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The EM Educator Series

Mini-Case: UA for all - Pearls & Pitfalls in the ED setting

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Mini-Cases:
1: A 24-year-old female presents with dysuria and frequency. Her VS are normal, and she otherwise feels well. She denies vaginal discharge or bleeding. You order a urinalysis, but question ordering a urine culture as well.

2: A 79-year-old male presents with frequent falls. He endorses generalized weakness but denies other symptoms including chest pain, abdominal pain, dyspnea, dysuria/frequency, and edema. A urinalysis sent from triage shows 4 WBCs, trace LE, and negative nitrites.

Questions for Learners:

1) What are the components of a urinalysis and urine dipstick, and what do they mean? (color / clarity / glucose / bilirubin / ketones / spec gravity / blood / pH / protein / urobilinogen / nitrite / LE / RBC/ WBC / bacteria / squam / hyaline casts)

2) What may cause false positive and false negative results for leukocytes, nitrites, ketones, and blood?

3) What is the relationship between squamous cells and contamination?

4) Does cloudy, smelly urine = UTI?

5) Does +LE and/or WBC diagnose UTI? What is the differential for sterile pyuria?

6) Is a positive nitrite diagnostic of UTI?

7) Is a urinary pregnancy test Pt states: my urine preg test is always negative, but the blood proves I'm pregnant

8) Who needs a urine culture?

9) When should you treat asymptomatic bacteriuria?

10) Elderly patients with recurrent falls or AMS… is a UTI responsible?

11) How does a urinary stent impact urinalysis testing and the diagnosis of UTI?

12) How do you interpret urinalysis in a catheterized patient, and how do you diagnose UTI?

Suggested Resources:

- ✓ Articles:
  - EP Monthly Part 1: The Lowly Urinalysis: How to Avoid Common Pitfalls
  - EP Monthly Part 2: Complicated UTI Part II: Understanding Special Populations
  - LITFL Urine Analysis
  - emDOCs: UTI – Pearls and Pitfalls in Urine Testing
  - ALiEM Uncomplicated Urinary Tract Infection in Older Adults: Diagnosis and Treatment (Part 1)
  - ALiEM Uncomplicated Urinary Tract Infections in Older Adults: Diagnosis and Treatment (Part 2)
  - emDOCs: Foley Catheter Patients: Common ED Presentations / Management / Pearls & Pitfalls
  - emDOCS: Pyelonephritis: It's not always so straightforward…
- ✓ Podcast:
  - EM Cases - Episode 94 UTI Myths and Misconceptions

Answers for Learners:

1) What are the components of a urinalysis and urine dipstick, and what do they mean? (color / clarity / glucose / bilirubin / ketones / spec gravity / blood / pH / protein / urobilinogen / nitrite / LE / RBC/ WBC / bacteria / squam / hyaline casts)

" Specific gravity is related to serum and urine osmolality, measuring the kidney's ability to concentrate or dilute urine. Normal values range from 1.003 to 1.030 (< 1.010 is associated with relative hydration, while > 1.020 is associated with relative dehydration). [3,4,12] Decreased values occur with excessive hydration, nephrogenic diabetes insipidus, glomerulonephritis, pyelonephritis, and acute tubular necrosis.

Increased levels are found in dehydration, SIADH, adrenal insufficiency, liver failure, nephrotic syndrome, and prerenal renal disease. [3,12] It can also occur with glycosuria, proteinuria, IV contrast, and urine contamination.

Fixed levels approaching 1.010 are common in end stage renal disease or chronic glomerulonephritis. Urinary pH in patients with normal metabolic activity ranges from 5.5-6.5 (though some regard 4.5-8 as normal). [3,4] High urinary pH is common in vegetarians, UTIs (due to urea-splitting bacteria), alkalemia, type 1 renal tubular acidosis, and drugs. Lower urinary pH is common in diets with high protein or fruit, acidemia (the normal renal response to acidosis is acid excretion in the urine), diabetes, starvation, diarrhea, and several metabolic disorders (Phenylketonuria). [13-15]

Protein is often excreted in the urine, though this should not be greater than 150 mg in 24 hours. Levels of 150 mg/day are significant. Dipstick is positive for protein at 5-10 mg/dL. [3,13] However, microalbuminuria (30-300 mg/day) is usually not detected on dipstick testing. Results of 1+ correspond to 30 mg/dL, 2+ to 100 mg/dL, 3+ to 300 mg/dL, and 4+ to 1,000 mg/dL. [16,17]

