Urinalysis, including interpretation and sediment evaluation

Components of the urinalysis:

1. Gross observation
2. Measurement of solute concentration (specific gravity and/or osmolality)
3. Chemical methods (i.e. reagent strips) to measure chemical constituents & pH
4. Sedimentation & microscopic evaluation of formed components.

Physical properties	Chemical properties	Sediment examination
USG	Glucose	RBCs
Color	Ketones	WBCs
Turbidity	Protein	Epithelial cells
Odor	Blood	Casts
Volume	Bilirubin	Crystals
	pH	Bacteria
	Urobilinogen	Fungi
	Leukocyte esterase	Parasites/ova
	Nitrate	Sperm
		Contaminants

****All components of the urinalysis must be completed for results to be meaningful.****

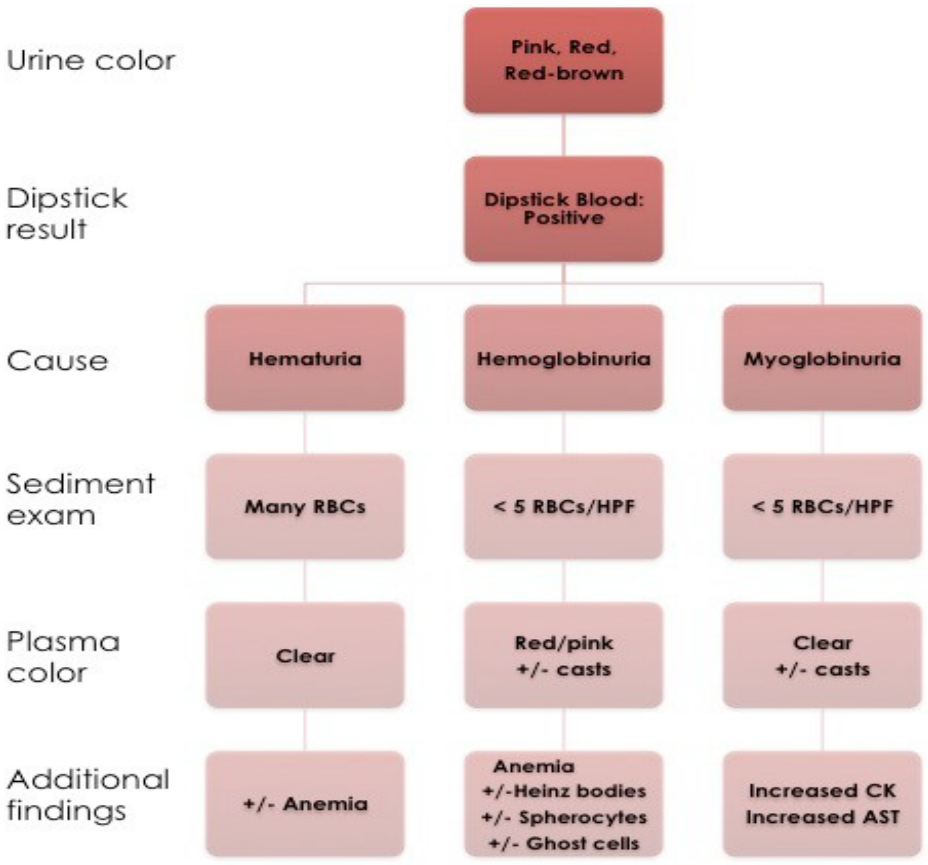
I. PHYSICAL PROPERTIES

- **a. Urine specific gravity**
  - **i.** Interpret USG considering patient hydration status, history, & clinical laboratory data.
    1. **USG values associated with adequate renal concentrating ability:**
       - **a. Cats > 1.035**
       - **b. Dogs > 1.030**
       - **c. Large animals > 1.025**
    2. **1.001 to 1.007 = Hyposthenuria**
       - **a.** Tubules able to dilute urine (less concentrated than original glomerular filtrate)
    3. USG of 1.008 to 1.012 = Isosthenuria (same SG as that of plasma)
       - **a.** Indicates no renal tubular concentration or dilution of glomerular filtrate
    4. USG > 1.012
       a. Indicates some concentrating ability; must interpret with patient's hydration

b. Color:

i. Normal urine varies from colorless to dark yellow (due to urochromes and urobilin).

