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*Case Report*

# N4-acetyl-sulfamethoxazole stone in a patient on chronic trimethoprim/sulfamethoxazole therapy: a case report and literature review

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**Abstract:** Though early antibiotic sulfonamides had poor urine solubility and resulted in urine crystalluria and urolithiasis, sulfamethoxazole urolithiasis is a rare phenomenon. In our case report, we describe a patient with N4-acetyl-sulfamethoxazole (metabolite of sulfamethoxazole) urolithiasis that developed after prolonged exposure to trimethoprim/sulfamethoxazole (TMP-SMX). Prior to stone formation, our patient had a total colectomy and end ileostomy created after an episode of toxic megacolon secondary *Clostridium difficile*. He also had benign prostatic hypertrophy and chronic urinary retention. These specific metabolic conditions, including dehydration leading to higher urinary concentration, urinary stasis, and low urinary pH may have predisposed our patient to this rare condition. Our patient's stones were then imaged under light microscopy and scanning electron microscopy (SEM). It was found to be comprised of rectangular shaped crystals. To our knowledge, this is the first time these stone crystals have been imaged with SEM.

**Keywords:** Kidney stone, urolithiasis, sulfamethoxazole, trimethoprim

## Introduction

Sulfamethoxazole in combination with trimethoprim has been a mainstay of antibiotic therapy since the 1970s. Both substrates target bacterial biosynthesis of folic acid [1] to inhibit bacterial growth. It is mostly available as an oral antibiotic and used to treat common bacterial infections of the urinary tract, respiratory tract, and skin. Early antibiotic sulfonamides developed in the 1930s had poor urine solubility and resulted in urine crystalluria and urolithiasis, which were well known complications of sulfonamide therapy at that time [2, 3]. Subsequently, sulfonamides with higher urine solubility have been developed and sulfa-drug induced crystalluria now occurs rarely [3-7]. Here we describe our case of a patient with N4-acetyl-sulfamethoxazole urolithiasis which developed after prolonged exposure to trimethoprim/sulfamethoxazole (TMP-SMX).

## Materials and methods

Our patient was a 72-year-old male who initially underwent L1-2, L2-3, L3-4, and L4-5 laminectomy surgery with hardware placed in February of 2020 (3 years prior) for lumbar spinal stenosis. His postoperative course was complicated by *Serratia marcescens* and *Candida parapsilosis* surgical site infections requiring multiple revision surgeries and antibiotic courses. In December of 2020, he developed fulminant *Clostridium difficile* colitis with toxic megacolon, ultimately requiring total colectomy and end ileostomy. Following this, he was placed on TMP-SMX and fluconazole indefinitely for suppression of his chronic spinal hardware infection. An abdominopelvic computed tomography (CT) scan in June of 2022 was normal, as part of routine preoperative imaging prior to ileostomy reversal. On the day of his planned ileostomy reversal in September 2022, Urology performed ureteral catheterization and bilateral retrograde pyelography to assist with intra-abdominal ureteral identification. On left retrograde pyelography, he was found to have severe left sided hydroureteronephrosis. An indwelling ureteral stent was left, and the Ileostomy reversal was aborted. A CT scan was performed in October of 2022 and showed a 1 cm left lower