Urine concentration can affect the semiquantitative results of the dipstick (dilute urine will result in underestimation of protein). A special indicator dye, Bromophenol blue, is most sensitive to albumin. However, it may not detect globulins and Bence-Jones proteins (secreted in multiple myeloma, lymphoma, and macroglobulinemia). [3,4,13] Urinary protein is elevated due to increased renal tubular secretion, increased filtration, pyelonephritis, glomerulonephritis, chronic hypertension, nephrotic and nephritic syndrome, drugs, CHF, exercise, fever, cold exposure, pregnancy, physiologic stress, and other conditions. [3,4,13]

Leukocyte esterase (LE) is an enzyme produced by neutrophils, and the presence of these cells is suggested with LE activity. A positive LE test is associated with pyuria, typically in the setting of > 10 WBCs per high powered field (hpf). [3,18,19] To properly evaluate for LE, the dipstick requires 30 seconds to 2 minutes of urine contact. There are many pitfalls with this test, which we will discuss later.

Nitrites are not normal in urine. These result from the conversion of urine nitrate to nitrite by bacteria, which typically requires approximately 4 hours of incubation within the bladder. [19,20] A positive nitrite test reflects the presence of gram-negative bacteria such as E. coli. A positive test is extremely specific, but not sensitive for UTI. [20,21]

Over 10,000 bacteria/mL urine is required to result in a positive nitrite test. Unfortunately, nitrite dipstick reagent strips are sensitive to air. After one week of exposure to air, up to 1/3 of strips provide a false positive result, which increases to 3/4 at two weeks. [22] Hematuria is defined by the presence of at least 3 RBCs/hpf on urinalysis. [3,4,23-25] Hemoglobin itself is typically poorly filtered, and the presence of hemoglobin in the urine occurs once haptoglobin is fully saturated and proximal reabsorption capacity is exceeded. On the other hand, myoglobin is smaller and not protein-bound. Urine dipsticks can also detect the presence of whole and lysed red blood cells through peroxidase activity.

Myoglobin and hemoglobin both catalyze this reaction (thus the positive test in rhabdomyolysis). A positive dipstick result may be due to trauma, infection, inflammation, calculi, neoplasm, clotting disorder, burns, cold, eclampsia, sick cell crisis, transfusion reaction, exercise, and infarction. Diets with high vitamin C can result in false negative results for hematuria, as vitamin C affects peroxidase activity. [3,4]

Glucose is typically filtered in the glomerulus and reabsorbed in the proximal tubule. However, glycosuria can occur when the filtered glucose exceeds the tubules ability to reabsorb (serum levels 180-200 mg/dL), seen in diabetes, Cushing's disease, liver disease, and several congenital/metabolic conditions. [3,4] Another cause is failure to resorb urinary glucose in the proximal tubule.

Ketones result from incomplete fat metabolism, accumulate in the serum, and are then excreted in the urine. Low carbohydrate diets, starvation, diabetes, alcoholism, hyperthyroidism, and eclampsia can result in increased urinary ketones. Other causes include insulin, isoniazid, and isopropyl alcohol overdose. Most labs use the nitroprusside test for detection of ketones, which is more sensitive to acetoacetic acid, rather than beta-hydroxybutyric acid (the predominant ketone in DKA). [3]

Bilirubin is not normally found in urine. Unconjugated bilirubin is not filtered, as it is not water soluble; however, conjugated bilirubin is water soluble. Its presence in urine is suggestive of liver or biliary dysfunction. Urobilinogen is present in small amounts in urine. This is the end product of bilirubin metabolism. Hemolysis and liver disease can increase urine urobilinogen amounts, while bile duct obstruction and specific antibiotics may decrease it."

2) What may cause false positive and false negative results for leukocytes, nitrites, ketones, and blood?

Table 1

Urine Component	False Positive	False Negative
Leukocytes	Contamination, trichomonas, drugs/foods coloring urine red, low urine specific gravity (increases cell lysis)	Recent antibiotic therapy, glycosuria, proteinuria, elevated urine specific gravity (impedes cell lysis), low bacteria urine count, high vitamin C, oxidizing drugs (cephalexin, nitrofurantoin, gentamicin, tetracycline)
Nitrites	Contamination, dipstick exposure to air, phenazopyridine	Drugs/foods coloring urine red, elevated urine specific gravity, high urobilinogen, pH < 6, high vitamin C, specific bacteria (S. saprophyticus, Pseudomonas, Acinetobacter, and enterococci (at least most))
Protein	Alkaline/concentrated urine, phenazopyridine	Acidic/dilute urine, protein that is not albumin (Bence Jones in multiple myeloma)
Blood	Dehydration, exercise, menstrual blood, myoglobinuria	Captopril, acidic urine, high vitamin C, elevated urine specific gravity
Glucose	Ketones, levodopa, bleach, hydrogen peroxide	Elevated urine specific gravity, uric acid, high vitamin C
Ketones	Acidic urine, elevated urine specific gravity, several drug metabolites, heavily pigmented urine	Delayed urine analysis, predominance of beta-hydroxybutyric acid