Abnormal Color	Cause
Red or red-brown (see flow chart below)	Hematuria or Hemorrhage • Red color clears on centrifugation • RBCs present on sediment exam • Early during voiding – suggests lower urinary tract • Late during voiding – suggests bladder or kidneys Hemoglobin • Serum/plasma color pink Myoglobin • Serum/plasma color clear – straw
Very dark red, brown or black	Methemoglobinuria from hemoglobin or myoglobin
Yellow-orange-brown	Bilirubin
Yellow-green	Biliverdin, P*seudomonas* sp. UTI, new methylene blue
White (may be cloudy)	Pyuria Crystalluria (esp. calcium carbonate)



c. Turbidity:

i. Urine is **normally clear** when voided but may become cloudy after standing due to crystal precipitation.

ii. Exceptions:

1. Horse, rabbit, guinea pig - contains calcium carbonate crystals +/- mucus

iii. Causes of cloudy urine: cells, crystals, mucus, bacteria, yeast, casts, sperm, lipid, radiocontrast media.

d. Odor

i. Normal urine has distinct odor, may be strong due to hormones or certain proteins (i.e. cauxin in cats)

ii. Pathologic odor changes include:

1. Ammonia: urea-splitting bacteria—UTI
2. Ketones: acetone aroma in ketosis
3. Drug excretion: penicillins, DMSO

e. Volume:

i. "Normal" varies with species, body weight, diet and feeding frequency, fluid intake, physical activity, and environmental conditions (temperature, humidity, etc)

ii. Only 1-2% of ultrafiltrate is excreted as urine.

iii. Terminology for volume of urine

1. **DIURESIS**: Non-pathologic increased urine production
    a. Increased water consumption, diuretic therapy, fluid or steroid administration
2. **POLYURIA**: Pathologic increased urine production.
    a. Acute/chronic renal disease, diabetes mellitus, diabetes insipidus, Cushings disease, pyometra, etc.
3. **OLIGURIA**: Decreased urine production.
    a. Pathologic: Dehydration, fever, acute renal failure, shock
    b. Non-pathologic: Increased ambient temperature, increased panting
4. **ANURIA**: Urine production of <2 ml/kg/day
    a. Obstructive diseases, toxic nephrosis
5. **POLLAKIURIA**: Increased frequency of urination; normal urine volume
    a. Bladder inflammation, bladder mass lesion, pregnancy, behavioral

II. CHEMICAL PROPERTIES

a. **Reagent Dipsticks:** First developed for use in humans. Several commonly included tests are **not** generally **valid** for interpretation in animals: **urobilinogen, nitrites, leukocyte esterase**
   i. Accuracy highly dependent upon technique!!
   ii. MUST TIME TEST: Test results based on color change by a specified time
      1. Mixing of reagents can produce erroneous results, therefore important to remove excess urine from test strip (if dipped into urine), or pipette single drop of urine onto each reagent test square (better).
      2. Temperature of urine can influence results –room temp best
      3. Resuspend to disperse sediment
      4. Watch expiration date & keep container closed!

