UpToDate® Official reprint from UpToDate®
www.uptodate.com ©2017 UpToDate®
Wolters Kluwer

Crystal-induced acute kidney injury (acute renal failure)

Author: Mark A Perazella, MD, FACP
Section Editor: Paul M Palevsky, MD
Deputy Editor: Alice M Sheridan, MD

All topics are updated as new evidence becomes available and our peer review process is complete.
Literature review current through: Mar 2017. | **This topic last updated:** Aug 10, 2016.

INTRODUCTION — Crystal-induced acute kidney injury (AKI) is caused by the intratubular precipitation of crystals, which results in obstruction. Crystal-induced AKI most commonly occurs as a result of acute uric acid nephropathy and following the administration of drugs or toxins that are poorly soluble or have metabolites that are poorly soluble in urine [1,2]. Other drugs or medications may be metabolized to insoluble products such as oxalate (ethylene glycol, vitamin C), which are associated with precipitation of calcium oxalate crystals within tubular lumens and kidney injury.

This topic review discusses drug-related crystal-induced AKI. Uric acid nephropathy and acute phosphate nephropathy are discussed elsewhere. (See "Uric acid renal diseases" and "Acute phosphate nephropathy".)

ETIOLOGY — Multiple drugs and toxins cause intratubular crystal-induced obstruction. Common agents include:

- Acyclovir
- Sulfonamide antibiotics
- Ethylene glycol
- Megadose vitamin C
- Methotrexate
- Protease inhibitors

Other agents that have been described in case reports to cause crystal-induced AKI include orlistat, oral sodium phosphate purgatives, ciprofloxacin, and high-dose amoxicillin [1,3].

CLINICAL PRESENTATION AND DIAGNOSIS — Patients with drug-related crystal-induced AKI are usually asymptomatic, and kidney injury is detected by an increased serum creatinine [4]. Occasionally, patients present within one to seven days after initiation of the offending drug with renal colic symptoms such as flank or abdominal pain, nausea, or vomiting.

Urinalysis often reveals hematuria, pyuria, and crystalluria [1,5]. Significant proteinuria (ie, >500 mg/day) is not commonly observed, unless the patient has underlying proteinuric kidney disease and subsequently develops crystal-induced AKI.

The diagnosis is suggested by the appearance of crystals in the urine, the morphology of which depends upon the specific causative drug (see 'Specific agents' below). However, crystalluria may also be observed in patients who have no evidence of AKI [5].

Definitive diagnosis is obtained by examination of histology obtained by biopsy. In general, however, a biopsy is not indicated in patients who present with AKI in the setting of starting a drug that is known to cause crystal-induced AKI, unless atypical features (such as significant proteinuria in a patient who does not have underlying proteinuric kidney disease) are present.

The differential diagnosis for crystal-induced AKI is AKI from any cause and, among patients who present with hematuria and even modest proteinuria, glomerulonephritis. The diagnostic approaches to these disorders are discussed elsewhere. (See "Diagnostic approach to the patient with subacute kidney injury in an outpatient setting" and "Differential diagnosis and evaluation of glomerular disease".)

Crystal-induced AKI is generally reversed following discontinuation of the drug, although temporary dialysis may be necessary in some cases, and chronic kidney disease (CKD) may be a long-term consequence of crystal-induced AKI [6].

RISK FACTORS — Risk factors for crystal-induced kidney injury include true and "effective" intravascular volume depletion, underlying kidney or liver disease, and metabolic perturbations that change urinary pH [1,2,6]. The effect of urine pH on crystal formation varies depending upon the specific causative agents. As an example, whereas sulfonamides tend to form crystals in acidic urine, protease inhibitors such as indinavir form crystals in alkaline urine.

Excessive drug dosing for a given glomerular filtration rate (GFR) may contribute to the risk of kidney injury [1].

OVERVIEW OF TREATMENT — The correction of volume depletion is critical to prevent crystal-induced AKI among patients at risk. Therapy of established crystal-induced AKI is supportive and consists of volume repletion, usually with isotonic saline, and administration of a loop diuretic in an attempt to wash out the obstructing crystals. The use of loop diuretics is of theoretical benefit only, and its efficacy has not been shown. Despite the absence of proven efficacy, we generally administer furosemide. Fluid loss induced by the diuretic must be replaced to prevent volume depletion and a late slowing of flow within the tubules.

In addition to volume repletion and loop diuretics, among patients with crystal-induced AKI due to specific medications (as, for example, sulfonamide antibiotics and methotrexate), adjusting the urine pH to achieve better solubility of the crystal may be of benefit. These issues and specific treatments, where indicated, are discussed below. (See 'Sulfonamide antibiotics' below and 'Methotrexate' below.)

SPECIFIC AGENTS

Acyclovir — Acyclovir is rapidly excreted in the urine (being both filtered and secreted) and has a relatively low solubility [5]. Thus, bolus intravenous (IV) therapy, especially if the patient is volume depleted, may lead to the deposition of acyclovir crystals in the tubules, resulting in intratubular obstruction and foci of interstitial inflammation [4,5]. Ganciclovir, another antiviral agent that is structurally related to acyclovir and is also excreted in the urine, appears to be associated with a much lower risk of crystal-induced AKI compared with acyclovir [5,7].

Renal function in affected patients typically begins to deteriorate within 24 to 48 hours after therapy with acyclovir is initiated [1,6]. Patients may complain of nausea and flank or abdominal pain at this time, presumably induced by the urinary tract obstruction [5]. In some cases, birefringent, needle-shaped acyclovir crystals, occasionally engulfed by white cells, can be seen in the urine, particularly under polarized light.

The decline in kidney function is usually mild but occasionally may be severe, with marked increases in the plasma creatinine concentration in some cases [8,9]. However, complete recovery typically occurs within four to nine days after acyclovir is discontinued.

It is likely that most cases of acyclovir nephrotoxicity, which is likely due in part to direct tubular toxicity and in part to luminal crystal-associated obstruction, can be prevented by prior volume repletion (with the urine output maintained above 75 mL/hour) and slow IV drug infusion over one to two hours. We generally administer IV isotonic saline at a rate of 125 mL/hour, starting at least one hour prior to the administration of acyclovir and continuing for six hours after the acyclovir infusion is finished. Patients who develop AKI can usually be safely rechallenged (if necessary) by limiting the dose to ≤250 mg/m^2 [5]. Oral therapy is usually well tolerated, presumably due to a less rapid rate of acyclovir excretion. Rarely, AKI can develop with oral

acyclovir in patients with underlying kidney disease (and excessive dosing) and severe volume depletion [10,11].

Therapy of established renal failure is supportive and consists of volume repletion, usually with isotonic saline and administration of a loop diuretic in an attempt to wash out the obstructing crystals. As noted above, although the use of loop diuretics is of theoretical benefit only and its efficacy has not been shown, we generally administer furosemide. Fluid loss induced by the diuretic must be replaced to prevent volume depletion and a late slowing of flow within the tubules. (See "Maintenance and replacement fluid therapy in adults".)