3) What is the relationship between squamous cells and contamination?

"Classically, a "good" urine sample contains less than 5 squamous epithelial cells (SECs)/low-power field (lpf). [18,19] Recommendations have previously been to obtain a repeat sample for samples with > 5 SECs/lpf. However, SECs are poor markers of urine culture contamination. [33] One study evaluated a quantitative threshold of SECs. [33] In that study, samples with fewer than 8 SECs/lpf demonstrated greater ability to predict bacteriuria on urinalysis (+LR 4.98), but SECs did not accurately identify contaminated urine. [33]

Samples with the absence of pyuria and nitrites perform similarly no matter the SEC count in the specimen. For culture, no threshold of SECs predicts contamination. [33]"

4) Does cloudy, smelly urine = UTI?

"Unfortunately, urine color, clarity, and odor cannot be used to diagnose UTI.19 One study found a 13% sensitivity for urine transparency to diagnose UTI. [35] As discussed, cloudy urine has a variety of causes and is common with crystals and purine-rich food. Foul-smelling odor cannot be used in spontaneously voiding or catheterized patients to diagnose UTI, and urine odor is primarily dependent on the patient's urea concentration in the urine and hydration status. [36,37]"

5) Does +LE and/or WBC diagnose UTI? What is the differential for sterile pyuria?

"Urinalysis with positive LE alone should not be used for diagnosis of UTI. [19] Positive LE demonstrates sensitivity 80-90% and specificity 95-98% for pyuria. [8,18,33] WBC counts of 6-10 cells/mL may be due to dehydration, and patients with oliguria or anuria also commonly have pyuria. [3,8,19] Many conditions can result in sterile pyuria, including contamination, interstitial nephritis, nephrolithiasis, tumor, interstitial cystitis, intraabdominal pathology, and presence of an atypical organism.

Overtreatment occurs in up to 44% of patients if WBC count alone is used with cutoff of 3 WBC/hpf. [8] True symptomatic UTI is associated with a significant number of WBCs in the urine (> 10/microL). [19] Hematuria can cause a false positive result for urine WBCs. Leukocytes and WBCs may be present in urine due to other conditions such as appendicitis, diverticulitis, sexually transmitted infection, and renal injury. False negatives can occur in neutropenic/leukopenic patients. [3,4] Rather than relying on UA alone, diagnosis should be based on patient symptoms."

6) Is a positive nitrite diagnostic of UTI?

"Positive urinalysis for nitrites possesses high specificity for gram-negative bacteriuria. [3,4] However, urine nitrites in isolation are not diagnostic of UTI. [19] Symptoms of UTI in association with positive nitrite are diagnostic of UTI. On the other hand, nitrite testing may be negative with insufficient urine dwell time in the bladder or infection with organisms unable to convert nitrate to nitrite. [3,4] In this setting, other components of the dipstick should be used in conjunction with symptoms of UTI for diagnosis.

Negative LE and nitrite can rule out UTI in uncomplicated and complicated patients with a sensitivity approaching 94%, and a patient with urinary symptoms and negative LE and nitrite should undergo evaluation for other causes of symptoms. [38] Positive LE and nitrite together display a sensitivity for bacteriuria of 48% and specificity of 93% in nursing home patients. [39] Specificity approaches 100% in other populations. [9]"

7) Is a urinary pregnancy test Pt states: my urine preg test is always negative, but the blood proves I'm pregnant

"Pregnancy testing can be completed on serum or urine samples. Urine testing is typically qualitative, though this is less sensitive than serum testing (which can be quantitative or quantitative). [40,41] While serum pregnancy tests can detect hCG levels of 5-10 milli-int. units/mL, and high sensitive quantitative serum tests are positive at 1-2 milli-int. units/mL, urine qualitative tests are not far behind, with positive results at 20-50 milli-int. units/mL – and these assessments are accurate and reliable with current assays. [40-42]

Importantly, other urine factors such as specific gravity have not been shown to affect qualitative urine testing for pregnancy, even with specimens diluted fivefold. [42-44] False negatives can occur in the setting of early

pregnancy in which the hCG is below the threshold of detection, or a hook effect, where a very high hCG is present and affects test reagents. [42,45]"

8) Who needs a urine culture?

