

Urine Sediment Examination in the Diagnosis and Management of Kidney Disease: Core Curriculum 2019

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Automated urine technology and centralized laboratory testing are becoming the standard for providing urinalysis data to clinicians, including nephrologists. This trend has had the unintended consequence of making examination of urine sediment by nephrologists a relatively rare event. In addition, the nephrology community appears to have lost interest in and forgotten the utility of provider-performed urine microscopy. However, it is critical to remember that urine sediment examination remains a time-honored test that provides a wealth of information about the patient's underlying kidney disease. This test performs very favorably as a urinary "biomarker" for a number of acute kidney diseases. When used properly, urine sediment findings alert health care providers to the presence of kidney disease, while also providing diagnostic information that often identifies the compartment of kidney injury. Urine sediment findings may also guide therapy and assist in prognostication. In this review of the role of urine sediment examination in the diagnosis and management of kidney disease, we seek to help experienced nephrologists maintain their competency in performing this test and encourage ongoing training of nephrology fellows and others less experienced in such analyses.

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The Role of Urine Sediment Analysis

When the patient dies the kidneys may go to the pathologist, but while he lives the urine is ours. It can provide us day by day, month by month, and year by year with a serial story of the major events within the kidney.

Dr. Thomas Addis (1881-1949)

Urine microscopy with examination of urine sediment is becoming a lost art for nephrologists. It seems to have fallen out of favor in recent decades as automated urine technology and centralized laboratory testing have become more widespread. While nephrologists continue to search for tests for more accurate identification and diagnosis of kidney disease, it is not yet time to abandon use of the reliable and time-tested examination of spun urine sediment. We have forgotten that this test is an excellent "biomarker" of kidney disease when used by a properly trained clinician.

Microscopic examination of spun urine sediment performed by an experienced nephrologist is an important tool for diagnosing and managing a number of conditions affecting the kidneys. It is an important adjunctive test in the evaluation of patients with acute and chronic kidney disease when used in concert with history and physical examination, directed serum tests, dipstick urinalysis, and genitourinary imaging. Urine sediment is especially helpful in assessing patients with acute kidney injury (AKI), as

well as those with proteinuria, hematuria, and leukocyturia identified on dipstick urinalysis.

Proficient microscopic examination of urinary sediment may provide important information that is not typically available when automated urinalysis and/or laboratory technician-performed urine examination data are used. Importantly, accurately observing urinary cell morphology, identifying cellular and noncellular casts, and recognizing various endogenous and drug-related crystals can enable rapid diagnosis of the acute or chronic kidney disease. Based on the information garnered from this bedside test, urine sediment provides a window into the kidneys such that it has been viewed as the noninvasive "liquid biopsy."

Although urine microscopy provides critical information in patients with kidney disease, clinicians also need to be cognizant of the limitations of this test. As discussed, urine sediment can sometimes be bland despite the presence of various intrinsic kidney diseases such as acute interstitial nephritis (AIN), proliferative lupus glomerulonephritis, and acute tubular injury/necrosis. In addition, cells and crystals observed in urine may not always be reflective of the underlying cause of kidney disease. Notable examples are the presence of uric acid, calcium oxalate, and drug-related crystals in urine of asymptomatic patients. As such, we would like to emphasize that the clinician's knowledge of clinical

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

context allows him or her to develop a pretest probability for a likely diagnosis to which the urine dipstick and sediment findings are applied. This allows the clinician, knowledgeable of the limitations of urine microscopy, to develop a probable diagnosis using the urinary data obtained, giving less weight to findings that are likely unrelated to the underlying kidney disease.

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Automated Versus Manual Urinalysis

Fully automated microscopic platforms have expanded in laboratory medicine. Diagnostic screening of urine samples is the third most common analysis performed by clinical laboratories and thus the balance of economic constraints and diagnostic accuracy is highly relevant. In an effort to standardize laboratory testing, in the United States, the Clinical Laboratory Improvement Amendments act mandated that only certified personnel perform urinalysis. As expected, the increased use of automated systems for the sake of cost and efficiency decreased reliance on manual microscopy. In automated systems, digitized images of urine sediment are generated for computer and technician-based analysis. Commonly used devices include IRIS iQ200, Sysmex UF-1000i, Cobas u701, and SediMax, which allow for rapid analysis of pathologic urine specimens.

There are clear economic advantages to centralized rapid analysis. According to one UK survey, 32% of laboratories needed fewer staff with automated systems, and increasingly fewer skilled technicians assume the responsibility for analyzing urine. Labor costs can account for up to 70% of the cost per test, coupled with relatively prolonged time to report a manual microscopic analysis (2.7 minutes per test) versus automated systems (20 seconds per test), which greatly improves turnover time.

The iQ200 system uses laminar flow technology, in which the digital imaging software identifies cells and particles in uncentrifuged urine. Hundreds of images are captured using a digital camera and characterized based on shape, contrast, and texture of the particle. The Cobas u701 system uses cuvettes and centrifuges the sample, and in 30 seconds, then captures 15 images and classifies them into various categories, including hyaline casts, pathologic casts,

crystals, and nonsquamous epithelial cells. The operator is also able to view the images and reclassify the specimen.

A small single-center study of 25 patients with a clinical diagnosis of acute tubular necrosis (ATN) compared the iQ200 automated system to manual microscopy for identification of pathologic casts. The iQ200 system was insensitive to ATN and failed to recognize a significant number of pathologic granular casts. Granular casts were identified in 24% of samples using the iQ200 system versus 72% ($P < 0.001$) of samples analyzed by a nephrologist with manual microscopy. Agreement between the methods occurred in only 40% of samples, which may be due in part to lack of centrifuged urine for automated analysis.

A small single-center study of 26 patients evaluated the accuracy of a laboratory and medical technologist interpretation of microscopy versus a nephrologist's interpretation of urine sediment. A significantly greater number of renal tubular epithelial cells (RTECs), granular casts, and dysmorphic red blood cells (RBCs) were seen by the nephrologist's use of manual urine microscopy. Even when blinded to the clinical history, the nephrologist performing urine microscopy made the correct diagnosis >90% of the time as compared to only 19% when a second nephrologist used the automated urinalysis and laboratory-based microscopy report.

Two Cobas 6500 and Iris IQ200 systems were compared with manual urine microscopy performed by laboratory technicians, who were considered as the gold standard for the study. Using the Cobas 6500 system, diagnostic sensitivity and specificity for white blood cells (WBCs) were 93% and 87%, respectively, and 82% and 81%, respectively for RBCs. Whereas the IQ200 system had similar sensitivity for WBCs (92%) and RBCs (90%), the system was less specific for WBCs (71%) and RBCs (63%). Automated systems showed good correlation for erythrocytes ($r = 0.87$; $P = 0.001$) and leukocytes ($r = 0.92$; $P = 0.001$); however, there was no correlation for pathologic nonepithelial cells ($r = 0.16$; $P = 0.049$) and very poor correlation for crystals ($r = 0.46$; $P = 0.001$). The authors concluded that automated systems were inadequate to identify and classify sediment particles such as casts and crystals in highly pathologic samples. In a test of the Cobas 6500 system and UX-2000 analyzer compared with manual microscopy in 258 urine specimens, sensitivity and specificity for pathologic casts were 39.2% and 98.1%, respectively, for the Cobas 6500 system and 45.1% and 93.7%, respectively, for the UX-200 system.

Although automated urinalysis systems with a certified central laboratory performing microscopy are time saving, standardized, and cost-effective, they are not reliable to diagnose various kidney diseases such as ATN, glomerulonephritis, vasculitis, or crystalline-related kidney disease. As such, clinicians should not depend on laboratory-reported urinalysis for clinical decision making in patients with kidney disease.

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Manual Urine Microscopy

Diagnosis of AKI is dependent on gathering an accurate history, changes in hemodynamics, medication exposure, urinary output and fluid balance, serum creatinine level trends, and urinalysis. Examination of urine sediment is inexpensive and relatively timely, but somewhat more labor intensive because in most centers, a skilled nephrologist must collect and analyze a fresh urine sample within 2 hours of collection. However, this test offers a great deal of information beyond what is yielded solely by automated urinalysis.