Although hemodialysis may remove substantial amounts of acyclovir [8], it has not been shown to reverse or limit the duration of acyclovir-induced AKI and is not indicated for this purpose. However, neurotoxicity may develop in patients who develop severe acyclovir-induced AKI [11-13], and, in this setting, hemodialysis may be indicated in order to remove the drug [8].

In addition, hemodialysis may be required to correct the metabolic sequelae of AKI. (See "Renal replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose".)

Sulfonamide antibiotics — Some sulfonamide antibiotics are relatively insoluble in acid urine, particularly sulfadiazine and sulfamethoxazole, which are used in high doses to treat toxoplasmosis and *Pneumocystis carinii* infection in immunocompromised patients [5,14-16]. Up to 29 percent of patients treated with sulfadiazine are at risk to develop AKI [1,14-17] because this drug is highly insoluble in urine with a pH of ≤5.5 [17]. Intrarenal sulfadiazine precipitation may also result in nephrolithiasis [16].

The risk of crystal precipitation increases with doses of sulfadiazine of 4 to 6 g/day and of sulfamethoxazole of 50 to 100 mg/kg/day [14-17]. Alkalinization of the urine to a pH >7.15 increases sulfadiazine solubility more than 20-fold [5,14].

Sulfonamide crystals can assume many shapes, in part dependent upon the specific sulfonamide present. The most common morphology includes needle-shaped crystals, rosettes, and those resembling shocks of wheat (picture 1). Sulfadiazine sludge or small calculi in the calyces can also be detected in some cases as bilateral, layered clusters of echogenic material on renal ultrasonography [5,17].

Intrarenal sulfadiazine precipitation may be prevented by maintaining fluid intake above 3 L/day, which may be administered orally or intravenously [16]. Patients who are receiving sulfadiazine should be monitored by serial urinalyses for the development of crystalluria. Among patients who develop crystalluria, we administer an IV bicarbonate solution to alkalinize the urine to ≥7.15 in order to prevent AKI. To patients who are euvolemic and have normal renal function and a normal serum sodium concentration, we give a solution containing 75 mEq sodium bicarbonate per liter of sterile water. If the patient is hypovolemic, we give an isotonic solution (containing 75 mEq sodium bicarbonate per liter of one-half isotonic saline). We generally give approximately 3 L/day (ie, infusion rate of 125 mL/hour).

Patients who are receiving prophylactic IV bicarbonate should be closely monitored by physical exam for volume overload and by daily measurement of serum creatinine and electrolytes for development of AKI, alkalosis, or other electrolyte abnormalities.

Some patients may develop AKI despite prophylactic volume repletion and alkalinization of urine. Among such patients, AKI usually resolves when the sulfonamide is discontinued. The treatment of established AKI is supportive. Volume depletion, if present, should be treated in all patients, usually with isotonic saline. The administration of loop diuretics may assist recovery of renal function by clearing obstructive casts from tubular lumen, although there are no published data that have demonstrated a benefit of loop diuretics.

Among patients with established AKI, a forced alkaline diuresis to a target urine pH >7.15 may provide benefit by increasing the solubility of sulfadiazine, although there are no published studies that show that this treatment reverses or limits the duration of established sulfonamide-associated AKI.

In addition to a lack of clear evidence of benefit, maintaining the urine pH >7.15 is difficult in patients with established AKI. There are also potential risks to alkalinization of the plasma, such as promoting calcium phosphate deposition (which is more likely if hyperphosphatemia is present) and inducing or worsening the manifestations of hypocalcemia by both a direct membrane effect and a reduction in ionized calcium levels [18]. Manifestations of severe hypocalcemia include tetany, seizures, and cardiac arrhythmias. (See "Clinical manifestations of hypocalcemia".)

Despite these limitations, patients who are appropriately monitored may benefit from IV bicarbonate therapy. For patients who have a urine pH ≤7.15, we generally administer a solution (mixed by the pharmacy) containing 140 mEq of sodium bicarbonate per liter of sterile water at a rate of 125 mL/hour along with a loop diuretic such as furosemide, providing patients are not oliguric and do not have hypocalcemia, metabolic alkalosis, or an indication for acute hemodialysis. (See "Renal replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose", section on 'Urgent indications'.)

Among patients with established AKI, the bicarbonate infusion should be discontinued if the urine pH does not rise above 7 after 12 hours or if metabolic alkalosis or volume overload develops.

There is no benefit to hemodialysis for the removal of sulfonamides.

Methotrexate — Approximately 90 percent of administered methotrexate is normally excreted unchanged in the urine. High-dose IV methotrexate can both precipitate in the tubules and cause direct tubular injury [19-21]. The risk of methotrexate-induced nephrotoxicity is increased with an acidic urine (since methotrexate is poorly soluble in an acidic urine) and with volume depletion (which decreases urine flow rate and increases the concentration of methotrexate in tubular fluid). In addition, the risk of methotrexate nephrotoxicity is higher when there is sustained elevation in the plasma methotrexate concentration [22].

The risk of developing AKI can be minimized by prior volume repletion (both to maintain a high urine flow and to lower the concentration of methotrexate in the tubular fluid) and by alkalinization of the urine to a pH >7, which can increase the solubility of methotrexate by as much as 10-fold [20]. Among all patients who are receiving IV methotrexate, we administer an IV bicarbonate solution to alkalinize the urine to ≥7 in order to prevent AKI. To patients who are euvolemic and have normal renal function and a normal serum sodium concentration, we give a solution containing 75 mEq sodium bicarbonate per liter of sterile water that is mixed by the pharmacy. If the patient is hypovolemic, we give an isotonic solution (containing 75 mEq sodium bicarbonate per liter of one-half isotonic saline). We generally give approximately 3 L/day (ie, infusion rate of 125 mL/hour). The bicarbonate infusion should be begun 12 hours before methotrexate administration and continue for 24 to 48 hours.

The incidence of methotrexate-induced AKI in the era of routine intravascular volume repletion and urinary alkalinization was reported to be 1.8 percent in an analysis of data from clinical trials in osteosarcoma [23].

Methotrexate-induced AKI is typically nonoliguric and usually reversible [21,22]. The plasma creatinine concentration usually peaks within the first week and returns well toward baseline levels within one to three weeks [21].

Treatment of methotrexate-induced AKI is directed at volume repletion, washing out the crystals within tubular lumens via the administration of a loop diuretic, and alkalinization of urine. There are no studies that have proven a benefit of either loop diuretics or alkalinization of urine, and these measures are of theoretical benefit only.

As described above, maintaining the urine pH above 7 is difficult in patients with AKI and is associated with potential risks, including calcium phosphate deposition and inducing or worsening the manifestations of hypocalcemia by both a direct membrane effect and a reduction in ionized calcium levels [18]. (See 'Sulfonamide antibiotics' above.)

