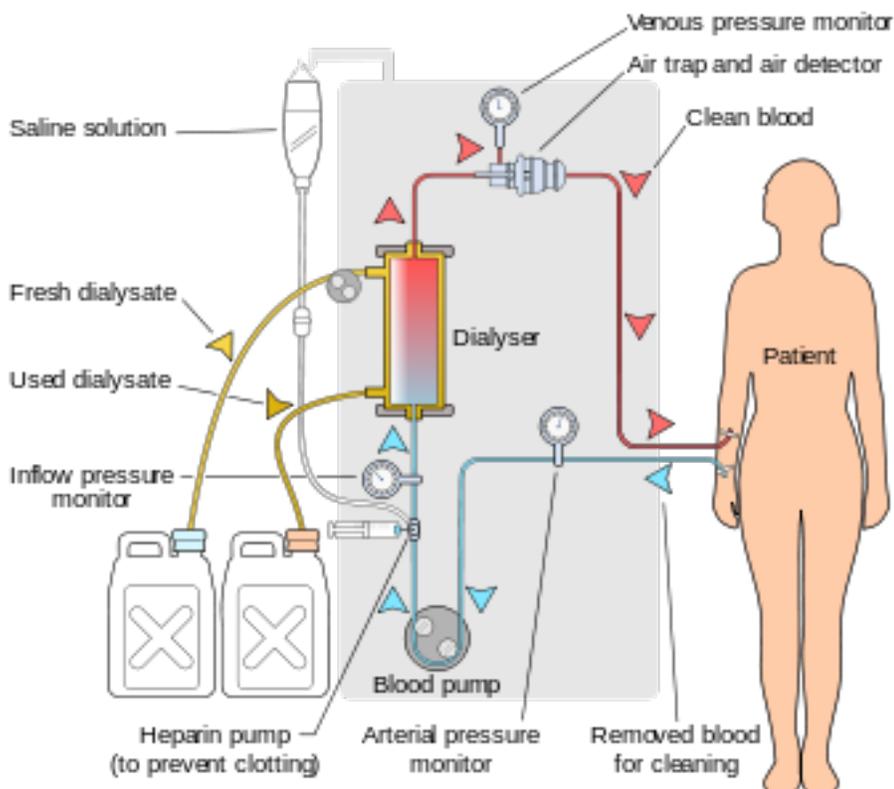
-Body surface area correction is common when tables are used.

c. True (Gold Standard) GFR using other test compounds that are administered i.v. specifically to determine GFR. Not used very much in the clinic. One of these is the inulin test. Inulin is an unnatural polysaccharide found in many plants that is neither reabsorbed or secreted by the kidneys.

3. Kidney Dialysis:

a. Close to 400,000 patients are on kidney dialysis. Dialysis occurs as often as daily for some but more often it is 3-4 times per week.

b. Dialysis consists of countercurrent exchange of low molecular weight compounds across a membrane with a standard solution of dialysis fluid. The dialysis fluid contains normal concentrations of most of the electrolytes but lacks those compounds like urea, creatinine and inorganic acids like sulfuric acid that are normally cleared by the kidney. Dialysate solutions are selected based upon each patient. Bicarbonate is often varied.



c. Many drugs, particularly low MW, low volume of distribution, low protein bound compounds are transferred to the dialysate and lost to the patient. Thus drug selection and dosing of drugs to patients on dialysis (renal and peritoneal) is extremely important and complicated.

1. Usually the drugs are dosed after dialysis.
2. The clearance of drug from blood into the dialysate is dependent on the type of membrane.

4. Dose Adjustments in Renal Disease:

a. The clearance of many drugs is significantly reduced in renal insufficiency. In most cases this is due to a high fraction of the total clearance due to renal elimination. One class of drugs where dose adjustments are often required is the antibiotics. The reference above has a nice summary of downward dose adjustments by drug class in different stages of kidney disease.

b. In some cases the clearance of an active metabolite is also reduced.

c. A good quick summary at <http://www.aafp.org/afp/2007/0515/p1487.pdf>

Table 4. Antihypertensive Agents: Dosing Requirements in Patients with Chronic Kidney Disease

Drug	Usual dosage*	Dosage adjustment (percentage of usual dosage) based on GFR (mL per minute per 1.73 m ²)		
		> 50	10 to 50	< 10
ACE inhibitors†				
Benazepril (Lotensin)	10 mg daily	100%	50 to 75%	25 to 50%
Captopril (Capoten)	25 mg every 8 hours	100%	75%	50%
Enalapril (Vasotec)	5 to 10 mg every 12 hours	100%	75 to 100%	50%
Fosinopril (Monopril)‡	10 mg daily	100%	100%	75 to 100%
Lisinopril (Zestril)	5 to 10 mg daily	100%	50 to 75%	25 to 50%
Quinapril (Accupril)	10 to 20 mg daily	100%	75 to 100%	75%
Ramipril (Altace) ⁵	5 to 10 mg daily	100%	50 to 75%	25 to 50%
Beta blockers				
Acebutolol (Sectral)	400 to 600 mg once or twice daily	100%	50%	30 to 50%
Atenolol (Tenormin)	5 to 100 mg daily	100%	50%	25%
Bisoprolol (Zebeta)§	10 mg daily	100%	75%	50%
Nadolol (Corgard) ⁵	40 to 80 mg daily	100%	50%	25%
Diuretics				
Amiloride (Midamor)	5 mg daily	100%	50%	Avoid
Bumetanide (Bumex) ⁵	No adjustment needed	—	—	—
Furosemide (Lasix) ⁵	No adjustment needed	—	—	—
Metolazone (Zaroxolyn)	No adjustment needed	—	—	—
Spironolactone (Aldactone) ⁵	50 to 100 mg daily	Every 6 to 12 hours	Every 12 to 24 hours	Avoid
Thiazides	25 to 50 mg daily	100%	100%	Avoid
Torsemide (Demadex) ⁵	No adjustment needed	—	—	—
Triamterene (Dyrenium)	50 to 100 twice daily	100%	100%	Avoid