"Urine testing and assessment in the ED is a part of every shift. While urine cultures can provide important information for some patients, the majority of UTIs do not require cultures. These cultures provide little to no utility in the ED for routine UTIs. Literature demonstrates 80-95% of UTIs are due to E. coli.(1-6) In the setting of infection due to S. saprophyticus, enterococci, or group B streptococci, the typical antimicrobials used provide adequate treatment.

On a routine basis, cultures do not affect patient outcomes and do not change management (1-4). So when should you obtain a urine culture? Urine cultures are recommended for patients with complicated infection (basically anyone with a UTI who is not a nonpregnant, reproductive-aged adult female), pyelonephritis,those on recent antibiotic therapy, or those with continued symptoms who have failed antibiotics (1-3). UTI in a patient with simple UTI does not require urine culture. Let's save the time of physicians everywhere and not order cultures unless they are specifically indicated."

9) When should you treat asymptomatic bacteriuria?

"The elderly patient with pyuria, bacteriuria, and UTI symptoms is straightforward. However, what happens when symptoms are not present? Bacteria in the urine without symptoms of UTI defines asymptomatic bacteriuria (ASB), specifically in women with two consecutive clean-catch voided specimens consisting of one organismin > 105 cfu/mL and in men with one specimen and the same organism count.(2,7) This finding does not definitively diagnose UTI, and ASB rates increase with age.(7-9) One study found 5% of sexually active young women to have ASB.(10) Rates of ASB approach 25-50% of women and 15-49% of men without indwelling catheters.(11) These rates increase in the elderly due to altered elimination, anatomical variations of the urogenital tract, poor hygiene, hormonal changes, and neurologic impairment.(7)

Many of these organismsare not harmful but rather commensal organisms.(9) Asymptomatic UTI in the elderly patient is less common than ASB,(12) and ASB is not associated with poor long term outcomes including pyelonephritis, sepsis, and renal failure.(13) Clinical signs and symptoms of UTI are needed for treatment, but many patients are not able to provide these.(9) Emergency physicians regularly evaluate older patients unable to provide history and exam. A study released in 2014 from JAMA recommended treatment for patients if they demonstrated bacteriuria and pyuria with two of the following: fever, worsening urinary frequency or urgency, acute dysuria, suprapubic tenderness, or costovertebral angle tenderness.(14) Another possible formula to differentiate UTI and bacteriuria is the following: pyuria + bacteriuria + nitrites = infection; bacteriuria but no pyuria = colonization/bacteriuria; pyuria alone but no bacteria = inflammation.(15)

Patients undergoing instrumentation or surgery of the bladder may require antibiotics in the setting of bacteriuria alone.(16) Treating patients without true UTI can increase antimicrobial resistance, as well as expose patients to dangerous side effects and diseases such as C. difficile colitis.(7,17,18) In fact, antibiotics are used inappropriately in close to half of patients with ASB.(19) However, educational programs and knowledge of ASB can effectively reduce inappropriate treatment.(19)"

10) Elderly patients with recurrent falls or AMS… is a UTI responsible?

"Altered mental status, "the dwindles," or recurrent falls in an elderly patient has a large differential.(9) The history and exam are often unrevealing, thus resulting in a fishing expedition with a net of tests. If UTI is a contributor, systemic signs or symptoms should be present, along with evidence of UTI such as dysuria.(20) In patients with clinical suspicion of UTI without a catheter, acute change in mental status was associated with bacteriuria and pyuria.(21)

However, several studies suggest falls without signs or symptoms of UTI are not associated with pyuria or bacteriuria.(22,23) It's challenging to evaluate a patient with chronic dementia and falls or a patient who is altered and can't provide a history of urinary symptoms. An exam evaluating for suprapubic or CVA tenderness in conjunction with UA canbe helpful, as UA with positive nitrites, pyuria, and bacteriuria is suggestive of UTI.(9,15) In patients for which history and exam are unreliable but exhibit no other explanation for AMS, one study recommends using bacteriuria with other markers of systemic inflammation including fever/hypothermia, elevated WBC/CRP, elevated blood glucose in absence of diabetes, and acutely altered mental status to diagnose UTI and begin treatment.(24) If a urine dipstick demonstrates negative LE and no nitrites, then UTI is not present.(24) Other causes of altered mental status (remember AEIOU TIPS) must be excluded before chalking altered mental status to UTI. If the patient meets criteria for sepsis or displays marker of inflammation and UA is consistent with UTI, then treatment is warranted.(9,24)"

11) How does a urinary stent impact urinalysis testing and the diagnosis of UTI?

