EDUCATIONAL COMMENTARY – URINARY CRYSTALS

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**Florida licensees, please note: This exercise is NOT intended to fulfill your state education for microscopy.

Learning Objectives

On completion of this exercise, the participant should be able to

- explain how the storage of urine can affect the formation of urinary crystals;
- identify types of urinary crystals;
- name crystals that can be found in a normal urine sample but also can indicate a pathologic condition;
- associate disease states that can produce urinary crystals; and
- how to differentiate crystals caused by x-ray contrast media from other urinary crystals

History of Urine Microscopy

Urinalysis is one of the oldest diagnostic tools. Although early physicians lacked microscopic examination, certain conditions such as diabetes, and possibly mental illness, could be diagnosed by physical observation. Physical properties such as taste (sweet indicates diabetes) and color (King George III had red-brown urine, indicating porphyria) were used. With the invention of the microscope, urine sediments, such as cells, microorganisms, and crystals, could be observed to aid in the diagnosis of disease. When physicians order a urinalysis with microscopy, the laboratorian’s ability to identify different urinary crystals is a vital part of the examination.

Crystal Formation

Most crystals are not present in freshly voided urine samples. Urine can be supersaturated with a crystalline compound that is soluble when the sample is freshly voided. Crystals may precipitate out of the sample owing to changes in the solubility of the crystal when the urine sample is allowed to cool at room temperature or when refrigerated. Changes in pH resulting from bacterial growth can also influence the formation of crystals.
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Types of Crystals

While urinary crystals can be divided into pathogenic and nonpathogenic, some of the nonpathogenic crystals can also indicate disease. For example, the presence of uric acid, triple phosphate, and calcium oxalate crystals can be considered normal, but they can also indicate a pathological process. The kidney maintains the acid/base balance in the blood by the secretion of hydrogen ions. The more hydrogen ions secreted, the lower the pH of the urine. Normal urine pH can range from 4.5 to 8.0. Urine is considered acidic when the pH is equal to or less than 6. Urine is considered alkaline when the pH is greater than 8.0. Crystals can be found in acid, neutral (pH, 6.5-7.5), and alkaline urine samples. To aid in identification, it is useful to categorize crystals as found in acid or alkaline urine (Table).

Table. pH of Normal and Abnormal Urinary Crystals

<table>
<thead>
<tr>
<th>Normal Crystals</th>
<th>pH</th>
<th>Abnormal Crystal</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium oxalate</td>
<td>Acid/Neutral</td>
<td>Bilirubin</td>
<td>Acid</td>
</tr>
<tr>
<td>Hippuric</td>
<td>Acid</td>
<td>Cholesterol</td>
<td>Acid</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>Alkaline</td>
<td>Leucine</td>
<td>Acid</td>
</tr>
<tr>
<td>Triple phosphate</td>
<td>Alkaline</td>
<td>Tyrosine</td>
<td>Acid</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Alkaline</td>
<td>Cystine</td>
<td>Acid</td>
</tr>
<tr>
<td>Ammonium biurate</td>
<td>Acid</td>
<td>Sulfonamide</td>
<td>Acid</td>
</tr>
<tr>
<td>Amorphous phosphates/urate</td>
<td>Alkaline/Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>Acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pathogenic Crystals

Uric Acid Crystals

Uric acid crystals are found in acid urine and form upon standing at room temperature for several hours. The crystals are usually amber and have various shapes, such as rhomboid plate, cubes, and barrels (Figure 1).
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Uric acid crystals, although usually considered normal, can also be considered abnormal. They can be found in the urine of individuals taking certain medications such as diuretics and may indicate gout, acute uric acid nephropathy, or nephrolithiasis.

**Bilirubin Crystals**

The crystals appear as needlelike clusters, granules, or, occasionally, plates and are found in acidic urine. They are highly pigmented with an orange to brown color (**Figure 2**). Bilirubin crystals are formed from conjugated bilirubin. The crystals are a result of increased bilirubin in the urine and can indicate hepatic diseases including hepatitis or liver failure. Because several crystals can have orange/brown pigmentation, correlation with a positive urine dipstick for bilirubin is important.

![Bilirubin crystals. Image taken from Shutterstock.com.](image)

**Figure 2.** Bilirubin crystals. Image taken from Shutterstock.com.

**Cholesterol Crystals**

These crystals appear as flat, colorless, plates with notches in the corner (**Figure 3**). Cholesterol crystals, found in acidic urine, are an indication of nephrotic syndrome and a sign of kidney damage. They can also be present when there is a thoracic or abdominal blockage to lymph drainage, called *chyluria*. Other findings that may be present with cholesterol crystals include proteinuria, low serum albumin with high cholesterol, and swelling of the limbs. Fat droplets, fatty casts, and oval fat bodies may be present.
Cystine Crystals

Cystine crystals appear as flat, colorless 6-sided plates and can have equal or unequal sides (Figure 4). Cystine crystals are found in acidic urine. Cystinosis is a rare inherited metabolic disorder in which there is a proximal tubular defect in the reabsorption of the amino acid cystine. Cystine crystals can be deposited in the tubules as calculi. Because cystine crystals resemble uric acid crystals, confirmatory testing should be done to verify the presence of cystine crystals. A chemical test using the cyanide-nitroprusside reaction may be used to confirm the presence of cystine crystals. If positive, a blue color will develop. Solubility in ammonia will also help differentiate cystine from uric acid crystals. Cystine crystals are soluble in ammonia whereas uric acid crystals are not (Table).
Leucine Crystals

Leucine crystals are oily, highly retractile, brownish, form concentric rings, and are found in acidic urine (Figure 5). Refrigeration is required to make the crystals visible. Leucine crystals are present in maple syrup urine disease, oasthouse urine disease, and in severe liver disease. In severe liver disease, tyrosine crystals may also be present.