GFR = glomerular filtration rate; ACE = angiotensin-converting enzyme.

*—Table provides general dosing information; dosages may be different for specific indications.

†—May need to use lower initial doses in patients receiving diuretics.

‡—Less likely than other ACE inhibitors to accumulate in patients with renal failure. A fixed-dose combination with hydrochlorothiazide should not be used in patients with a creatinine clearance less than 30 mL per minute (0.5 mL per second).

§—Maximal dosage in patients with renal impairment is 10 mg daily.

||—Thiazides should not be used in patients with a creatinine clearance less than 30 mL per minute; however, thiazides are effective in these patients when used with loop diuretics.

Information from references 4 and 5.

5. Drug Induced Kidney Toxicity: <http://www.aafp.org/afp/2008/0915/p743.pdf>

The renal tubule cells, particularly the proximal tubules can be exposed to high concentrations of drugs and toxic metabolites due to the concentrating effect of the kidney. Toxicity is often acute and reversible.

- a. Toxicity can be due to mitochondrial toxicity, oxidative stress and damage from free radicals. Examples are the aminoglycosides, anti-retrovirals and amphotericin B.

- b. Toxicity can be due to an inflammatory response arising from drugs that bind to antigens in the kidney or act as antigens. NSAIDs can cause acute nephritis particularly in children.
- c. Some drugs can crystallize in the distal tubules reducing urine flow and leading to interstitial nephritis and other kidney issues. Chemotherapeutics and antibiotics. Urine volume, hydration and urinary pH are factors here.
- d. Drugs that cause rhabdomyolysis such as the statins can cause renal injury in a number of locations due to the high load of muscle intracellular contents caused by overwhelming cell lysis.
- e. Drugs of abuse (see example below)

Kidney Damage Reported After Synthetic Cannabinoid Use

Sixteen patients in six states have been hospitalized with acute kidney injury (AKI) after using synthetic cannabinoids (SCs), according to the Centers for Disease Control and Prevention.

Details of these AKI cases appear in the CDC's Morbidity and Mortality Weekly Report (2013;62:93-98). The cases include 15 male patients aged 15-33 years and one 15-year old girl. *All but one presented with nausea and vomiting, and 12 had abdominal, flank, and/or back pain.* None had previous kidney problems or used medications that have been linked to renal dysfunction.

The patients' *peak serum creatinine concentrations range from 3.3 to 21.0 mg/dL* , and the apex occurred between one and six days after symptom onset. Furthermore, *eight of the patients had proteinuria, five had casts in the urine, nine had pyuria, and eight had hematuria.* Eight underwent renal biopsy and six had acute tubular injury, while three had acute interstitial nephritis. Most had full recovery of kidney function within three days of the creatinine peak. *Five required hemodialysis, but none died.* No single SC product explained all 16 cases.

B. Urinalysis

Simple POC values can be determined using dipsticks.

2161 Bayer Corporation, Elkhart, IN 46515 USA AG16516C Rev. 10/97 USA EXP. 2009-12 LOT: 8F06C



Multistix® 10 SG
Reagent Strips for Urinalysis

Glucose
Bilirubin
Ketone (Acetoacetic Acid)
Specific Gravity
Blood
pH
Protein
Urobilinogen
Nitrite
Leukocytes