ATN is one of the most common causes of hospital-acquired AKI and the clinical differentiation of prerenal AKI and ATN can often be challenging. However, the distinction is crucial because therapies and outcomes are often dramatically different. The accuracy of a history of volume depletion or hypotension, urine volume, and fractional excretion of sodium/urea results are sometimes unreliable to differentiate prerenal AKI and ATN. It has previously been shown that manual urine microscopy conducted with a urinary sediment scoring system is highly predictive of final diagnosis and capable of differentiating the clinical entities. A 2008 study used a urine sediment scoring system in 231 patients with hospital-acquired AKI due to either ATN or prerenal AKI diagnosed. A score ≥ 2 (1-5 granular casts/low-power field [LPF] or RTECs/high-power field [HPF]) along with a premicroscopy diagnosis of ATN carried a positive predictive value of 100% for final diagnosis of ATN. Conversely, a premicroscopy diagnosis of prerenal AKI with a score of 1 (absence of RTECs or granular casts on microscopy) carried a negative predictive value of 91%. With use of manual microscopy, 23% of patients with premicroscopic diagnosis of prerenal AKI were subsequently changed to a diagnosis of ATN, and 14%, from ATN to prerenal AKI. A limitation of this study is observer bias because the microscopists were not blinded to initial diagnostic impression. Final diagnosis was not based on kidney biopsy but on various clinical parameters

such as kidney function response to fluids and other maneuvers.

The urine microscopy scoring system not only carries diagnostic utility, but also maintains prognostic value for relevant clinical outcomes. In a study of 197 patients with AKI who were stratified by AKI Network (AKIN) staging with a modified RTEC/granular cast-based scoring system, higher urine sediment scores were shown to have higher dose-dependent relative risk for worsening AKI (higher AKIN stage, dialysis therapy, or death), with an adjusted relative risk of 7.3 (95% confidence interval, 3.8-9.6) for urine sediment score ≥ 3 versus 0.

In a pilot study of 30 patients, a simplified granular cast scoring index was used to evaluate renal outcomes in patients with a clinical diagnosis of ATN. Of the 18 patients with ATN for whom urinary sediment was assessed for outcomes, 61.1% did not recover kidney function and the mean cast scoring index was 2.2. Patients without renal recovery had a higher cast scoring index as compared with patients who recovered kidney function (2.55 ± 0.93 vs 1.57 ± 0.79 ; $P = 0.04$). Receiver operating characteristic area under the curve for the cast scoring index to diagnose lack of renal recovery was 0.79.

These studies suggest that examination of spun urine sediment is valuable for both diagnosis and prognosis in patients with hospital-acquired AKI, for which automated urinalysis would likely fall short. Although most microscopes are not equipped with integrated cameras to capture the images of manual microscopy, the current era has made it possible to take high-quality point-of-care urine images with cell phone cameras that can be uploaded into the electronic health record in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner. Provider-performed microscopy certification is required to use images in the medical record.

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Performing Urine Sediment Analysis

Manual urine microscopy should be carried out in a standardized fashion to allow reliable results to be interpreted for clinical patient care and used in the study setting. Fresh urine samples should be examined after

spontaneous voiding when possible, whereas urine collection in patients with indwelling bladder catheters should be from the tube to avoid old urine that has been sitting in the bag. To avoid cell and cast degradation, urine should be examined within 1 to 2 hours of collection or quickly refrigerated to allow viewing over the next 8 hours. Urine should be inspected for color, clarity, and turbidity before centrifugation. Abnormal urine colors will point to potential endogenous (pigmenturia, lipids, etc) or exogenous (drugs, foods, etc) processes.

Ten milliliters of urine is centrifuged for at least 5 minutes with at least 1,500 rpm to maximize yield. After removal by suction of 9.5 mL of supernatant urine (or carefully decanting the urine), gentle manual agitation of the test tubes or gentle suction and expulsion of the sediment by pipette is performed, and a single drop of urine sediment is placed on a standardized glass slide and cover slipped. The sediment field is examined at low (original magnification $\times 10$) and high power (original magnification $\times 40$) using brightfield or phase contrast microscopy with a minimum of 10 fields (20 fields optimal) observed under each power. Urine dipstick findings, in particular pH and osmolality, should also be noted at the time of analysis because erythrocyte and leukocyte size and shape can change depending on osmotic forces. For example, RBCs can shrink and become crenated with high osmolality or swell with low osmolality. Leukocytes can similarly shrink or swell and make proper identification difficult. In addition, cast survival time is pH dependent and they may degrade more quickly with alkaline pH. The cover slip edges tend to accumulate more casts and should be included as a part of the sediment field examination.

Urine Sediment Examination by Kidney Syndrome

Urine sediment is analyzed for various formed elements, which include but are not limited to cells, casts, and crystals. Erythrocytes are small and anucleate and may be isomorphic or dysmorphic. Three separate leukocytes can be found in urine. Neutrophils are round and granular, with a multilobed nucleus. Eosinophils have a bilobar nucleus and granules that occupy the cytoplasm. Rarely seen lymphocytes are smaller cells with a large nucleus better identified using special staining. RTECs are round to oval with a large central nucleus. Casts are cylindrical elements formed in the distal tubules and collecting ducts, they may be acellular, contain granular or waxy material, or contain various cell types (erythrocytes, leukocytes, and RTECs). Crystal formation is a marker of urine supersaturation of substances produced in metabolic and inherited diseases or with drug exposure. Crystal formation is often pH dependent, information that facilitates accurate crystal characterization. Crystal color, morphology, and birefringence under polarization

should be noted. [Table 1](#) describes the most common urine sediment and dipstick findings seen in various kidney syndromes.

Case: A 73-year-old woman with history of hypertension, coronary artery disease, diastolic heart failure, chronic obstructive pulmonary disease, gout, and stage 3a chronic kidney disease was admitted to the intensive care unit with community-acquired bilobar pneumonia complicated by hypotension and acute respiratory failure requiring biPAP. She was treated empirically with intravenous ceftriaxone and azithromycin and received fluid resuscitation with 4 L of normal saline solution and low-dose norepinephrine for blood pressure support. Blood cultures grew *Streptococcus pneumoniae* and azithromycin treatment was discontinued. Examination revealed right middle and lower lung crackles with consolidative changes. There were no skin rash, petechiae, or purpura. Serum creatinine level initially increased from a baseline of 1.3 mg/dL to 1.9 mg/dL over the next 3 days, stabilized at this level for the next 4 days, and then increased to 2.7 mg/dL on day 9, increasing further to 4.1 mg/dL on day 10. Renal ultrasound revealed bilateral 10-cm kidneys without hydronephrosis. Automated urinalysis showed specific gravity of 1.012, pH of 5.5, protein (1+), blood (1+), and leukocyte esterase (1+) and gave negative results for nitrite, glucose, and urobilinogen. Urine chemistries revealed fractional excretion of sodium of 2.3% and fractional excretion of urea of 55%, while urine eosinophils (based on Hansel stain) were $<1\%$. The nephrology team examined the spun urine sediment, which showed 3 to 8 isomorphic RBCs/HPF, 10 to 15 WBCs/HPF, 10 to 15 RTECs/HPF, 2 to 4 granular casts/LPF, 0 to 1 WBC cast/HPF ([Fig 1A](#)), and numerous uric acid crystals ([Fig 1B](#)).

Question 1: Using the clinical data and urine studies, what is the most likely cause of the increase in serum creatinine level to 4.1 mg/dL?

- a) Acute tubular injury/necrosis
- b) Acute infectious glomerulonephritis
- c) AIN
- d) Acute uric acid nephropathy

For answer, see the following text.

The patient underwent kidney biopsy, which revealed inflammatory cells consisting of lymphocytes, plasma cells, and eosinophils diffusely within the interstitium along with tubulitis, consistent with AIN. In this case, urine sediment had RBCs, WBCs, granular casts, a rare WBC cast, and uric acid crystals potentially suggesting a glomerular (RBCs), tubular (RTECs and granular casts), or interstitial (WBCs and WBC casts) disease. Uric acid crystals raised the possibility of crystalline-related AKI. However, urine sediment findings need to be interpreted in the context of the case. AIN is an inflammatory lesion that injures tubular epithelium, and not uncommonly, RBCs, WBCs/WBC casts, RTECs, and granular casts may be seen. Thus, as discussed in the following sections, the correct answer is (c), AIN.