Despite these limitations, given the potential benefit of bicarbonate therapy, we administer a bicarbonate infusion to all patients who have methotrexate-related AKI, providing they are not oliguric and do not have hypocalcemia, metabolic alkalosis, or an indication for acute hemodialysis. (See "Renal replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose", section on 'Urgent indications'.)

We generally administer a solution containing 140 mEq sodium bicarbonate per liter of sterile water at a rate of 125 mL/hour intravenously, along with a loop diuretic such as furosemide, providing patients are not oliguric and do not have hypocalcemia, metabolic alkalosis, or an indication for acute hemodialysis. (See "Renal replacement therapy (dialysis) in acute kidney injury in adults: Indications, timing, and dialysis dose", section on 'Urgent indications'.)

The bicarbonate infusion should be discontinued if the urine pH does not rise above 7 after 12 hours or if metabolic alkalosis develops.

AKI often results in an elevated plasma methotrexate concentration [22]. This is clinically very important since it may increase the toxicity of methotrexate as decreased urinary excretion results in elevated plasma drug levels that can last for as long as two to three weeks [21]. Leucovorin rescue with or without thymidine is effective in this setting, although higher-than-usual doses are often required and are generally based on the plasma methotrexate concentration [19,21]. Leucovorin should be continued until levels of methotrexate fall below 0.05 micromolar. (See "Major side effects of low-dose methotrexate".)

Glucarpidase, which rapidly metabolizes folic acid and chemically similar antifolates such as methotrexate to inactive metabolites, may prevent systemic methotrexate toxicity by rapidly lowering serum methotrexate levels that remain unacceptably high despite adequate hydration and urinary alkalinization [24-26]. In one report, for example, 65 patients with renal insufficiency and an elevated serum methotrexate concentration 36 to 42 hours after methotrexate infusion were treated with a single dose of glucarpidase [26]. Fifteen minutes following glucarpidase treatment, serum methotrexate levels decreased by a median of 87 percent.

Glucarpidase also metabolizes leucovorin, which should be continued for two days after glucarpidase administration [22].

Glucarpidase was approved in the US in January 2012 for treatment of toxic methotrexate plasma concentrations (>1 micromol/L [>1 microm]) in patients with delayed methotrexate clearance due to impaired renal function [27]. Recommendations for the use of glucarpidase among patients with renal dysfunction and elevated methotrexate levels are discussed elsewhere. (See "Therapeutic use and toxicity of high-dose methotrexate", section on 'Glucarpidase (carboxypeptidase G2)'.)

Drug removal by hemodialysis, charcoal hemoperfusion, or plasma exchange is generally of limited value since methotrexate is both protein bound (and therefore not readily dialyzable) and has a relatively large extravascular volume of distribution [19,28]. However, in one small case series, daily hemodialysis with high-flux membranes for four to six hours improved methotrexate clearance [29]. In one patient who was dialysis dependent prior to high-dose methotrexate therapy, 63 percent of the drug was cleared in six hours. Analysis of seven separate methotrexate treatments in this patient demonstrated complete drug removal after an average of 5.6 days [29].

Limited data also suggest that albumin-based continuous venovenous hemodialysis (CVVHD) may provide better methotrexate clearance than CVVHD without albumin, presumably due to the effect of better removal of protein-bound methotrexate [30].

Protease inhibitors

Indinavir — Indinavir, a protease inhibitor used in the treatment of human immunodeficiency virus (HIV) infection, commonly causes asymptomatic crystalluria and may cause AKI associated with crystal deposition and/or nephrolithiasis (picture 2) [2,31-40].

- One report described 29 patients in whom stones either passed spontaneously or were removed by ureteroscopy [39]. Mass spectrometry demonstrated that the stones consisted of indinavir base monohydrate.

- In another study, among 240 patients, 8 percent experienced urologic symptoms, and 3 percent had nephrolithiasis due to indinavir stones [31]. In addition, among 142 patients who provided urine samples, 20 percent had urinary crystals consisting of indinavir (picture 2).

However, one retrospective study of 24 patients with nephrolithiasis and HIV infection found that indinavir-containing stones were found in only 4 of 14 patients taking indinavir [41]. The other individuals had stones consisting of a variety of other substances (calcium oxalate and others), with metabolic evaluation suggesting a variety of abnormalities. This suggests that, among HIV patients administered indinavir, nephrolithiasis may result from something other than the protease inhibitor.

The mechanism by which indinavir causes both AKI and nephrolithiasis is by the precipitation of indinavir crystals. Indinavir has a low solubility (0.03 mg/mL) at a pH of 6, but is much more soluble at lower pH values (100 mg/mL at pH 3.5). In a study of 54 patients on indinavir, patients with urine pH >6 were much more likely to have indinavir crystals on urinalysis than those with lower urinary pH, particularly if the urine was also concentrated [42]. However, although acidification of urine may increase the solubility of indinavir, this is difficult to achieve and potentially harmful [31,36,39]. Thus, acidification of urine is not recommended. (See "Overview of antiretroviral agents used to treat HIV", section on 'Protease inhibitors (PIs)'.)

Increased fluid intake prior to each oral dose of indinavir may decrease the risk of crystal formation. However, increased fluid intake may not be entirely protective. In a prospective study of 105 patients taking indinavir, a renal stone occurred in approximately 12 percent of patients after a median treatment duration of 22 weeks despite enhanced fluid intake, documented by continuous monitoring [40].

The radiologic imaging procedures typically used in the diagnosis of ureteral stones appear to be **unreliable** in the diagnosis of nonopaque stones due to indinavir. (See "Diagnosis and acute management of suspected nephrolithiasis in adults".)

In a retrospective study of 36 patients treated with indinavir who presented with signs of renal colic (ipsilateral flank pain, dysuria, urgency, hematuria), abdominal radiography failed to identify a renal stone in any individual, while only 1 of 13 excretory urograms, 4 of 11 renal ultrasonographic examinations, and 0 of 12 computed tomography (CT) scans were diagnostic of nephrolithiasis [43]. Contrast-enhanced CT scanning may suggest the diagnosis by showing a filling defect in a ureter, delayed excretion, or a persistent nephrogram [44].

These renal and urologic complications with indinavir appear to require discontinuation of the agent in one-third of patients [45]. To help prevent nephrolithiasis and AKI, we suggest an oral fluid intake of at least 1.5 liters of water daily [46].

Chronic kidney disease (CKD) from protease inhibitors may also result from interstitial fibrosis and renal atrophy [33-38].

Atazanavir — Like indinavir, the protease inhibitor, atazanavir, can lead to stone formation and, less commonly, AKI due to its relative insolubility in the urine [47-49].

An initial case series described 11 patients who developed nephrolithiasis while taking atazanavir [48]. Analysis of the stones demonstrated crystals of atazanavir base, but not metabolites. Eight stones contained a core of atazanavir, while four had a core of calcium oxalate (one patient had two stones).