For In Vitro Diagnostic Use
100 Strips

TESTS AND READING TIME

Test	Reading Time	Color Scale	Quantitative Scale
Leukocytes	2 minutes	Negative (light green), Small (yellow), Trace (orange), Moderate (red), Large (dark red)	None
Nitrite	60 seconds	Negative (light green), Positive (any degree of yellow to pink color)	None
Urobilinogen	60 seconds	Negative (light green), 0.2 (orange), 1 (red), 2 (dark red), 4 (purple), 8 (dark purple), 2000 or more (black)	mg/dL Urine (1 mg = approx. 1 EU)
Protein	60 seconds	Negative (light green), Trace (yellow), 30 (orange), 100 (red), 300 (dark red), 2000 or more (black)	mg/dL
pH	60 seconds	8.0 (dark blue), 7.5 (blue), 7.0 (green), 6.5 (yellow-green), 6.0 (yellow), 5.5 (orange), 5.0 (red)	None
Blood	60 seconds	Negative (light green), Non-hemolyzed (yellow), Hemolyzed (orange), Trace (red), Small (dark red), Moderate (purple), Large (black)	None
Specific Gravity	45 seconds	1.000 (light green), 1.005 (yellow), 1.010 (orange), 1.015 (red), 1.020 (dark red), 1.025 (purple), 1.030 (black)	None
Ketone	40 seconds	Negative (light green), Trace (yellow), Small (orange), Moderate (red), Large (dark red)	mg/dL
Bilirubin	30 seconds	Negative (light green), Small (yellow), Moderate (orange), Large (red)	None
Glucose	30 seconds	Negative (light green), 1/10 (yellow), 1/5 (orange), 1/2 (red), 1 (dark red), 2 or more (black)	g/dL (%)

READ PRODUCT INSERT BEFORE USE. IMPORTANT: Do not touch test areas. Store at temperatures between 15°-30°C (59°-86°F) and out of direct sunlight. Do not use product after expiration date. Do not remove desiccant. Remove only enough strips for immediate use. Replace cap immediately and tightly. Intended for use in the U.S.A.

1. pH (normal range 4.5 – 8.0; average 6.0)

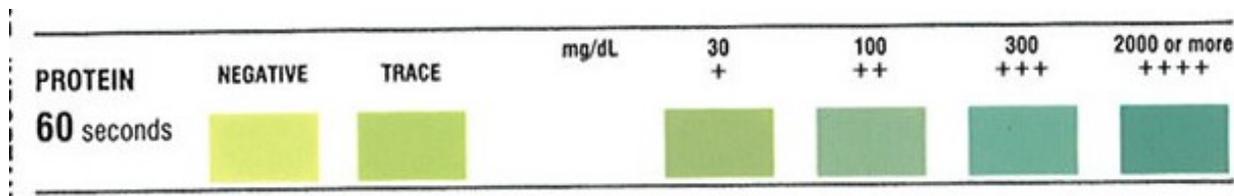
The primary acid produced by cellular metabolism is sulfuric acid which is excreted by the kidney so, on average, the pH of the urine is more acidic than the blood.

The pH of the urine is affected by some drugs, diet, metabolic and kidney disorders. It can be measured using test strips to an accuracy of 0.5 units.

Acidic Urine: Metabolic acidosis, cranberries and fruit juices, lactic- and keto-acidosis, ascorbic acid, compensatory ammonium ion excretion.

Alkaline Urine: Post prandial, metabolic or respiratory alkalosis, some UTIs, acetazolamine, bicarbonate salts, thiazide diuretics.

2. Protein in urine is best when normalized to creatinine in urine: Normal values are total protein/creatinine ratio < 200 mg/gram; albumin/creatinine <30 mg/gram.



a. *Normal function:* Trace (<30 mg/dL (+) on dipstick) Glomerular filtration of large MW proteins such as albumin is low to non-existent. MW cut-off is 30-40 kD. Smaller proteins and peptides are filtered endocytosed by the cells lining the proximal tubules where they undergo proteolysis and the amino acids returned to the blood. Small peptides and amino acids are transported back into the blood using the same set of co-transporters that are present on the enterocytes. Healthy individuals excrete 80-100 mg protein per day (5 mg/dL).

b. *Abnormal function:* Proteinuria staging and examples

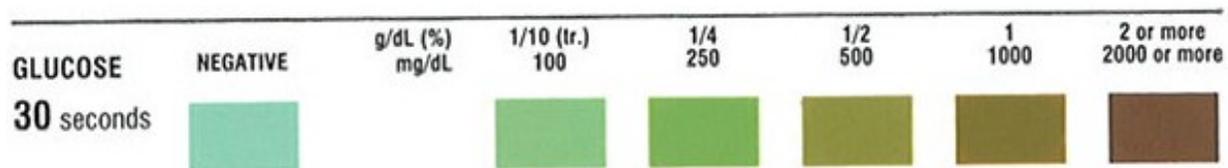
Mild (< 0.5 g/day) High blood pressure, UTI, exercise

Moderate (0.5-3 g/day) Glomerulonephritis (acute/chronic), CHF, diabetic nephropathy, pre-eclampsia

Significant (>3 g/day) Amyloidosis, severe glomerulonephritis, diabetic nephropathy

c. Various dipsticks provide total protein in mg/dL and albumin/creatinine.