Table 1. Urine Sediment and Associated Kidney Injury Syndromes

Kidney Lesion/Syndrome	Urine Sediment	Urine Dipstick
Prerenal azotemia	Bland, hyaline casts, few finely granular casts, occasional RTECs	-/+ protein
Acute tubular injury	RTECs, RTEC casts, coarse granular casts, "muddy brown" casts	-/+ protein
Acute interstitial nephritis	WBCs, WBC casts, RTECs, RTEC casts, RBCs, occasional RBC casts	-/+ protein, +/+++ LE, +/+++ blood
Nephritic syndrome	Dysmorphic RBCs (acanthocytes), isomorphic RBCs, WBCs, RBC casts, WBC casts	+/+++ protein, ++/++++ blood
Nephrotic syndrome	Lipid droplets, oval fat bodies, birefringent Maltese cross, lipid laden casts, cholesterol crystals	+++ /++++ protein
Crystalline nephropathy	Various endogenous or drug-related crystals, RTECs, RBCs, WBCs, some WBCs engulfing crystals	-/+ blood, -/+ LE
Osmotic nephropathy	Swollen RTECs with cytoplasmic vacuoles, RTEC/granular casts	-/+ protein

Abbreviations: LE, leukocyte esterase; RBCs, red blood cells; RTECs, renal tubular epithelial cells; WBCs, white blood cells.

Acute Kidney Injury

Overview

Although prerenal AKI is a fairly common cause of AKI in hospitalized patients, tubular injury by an ischemic, toxic, or combined insult is also a common cause of AKI in this setting. As such, examination of urine sediment for various cell types and casts is useful in diagnosing the cause of AKI in the hospitalized patient. A purely prerenal cause of AKI often results in urinary sediment that is bland or characterized by hyaline casts. A small number of RTECs may also

be present. Ischemic and/or toxic acute tubular injury leading to AKI is classically defined by the presence of cells and casts indicative of tubular injury and necrosis. Numerous RTECs may be seen alone or with casts. Leukocytes and RBCs may be present but may be the result of another cause, such as infection/stone or a concomitant lesion elsewhere in the glomerulus or interstitium. RTEC casts may be seen along with RTECs and suggest a relatively recent tubular injury. Fine or coarse granular casts may be seen alone or with RTECs and indicate significant tubular injury. In addition, the higher the number of

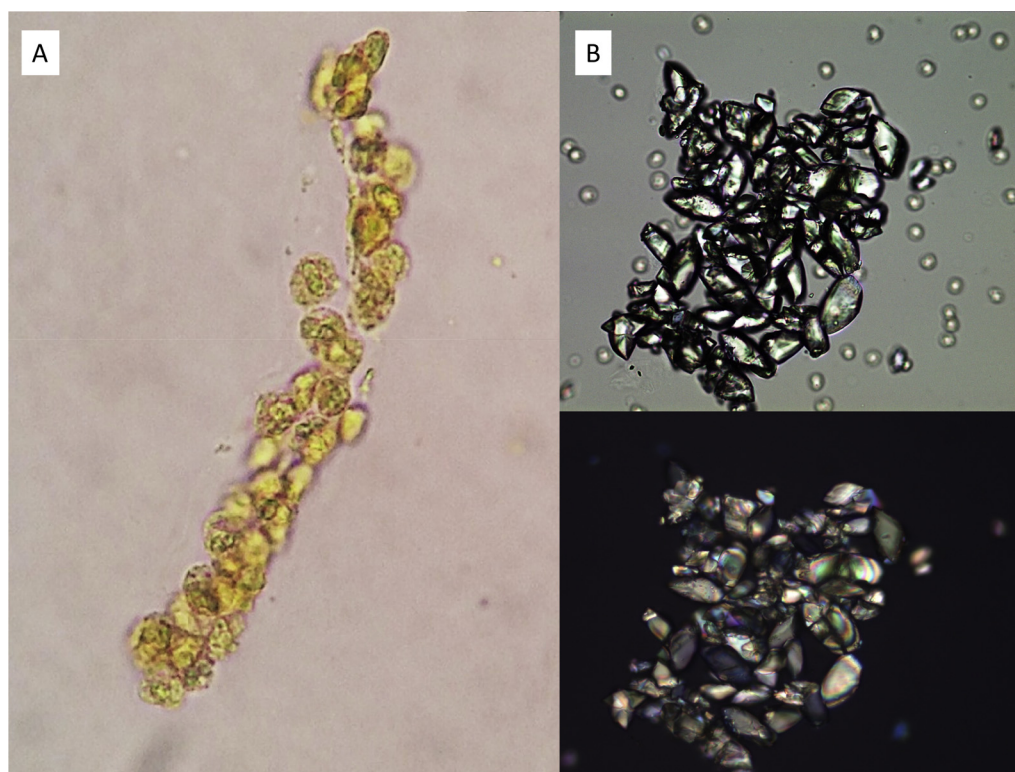


Figure 1. Urine sediment shows (A) white blood cell cast and (B) uric acid crystals (lower panel: polychromatic appearance under polarization). (A) Reproduced with permission from Perazella MA. The urine sediment as a biomarker of kidney disease. *Am J Kidney Dis.* 2015;66(5):748-755.

RTECs/HPF and RTEC casts or granular casts/LPF, the more severe the AKI and likelihood of progression to a higher AKIN stage, need for dialysis therapy, or death.

RTECs and Casts

Tubular cells in the various nephron segments have different morphology and when shed into urine, they will have varied shapes, profiles, nuclei, and organelle abundance. The finding of RTECs and casts in sediment reflects that they have undergone necroptosis from ischemic and/or toxic injury. Identifying these cells in urinary sediment using conventional brightfield microscopic analysis without staining can sometimes be challenging for the novice and untrained eye. Urinary RTECs (Fig 2A) can be round, oval, polygonal, or columnar and typically have a high nucleolar to cell diameter ratio (mean nuclear diameter, $7.7 \pm 1.1 \mu\text{m}$, with cell diameter of $13.2 \pm 2.2 \mu\text{m}$) compared with superficial transitional uroepithelial cells (mean nuclear diameter, $10.1 \pm 1 \mu\text{m}$, with cell diameter of $31.2 \pm 9 \mu\text{m}$). A size comparison can be made to a neighboring erythrocyte, which is typically half the diameter of an RTEC ($\sim 6 \mu\text{m}$). It can be difficult to differentiate round RTECs from deep uroepithelial cells, which have similar cell diameter and nucleolar size ratios. However, the company that cells keep is important. For example, if renal parenchymal elements such as RTEC casts (Fig 2B) or granular casts are also present or the patient has proteinuria and an increasing serum creatinine level, these cells are likely RTECs rather than uroepithelium. The absence of elements makes the cells more likely uroepithelium, but this approach is not perfect. With more severe tubular injury, the number of RTECs and casts and/or granular casts observed on sediment examination increase.

Granular Casts

In general, the presence of urinary casts suggests some form of acute or chronic kidney injury or disease. Casts are cylindrical and can be acellular (hyaline, proteinaceous, or granular) or contain various cell types reflective of the type of kidney injury (RBCs, WBCs, RTECs, crystals, lipids, or micro-organisms). Casts may be short or long and thin or wide depending on the diameter and length of the nephron segment in which they were formed. All casts are composed of a backbone of uromodulin. As a result, all casts begin to form in the loop of Henle and further develop in the distal tubular lumens. Granular casts, which may be fine, coarse, or mixed (hyaline-granular cast), generally reflect tubular injury. These casts may be composed of degraded cell lysosomes (seen as granules on electron microscopy) admixed with ultrafiltered serum proteins or particles from degenerated RTECs admixed with uromodulin. When granular casts are dense and brownish/burnt umber, they are called “muddy brown casts” (Fig 3). When hospitalized patients with AKI have large numbers of these casts, they are thought to be

pathognomonic for severe ATN. However, the presence of granular casts does not always confirm a diagnosis of ATN because they can be seen with AIN, thrombotic microangiopathy, and other kidney lesions.