b. Individual dipstick tests:
   i. pH
      1. Reflects $[H^+]$ in urine & acid-base status of the patient
      2. Influenced by renal & extrarenal factors
   ii. Glucose
      1. Glucose passes through the glomerulus (freely-filtered)
      2. Reabsorbed in the proximal tubule normally
      3. Proximal renal tubule has a 'transport maximum' which varies by species; once this is reached, excess glucose enters the urine resulting in glucosuria:
         a. Dog: > 180-220 mg/dl
         b. Cat: > 280-290 mg/dl
         c. Horse: > 150 mg/dl
         d. Cattle: > 100 mg/dl (in calves > 150 mg/dl)
      4. Differentials when positive (glucosuria):
         a. Causes of persistent or transient hyperglycemia:
            i. Diabetes mellitus, acute pancreatitis, post-prandial, Cushings, fear or stress, drug therapy (steroids, xylazine, ketamine)
         b. Tubular disease resulting in euglycemic glucosuria
            i. Acquired—toxic insult, necrosis to proximal renal tubules
            ii. Inherited—Fanconi syndrome (basenji, sheltie, others)
      5. False results:
         a. Positive: contamination with bleach or peroxide (may happen if sample collected off of floor or exam table)
         b. Negative: refrigeration, concurrent ketonuria, others

   i. Ketones
      1. Dipstick test: Increased fat metabolism &/or decreased carbohydrate metabolism
         a. Ketones include: acetoacetate, beta hydroxybutyrate, acetone
            i. Beta-hydroxybutyrate does not have chemical structure of ketone so is NOT detected by reagent strip

2. Differentials when positive:
    a. Ketosis due to:
        i. Complicated diabetes mellitus (+/- acidosis)
        ii. Negative energy balance—cattle
        iii. High fat/low carbohydrate diet
        iv. Pregnancy toxemia (ewes)
        v. Starvation (young animals)
    b. False results:
        i. Positive: Highly pigmented urine, some drugs

ii. Blood or hemoglobin
1. Dipstick 'blood' pad detects RBCs, hemoglobin & myoglobin
    a. CONFIRMATION with sediment exam for presence or absence of RBCs a must
    b. See flow chart above as urine may be red or pink-tinged
    c. RBCs—form button when centrifuged
    d. HGB or myoglobin—no button forms
2. Differentials when positive:
    a. Hematuria (RBCs)
        i. Coagulopathy, trauma (i.e. HBC), neoplasia, UTI, etc
    b. Hemoglobinuria
        i. RBCs can lyse in the vasculature or in the urine
        ii. Hemolysis (in vessels)
        iii. Hemolytic anemia (see RBC section)
            1. Pink-tinged plasma
    c. In urine (RBCs lyse) due to low USG (Hyposthenuria)
    d. Myoglobinuria
        i. Severe muscle injury (extreme exertion, etc)
        ii. High CK, increasing AST; clear plasma color
    e. False results:
        i. Positive—bleach
        ii. Negative—vitamin C

iii. Protein
1. Amount of protein present in urine determined by:
    a. Types/amounts of small proteins present in plasma
    b. Glomerular function
    c. Tubular function
    d. Presence of urinary tract disease (i.e. neoplasia or UTI)
2. Dipstick detects: albumin > globulin, hemoglobin, mucoproteins
3. A small amount of protein in the urine can be normal—when & why?
    a. In highly concentrated urine samples (dogs primarily)
    b. May result in trace or 1+ positive protein dipstick results
    c. Due to Tamm-Horsfall protein (a mucoprotein)
    d. Can result in formation of hyaline casts
4. Cats—dipstick protein results highly variable in cats with frequent false positives due to non-albumin protein cauxin
5. Interpret degree of proteinuria in light of USG
    a. 1+ urine protein in USG of 1.012 vs. 1.045

i. To get the same result of 1+ means there is a lot more protein in the more dilute urine = likely pathologic proteinuria