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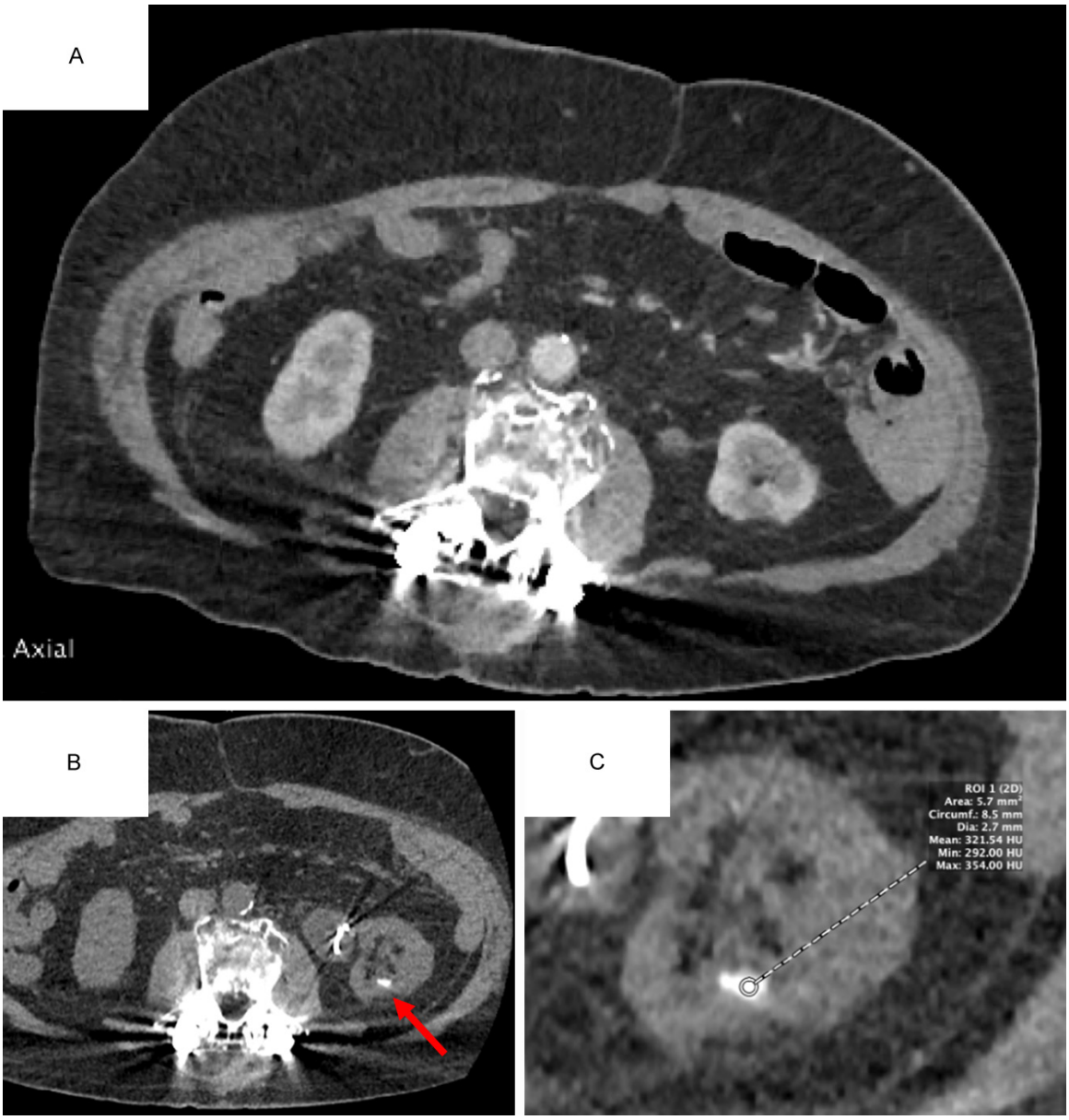


**Figure 1.** A. Computed tomography (CT) of the abdomen demonstrates no stone in the left kidney. B. CT of the abdomen demonstrates a left lower pole (red arrow) stone 4 months later. C. Left lower pole stone measures 321 Hounsfield units (HU).

pole stone (mean Hounsfield units (HU) 321; **Figure 1**). This was treated with ureteroscopy/stone extraction. A stone analysis was not performed at that time, as there was not an adequate specimen. No anatomic anomaly of the left ureter was identified, and the hydronephrosis resolved. Despite complete stone clearance, he developed a new 13 mm left lower pole stone (mean HU 206) and two small right renal stones in the span of 1 month (**Figure 2**). He also developed bladder stones during this time. He had a history of BPH, TURP, urethral stricture disease with prior dilation, and bladder dysfunction with significant bladder trabeculations. He elected for surveillance at that time. He notably passed multiple stones in the ensuing months. He brought these stones in during his follow up visit in May of 2023, and stone analysis (infrared spectroscopy, Quest Diagnostics©, Secaucus, NJ) revealed N4-Acetyl-Sulfamethoxazole (**Figure 3**). At that point, antimicrobial therapy was discontinued