Hyaline Casts

Prerenal AKI from true or effective volume depletion is generally not associated with tubular injury/necrosis. In this setting, urine sediment is usually bland with no/few cells and casts. Hyaline casts (Fig 4) are composed primarily of uromodulin produced by loop of Henle cells and may be seen when the decline in renal perfusion leads to sluggish urinary flow. Hyaline casts may also be seen with exercise, indicating the presence of dehydration. Sometimes severe renal hypoperfusion can induce “patchy” tubular injury, which can coexist with prerenal physiology creating a hybrid form of AKI. Clinically, the patient may have a partial response to treatment of the prerenal process while urine sediment shows hyaline casts along with few scattered RTECs and hyaline-granular casts. In this case, correcting the prerenal parameters while also supporting the underlying ATN is pursued.

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Case, continued: Ceftriaxone was considered the most likely drug responsible for AIN and was switched to levofloxacin to finish the course of therapy. Kidney function continued to worsen, with serum creatinine level increasing to 6.5 mg/dL 3 days after ceftriaxone treatment discontinuation. Prednisone, 60 mg, daily was administered and during the next 8 days, serum creatinine level improved, declining to 1.5 mg/dL.

Question 2: Which of the following urinary findings is specific for AIN?

- a) Urine eosinophils > 1% using Hansel stain
- b) WBC casts on urine sediment examination
- c) Numerous urinary WBCs with negative urine culture
- d) None of the options are specific for acute interstitial nephritis

For answer, see the following text.

Acute Interstitial Nephritis

None of the listed urinary findings in the question are specific for AIN (thus, the answer is “d”). A clinical diagnosis of AIN is notoriously difficult to make and kidney biopsy is often required. Biopsy-proven AIN occurs in

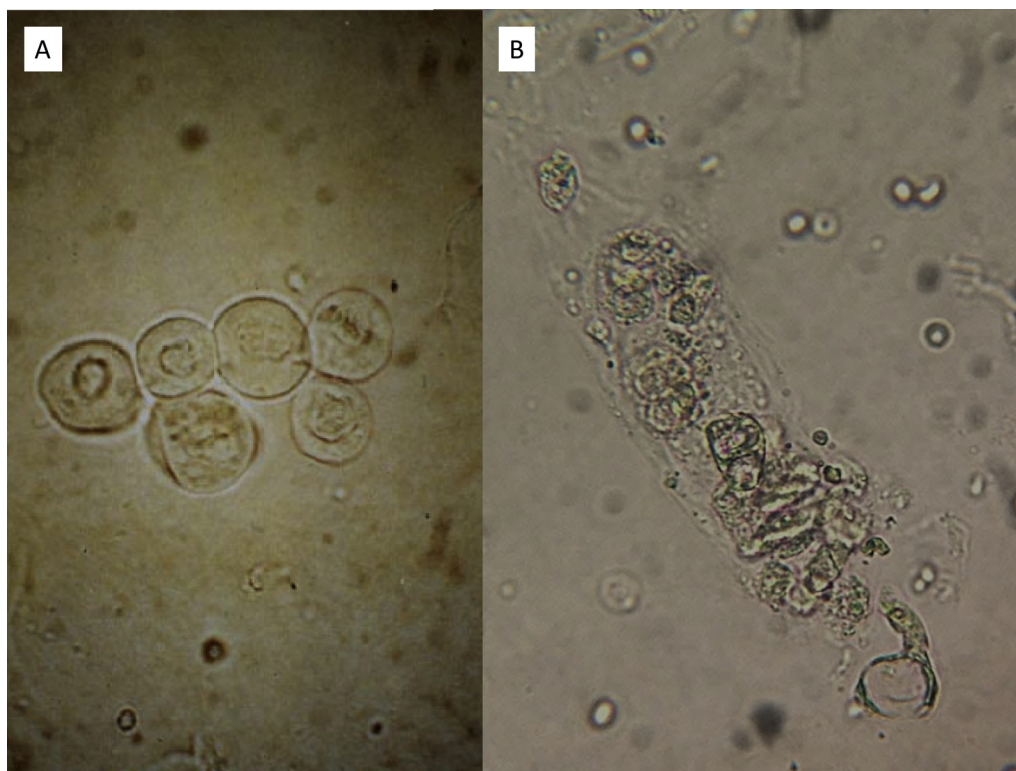


Figure 2. Urine sediment shows (A) renal tubular epithelial cells (RTECs) with a single nucleus and (B) RTEC cast, with multiple RTECs within the cast matrix.

approximately 10% to 15% of hospital-acquired AKI and appears to be increasing, likely reflecting ever-increasing drug exposure, which accounts for >70% of AIN. AIN on biopsy is characterized by an inflammatory cell infiltrate consisting of lymphocytes, plasma cells, eosinophils, and polymorphonuclear cells, along with interstitial edema with tubulitis and varying degrees of interstitial fibrosis. It seems logical that urinalysis with urine sediment examination would reflect the biopsy findings observed with AIN: WBCs, eosinophiluria, and WBC casts. However, this is not always the case with AIN. A retrospective study of biopsy-proven AIN noted that leukocyte esterase was positive in >80% of patients; however, a case series of biopsy-proven AIN observed WBCs in only 57% of manual urine microscopy examinations. The published literature shows a wide variation in leukocyturia (average of ~70%, with a range of 20%-80%). Hematuria is also seen in ~50% of AIN cases, with a similar wide range.

Eosinophiluria, a widely touted test used to evaluate AIN, has recently been debunked. The Mayo Clinic published a large series of patients with various kidney diseases on biopsy who also underwent urine eosinophil testing. Using both >1% and >5% as thresholds for positive results, eosinophiluria failed to separate AIN from other kidney diseases such as ATN, proliferative glomerulonephritis, diabetic nephropathy, and cast nephropathy. This is particularly problematic when one considers that hospital-acquired AKI often has many of these in the differential diagnosis.

In regard to WBC casts, the data are even weaker. In a case series of biopsy-proven AIN, only 14% of patients (3/21) had WBC casts, making these casts a very insensitive test for AIN. That is also our clinical experience. It may be that these casts break down or clump together, making their identification in sediment limited. Interestingly, >90% had other casts (RTEC, hyaline, granular, or hyaline granular) and 28.5% (6/21) had RBC casts. Notably, none

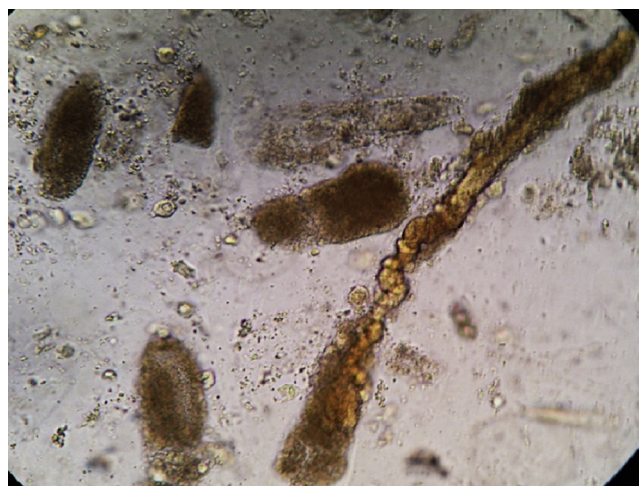


Figure 3. Granular or muddy brown casts of various widths and lengths are seen in a patient with acute kidney injury due to septic shock.



Figure 4. A hyaline cast is noted in a patient with acute kidney injury in the setting of decompensated heart failure.

of the 21 biopsy specimens had evidence of glomerular disease on light, immunofluorescence, or electron microscopy to explain the RBC casts. In addition, WBC casts are not highly specific because other inflammatory kidney lesions (proliferative glomerulonephritis and acute papillary necrosis) may have them. However, their presence should raise the clinician's suspicion for AIN and likely prompt kidney biopsy.

In our experience, urine sediment in AIN often contains RTECs, granular casts, and WBCs (with negative urine culture results). This likely reflects tubular injury/tubulitis from the inflammatory interstitial process. WBC casts are rare, but when present are highly suggestive of AIN in the absence of acute/chronic pyelonephritis. However, dysmorphic RBCs and RBC casts along with pyuria or WBC casts pushes the diagnosis toward proliferative glomerulonephritis.