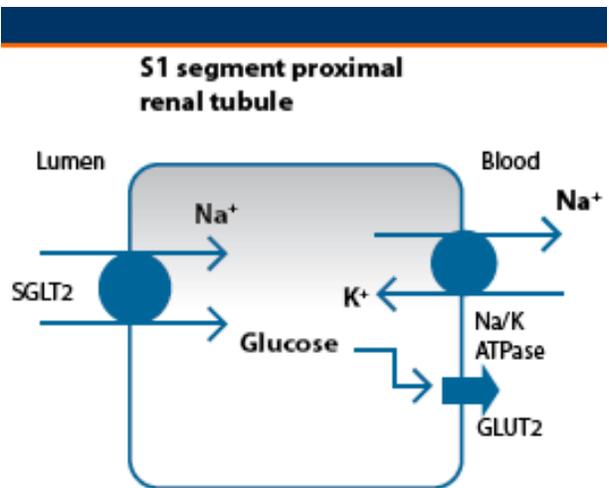
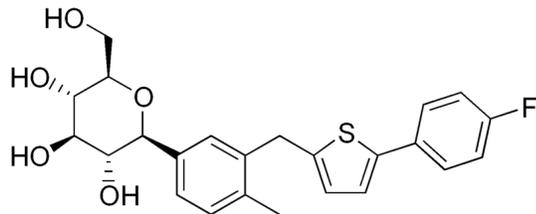
3. Glucose (no reference range) High levels called glucosuria which is accompanied by dehydration due to polyuria.



a. The test strips use the glucose oxidase method (detection limit 100 mg/dL). This test is based upon the enzymatic glucose oxidase/oxidase (GOD/POD) method. Glucose oxidase catalyzes the formation of gluconic acid and hydrogen peroxide from the oxidation of glucose. A second enzyme, peroxidase, catalyzes the reaction of hydrogen peroxide with a potassium iodide chromogen (green to blue) or other chromagen (green to brown above) to oxidize the chromogen to colors.

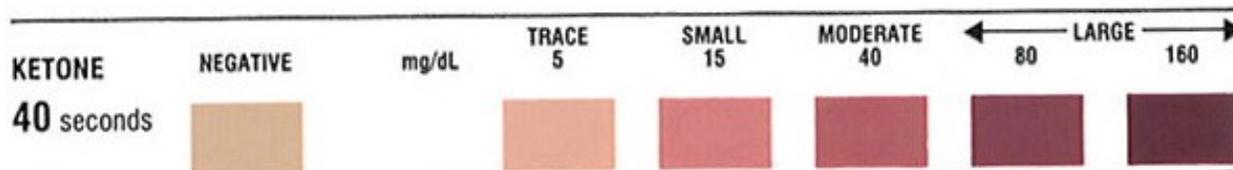
b. Glucose is found in the urine when blood glucose exceeds 180 mg/dL (10 mM) or when there is kidney disease in the proximal tubules. Glucose in the urine is not recommended currently to screen or monitor diabetes.

c. Interestingly, a new drug (canagliflozin: Invokana; JNJ; Janssen) has been approved by the FDA that acts by inhibition of the proximal tubule SGLT-2 transporter. An additional reduction in HBA_{1C} of 0.8% when added to metformin is observed. Urinary excretion of glucose can increase by as much as 70 grams/day. There is some concern about a higher incidence of UTIs and interest as a potential weight loss drug (280 calories down the drain).

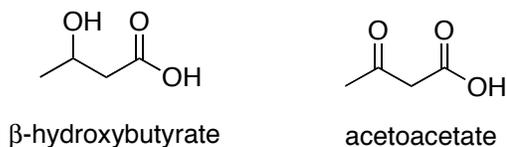


4. Ketone Bodies (no reference range)

The ketone bodies are 4 carbon weak acids produced by the liver when fatty acid levels are high in the blood. Normally they are present in urine only in trace amounts.



a. High serum concentrations of the ketone bodies acidify the blood (ketonemia) and can contribute to diabetic ketoacidosis (serum ketones > 1.1 mM or 12 mg/dL). The value can rise to as high as 15-25 mM! which is toxic. Diabetic ketoacidosis is a metabolic acidosis with a high anion gap. The most common cause of ketonuria is poor glycemic control in diabetes, particularly Type I, and the urine pH is low.

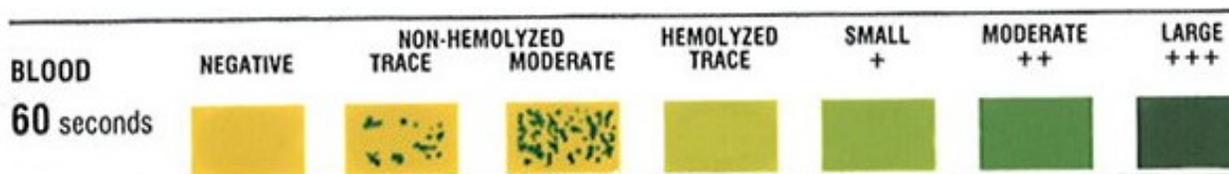


b. There are many dipstick products for ketone bodies. This test is based upon the reaction between acetoacetate and sodium nitroprusside in an alkaline medium. A positive result is indicated by a color change on the reagent pad from beige to violet. The most sensitive tests now detect both ketone bodies rather than just acetoacetate (limits of detection are 5 mg/dL). Some diets that try to force up free fatty acids in the blood as a strategy for weight loss recommend using ketosticks.

c. Other conditions that can cause ketonuria include pregnancy, low carb diets and starvation.