Several case reports and 30 cases of atazanavir-associated nephrolithiasis were subsequently reported upon review of the US Food and Drug Administration Adverse Event Reporting System (FAERS) database [41,50]. One study estimated a prevalence of atazanavir stones of 0.97 percent among those taking the drug [48].

One case of AKI due to atazanavir-associated crystal nephropathy has been reported [51]. In this case, rod-like atazanavir crystals were noted on urine microscopy (picture 3), as well as within tubular lumens and renal interstitium (along with granulomata) on renal biopsy (picture 4).

Fluid intake of ≥1.5 L/day should be encouraged among patients taking atazanavir.

Oxalate — AKI due to oxalate deposition in the kidney has been described in several settings:

- Primary hyperoxaluria (see "Primary hyperoxaluria")
- Ethylene glycol poisoning (see "Methanol and ethylene glycol poisoning")
- Secondary hyperoxaluria due to pancreatic insufficiency, inflammatory bowel disease, bowel resection, or gastric bypass (see "Chronic complications of the short bowel syndrome in adults")
- Orlistat therapy (see "Nephrocalcinosis", section on 'Hyperoxaluria')
- High doses of vitamin C [52,53]

Orlistat, a weight-loss drug that induces fat malabsorption, has been associated with intratubular calcium-oxalate deposition and AKI [54-56]. (See "Nephrocalcinosis", section on 'Hyperoxaluria'.)

Oral sodium phosphate purgatives — Oral sodium phosphate preparations have been used as laxatives or purgatives for bowel cleansing before colonoscopy, CT virtual colonoscopy, or bowel surgery. AKI secondary to acute phosphate nephropathy has been reported following the use of oral sodium phosphate preparations. Acute phosphate nephropathy is discussed elsewhere. (See "Acute phosphate nephropathy".)

Ciprofloxacin — The widely used fluoroquinolone antibiotic, ciprofloxacin, is known to cause AKI from acute interstitial nephritis [57-59]. Ciprofloxacin has also been reported to cause crystalluria in experimental animals [60] and both crystalluria [61-63] and crystal-induced AKI [64-68] in humans. In all reports, patients developed oliguric AKI within two days to two weeks of ingestion of oral ciprofloxacin. All case reports except one described patients who were ≥70 years of age, and two described patients who were on angiotensin-converting enzyme (ACE) inhibitors [68]. Urinalysis revealed crystals of varying shapes, which were composed of ciprofloxacin salt (picture 5).

Ciprofloxacin crystals typically precipitate in an alkaline pH [61,69]. However, crystals have been described in association with acidic urine pH in several case reports [64,67]. Ciprofloxacin crystals have been shown to display a wide array of appearances, including needles, sheaves, stars, fans, butterflies, and other unusual shapes. All crystals have had a lamellar structure, with sizes ranging from 30 x 5 microm to 360 x 237 microm, and are strongly birefringent under polarizing light [70]. Histology obtained by renal biopsy in three patients revealed needle-shaped birefringent crystals within the tubules (picture 6) without evidence of acute or chronic interstitial nephritis [67,68]. In all patients, renal function returned to baseline upon withdrawal of ciprofloxacin.

Risk factors for AKI include impaired kidney function, volume depletion, and a urine pH >6 (although acidic urine pH does not preclude a diagnosis of ciprofloxacin-induced crystal deposition). To prevent ciprofloxacin crystal-induced AKI, ciprofloxacin should be dose adjusted for level of glomerular filtration rate (GFR), the patient should be volume replete, and alkalinization of the urine should be avoided [71].

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Acute kidney injury in adults".)

SUMMARY AND RECOMMENDATIONS

- Acute kidney injury (AKI) due to intratubular crystal precipitation is observed in association with many medications. Patients are generally asymptomatic, although occasionally present with flank pain.

Urinalysis may show hematuria, pyuria, and crystals with a characteristic morphology. (See 'Introduction' above and 'Clinical presentation and diagnosis' above.)

- The maintenance of optimal volume status and correction of volume depletion is critical in the prevention of crystal-induced AKI from all causes. The alkalinization of urine may help prevent crystal-induced AKI secondary to sulfadiazine antibiotics and methotrexate. We suggest the following approach for patients who are receiving specific agents:

  - Among patients who are receiving intravenous (IV) acyclovir, we suggest the administration of IV isotonic saline at a rate of 125 mL/hour, starting at least one hour prior to the administration of acyclovir and continuing for six hours after the acyclovir infusion is finished (**Grade 2C**). (See 'Acyclovir' above.)

  - Among patients who are receiving high-dose IV sulfonamide antibiotics and develop crystalluria, we suggest the administration of IV sodium bicarbonate to prevent AKI (**Grade 2C**). (See 'Sulfonamide antibiotics' above.)

  - Among all patients who are receiving methotrexate, we recommend the administration of IV sodium bicarbonate to prevent AKI (**Grade 1B**). (See 'Methotrexate' above.)

- The maintenance of optimal volume status and correction of volume depletion is critical in the treatment of established AKI. Among all patients with established crystal-induced AKI from any cause, we recommend the correction of volume depletion with IV fluid (**Grade 1B**). In the absence of an indication for IV bicarbonate, such as for the treatment of sulfonamide- or methotrexate-induced AKI, the preferred IV fluid is usually isotonic saline.

- A loop diuretic may be effective in clearing obstructing casts in crystal-induced AKI. Among all volume-replete patients with established crystal-induced AKI from any cause, we suggest administration of a loop diuretic (**Grade 2C**). Fluid loss induced by the diuretic must be replaced to prevent volume depletion and a late slowing of flow within the tubules. (See 'Risk factors' above and 'Overview of treatment' above.)

- Crystals from sulfonamide antibiotics and methotrexate are more likely to form in acidic urine. Alkalinization of urine may provide benefit in established AKI from sulfonamide antibiotics or methotrexate.

  - Among patients with established sulfonamide-associated AKI who are not oliguric and do not have hypocalcemia or metabolic alkalosis or an indication for acute hemodialysis, we suggest the administration of IV bicarbonate with a target urine pH of >7.15 (**Grade 2C**). (See 'Sulfonamide antibiotics' above.)

  - Among patients with established methotrexate-associated AKI who are not oliguric and do not have hypocalcemia or metabolic alkalosis or an indication for acute hemodialysis, we suggest the administration of IV bicarbonate with a target urine pH of >7 (**Grade 2C**). (See 'Methotrexate' above.)

- Crystals from protease inhibitors such as indinavir or atazanavir are more likely to form in alkaline urine. However, it is difficult and potentially dangerous to acidify the urine among patients with established AKI. We recommend **not** acidifying the urine for the treatment of crystal-induced AKI from any cause (**Grade 1B**).