Leukocytes and WBC Casts

Drug-induced AIN is often included in the differential diagnosis of hospital-acquired AKI because patients are exposed to numerous potential offending agents. In most cases, the only clue to AIN is an increase in serum creatinine level and abnormalities in urine. Urinalysis may show low-grade proteinuria with positive blood and leukocyte esterase in the setting of a negative urine culture result. Urinary sediment may reveal a variety of cellular elements, including WBCs (Fig S1), RBCs, and RTECs. Urinary casts may also be present; RTEC, granular, and WBC casts have all been described. Leukocyte casts can be very difficult to distinguish from RTEC casts. Closely examining cellular structure (single vs multilobed nucleus) and size (RTEC larger than WBC) often allows one to make the correct call. In general, neutrophils are the most common WBC in urine (urinary infection) but can also be seen with inflammatory kidney lesions. They are about 10 to 15 μm in diameter (larger than RBCs [$\sim 6 \mu\text{m}$] and smaller than RTECs [$\sim 15\text{--}30 \mu\text{m}$]) and have a multilobed

nucleus. They can sometimes be difficult to identify in dilute or concentrated urine because the cell swells and shrinks and distorts the nuclei. Moreover, in alkaline urine and with delayed viewing, the cells can degenerate, making differentiation of nucleus from cytoplasmic granules difficult and challenging to distinguish from RTECs. In addition, leukocytes can form blebs, which to the untrained eye can be mistaken for dysmorphic RBCs. For these same reasons, WBC casts (Fig 1A) can also be difficult to distinguish from RTEC casts.

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Nephritic and Nephrotic Sediment

Nephritic syndrome is defined by hematuria with active urine sediment, proteinuria, hypertension, and decreased glomerular filtration rate (GFR). Proliferative glomerulonephritis, small-vessel vasculitis, and anti-glomerular basement membrane (anti-GBM) disease are common causes of nephritic syndrome and when severe are termed rapidly progressive glomerulonephritis. The nephritic sediment is characterized by a large number of erythrocytes and RBC casts. One of the hallmarks of glomerular bleeding is dysmorphic RBCs, including acanthocytes, or G1 cells. Dysmorphic RBCs and acanthocytes are fairly specific for glomerular injury, but lack sensitivity because isomorphic RBCs are often seen with glomerulonephritis. Dysmorphic RBCs making up $>5\%$ of total RBCs support glomerular bleeding. One study demonstrated 12.4% acanthocytes in biopsy-proven glomerular disease. Patients with proliferative lupus nephritis (classes III or IV \pm V) were reported to show a higher median number of acanthocytes and erythrocytes compared to pure lupus membranous nephritis. The optimal threshold for acanthocytes, $3.34 \times 10^4/\text{mL}$, yielded sensitivity of 85%, specificity of 67%, positive predictive value of 82%, and negative predictive value of 71% for detecting proliferative lupus nephritis while also correlating with lupus activity ($r = 0.62$; $P = 0.0001$). In our experience, sterile pyuria and/or WBC casts in patients with dysmorphic RBCs and/or RBC casts suggests a proliferative glomerulonephritis (lupus, vasculitis, membranoproliferative glomerulonephritis, etc) versus a nonproliferative glomerular disease (immunoglobulin A [IgA] nephropathy, thin basement membrane disease, etc). Along the same lines, mixed cellular (WBCs/RBCs) casts reflect proliferative glomerulonephritis.

In addition to diagnosis, monitoring urine for hematuria, dysmorphic RBCs, and RBC casts is useful for surveillance of patients with known glomerular disease

(glomerulonephritis and small-vessel vasculitis) to gauge response to therapy and recurrence of disease. To this point, persistent hematuria has been found to be associated with increased likelihood of antineutrophil cytoplasmic antibody vasculitis relapse. In addition, progression of IgA nephropathy has been reported to be associated with persistently high time-averaged hematuria (end-stage kidney disease: 30% vs 10.6%; estimated GFR reduction of 50%: 27% vs 15.2%). Unfortunately, these findings were based solely on dipstick hematuria and it would have been interesting to see how dysmorphic RBCs and RBC casts would have fared in predicting progression.

In contrast to nephritic syndrome, nephrotic syndrome is defined by edema, hypoalbuminemia, high-grade proteinuria (protein excretion ≥ 3.5 g/d), and hypercholesterolemia. In general, patients with nephrotic syndrome have relatively bland (acellular) urine sediments. Glomerular lesions are typically nonproliferative on histopathology and characterized by a leaky GBM. Common causes include the podocytopathies (minimum change disease and focal segmental glomerulosclerosis) and membranous nephropathy. Examination of urine sediment may demonstrate findings that support nephrotic syndrome, such as lipiduria and lipid casts. Mixed syndromes, such as diseases associated with nephritic/nephrotic findings, will have urinary features of both syndromes.

Erythrocytes and RBC Casts

Glomerular hemorrhage bespeaks various forms of glomerular injury and disease. Urinalysis and urine sediment examination are excellent tests to indicate new or ongoing glomerular injury. Most experts believe that phase contrast microscopy is superior to brightfield microscopy in visualizing urinary RBC morphology. Improved identification of RBC morphology with brightfield microscopy can be achieved with lowering the condenser lens. Isomorphic RBCs (Fig S2) are $\sim 6 \mu\text{m}$ and appear as erythrocytes observed on a peripheral-blood smear. However, isomorphic RBCs are not specific to glomerular disease and can be seen with a number of extraglomerular (AIN and renal cell carcinoma) and extrarenal processes (nephrolithiasis, urologic cancers, urinary tract infections, excessive anticoagulation, etc). RBCs and RBC casts can also appear after vigorous exercise. Dysmorphic RBCs including acanthocytes (Fig 5A), also known as G1 cells, tend to be more specific for glomerular injury, but are an insensitive test. Dysmorphic RBCs may have many different shapes, with a ring shape and single or multiple blebs or protrusions. Due to loss of membrane, these cells are typically smaller ($\sim 3 \mu\text{m}$) than isomorphic RBCs. The process underlying the formation of dysmorphic RBCs is not definitely known, but it is likely a consequence of multiple injuries experienced by RBCs as they pass through gaps in an injured GBM and are then exposed to a hostile tubular environment (osmotic changes and acidic urine). It can be challenging to differentiate acanthocytes from

dysmorphic non-G1 cells or pseudo-G1 cells (echinocytes, stomatocytes, schistocytes, sickled cells, poikilocytes, etc). There are no defined morphologic criteria for G1 cells, but they will have membranous blebs, a doughnut shape with target configuration, and fragmented cell contours. Isomorphic erythrocytes can become crenated in concentrated urine, and it is important to recognize that these cells are not dysmorphic RBCs. Another urinary RBC is the ghost cell, which is an RBC with low hemoglobin content and has a low refractile index. This cell carries no specific meaning to suggest underlying pathology.

In the vast majority of cases, erythrocyte casts (Fig 5B) represent glomerular injury. RBCs that pass through GBM gaps admix with uromodulin produced in the loop of Henle and from casts that are excreted into urine. As with dysmorphic RBCs, erythrocyte casts are specific for glomerular injury but are difficult to find and often not present, making them an insensitive test. As noted, RBC casts have been described with AIN, but this is not likely a common finding. In addition, WBC casts may also be seen with inflammatory glomerular lesions. Thus, the presence of hematuria, low-grade proteinuria, and WBC casts may indicate either glomerulonephritis or AIN. In this circumstance, kidney biopsy is warranted.

Lipiduria and Lipid casts

High-grade or nephrotic proteinuria is part of the definition of nephrotic syndrome. Dipstick urinalysis generally gives negative results except for proteinuria (3+ or 4+). Urine sediment, in contrast, may contain a number of findings in this setting. Free lipid droplets, oval fat bodies, lipid casts, and cholesterol crystals may be observed. Circular fat droplets containing cholesterol esters will produce birefringent Maltese crosses under polarized light. Oval fat bodies are either macrophages or RTECs that are engorged with fat droplets that these cells have endocytosed. Free lipid droplets, cholesterol crystals, and/or oval fat bodies can be embedded in a cast matrix, forming a lipid or “fatty” cast (Fig S3).