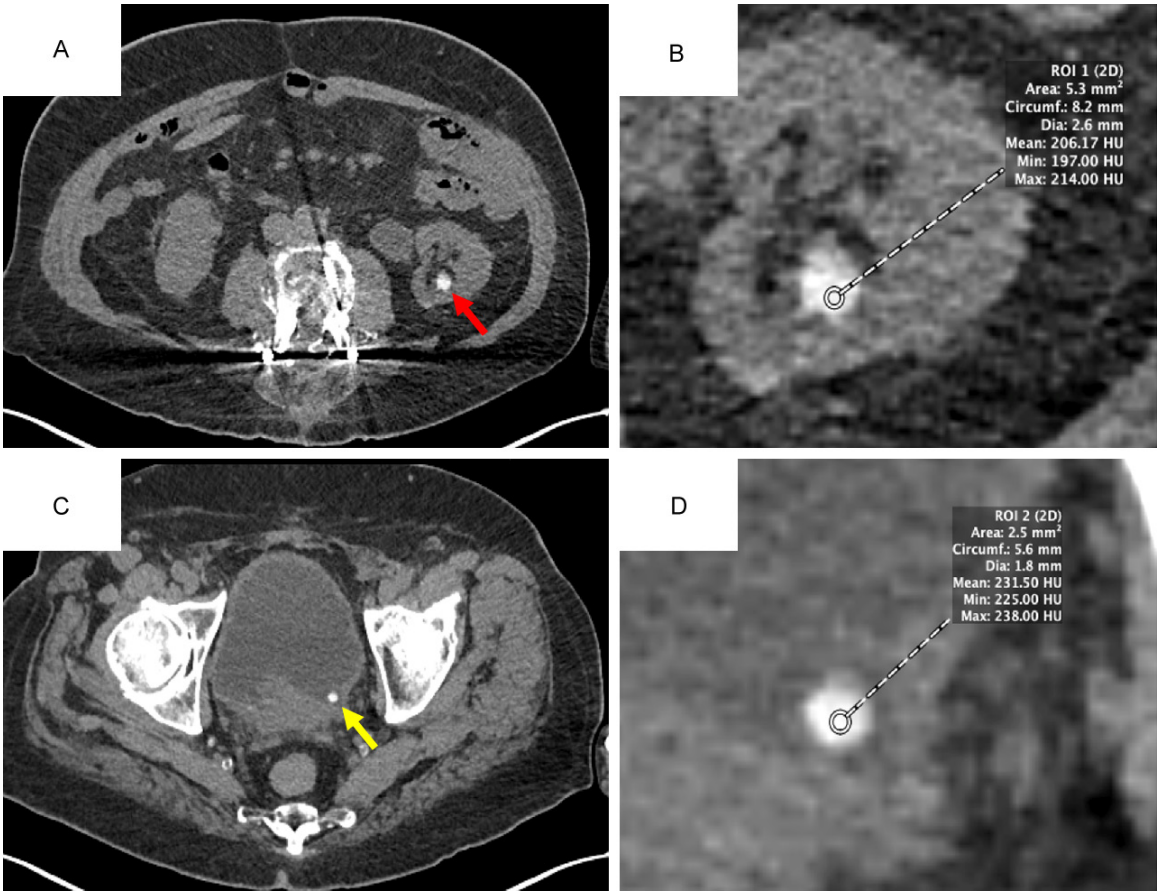


**Figure 2.** A. CT of the abdomen and pelvis demonstrates new stone growth (red arrow) in the left kidney 1 month after treatment. B. Left kidney stone averages 206 HU. C. The same CT study demonstrates a bladder stone (yellow arrow). D. The bladder stone averages 232 HU.

due to risk of ongoing therapy outweighing potential benefits. He last passed a stone shortly after stopping trimethoprim/sulfamethoxazole in June 2023. Surveillance renal/bladder ultrasounds in July 2023 and March 2024 did not show any evidence of stone, and he has had no recurrence of infection symptoms related to his spine.

## Discussion

Early sulfonamides were commonly implicated in urolithiasis formation, dating back to the 1940s [8]. Specifically, acetylated metabolites had a tendency to precipitate and crystalize in renal tubules, causing oliguria or anuria, or in the collecting system resulting in stone formation [9]. The development of sulfonamides with greater solubility has decreased the incidence of sulfonamide-induced urolithiasis substantially. Sulfamethoxazole was introduced in 1961, and now, in combination with trimethoprim, is on the World Health Organization Model List of Essential Medicines [10]. Urolithiasis derived from sulfamethoxazole is rare despite widespread use of sulfamethoxazole throughout the world. Sulfamethoxazole and N4-acetyl-sulfamethoxazole have losangic shaped crystals, which may contribute to low lithogenic potential [8]. Factors that may predispose patients to sulfonamide crystallization include urine concentration, degree of acetylation, urinary stasis, urine pH (acidic), and urine temperature [11]. We know the degree of acetylation for our known stone compound, and we can assume that our patient's temperature remained relatively constant. We therefore will focus on urinary concentration, urinary stasis, and urine pH in examining our patient's predisposition for calculus formation.

Given the rapid absorption of sulfamethoxazole after oral administration (peak serum concentration is 1-4 hours after administration, and $T_{½}$

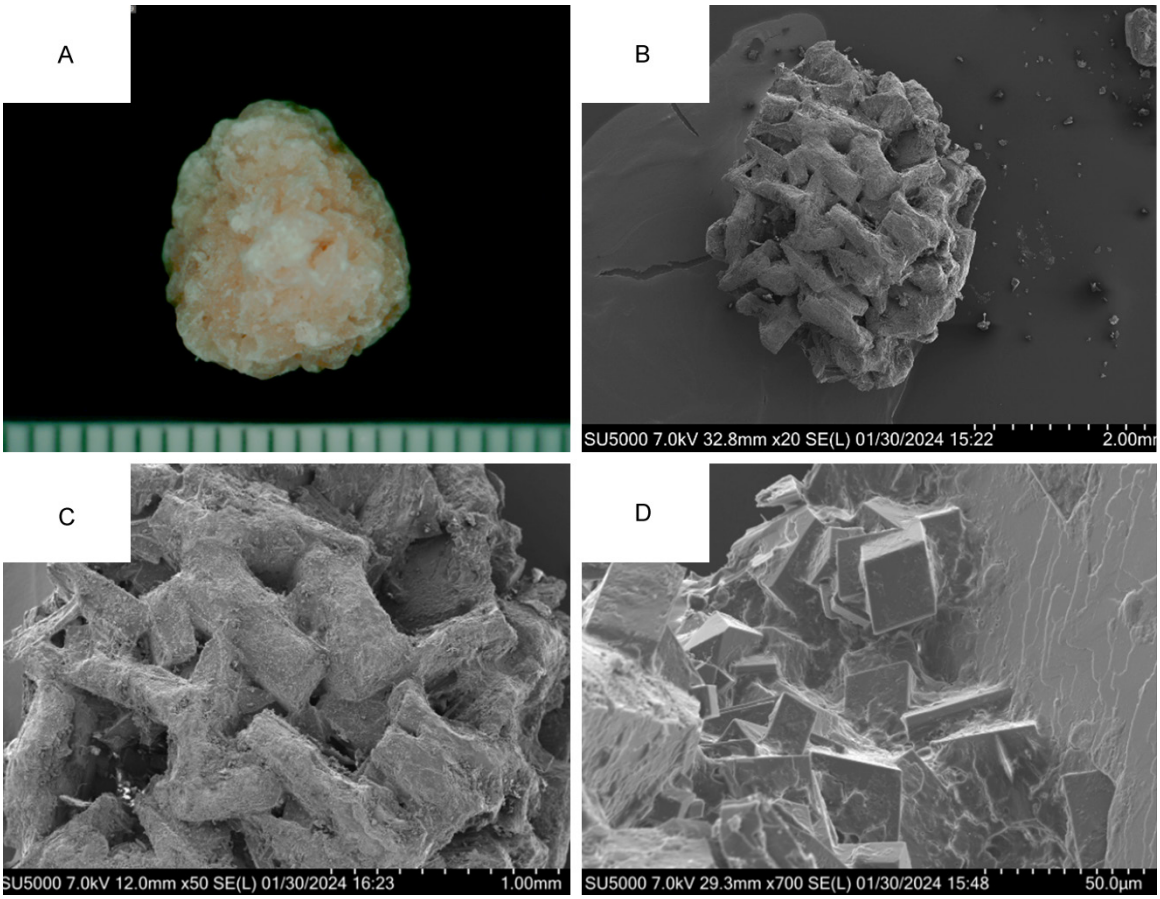


**Figure 3.** A. N4-acetyl-sulfamethoxazole stone under light microscopy. B. Scanning electron microscopy (SEM) ×20 of the N4-acetyl-sulfamethoxazole stone. C. SEM ×50 of the N4-acetyl-sulfamethoxazole stone. D. SEM ×700 of the N4-acetyl-sulfamethoxazole stone.

is 10 hours), our patient's colonic resection is unlikely to have altered absorption of sulfamethoxazole significantly [12, 13]. Once absorbed, sulfamethoxazole is metabolized in the liver by cytochrome P450 2C9 (CYP2C9) to N4-acetyl, N4-hydroxy, 5-methylhydroxy-, N4-acetyl-5-methylhydroxy-sulfamethoxazole metabolites, and an N-glucuronide conjugate. Notably, our patient was also taking fluconazole, which is an inhibitor of CYP2C9. This would therefore decrease conversion to the N4-acetyl-sulfamethoxazole and not further predispose to crystal formation.

Sulfamethoxazole and its metabolites are excreted renally via glomerular filtration and tubular secretion. Impaired renal function will increase half-life. Normal breakdown of sulfamethoxazole and its metabolites are excreted as follows: 20% excreted as sulfamethoxazole, 15-20% N-glucuronide conjugate, and 50-70% N4-acetyl-sulfamethoxazole [14]. The longer half-life in our renally impaired patient might have provided a greater opportunity for conversion of sulfamethoxazole to N4-acetyl-sulfamethoxazole, increasing renal concentration. Dehydration from his colonic resection may also further concentrate urine and predispose to crystal formation.

Our patient has a long history of benign prostatic hypertrophy (BPH) and underwent transurethral resection of prostate in 2014 and again in 2018. During his hospitalization for toxic megacolon, he was found to be in acute urinary retention requiring foley catheter placement. In subsequent follow up visits, he passed his voiding trial, but he consistently had elevated post-void residual volume of around 100 mL. He also had chronic left sided hydronephrosis, though there was no evidence of left sided ureteral obstruction. Each of these condi-

tions could represent some degree of urinary stasis, predisposing to urolithiasis. Additionally, our patient's pH on urinalysis was consistently 5.5 and 5, further predisposing to sulfonamide crystallization.

After the stone analysis was performed, the stones were then imaged under light microscopy and scanning electron microscopy (SEM). It was found to be comprised of rectangular shaped crystals (**Figure 3**). To our knowledge, this is the first time these stone crystals have been imaged with SEM.

## Conclusion

Sulfamethoxazole-derived urolithiasis is rare. In this case report, we describe our patient with N4-acetyl-sulfamethoxazole renal and bladder calculi. In addition to long-term antimicrobial prophylaxis with TMP-SMX, specific metabolic factors, including dehydration leading to higher urinary concentration, urinary stasis secondary to chronic urinary retention and chronic unilateral hydronephrosis, and urinary acidity may have predisposed our patient to this rare condition.

## Disclosure of conflict of interest

None.

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