"Urinary stents consist of an indwelling, hollow, endoluminal splint within the ureter to facilitate urine drainage from the kidney to the bladder.(25-27) Several indications include benign or malignant obstruction, urolithiasis therapy, perioperative management, and urinary leak.(25-27) These stents are associated with several complications, most commonly irritative symptoms in up to 80-90% of patients.(25,26)

Suprapubic pain is also common, as is hematuria. Complications include UTI, stent migration, encrustation, stent fracture, ureteral erosion/fistulization, incontinence, vesicorenal reflux, and inadequate relief of obstruction.(25-27)

UTI develops as a result of instrumentation or later as an underlying disease process, and organisms causing the infection are associated with development of a biofilm. Newer coatings and stent materials may reduce the risk ofinfection.(25,26) For patients with systemic findings of UTI or symptoms consistent with UTI in the setting of evidence on urinalysis/dipstick (pyuria, positive nitrites, positive LE), antibiotics are likely warranted. The patient should be discussed with urology as well."

12) How do you interpret urinalysis in a catheterized patient, and how do you diagnose UTI?

"Patients with indwelling catheters often present to the ED with catheter-associated issues. Unfortunately, catheter-associated UTI (CA-UTI) is one of the most common nosocomial infections, defined by signs or symptoms of UTI with > 103 colony forming units/mL from a single catheter specimen or midstream voided specimen, andthe catheter must have been in place > 2 days.(32-36) Close to 100% of patients with indwelling Foley catheter are colonized by 2-5 organisms within 2 weeks (77% polymicrobial) of catheter placement.(9,32-34) The rate of bacteriuria from urinary catheter is close to 10% per day, and of these,10-25% of patients develop symptoms of UTI.(20,33-36)

CAUTI is also associated with significant risk of bacteremia.Close to 20% of hospital-acquired bacteremia comes from the urinary tract with mortality approaching 10%.(32,34,37) The presence of a urinary catheter is also a predisposing factor to septic shock with UTI,(38-41) and a greater number of patient comorbidities increases the risk of septic shock in patients with indwelling catheter.(42)

UTI in the setting of a catheter occurs with greater frequency in females, older patients, diabetes, bacteria colonization in the drainage bag, and errors in care of the catheter.(32,43-45) UTI can be extraluminal (66%) or intraluminal (34%), with extraluminal occurring from bacteria entry into the bladder from the catheter biofilm and intraluminal occurring due to urinary stasis or contamination of the collection bag.(20,46-50) Signs and symptoms of CA-UTI include new or worsening fevers, rigors, altered mental status, malaise, lethargy, flank pain, CVA tenderness, new hematuria,and pelvic discomfort.(9,32) Fever is the most common symptom. Pyuria is not

diagnostic, but the absence of pyuria strongly suggests a diagnosis other than CA-UTI.(9,32,51) If LE and nitrites are absent with < 10 WBCs/hpf, CA-UTI
can be excluded.(51)

Treatment is a little more complex than your run-of-the-mill UTI. The IDSA recommends obtaining a urine culture before treatment.(32) If the catheter has been in place for over two weeks at the time of the UTI and the catheter is needed, then the catheter should be replaced and urine obtained from the new catheter before antibiotics are provided.(9,32) Patients with signs and symptoms of UTI including fever and suprapubic pain or tenderness should be treated by removal of the catheter, if possible, and antibiotics.

Unfortunately due to the catheter, dysuria is not reliable alone for diagnosis of UTI. Overtreatment can result in selection of more resistant bacteria, and prophylactic therapy is not recommended for patients with long term catheters (more than 2 weeks).(9,32,51-54) Candiduria is also common in patients with catheters, most commonly due to colonization.(9,32,55) Treatment with antifungals is only needed in
specific situations including signs of infection and no other source of infection.(32,55) If the patient is immunocompromised (transplant patient or those receiving chronic steroids), candiduria should be treated with antifungals. Otherwise, conservative management with catheter exchange and observation is recommended.(52)”