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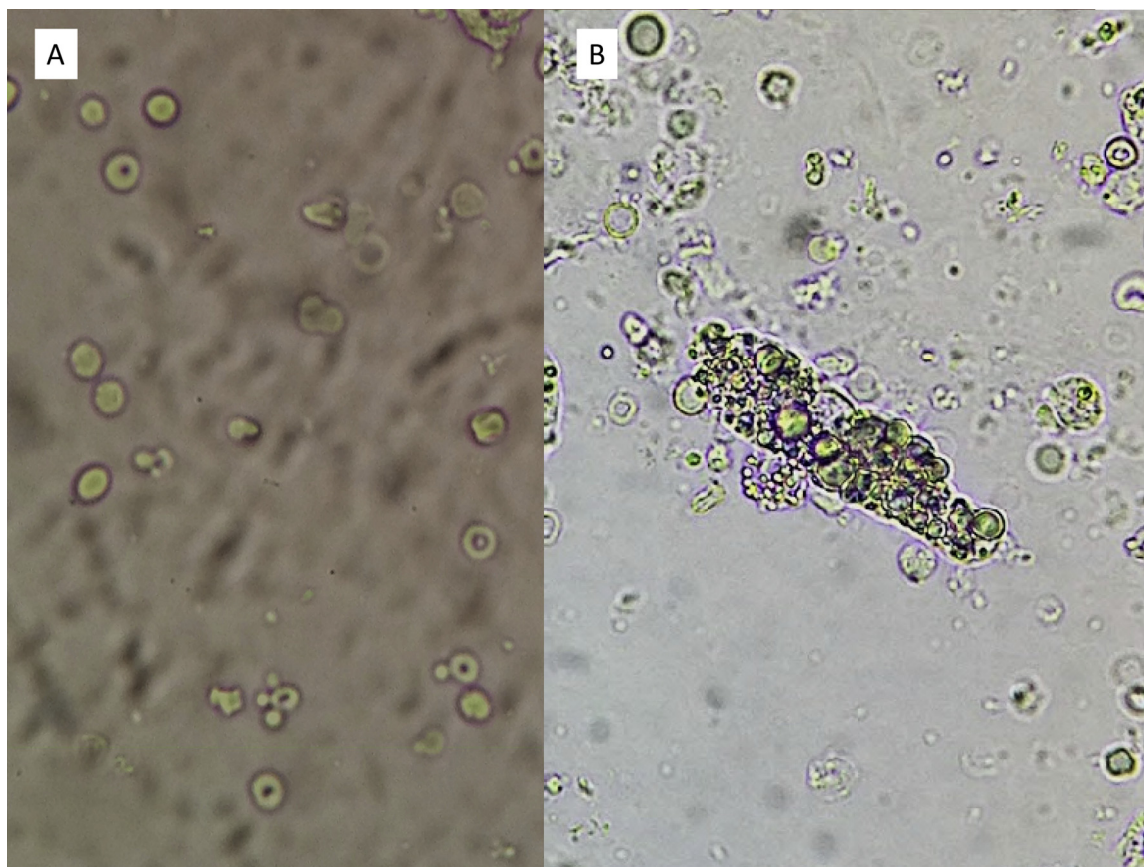


Figure 5. Urine sediment of a patient with infection-related glomerulonephritis reveals (A) dysmorphic red blood cells (RBCs), including acanthocytes and isomorphic RBCs, and (B) RBC cast.

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Crystalluria

Overview

Various crystals may be seen in urine sediment. Fogazzi notes that crystals are present in 8% of specimens examined in his laboratory. They may be nonpathologic or may be the cause of kidney disease (nephrolithiasis, AKI, etc) resulting from endogenous crystal production or exogenous drug exposure. Crystal formation with crystalluria can be secondary to inherited diseases, metabolic disorders, and drug exposure. It is important to view the sediment without excessive delay (>2 hours) because incidental precipitation of some compounds (uric acid) will occur even in urine from healthy patients if it is left to stand. Sediment examination for crystals starts with brightfield or phase contrast microscopy under low and high powers to observe crystal appearance followed by polarization to determine birefringence and help identify crystals. For example, uric acid, monohydrated calcium

oxalate, calcium phosphate, and triple phosphate crystals are 100% birefringent. In addition to these maneuvers, it is important to note pH because certain crystals tend to form in acid or alkaline pH (Table 2).

Crystalluria may appear in bland urine sediment or be associated with concomitant hematuria and leukocyturia due to the abrasive effect of crystals on renal parenchyma and uroepithelium. As noted, not all crystalluria is pathologic. However, active urine sediment, nephrolithiasis, and AKI strongly raise the possibility of pathologic crystals. In this setting, the underlying clinical and laboratory data suggestive of inherited or metabolic diseases associated with crystalluria and thorough review of the medication list will help in identifying whether crystalluria is pathologic and the cause of crystalline nephropathy and/or nephrolithiasis. A few select endogenous crystals and drug-related crystals are discussed next.

Select Endogenous Crystals

Calcium Oxalate

Calcium oxalate crystals can be found in urine pH values ranging from <5.5 to 6.7 but are seen mostly with pH < 5.8. There are 2 main types of crystals; monohydrated and dihydrated calcium oxalate. Monohydrated

Table 2. Description of Common Urine Crystals

	Morphology	pH Range	Birefringence
Endogenous			
Calcium oxalate	Monohydrated: colorless ovoid, dumbbells, rods Dihydrated: colorless bipyramidal	5.4-6.7 5.4-6.7	Strong (mono) Weak (di)
Calcium phosphate	Prisms, sticks, needles, stars, rosettes in isolation or in aggregates	6.7-7.0	Strong
Triple phosphate	Trapezoids, prisms, feather-like, "coffin lids"	6.2-7.0	Strong
Uric acid	Amber with variety of shapes: rhomboids, barrels, rosettes, needles, 6-sided plates	5.4-5.8	Strong polychromatic
Cystine	Colorless hexagonal plates with irregular sides	5.5	Weak
Leucine	Yellow-brown spheres with concentric striations	5.5-6.5	Maltese cross
2,8-Dihydroxyadenine	Reddish-brown round with central spicules and dark outline	5.5-7.0	Maltese cross
Tyrosine	Colorless to yellow thin needles in bundles or rosettes	5.5-6.5	Strong
Cholesterol	Thin plates with well-defined edges	5.5	Negative
Ammonium biurate	Yellow-brown spheres with spicules, thorn apples	5.5-7.0	Strong
Calcium carbonate	Dumbbells, thick rods, 4-leaf clover	7.0	Strong
Bilirubin crystals	Yellow needle-like crystals, attach to cell surfaces	5.5	Weak
Drug-Related			
Sulfadiazine	Amber as shocks or sheaves of wheat, shells	5.5	Strong
Acyclovir	Thin needles with sharp or blunt ends	5.5-7.0	Strong
Atazanavir	Thin needles in isolation or as aggregates	6.0-7.0	Strong
Methotrexate	Yellow-brown	5.4-6.0	Strong
Vitamin C (calcium oxalate)	Same as for monohydrated calcium oxalate	5.4-6.7	Strong
Triamterene	Brown and other colors (green/orange/red); spheres	5.5	Maltese cross
Ciprofloxacin	Colorless needles, stars, fans, sheaves	>7.0	Strong
Amoxicillin	Colorless thin needles, broom/brush-like	5.5-6.5	Strong

crystals (Fig 6A) are colorless; can be ovoid, biconvex, dumbbells, and rods; and are strongly birefringent. In contrast, dihydrated crystals (Fig 6B) appear as bipyramidal colorless crystals of varied size and typically are not birefringent. Generally, only one type of calcium oxalate crystal is present in urine, but occasionally both may be seen. Calcium oxalate crystalluria does not always represent disease and may be seen in healthy individuals, especially those ingesting foods containing high oxalate content (chocolate, rhubarb, almonds, and spinach). Calcium oxalate nephrolithiasis is the most common stone type and is due to altered metabolism favoring calcium oxalate crystallization and stone growth. Primary and secondary hyperoxaluria also lead to crystalline nephropathy and nephrolithiasis. Enteric hyperoxaluria can develop from various gastric bypass surgeries (Roux-en-Y) or other causes of malabsorption (orlistat, pancreatitis, etc). Exogenous causes of oxalate nephropathy include drugs that are metabolized to calcium oxalate, including megadose intravenous doses of vitamin C, ethylene glycol, and nifedipine. Monohydrated calcium oxalate crystals may be seen with ethylene glycol toxicity. In addition, some foods/drinks containing large amounts of oxalate,

such as star fruit, and green smoothie cleansing may cause acute oxalate nephropathy. The clinical context must be considered with calcium oxalate crystalluria, remembering that their presence are not always pathologic.