- Methotrexate-induced AKI often results in an elevated plasma methotrexate concentration, which may increase the systemic toxicity of methotrexate. Leucovorin rescue, with or without thymidine or glucarpidase, may be effective in this setting. (See 'Methotrexate' above and "Major side effects of low-dose methotrexate" and "Therapeutic use and toxicity of high-dose methotrexate", section on 'Glucarpidase (carboxypeptidase G2)'.)

Use of UpToDate is subject to the Subscription and License Agreement.

REFERENCES

1. Perazella MA. Crystal-induced acute renal failure. Am J Med 1999; 106:459.
2. Teichman JM. Clinical practice. Acute renal colic from ureteral calculus. N Engl J Med 2004; 350:684.
3. Hentzien M, Lambert D, Limelette A, et al. Macroscopic amoxicillin crystalluria. Lancet 2015; 385:2296.
4. Sawyer MH, Webb DE, Balow JE, Straus SE. Acyclovir-induced renal failure. Clinical course and histology. Am J Med 1988; 84:1067.
5. Berns JS, Cohen RM, Stumacher RJ, Rudnick MR. Renal aspects of therapy for human immunodeficiency virus and associated opportunistic infections. J Am Soc Nephrol 1991; 1:1061.
6. Brigden D, Rosling AE, Woods NC. Renal function after acyclovir intravenous injection. Am J Med 1982; 73:182.
7. Morbidity and toxic effects associated with ganciclovir or foscarnet therapy in a randomized cytomegalovirus retinitis trial. Studies of ocular complications of AIDS Research Group, in collaboration with the AIDS Clinical Trials Group. Arch Intern Med 1995; 155:65.
8. Krieble BF, Rudy DW, Glick MR, Clayman MD. Case report: acyclovir neurotoxicity and nephrotoxicity--the role for hemodialysis. Am J Med Sci 1993; 305:36.
9. Obada EN, Level G, Mathieu P, et al. [Acute renal failure following a treatment with acyclovir]. Nephrol Ther 2010; 6:125.
10. Giustina A, Romanelli G, Cimino A, Brunori G. Low-dose acyclovir and acute renal failure. Ann Intern Med 1988; 108:312.
11. Eck P, Silver SM, Clark EC. Acute renal failure and coma after a high dose of oral acyclovir. N Engl J Med 1991; 325:1178.
12. Spiegal DM, Lau K. Acute renal failure and coma secondary to acyclovir therapy. JAMA 1986; 255:1882.
13. Cohen SM, Minkove JA, Zebley JW 3rd, Mulholland JH. Severe but reversible neurotoxicity from acyclovir. Ann Intern Med 1984; 100:920.
14. Simon DI, Brosius FC 3rd, Rothstein DM. Sulfadiazine crystalluria revisited. The treatment of Toxoplasma encephalitis in patients with acquired immunodeficiency syndrome. Arch Intern Med 1990; 150:2379.
15. Carbone LG, Bendixen B, Appel GB. Sulfadiazine-associated obstructive nephropathy occurring in a patient with the acquired immunodeficiency syndrome. Am J Kidney Dis 1988; 12:72.
16. Hein R, Brunkhorst R, Thon WF, et al. Symptomatic sulfadiazine crystalluria in AIDS patients: a report of two cases. Clin Nephrol 1993; 39:254.
17. Sasson JP, Dratch PL, Shortsleeve MJ. Renal US findings in sulfadiazine-induced crystalluria. Radiology 1992; 185:739.
18. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore) 2005; 84:377.
19. Garrick, MB, Mayer, RJ, Abelson, HT. Acute renal failure associated with cancer treatment. In: Acute Renal Failure, 2nd ed, Brenner, BM, Lazarus, JM (Eds), Churchill Livingstone, New York 1988. p.636.
20. Pitman SW, Frei E 3rd. Weekly methotrexate-calcium leucovorin rescue: effect of alkalinization on nephrotoxicity; pharmacokinetics in the CNS; and use in CNS non-Hodgkin's lymphoma. Cancer Treat Rep 1977; 61:695.
21. Abelson HT, Fosburg MT, Beardsley GP, et al. Methotrexate-induced renal impairment: clinical studies and rescue from systemic toxicity with high-dose leucovorin and thymidine. J Clin Oncol 1983; 1:208.

22. Widemann BC, Adamson PC. Understanding and managing methotrexate nephrotoxicity. Oncologist 2006; 11:694.
23. Widemann BC, Balis FM, Kempf-Bielack B, et al. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. Cancer 2004; 100:2222.
24. Krause AS, Weihrauch MR, Bode U, et al. Carboxypeptidase-G2 rescue in cancer patients with delayed methotrexate elimination after high-dose methotrexate therapy. Leuk Lymphoma 2002; 43:2139.
25. Widemann BC, Balis FM, Murphy RF, et al. Carboxypeptidase-G2, thymidine, and leucovorin rescue in cancer patients with methotrexate-induced renal dysfunction. J Clin Oncol 1997; 15:2125.
26. Buchen S, Ngampolo D, Melton RG, et al. Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. Br J Cancer 2005; 92:480.
27. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125327lbl.pdf?et_cid=28599956&et_rid=463638624&linkid=http%3a%2f%2fwww.accessdata.fda.gov%2fdrugsatfda_docs%2flabel%2f2012%2f125327lbl.pdf (Accessed on January 18, 2012).
28. Garella S. Extracorporeal techniques in the treatment of exogenous intoxications. Kidney Int 1988; 33:735.
29. Wall SM, Johansen MJ, Molony DA, et al. Effective clearance of methotrexate using high-flux hemodialysis membranes. Am J Kidney Dis 1996; 28:846.
30. Pasko DA, Grio M, Thomas S, et al. Methotrexate transmembrane clearance during albumin based continuous veno-venous hemodialysis. Blood Purif 2005; 23:165.
31. Kopp JB, Miller KD, Mican JA, et al. Crystalluria and urinary tract abnormalities associated with indinavir. Ann Intern Med 1997; 127:119.
32. Gagnon RF, Tecimer SN, Watters AK, Tsoukas CM. Prospective study of urinalysis abnormalities in HIV-positive individuals treated with indinavir. Am J Kidney Dis 2000; 36:507.
33. Jao J, Wyatt CM. Antiretroviral medications: adverse effects on the kidney. Adv Chronic Kidney Dis 2010; 17:72.
34. Tashima KT, Horowitz JD, Rosen S. Indinavir nephropathy. N Engl J Med 1997; 336:138.
35. Martinez F, Mommeja-Marin H, Estepa-Maurice L, et al. Indinavir crystal deposits associated with tubulointerstitial nephropathy. Nephrol Dial Transplant 1998; 13:750.
36. Perazella MA, Kashgarian M, Cooney E. Indinavir nephropathy in an AIDS patient with renal insufficiency and pyuria. Clin Nephrol 1998; 50:194.
37. Sarcletti M, Petter A, Romani N, et al. Pyuria in patients treated with indinavir is associated with renal dysfunction. Clin Nephrol 2000; 54:261.
38. Daugas E, Rougier JP, Hill G. HAART-related nephropathies in HIV-infected patients. Kidney Int 2005; 67:393.
39. Daudon M, Estépa L, Viard JP, et al. Urinary stones in HIV-1-positive patients treated with indinavir. Lancet 1997; 349:1294.
40. Reiter WJ, Schön-Pernerstorfer H, Dorfinger K, et al. Frequency of urolithiasis in individuals seropositive for human immunodeficiency virus treated with indinavir is higher than previously assumed. J Urol 1999; 161:1082.
41. Nadler RB, Rubenstein JN, Eggener SE, et al. The etiology of urolithiasis in HIV infected patients. J Urol 2003; 169:475.
42. Gagnon RF, Alli AI, Edwardes MD, et al. Low urine pH is associated with reduced indinavir crystalluria in indinavir-treated HIV-infected individuals. Clin Nephrol 2006; 65:13.
43. Schwartz BF, Schenkman N, Armenakas NA, Stoller ML. Imaging characteristics of indinavir calculi. J Urol 1999; 161:1085.