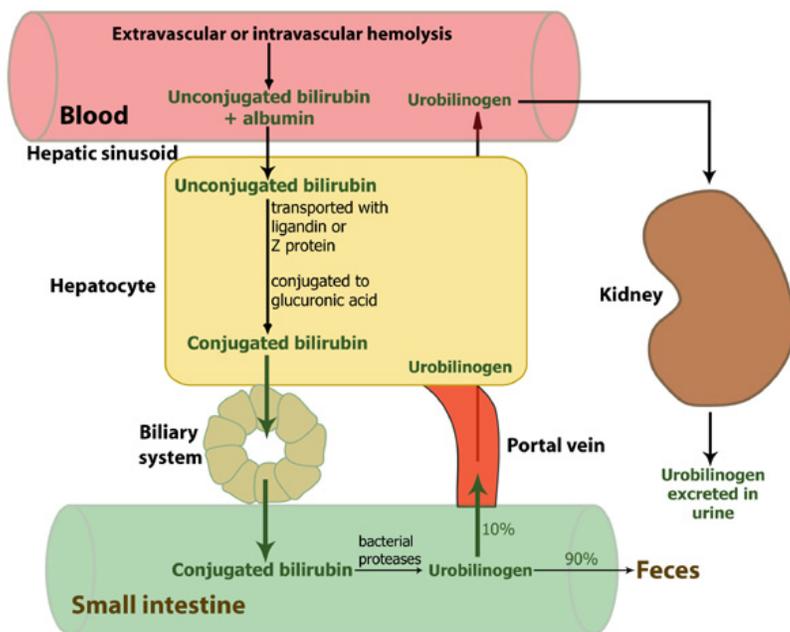
5. Hemoglobin and RBCs (hematuria)

- a. The presence of hemoglobin inside red blood cells (non-hemolyzed) and after lysis is observed. The test for intact red blood cells is sensitive and can pick up small numbers (2-3) that would be observed under a high power microscope. While red blood cells in urine can be observed after exercise, trauma or fever.
- b. RBC in the urine can be due to glomerulonephritis, infection, tumors, stones and coagulopathies. Bladder infections can also produce hematuria.
- c. This test is based upon hemoglobin reacting as peroxidase. Intact erythrocytes hemolyze on the test pad and the hemoglobin released produces a green dot. Scattered green dots on the yellow test pad are indicative of intact erythrocytes. A uniform green color is indicative of released hemoglobin, myoglobin, or hemolyzed erythrocytes. The colors produced range from orange yellow through green. Myoglobin will also produce a positive test.

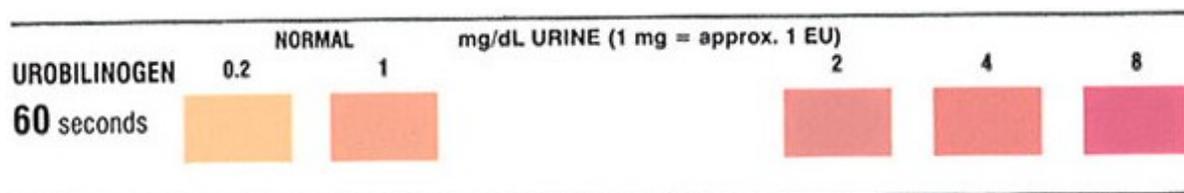
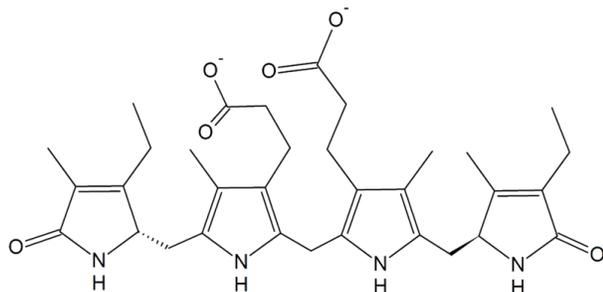


6. Bilirubin and Urobilinogen

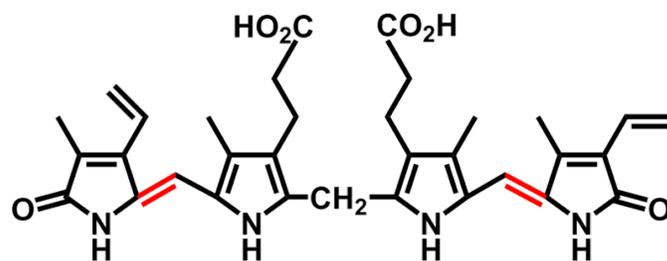
- a. Bilirubin is produced by normal oxidation of heme and transported to the liver for conjugation and excretion as the diglucuronide in the bile. Urobilinogen is produced in the gut by bacteria.



a. *Urobilinogen* is produced by gut bacteria oxidation of bilirubin diglucuronide. It is normally partially reabsorbed in the lower GI and excreted in the urine. High levels in urine indicate hemolysis, cirrhosis or acute hepatitis. Urobilinogen can rise before bilirubin in the urine. Low levels are seen in cholestasis (totally blocked bile flow). Urobilinogen is not colored.



b. *Bilirubin* is normally excreted as the diglucuronide in the bile. A dark yellow to green-brown color in the urine suggests bilirubin (the extra double bonds in red give the color). If you can recall, serum levels of bilirubin is called indirect bilirubin while levels of bilirubin diglucuronide is called direct bilirubin because it reacts with the color reagent in the absence of a detergent. Bilirubinuria is seen with intrahepatic cholestasis, bile duct obstruction, acute or chronic hepatic disease and drug induced hepatotoxicity. High serum levels of bilirubin seen in jaundice produce a yellow tinge to the skin.