6. Additional diagnostic testing options (see end of UA section also):
    a. SSA aka bumin test
    b. Urine Protein: Urine creatinine (UPC)
7. Causes of proteinuria:
    a. Pre-renal – Overflow proteinuria (small proteins pass through glomerulus)
        i. Hemoglobinuria (from intravascular hemolysis)
        ii. Myoglobinuria (from muscle necrosis
    b. Functional or physiologic (Pre-renal cause with renal effect on glomerulus)
        i. Fever, seizures, strenuous exercise (@15% of dogs)
    c. Renal
        i. Glomerular, tubular or a combination
            1. Selective glomerular wall usually permits only small molecules through (albumin mostly excluded)
            2. Tubules—protein that passes through glomerulus & enters into tubular fluid will be reabsorbed by proximal tubular epithelial cells
            3. Increased protein presented to tubular cells leads to damage, worsens proteinuria
        ii. Glomerular more common & tends to be more severe although need renal biopsy to confirm type & severity of renal disease
            1. Glomerulonephritis
                a. Numerous types, i.e. immune complex disease, antibodies to glomerular basement membrane
            2. Amyloidosis (e.g. inherited—Siamese cats or acquired)
        iii. Tubular—especially with acute injury toxins, inflammation, excess protein
        iv. Renal proteinuria is also called protein-losing nephropathy
    d. Post-renal
        i. Hemorrhage or inflammation within the distal renal tubules, ureters, bladder, urethra & reproductive tract sources (i.e. prostate, estrus)
        Check urine sediment for RBCs, WBCs & evidence of neoplasia
            1. Hemorrhage: Coagulopathy, neoplasia, UTI, trauma
            2. Inflammatory: UTI
    e. False results:
        i. Positive—Highly alkaline urine, highly pigmented urine, prolonged immersion of dipstick in urine
        ii. Negative—albumin concentration < 30mg/dl (microalbuminuria)

iv. Bilirubin
1. Dipstick test: detection of conjugated (direct) bilirubin which is water soluble
2. Unconjugated bilirubin is bound to albumin so should not be present in urine (given glomerular selectivity)
3. Dogs—
    a. Low renal threshold so see bilirubinuria before hyperbilirubinemia
4. Differentials when positive:
    a. Normal
        i. In highly concentrated urine from dogs (male > female) due to low renal threshold—usually < 2+
        ii. Trace bilirubinuria in cattle (@ 25%)

b. Hyperbilirubinemia due to:
    i. Cholestasis or bile duct obstruction
        1. Bilirubin normally excreted into biliary tree
    ii. Hemolysis (intra- &/or extravascular)
        1. Look for concurrent anemia + cause for hemolysis
5. False results:
    a. Positive: Highly colored urine
    b. Negative: Delayed sample analysis

v. Urobilinogen
1. See liver notes for origin of urobilinogen
2. Absence of urobilinogen could indicate complete bile duct obstruction, but:
    a. May not be detected in normal animals
    b. Poorly correlated with liver disease

vi. Nitrite ➔INVALID

vii. Leukocyte esterase ➔INVALID

III. SEDIMENT EXAMINATION

a. Basic procedure to prepare sediment sample:
   i. 5-10 ml urine in centrifuge tube
   ii. Centrifuge at low speed (< 1000 rm) for @ 5 minutes
   iii. Pour off most of supernatant
   iv. Resuspend small pellet in remaining supernatant
   v. Place 1 drop of urine on clean slide; apply coverslip

b. Considerations in Evaluating Urine Sediment:
   i. Quantitative analysis is entirely dependent upon volume of urine evaluated. Must use a **consistent volume** in sediment examination for meaningful results!

   ii. Method of collection can influence findings:
      1. Catheterized or free catch: More squamous epithelial cells
      2. Cystocentesis: Iatrogenic hemorrhage possible

c. Evaluation of unstained sediment smear:
   i. 10x – casts, overall cellularity, larger structures (hyphae, microfilaria)
   ii. 40x –cellular component (RBCs, WBCs, epithelial cells), infectious agents, crystal types, etc.

d. Stain vs. Unstained sediment?
   i. Unstained better—takes practice!
      1. LOWER the condenser (light source just under the stage) for unstained specimens.
   ii. Disadvantages of using sediment stain include:
      1. Uneven staining can confuse interpretation.
      2. Stains may be contaminated with bacteria or may contain precipitates which confuse interpretation.
   iii. If stained sample is desired, BEST option is to prepare a thin, dried sediment smear & stain with Diff Quick.