Uric Acid

Uric acid crystals (Fig 1A) are invariably found in acidic urine and come in a wide array of sizes and shapes, which include rhomboids, barrels, rosettes, plates, and needles. They often are amber and have strong polychromatic birefringence with polarization, which helps distinguish uric acid crystals from other crystals. The presence of uric acid crystals in urine does not confirm the diagnosis of uric acid nephropathy: they may occur in samples from healthy patients, especially when urine sits around or is refrigerated before examination. Uric acid crystalluria may be observed in those with uric acid nephrolithiasis and patients with rhabdomyolysis or lymphoproliferative disorders complicated by tumor lysis syndrome. The presence of uric acid crystal casts strongly suggests crystalline nephropathy as the cause of AKI. It is important to remember that the diagnosis of uric acid as the cause of disease depends on the clinical context in which the crystals are seen.

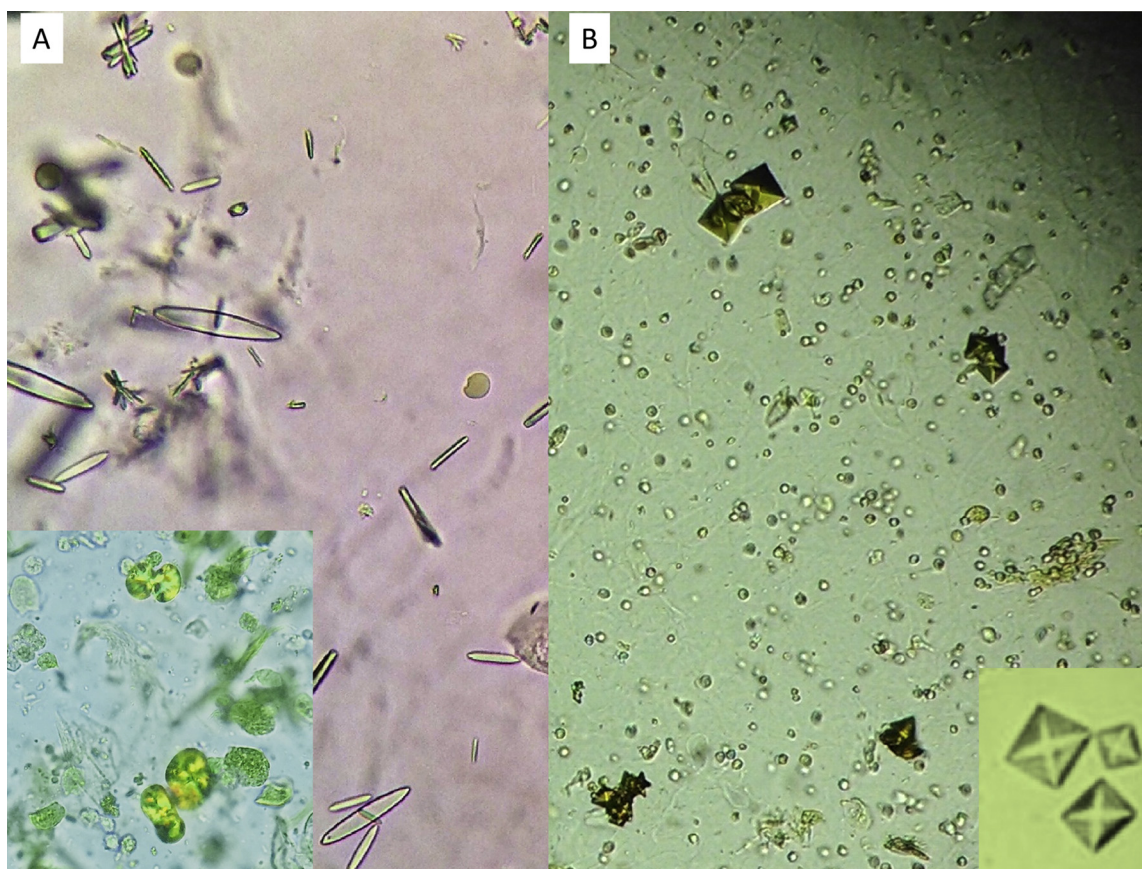


Figure 6. Crystals of: (A) calcium oxalate monohydrate and (B) calcium oxalate dihydrate. The former are biconvex rods or sticks but may also appear as dumbbells (inset), while the latter are bipyramidal and look like “envelopes” (particularly visible in the inset).

Amorphous urates within urine may be found in urine from healthy individuals and less commonly in pathologic conditions.

Calcium Phosphate and Triple Phosphate

As with calcium oxalate crystals, calcium phosphate crystals may be seen in urine from healthy individuals and stone formers. They are seen in alkaline urine and manifest as a wide spectrum of shapes, including prisms, rosettes, stars, needles, or sticks/rods. The crystals are strongly birefringent and may be seen with amorphous phosphates, which appear more like uric acid crystals, but are not birefringent. Calcium phosphate crystals have been rarely seen with phosphate nephropathy following oral sodium phosphate purgative for bowel cleansing.

Triple phosphate crystals are composed of magnesium ammonium phosphate and are found in alkaline urine. One of the most common shapes is a “coffin lid,” with other forms including elongated prisms, trapezoids, and feather-like structures. Birefringence can be weak or strong under polarized microscopy. These crystals are not seen in urine from healthy individuals and typically occur in urine infected

with urease-producing microorganisms such as *Ureaplasma urealyticum* and *Corynebacterium urealyticum*. These crystals should prompt a search for infection with a urea-splitting organism.

Cystine

Cystine crystals are observed only in patients with cystinuria, a recessive inherited disease due to deficient renal tubular absorption of cystine and other dibasic amino acids leading to nephrolithiasis. The crystals, which are colorless hexagonal plates (Fig S4) with weak birefringence, form in acidic urine. They can be seen alone or heaped onto one another.

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Select Drug Crystals

Sulfonamides

Sulfadiazine is the most common sulfonamide associated with crystalluria and crystalline nephropathy. The drug is rapidly excreted by the kidneys and is insoluble in acidic urine. Sulfadiazine crystals (Fig 7) appear as shocks or sheaves of wheat or shells with an amber color and radial striations and are strongly birefringent. Other sulfonamides, such as sulfamethoxazole, sulfasalazine, and acetazolamide, may also cause crystalluria, albeit less commonly. The crystals may be seen alone or with RBCs and leukocytes. Asymptomatic crystalluria, crystalline nephropathy, and nephrolithiasis can occur with sulfadiazine. Large intravenous doses (4-6 g/d of sulfadiazine or 50-100 mg/kg/d of sulfamethoxazole), volume depletion, acidic urine, and underlying acute or chronic kidney disease increase the risk for crystalline nephropathy. Intravenous fluids and urinary alkalization prevent or reduce this adverse effect. Calculi containing N-acetyl-sulfadiazine suggests that rapid N-acetylation decreased sulfonamide solubility.

Atazanavir

Atazanavir is a protease inhibitor commonly used in antiretroviral regimens for the treatment of human immunodeficiency virus (HIV) infection. Like its forerunner

indinavir, atazanavir also causes crystalluria, nephrolithiasis, crystalline nephropathy, and acute and chronic interstitial nephritis. The drug is extensively metabolized by the liver and undergoes predominantly biliary excretion, with 7% excreted by the kidneys. It is maximally soluble at pH of 1.9, and risk for crystal precipitation and calculi formation increases as pH becomes more alkaline. Other risk factors for crystalline nephropathy and nephrolithiasis include prolonged duration of therapy (~2-3 years), ritonavir boosting, previous nephrolithiasis with indinavir, and elevated bilirubin levels. Atazanavir crystals are needle shaped and mildly birefringent, whereas calculi are radiolucent and typically beige to yellow. Biopsy-proven crystalline nephropathy and AIN secondary to atazanavir have been shown in a number of case reports.