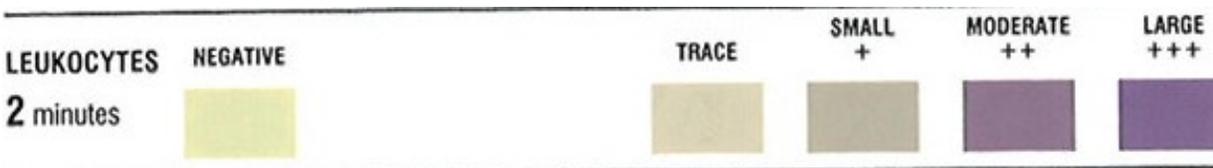


7. Nitrites, Leukocytes and Infection

a. *Nitrites*: The presence of nitrites in the urine is an indirect indicator of a urinary tract infection. Most, but not all, bacteria can reduce endogenous nitrates (one source is nitric oxide (NO) decomposed to nitrate) that are normally excreted in the urine to nitrites which are recognized by this test. The first morning urine is best as the bacteria have had time to produce large amounts of the nitrites. A follow-up urine culture is indicated by a positive test.



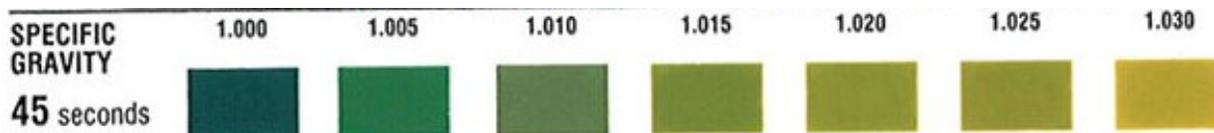
b. *Leukocytes (leukocyte esterase)* WBCs have an esterase that can be detected by a colorimetric assay for a colored product of the enzyme with a test substrate. A positive test is indicative of pyuria (pus in the urine).



8. Specific Gravity (1.001 to 1.035; normal (isosthenuric) is 1.010-1.025)

a. The osmolality of the blood is maintained by the kidneys. Normal blood osmolality is 285-300 mOsm/kg. Urine osmolality and specific gravity are positively correlated. The major osmolytes are sodium, sulfate, urea and phosphate. The kidneys can dilute urine relative to serum to a specific gravity of 1.001 and concentrate it to a value of 1.035. The knowledge of the specific gravity or osmolality of urine is best applied when the osmolality of serum is also known. Overall the osmolality of urine and blood are almost identical and must be in order for the kidneys to do their job.

b. Specific gravity can be measured with instruments called urinometers. The test strips are totally miraculous if you ask me. They have a polymeric acid embedded in the strip which changes ionization based on specific gravity. The resulting change in pH is detected using a pH color change with a pH indicator.



c. Specific gravity is most informative when paired with serum data. In general problems are associated with states where the two measures are opposite (high serum osmolality-low urine specific gravity). High specific gravity is often observed with CHF and dehydration. Low specific gravity is observed in diuresis and excess IV fluids. Patients with renal disease are usually only able to produce urine with the same osmolality as the blood. Their kidneys can neither concentrate or dilute the glomerular filtrate.

9. Microscopic Examination: The urine can be examined for color, turbidity and for cells, crystals and casts via a high power microscope.

a. Cells that may be observed are

RBC's (hematuria) due to kidney disease, UTI, kidney stones. 3 or 4 per high power field is normal after exercise, trauma or fever.

WBC (leucocytes) Pyuria is defined as 3 or more WBC's per high powered microscope field. Inflammatory diseases such as glomerulonephritis.