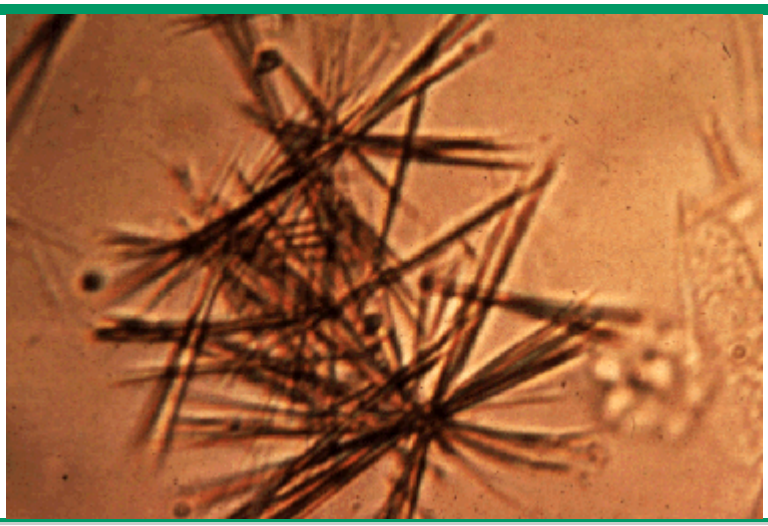
44. Blake SP, McNicholas MM, Raptopoulos V. Nonopaque crystal deposition causing ureteric obstruction in patients with HIV undergoing indinavir therapy. AJR Am J Roentgenol 1998; 171:717.
45. Voigt E, Wickesberg A, Wasmuth JC, et al. First-line ritonavir/indinavir 100/800 mg twice daily plus nucleoside reverse transcriptase inhibitors in a German multicentre study: 48-week results. HIV Med 2002; 3:277.
46. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2005; 40:1559.
47. Brewster UC, Perazella MA. Acute interstitial nephritis associated with atazanavir, a new protease inhibitor. Am J Kidney Dis 2004; 44:e81.
48. Couzigou C, Daudon M, Meynard JL, et al. Urolithiasis in HIV-positive patients treated with atazanavir. Clin Infect Dis 2007; 45:e105.
49. Chang HR, Pella PM. Atazanavir urolithiasis. N Engl J Med 2006; 355:2158.
50. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. AIDS 2007; 21:1215.
51. Izzedine H, M'rad MB, Bardier A, et al. Atazanavir crystal nephropathy. AIDS 2007; 21:2357.
52. Swartz RD, Wesley JR, Somermeyer MG, Lau K. Hyperoxaluria and renal insufficiency due to ascorbic acid administration during total parenteral nutrition. Ann Intern Med 1984; 100:530.
53. Nakamoto Y, Motohashi S, Kasahara H, Numazawa K. Irreversible tubulointerstitial nephropathy associated with prolonged, massive intake of vitamin C. Nephrol Dial Transplant 1998; 13:754.
54. Courtney AE, O'Rourke DM, Maxwell AP. Rapidly progressive renal failure associated with successful pharmacotherapy for obesity. Nephrol Dial Transplant 2007; 22:621.
55. Singh A, Sarkar SR, Gaber LW, Perazella MA. Acute oxalate nephropathy associated with orlistat, a gastrointestinal lipase inhibitor. Am J Kidney Dis 2007; 49:153.
56. Weir MA, Beyea MM, Gomes T, et al. Orlistat and acute kidney injury: an analysis of 953 patients. Arch Intern Med 2011; 171:703.
57. Hootkins R, Fenves AZ, Stephens MK. Acute renal failure secondary to oral ciprofloxacin therapy: a presentation of three cases and a review of the literature. Clin Nephrol 1989; 32:75.
58. Connor JP, Curry JM, Selby TL, Perlmutter AD. Acute renal failure secondary to ciprofloxacin use. J Urol 1994; 151:975.
59. Markowitz GS, Perazella MA. Drug-induced renal failure: a focus on tubulointerstitial disease. Clin Chim Acta 2005; 351:31.
60. Ball P. Ciprofloxacin: an overview of adverse experiences. J Antimicrob Chemother 1986; 18 Suppl D:187.
61. Thorsteinsson SB, Bergan T, Oddsdottir S, et al. Crystalluria and ciprofloxacin, influence of urinary pH and hydration. Chemotherapy 1986; 32:408.
62. Thorsteinsson SB, Bergan T, Rohwedder R. Tolerance of intravenously administered ciprofloxacin. Chemotherapy 1988; 34:256.
63. Ball P, Tillotson G. Tolerability of fluoroquinolone antibiotics. Past, present and future. Drug Saf 1995; 13:343.
64. Chopra N, Fine PL, Price B, Atlas I. Bilateral hydronephrosis from ciprofloxacin induced crystalluria and stone formation. J Urol 2000; 164:438.
65. Dharnidharka VR, Nadeau K, Cannon CL, et al. Ciprofloxacin overdose: acute renal failure with prominent apoptotic changes. Am J Kidney Dis 1998; 31:710.

66. Sedlacek M, Suriawinata AA, Schoolwerth A, Remillard BD. Ciprofloxacin crystal nephropathy--a 'new' cause of acute renal failure. Nephrol Dial Transplant 2006; 21:2339.
67. Stratta P, Lazzarich E, Canavese C, et al. Ciprofloxacin crystal nephropathy. Am J Kidney Dis 2007; 50:330.
68. Montagnac R, Briat C, Schillinger F, et al. [Fluoroquinolone induced acute renal failure. General review about a case report with crystalluria due to ciprofloxacin]. Nephrol Ther 2005; 1:44.
69. Schluter G. Ciprofloxacin: toxicologic evaluation of additional safety data. Am J Med 1989; 87:37S.
70. Fogazzi GB, Garigali G, Brambilla C, Daudon M. Ciprofloxacin crystalluria. Nephrol Dial Transplant 2006; 21:2982.
71. Christ W, Lehnert T, Ulbrich B. Specific toxicologic aspects of the quinolones. Rev Infect Dis 1988; 10 Suppl 1:S141.