![Figure 5. Leucine crystals. Image taken from Shutterstock.com.](image)

Tyrosine Crystals

Tyrosine crystals form highly retractile colorless needlelike structures and are found in acidic urine (Figure 6). When bilirubin is present in the urine, the tyrosine crystal can appear yellow and resemble bilirubin crystals. To differentiate, bilirubin crystals are soluble in chloroform, acidic solutions, alkaline solutions, and acetone, while tyrosine crystals are not. To further help differentiate, tyrosine crystals are soluble in ammonium hydroxide, hydrochloric acid, and dilute mineral oil, whereas bilirubin crystals will not dissolve in these. Tyrosine crystals may also be confused with calcium phosphate crystals. However, calcium phosphate crystals are found in alkaline urine, whereas tyrosine crystals are found in acidic urine.

![Figure 6. Tyrosine crystal. Image taken from Shutterstock.com.](image)
Sulfonamide Crystals

Sulfa crystals can appear as needlelike sheaves (Figure 7). They can be clear or brown and are found in acidic urine. The crystals can be seen in patients taking sulfadiazine, indinavir, intravenous acyclovir, and triamterene. These drugs can cause renal damage when given in high volumes or to volume-depleted patients.

Figure 7. Sulfonamide crystals. Image taken from Shutterstock.com.

Non-pathologic Crystals

Amorphous Urate and Amorphous Phosphate Crystals

Amorphous urate and amorphous phosphates crystals appear as small granular crystals and may be confused with bacteria (Figure 8). Amorphous urates are found in acidic urine whereas amorphous phosphate crystals are found in alkaline urine. These crystals are not found in freshly voided urine but will appear when the sample cools to room temperature or when refrigerated.

Figure 8. Amorphous phosphate crystals and a triple phosphate crystal (arrow). Image taken from Shutterstock.com.
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Calcium Oxalate Crystals

Calcium oxalate crystals can take several shapes, including dumbbell (monohydrate) and 4-sided envelope (dihydrate) and may be observed at any pH (Figures 9 and 10). Calcium oxalate crystals form when oxalate joins with calcium in the renal tubules. When conditions are right, the calcium oxalate will precipitate out as crystals. These crystals can also be seen in pathologic conditions such as nephrolithiasis and in cases of acute ethylene glycol ingestion.

![Calcium oxalate dihydrate crystals. Image taken from Shutterstock.com.](image1)

*Figure 9. Calcium oxalate dihydrate crystals. Image taken from Shutterstock.com.*

![Calcium oxalate monohydrate crystals. Image taken from Shutterstock.com.](image2)

*Figure 10. Calcium oxalate monohydrate crystals. Image taken from Shutterstock.com.*

Triple Phosphate Crystals

Triple phosphate crystals appear as easily recognized coffin lid–shaped crystals (Figure 11). Although the crystals are usually non-pathogenic, they may be seen in urinary tract infections that are caused by urea-splitting bacteria, such as *Proteus* species, chronic cystitis, and chronic pyelitis. They can also form urinary calculi.
Calcium Carbonate Crystals

Calcium carbonate crystals are found in alkaline urine and their sizes range from small crystals, which are slightly larger than amorphous crystals, to large granular masses (Figure 12). They may be amorphous or can have a dumbbell shape. When they appear as the amorphous type, they may be differentiated from bacteria with the use of polarized light. Calcium carbonate crystals are birefringent, while bacteria are not. These crystals do not indicate any pathologic condition.

Calcium Phosphate Crystals

Calcium phosphate crystals are found in acidic urine and form needlelike clumps (Figure 13). Although found in normal urine samples, they can also form calculi.
Hippuric Acid Crystals

The size and shape of Hippuric acid crystals varies from small needlelike to long prism-like forms (Figure 14). They are found in acidic, neutral, and alkaline urine. These are rarely seen and have no clinical significance.

Ammonium Biurate Crystals

Ammonium biurate crystals appear as yellow-brown, smooth or prickly spheres, and are found in alkaline urine (Figure 15). Ammonium biurate crystals can precipitate out during prolonged storage at room temperature. Sample collection and storage should be investigated when these crystals are seen. When found in fresh urine, they may result from in vivo precipitation. This is clinically significant because the crystal can cause renal tubular damage.
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![Image of Ammonium biurate crystals.](image.png)

**Figure 15.** Ammonium biurate crystals. Note the several prickly spheres. Image taken from Shutterstock.com.

X-ray Contrast Media Crystals

Intravenous x-ray contrast media may produce crystals in the urine. These crystals can mimic various crystals found in pathologic and non-pathologic states. When x-ray contrast media is present, the specific gravity of the urine sample is usually greater than 1.040. This finding will aid in differentiating the crystals of the contrast media from crystals caused by physiological conditions.

Conclusion

Urine microscopy is a valuable tool in today’s laboratory. Being able to identify crystals is an important component of urine microscopy. A competent microscopist must be able to identify crystals to aid the health care clinician in making an accurate diagnosis. Although most urinary crystals do not fit easily into pathologic/non-pathologic subtypes, some crystals are present only in pathologic conditions. Other crystals may be found in normal urine but can also indicate pathology, such as renal calculi or cystitis.

References


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