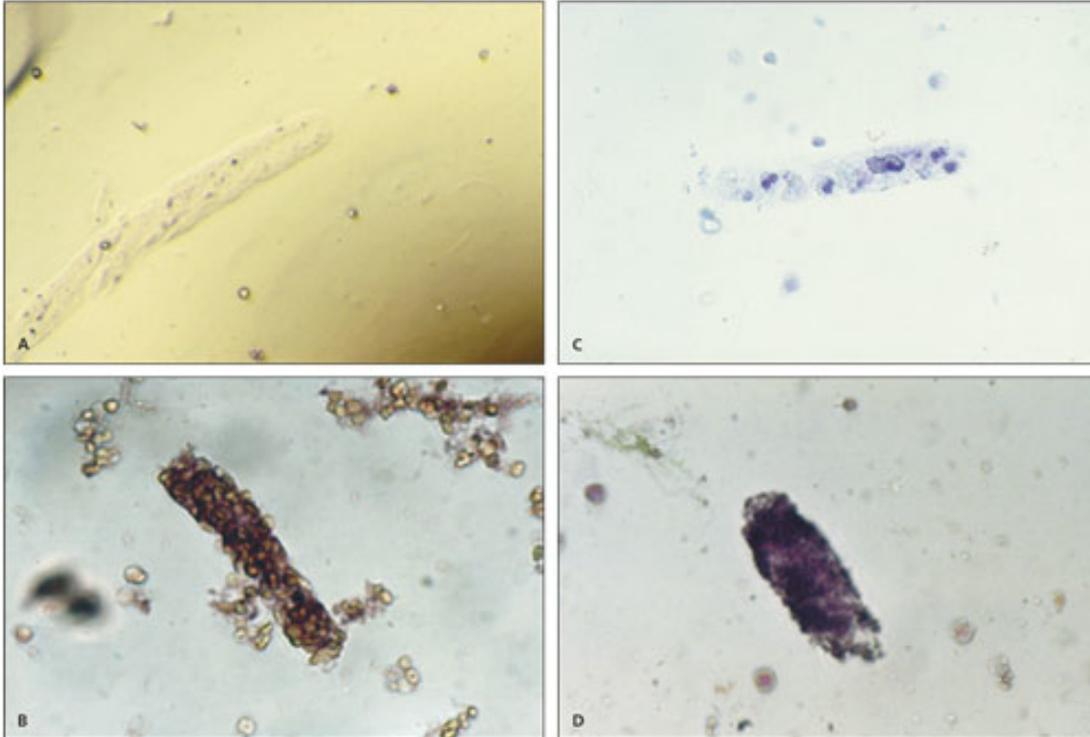
Tubular cells are small oval cells that are readily identified. More than one per high power field is cause for concern and may indicate tubular necrosis, interstitial nephritis or glomerulonephritis.

b. Casts are cylindrical glycoproteins that conform to the shape of the tubule lumen. A few clear casts are normal.

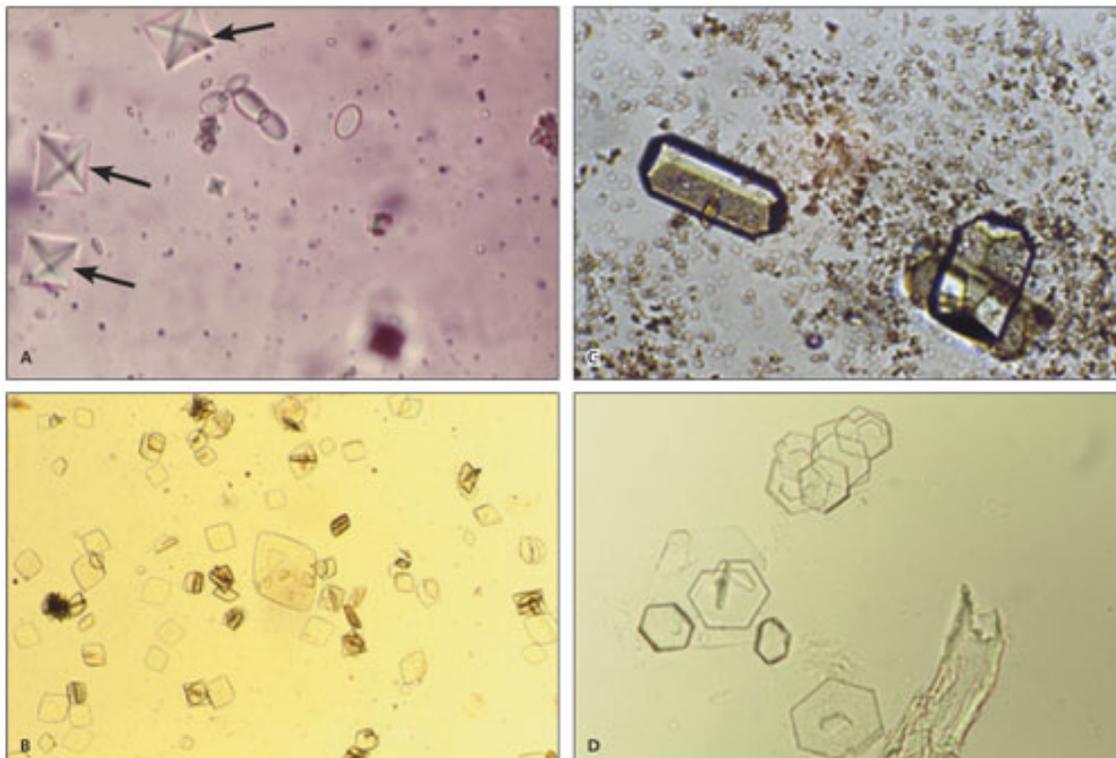
Hyaline casts: Clear casts difficult to see in a microscope. Seen in concentrated urine and also as a result of some diuretics (A).

Cell casts ((B) is RBC and (C) is WBC) are formed when cells become entrapped in the gelatinous mass lining the tubules. The cause and diagnosis of the casts is similar to what is observed for free cells.

Granular and waxy casts are seen in many conditions.