Topic 7229 Version 12.0

GRAPHICS

Photomicrograph showing urine sediment of a patient with sulfonamide crystalluria

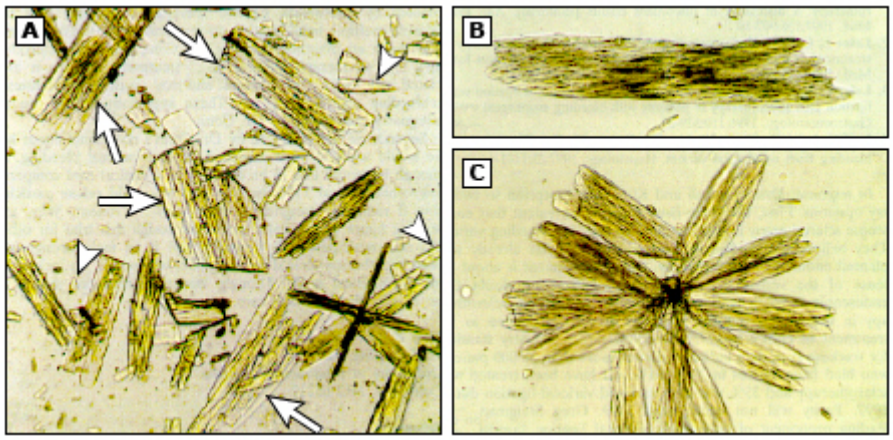


Urine sediment showing sulfonamide crystals with a needle-shaped appearance. Other forms that may be seen include rosettes and a shock of wheat appearance.

Courtesy of Harvard Medical School.

Graphic 56708 Version 3.0

Photomicrographs showing urine sediment of a patient with indinavir sulfate crystalluria

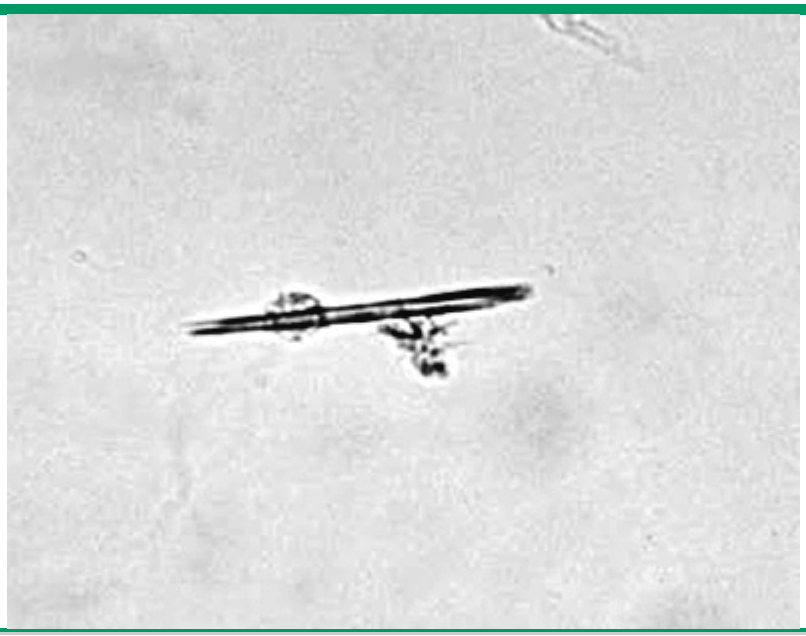


Light microscopic photographs of a fresh unstained preparation of urinary sediment showing three different forms of indinavir sulfate crystals.
(A) Rectangular plates of various sizes containing needle-shaped crystals. The plates have irregular borders with occasional tapering, and internal layering evident in the largest forms (arrows). Small, triangular pieces (arrowheads) represent broken ends of needles.
(B) A sheaf of densely packed indinavir sulfate needles.
(C) Several indinavir crystal groupings are arranged in a rosette.

Reprinted with permission from: Gagnon RF, Tsoukas CM, Watters AK, Ann Intern Med 1998; 128:321.

Graphic 70939 Version 4.0

Photomicrograph showing urine sediment of a patient with atazanavir crystalluria

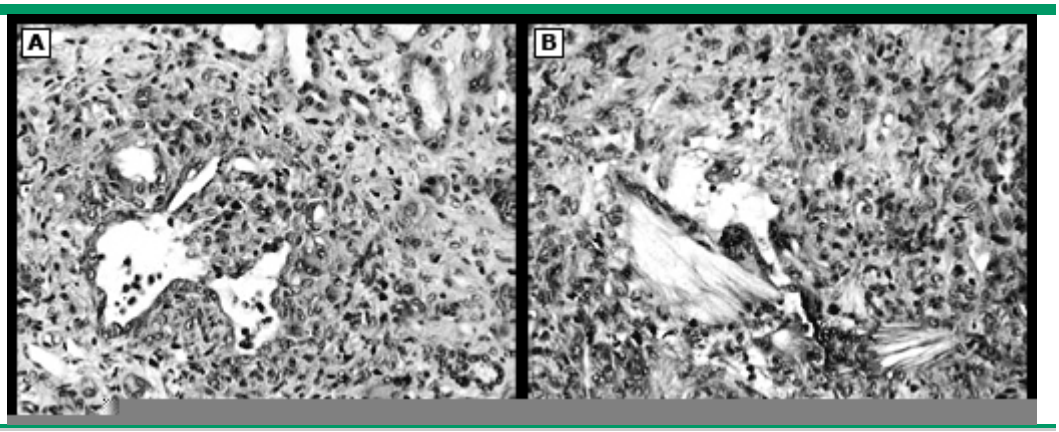


Urine sediment of a patient with atazanavir crystalluria demonstrates a needle-shaped crystal with bright field microscopy.

Reproduced with permission from: Izzedine H, M'rad MB, Bardier A, et al. Atazanavir crystal nephropathy. AIDS 2007; 21:2357. Copyright © 2007 Lippincott Williams & Wilkins.