Ciprofloxacin

Ciprofloxacin is a widely used antibiotic described in case reports to cause AIN and crystalline nephropathy. Ciprofloxacin crystals can have varied morphologies, including needles, sheaves, stars, fans, butterflies, and other unusual shapes. Crystals are typically colorless or brownish and are strongly birefringent. Large intravenous doses, older age, underlying kidney disease, and alkaline urine increase risk

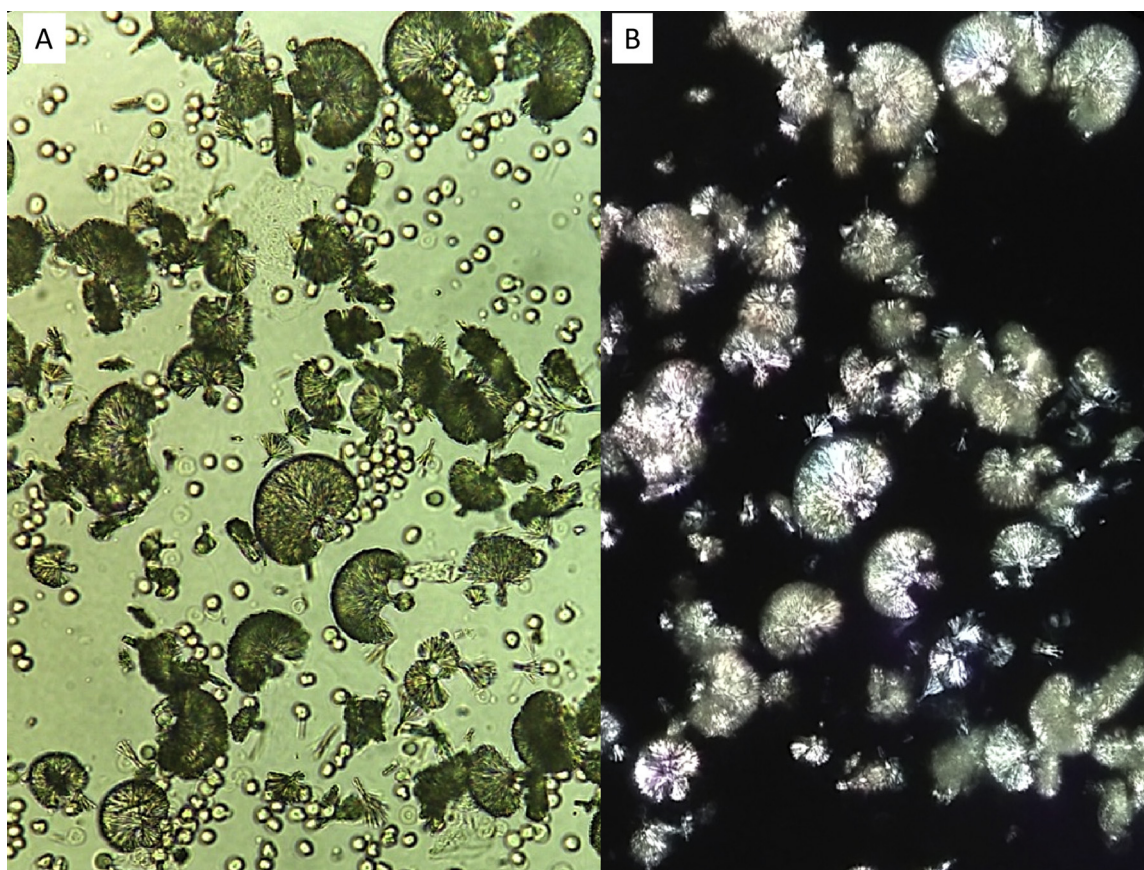


Figure 7. Urine sediment examination of a patient receiving intravenous sulfadiazine who developed acute kidney injury on day 4 of therapy reveals (A) sulfadiazine crystals that are (B) strongly birefringent with polarization.

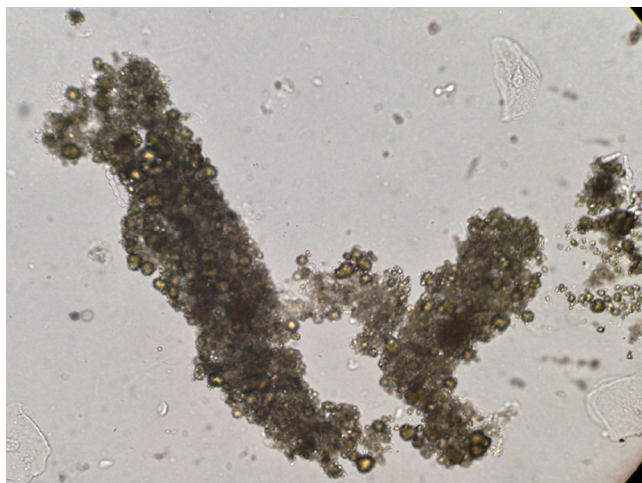


Figure 8. Methotrexate crystals are seen in urine sediment of a patient who developed acute kidney injury following therapy with high-dose intravenous methotrexate.

for crystal precipitation, although crystalline-induced AKI has occurred with standard doses and physiologic urine pH.

Acyclovir

Acyclovir is a common antiviral agent and can cause crystalline-induced AKI in some patients. The prodrug valacyclovir is a rare cause of crystalline nephropathy. The drug is rapidly excreted into urine by both tubular secretion and glomerular filtration, reaching high tubular concentrations in the distal nephron. This enhances risk for intratubular crystal precipitation. Risk factors for AKI include high doses ($>1,500$ mg/m²/d), bolus intravenous administration, pre-existing kidney disease, and volume depletion. Acyclovir crystals are needle shaped (Fig S5), birefringent, and accompanied by leukocytes, which may engulf the crystals. Prevention of AKI is aimed at reducing drug concentration in the tubular lumen by establishing urinary output of 100 to 150 mL/h, avoiding rapid infusions, and large doses.

Methotrexate

Methotrexate is an antimetabolite commonly prescribed in high doses in patients with various malignancies. Methotrexate and its metabolite 7-hydroxy-methotrexate are excreted predominantly in urine. Due to the limited solubility of drug and metabolites in acidic urine, intratubular precipitation of these substances can lead to AKI from crystalline nephropathy. The substances are 6- to 8-fold more soluble when urine pH is increased from 6.0 to 7.0. Intravenous fluids and urinary alkalization are used to prevent/reduce crystal precipitation and AKI. Urine microscopy can sometimes reveal compact or needle-shaped golden-brown crystals arranged in annular structures, free or within casts (Fig 8). The crystals are strongly birefringent. The presence of methotrexate crystals in urine of a patient with AKI following methotrexate therapy is diagnostic for crystalline nephropathy.

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Conclusions

Microscopic urine sediment examination is a fundamental diagnostic tool for the practicing nephrologist. It is superior to automated urinalysis in the diagnosis of AKI and often guides further diagnostic and therapeutic interventions. It is also a valuable tool in prognosticating outcomes in AKI and can clue the nephrologist in on impending need for dialysis therapy. In an era in which cost, efficiency, and quality are of increasing importance, it is surprising that physician-performed urine microscopy has become de-emphasized. We believe that urine microscopy offers a glimpse in real time into the anatomy and pathophysiology of kidney injury. It may also generate interest in our subspecialty and inspire future nephrologists. Use of modern technology such as smart phones, electronic health records, and social media may allow urine sediment to spark renewed interest in one of the oldest and most reliable diagnostic tests.

Supplementary Material

Figure S1: WBCs (with negative urine culture) are seen in the urine of a patient with AIN.

Figure S2: Isomorphic RBCs along with crenated RBC forms are observed in a patient with high urine specific gravity.

Figure S3: A lipid casts is seen under (A) phase contrast microscopy in a patient with nephrotic syndrome; (B) polarization shows strong birefringence with Maltese cross forms within the cast.

Figure S4: Cystine crystals in a patient with multiple kidney stones confirm a likely diagnosis of the inherited disorder cystinuria.

Figure S5: Urine sediment of a patient with AKI following intravenous acyclovir shows (A) acyclovir crystals that are (B) strongly birefringent with polarization.

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