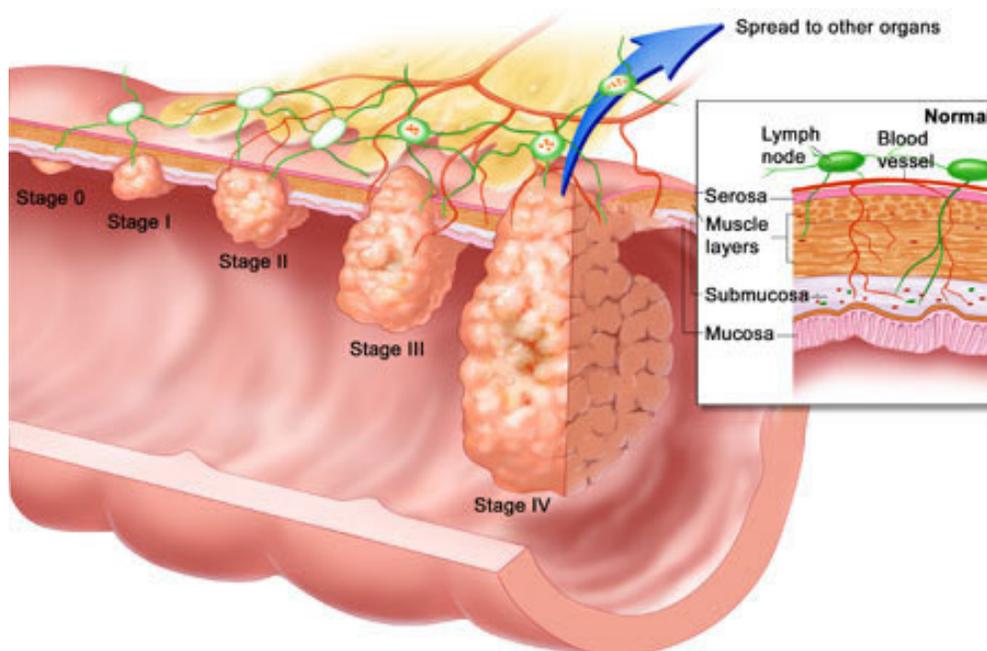


c. Crystals are formed due to high concentrations of solutes and are recognizable by their morphology. (A) Calcium oxalate (B) uric acid (C) triple phosphate (D) cystine.



C. Colorectal Cancer Screening

Colorectal cancer (CRC) is the second leading cause of cancer. There are approximately 130,000 cases per year and 50,000 deaths per year in the US. If diagnosed early there is a 90% survival rate. Annual screening for signs of cancer is recommended starting at the age of 50 unless there is a familial history for the disease. In addition to tests of fecal material discussed here sigmoidoscopy or colonoscopy are recommended at 5 year intervals.



1. Fecal Occult Blood Tests (FOBT): This is a surveillance test for colorectal neoplasias which targets blood loss into the feces due to tumor advancement. There are a range of tests available however most are targeted towards estimation of excess hemoglobin in the feces. We look briefly at 2 of the 3 kinds.

MAYO CLINIC
Mayo Medical Laboratories

Fecal Occult Blood Tests

	Guaiaic <i>Hemoccult</i>	Immuno <i>FIT</i>	Porphyrin <i>HemoQuant</i>
Hemoglobin analyte	heme	globin	heme + HDP
Quantitative	no	yes/no	yes
Detection rate			
Upper GI bleed	low	very low	high
Lower GI bleed	mod	high	high
Should be tested in lab	yes	yes	yes
List price	\$24	\$95	\$74
Medicare pays	\$22	\$22	\$22
Results back	Same/next day	Same/next day	Next day

Fecal Occult Blood Testing
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a. *gFOBT (Guaiac Test)* This is a colorimetric peroxidase test for heme in the feces. The test does not differentiate between heme obtained in the diet that escapes duodenal transport into the blood, heme due to upper GI bleeding (ulcers, aspirin), and heme from colorectal bleeds. The sample is exposed to hydrogen peroxide in the presence of guaiac resin. A blue color indicates heme. Multiple samplings should be tested as the detection percentage increases dramatically to 92%. Standard sensitivity is 10 ml of occult blood although more sensitivity is observed with some tests. Interestingly it is important that the reader of the test be tested for color-blindness.



b. *IFOBT [FIT (Immunochemical test for hemoglobin protein)]* This is an immunochemical test (ELISA) for human hemoglobin protein. “The sample is brought into contact with the test strip which initiates chromatographic flow. The sample flows down the test strip, rehydrates the colloidal gold anti-human hemoglobin antibody conjugate and, if hemoglobin is present in the sample, forms a hemoglobin-conjugate immune complex. The complex is then captured on the test strip in a zone containing anti-human hemoglobin antibodies to form a visible Test Line – a positive test.” The polyclonal antibody is raised to Hb in goats. Dietary hemoglobin and heme interference is minimized so diet before the test is less of a problem. This test is more sensitive (detects 0.3 ml of fecal blood) and selective. Most of the globin from Upper GI bleeds is digested to amino acids and the test does not differentiate.

2. Fecal Screening for Mutations: Developing technologies include detection of common DNA mutations in fecal samples and identification of certain proteins that are highly expressed in colorectal cancer.