e. CELLS
   i. RBCs: <5/HPF is normal
   ii. WBCs <5/HPF is normal
   iii. Epithelial cells:
      1. Squamous—from urethra, vagina/prepuce; minimal significance
      2. Transitional—from proximal urethral, bladder, ureters, renal pelvis
         a. Variable morphology (hence the name 'transitional'
         b. Hyperplasia from UTI, stones, etc results in abnormal morphology
            i. Correct underlying disease & reassess
      3. Renal tubular epithelial cells—rarely seen, may be present in casts with tubular damage
   iv. With high USG, cells crenate; with low USG, cells may lyse (esp. RBCs)

f. CASTS
   i. Composed of mucoprotein (normally made in distal tubule) matrix (Tamm-Horsfall protein) +/- cellular components that take on shape of tubule where it forms (i.e. a 'cast' of the tubule)
   ii. More likely to form in distal tubules where more concentrated
   iii. Types:
      1. Hyaline—homogenous mucoprotein matrix (hard to see); proteinuria
      2. Cellular—Renal tubular epithelial cells, can reflect tubular injury (renal tubular epithelial cells slough off
      3. Granular—coarsely or finely granular, reflects later stage of cellular cast
      4. Waxy—degenerated granular or cellular cast, more chronic tubular lesion
      5. RBC or WBC—reflects renal tubular hemorrhage or inflammation

g. CRYSTALS
    i. Form both before & after urine collection (i.e. crystals can be artifacts from a processingdelay!)
    ii. Formation depends on urine pH & solutes present in urine
    iii. Presence of crystals ≠ urolithiasis (urinary stones) although can be associated
    iv. Calcium carbonate crystals normal in horses, rabbits, guinea pigs

Name	Clinical significance
Ammonium (bi)urate	Hyperammonemia due to a portosystemic shunt or hepatic failure.
Amorphous phosphateor urate	No clinical significance.
Bilirubin	Indicate some degree bilirubinuria.
Calcium oxalate: dihydrate	Forms in acidic urine. Can be a normal finding.
Calcium oxalate: monohydrate	Hyperoxaluria due to ethylene glycol (EG) toxicosis or ingestion of oxalate-richfoods. Not always present with EG toxicosis.
Cystine	Indicates cystinuria, an inherited defect in urinary cystine transport. Newfoundland, English Bulldog, and others. Acidic increases likelihood of urolith formation and obstruction.
Drug associated	Reported with ampicillin, sulfa drugs, ciprofloxacin, radiographic contrast agents
Triple phosphate (magnesium ammonium phosphate; struvite)	Often of no clinical significance. May accompany urinary tract infection (urease-splitting bacteria).More likely to form in alkaline urine, refrigerated specimens.
Uric acid	Inherited defect in purine metabolism ➔increased uric acid. Dalmatians & bull dogs. Increases risk of uric acid uroliths (stones), especially in acidic urine.

h. MICROORGANISMS
    i. Bacteria (most common!)
        1. Consider method of collection
        2. Free catch or catheter-obtained—more likely to be a contaminant UNLESS there issignificant pyuria (inflammation) or a uniform population
        3. Diff-Quick stained air-dried urine sediment is best for confirming bacteriuria
        4. Culture & sensitivity for confirmation; cystocentesis-obtained samples recommended
    i. Microfilaria (Heartworm infection)
    ii. Bladder worm—*Pearsonema plica*
    iii. Kidney worm—*Dioctophyma renal*
    iv. Fecal contamination or inadvertent enterocentesis (during cystocentesis):
    v. *Giardia* sp., *Dipylidium* sp. egg packet
    vi. Fungi

1. Candida (normal flora of urogenital tract so overgrowth possible)
2. May just be a contaminant if present in low numbers
3. Systemic fungal disease (e.g. Blastomycosis) can be detected infrequently in urinarysediment in patients with renal or prostate involvement

vii. Other

1. Prototheca (uncommon)

i. MISCELLANEOUS FINDINGS

i. Sperm
ii. Lipid (looks similar to both RBCs & yeast but sits in a different plane of focus)
iii. Mucus