Graphic 77620 Version 12.0

Light micrograph of kidney biopsy with atazanavir crystals within tubular lumen and renal parenchyma

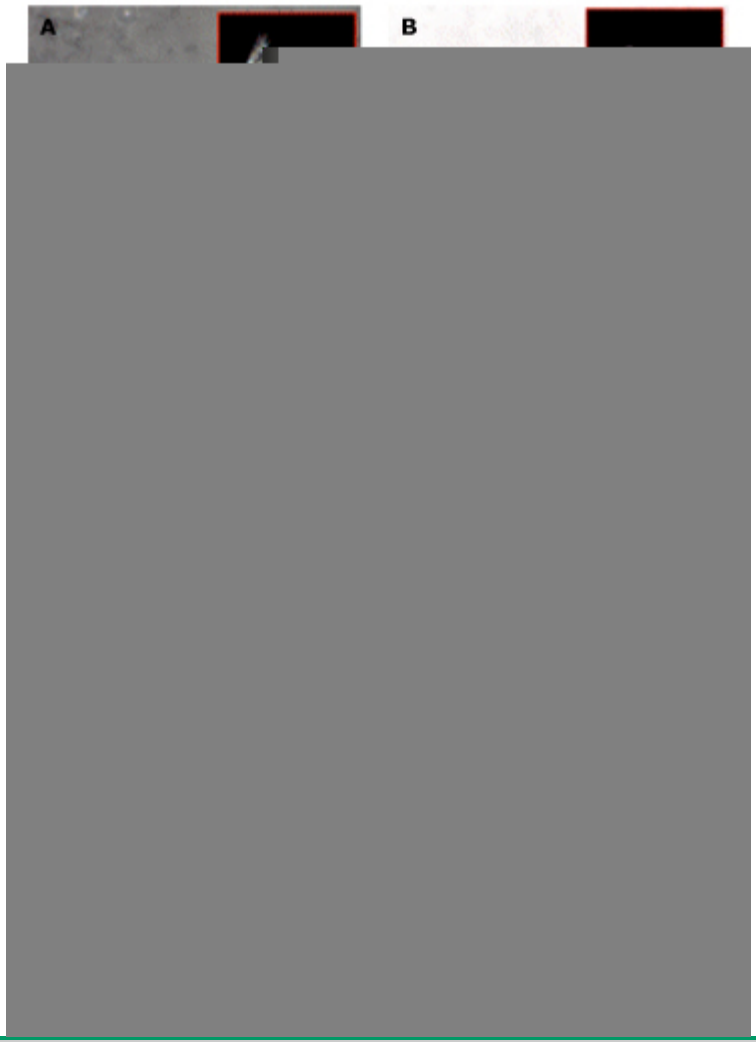


Renal biopsy from a patient treated with atazanavir demonstrates crystals within the tubular lumen and renal parenchyma.
(A) Needle-shaped atazanavir crystals within the tubular lumen.
(B) Atazanavir crystals within the renal parenchyma associated with granuloma formation.

Reproduced with permission from: Izzedine H, M'rad MB, Bardier A, et al. Atazanavir crystal nephropathy. AIDS 2007; 21:2357. Copyright © 2007 Lippincott Williams & Wilkins.

Graphic 77824 Version 12.0

Photomicrographs showing urine sediment of a patient with ciprofloxacin crystalluria

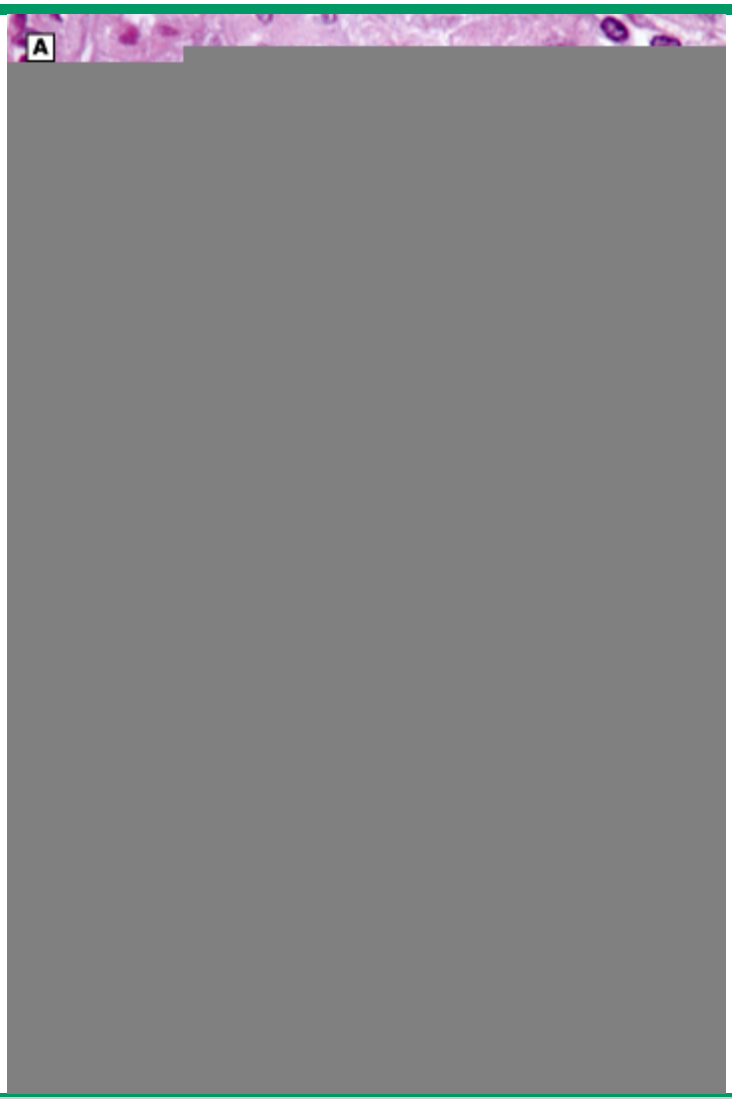


(A) Needles, (B) sheaves, (C) stars, and (D) bizarre shape. Crystals in A, C, and D are visualized under phase contrast microscopy, while those in B are seen with bright field microscopy. The crystals are shown with polarizing microscopy on the inset panels.

Reproduced with permission from: Fogazzi, GB, Garigali, G, Brambilla, C, Daudon, M. Ciprofloxacin crystalluria. Nephrol Dial Transplant 2006; 21:2982. Copyright ©2006 Oxford University Press.

Graphic 50067 Version 4.0

Light micrograph of kidney biopsy with ciprofloxacin crystals within tubular lumen



(A) Hematoxylin and eosin staining shows needle-shaped stellate crystals.
(B) Ciprofloxacin crystals within the tubule polarize.

Reproduced with permission from: Stratta, P, Lazzarich, E, Canavese, C, et al. Ciprofloxacin crystal nephropathy. Am J Kidney Dis 2007; 50:330. Copyright ©2007 Elsevier.

Graphic 62878 Version 4.0

Contributor Disclosures

Mark A Perazella, MD, FACP Nothing to disclose **Paul M Palevsky, MD** Grant/Research/Clinical Trial Support: Spectral Medical [Sepsis (Endotoxin assay)]. Consultant/Advisory Boards: Baxter [Dialysis (Hemodialysis equipment, peritoneal dialysis equipment and supplies, continuous renal replacement therapy equipment and solutions)]; Stealth Biotherapeutics [AKI]. **Alice M Sheridan, MD** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy