

# Cefazolin-Related Acute Interstitial Nephritis with Associated Nephrotic-Range Proteinuria: A Case Report

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**Abstract** A 67-year-old male with history of well controlled type 2 diabetes mellitus and hypertension developed acute interstitial nephritis (AIN) with nephrotic-range proteinuria during treatment with cefazolin for methicillin-sensitive *Staphylococcus aureus* and Group B *Streptococcus* (GBS) bacteremia. The patient received intravenous cefazolin 2 g every 8 h for 4 weeks prior to presentation to the emergency department with abdominal distension, nausea, and vomiting. Investigations revealed a serum ascites albumin gradient of 1.0 with total protein of 1.8 g/dL suggestive of nephrotic syndrome, which was confirmed with a spot urine protein/creatinine ratio that estimated 7.95 g of protein per day. Serum creatinine was elevated compared with baseline. Urine studies showed sterile pyuria with 3+ protein and eosinophiluria. The patient was diagnosed with AIN with nephrotic-range proteinuria associated with cefazolin use. Cefazolin was discontinued and, within a couple of days, the patient's creatinine stabilized. He was discharged with prednisone 60 mg once a day for 10 days with a taper over 2 weeks for his AIN. The patient's creatinine and proteinuria slowly decreased over the next couple of weeks, however, did not recover to baseline. A Naranjo assessment score of 6 was obtained, indicating a probable relationship between the patient's AIN with nephrotic-range proteinuria and his use of cefazolin.

## Abbreviations

AIN Acute interstitial nephritis

MSSA Methicillin-sensitive *Staphylococcus aureus*  
GBS Group B streptococcus

## Key points

Patients on cefazolin may develop acute interstitial nephritis (AIN) with associated nephrotic-range proteinuria.

Although nephrotic-range proteinuria is rare with AIN, its presence should not delay discontinuation of the suspected drug if AIN is clinically suspected.

Given that AIN can present with minimal symptoms, it can be helpful to monitor creatinine when starting a new medication that has been implicated to cause AIN.

## Introduction

Acute interstitial nephritis (AIN) is an under-diagnosed cause of acute to subacute kidney injury. The most common etiology of AIN is drug induced. Many classes of drugs can cause AIN, including but not limited to antibiotics, antivirals, anticonvulsants, analgesics, proton pump inhibitors, and diuretics [1]. AIN with associated nephrotic-range proteinuria is very rare, occurring in < 1% of cases of AIN [2]. This is the first case report of a patient who developed AIN with nephrotic-range proteinuria during treatment with cefazolin.

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## Case Report

A 67-year-old male with history of well controlled type 2 diabetes mellitus and hypertension presented to the emergency department for abdominal distension with nausea and vomiting. One month prior to presentation, the patient was hospitalized for methicillin-sensitive *Staphylococcus aureus* (MSSA) and Group B *Streptococcus* (GBS) bacteremia and was discharged on intravenous cefazolin 2 g every 8 h. The patient's creatinine and complete blood count were monitored weekly as an outpatient during his antibiotic therapy. Two weeks after being on home intravenous cefazolin, his creatinine increased from a baseline of 1.0 to 2.3 mg/dL. He developed progressively worsening nausea and vomiting with abdominal pain, eventually leading to inability to tolerate oral intake.

On physical exam, vitals were within normal limits except for blood pressure in the 180 s/90 s. No jaundice was noted. Abdominal exam showed a tense, distended abdomen that was diffusely tender to palpation with fluid waves. Extremities revealed bilateral 2+ pitting edema up to the thighs. The rest of the physical exam was unremarkable.

The patient had a normal leukocyte count with eosinophilia (white blood cell [WBC] 5600/ $\mu$ L; eosinophils 7.0%) thrombocytopenia (103,000/ $\mu$ L), and normocytic anemia (hemoglobin 9.3 g/dL; mean corpuscular volume [MCV] 95 pg). He had low albumin (2.2 g/dL), elevated blood urea nitrogen (56 mg/dL), and elevated creatinine (1.8 mg/dL with baseline creatinine of 1.0) but normal electrolytes and liver enzymes. Urinalysis displayed 3+ protein, 2+ blood, 19 WBC, and eosinophiluria. Urine sediment exam revealed many WBCs with WBC casts, red blood cells (RBCs) but no RBC casts. Urine spot protein/creatinine ratio gave an estimation of 7.95 g of protein per day. Diagnostic paracentesis showed 28 neutrophils and a serum albumin ascites gradient of 1.0 with a protein of 1.8 mg/dL, which suggested that the ascites was likely secondary to nephrotic syndrome (Table 1).

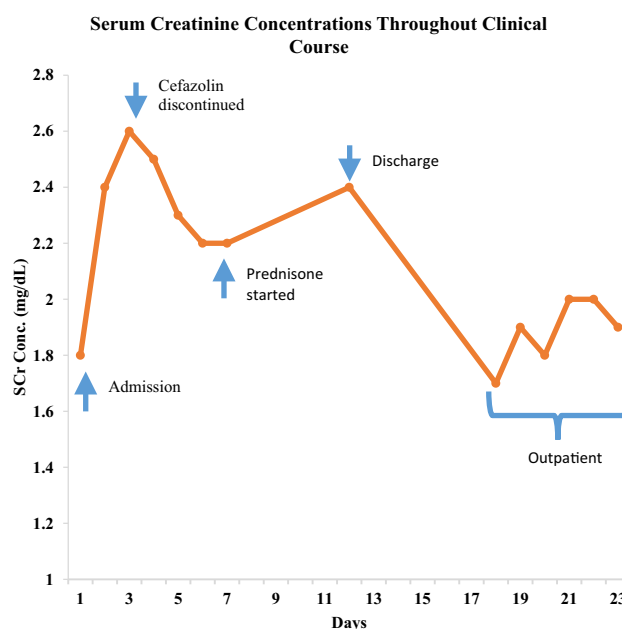
The findings were consistent with AIN caused by cefazolin as the time course of the acute kidney injury

**Table 1** Interpretation of ascites fluid based on ascites fluid analysis (serum albumin ascites gradient of 1.0 with a protein of 1.8 mg/dL); our patient had fluid consistent with nephrotic syndrome

Interpretation of ascites fluid	Serum ascites albumin gradient	
	< 1.1 g/dL	$\geq$ 1.1 g/dL
Total protein (g/dL)		
< 2.5	Nephrotic syndrome	Cirrhosis
$\geq$ 2.5	Cancer, tuberculosis	Heart failure

coincided with the use of the antibiotic. This was further supported by the peripheral eosinophilia, eosinophiluria (not quantified) with sterile pyuria, and microhematuria. However, AIN very rarely causes nephrotic-range proteinuria so an extensive workup of the nephrotic syndrome was done. Although the patient had a history of type 2 diabetes mellitus and hypertension, diabetic and hypertensive nephropathies were less likely given the subacute process of the acute kidney injury. The patient had a stable creatinine with intermittent trace proteinuria for years including during his last admission for the MSSA/GBS bacteremia 4 weeks prior. Rapid plasma reagin (RPR) and HIV tests were negative. C4 was normal, C3 was mildly low (69 mg/dL). Serum and urine electrophoresis and Free Kappa/Lambda light chain tests were unremarkable. Renal ultrasound showed no hydronephrosis.

The patient refused a kidney biopsy for definitive diagnosis; however, given the clinical picture, we hypothesized that cefazolin was related to the AIN with nephrotic range proteinuria. The diagnosis was delayed because of a combination of factors: the nephrotic syndrome workup, consultation with infectious disease services to discuss the safety of discontinuing the antibiotic, and the fact that cefazolin causing AIN was incredibly rare in the literature. The patient was initially continued on cefazolin during which time his creatinine worsened from 1.8 to 2.6 mg/dL. Once the diagnosis was made, cefazolin was discontinued immediately, and his creatinine stabilized and decreased to 2.4 mg/dL on discharge (Fig. 1).



**Fig. 1** Plot of the patient's serum creatinine throughout his clinical course from admission to primary-care outpatient follow up

Patient was discharged with prednisone 60 mg once a day for 10 days with a subsequent taper to 40 mg to 30 mg-20 mg-10mg-5 mg once a day for 3 days for his AIN. Patient's creatinine slowly decreased over the next couple of weeks, reaching a nadir of 1.7 mg/dL, however, did not recover to baseline. Unfortunately, the patient was lost to nephrology outpatient follow-up so a repeat urine spot protein/creatinine ratio was not repeated. Repeat urine dipstick done at a primary-care appointment showed improved proteinuria from 3+ (threshold of 300 mg/dL) to 2+ (threshold of 100 mg/dL) within 2 weeks of discharge.

## Discussion

AIN is primarily iatrogenic. Although other etiologies include infectious, autoimmune, and idiopathic, drug-induced AIN accounted for 71.1% of all cases of AIN according to a large retrospective pooled study by Baker and Pusey [3]. Methicillin was one of the first drugs to be implicated as a cause of AIN, with one study showing 17% of patients developing AIN if on methicillin for more than 10 days [4].

AIN is classically thought to have a triad of rash, eosinophiluria, and fever; however, a recent retrospective pooled study showed that rash, eosinophiluria, and fever were only present 22, 35, and 36% of the time, respectively [2]. One study showed that eosinophiluria, by itself, only had a sensitivity of 40% and a positive predictive value of around 38% [5]. The more common abnormal studies were microhematuria and sterile pyuria, which were reported 67 and 82% of the time, respectively [2]. Our patient's urinalysis revealed sterile pyuria, microhematuria, and eosinophiluria, all of which are present in AIN. Additionally, cefazolin was the only change that occurred prior to admission, and once cefazolin was discontinued, there was immediate stabilization and improvement in creatinine. This was highly suggestive that cefazolin caused the acute kidney injury.

This case report illustrates that AIN can commonly present with little to no symptoms. Although our patient's creatinine rose from a baseline of 1.0 to 2.3 mg/dL within 2 weeks, the only reason that the patient presented to the emergency department was because of his tense ascites secondary to his nephrotic-range proteinuria. Physicians should have high index of suspicion for AIN, especially if the patient recently started a new medication.

There are dozens of classes of drugs that have been reported to cause AIN; however, only a select few have been known to cause AIN with nephrotic-range proteinuria, the most well established being non-steroidal anti-inflammatory drugs (NSAIDs). AIN causes interstitial edema that, over time, can spread to and damage the tubules

causing proteinuria. Specifically, cephalosporins have been implicated in causing a hypersensitive allergic reaction and mitochondria injury to the tubular cells via inhibition of fatty acid and carnitine transport systems [6]. Although glomerular damage is rare, the interstitial inflammatory response, over time, can spread to Bowman's capsule. NSAIDs are hypothesized to cause AIN via an alternative pathway by shunting arachidonic acid metabolites into immune-modifying pathways causing glomerular damage and nephrotic-range proteinuria [7]. Although cefazolin has not been implicated in a similar mechanism of action, we believe that the length of treatment (4 weeks) prior to diagnosis of AIN may have contributed to a more severe kidney injury with spread of the interstitial inflammatory response to the glomeruli causing nephrotic-range proteinuria.

Cefazolin has been associated with AIN in only a handful of reported cases, none of which had a nephrotic-range proteinuria. A case report by Fredericks et al. described a case of acute renal failure after initiation of cefazolin and gentamicin therapy [8]. Urine protein analysis only showed trace proteinuria. The patient fully recovered his renal function after discontinuation of both antibiotics.

Treatment of drug-induced AIN consists primarily of discontinuing the offending agent and supportive care [9]. Our patient's blood counts and renal function were monitored while on cefazolin, as per the Infectious Diseases Society of America (IDSA) guidelines. His nephrotic syndrome initially undermined the diagnosis of AIN, which led to the delay of cefazolin discontinuation. Steroids are often used to treat AIN; however, the evidence is mixed with one retrospective study in Spain showing significant improvement in serum creatinine with steroid use and another in the United States revealing no benefit [10, 11]. Unfortunately, 30–70% of all patients who developed AIN never regained their baseline kidney function [2].

## Conclusion

This case report presents a patient with cefazolin-induced AIN with associated nephrotic-range proteinuria. AIN should be suspected whenever there is an unexplained increase in creatinine, especially after initiation of a new medication. Although nephrotic-range proteinuria is rare with AIN, its presence should not delay discontinuation of the causative drug if AIN is clinically suspected. Hence, for patients who need to be treated with outpatient parenteral antibiotic(s) for 4–6 weeks, it is imperative to monitor weekly laboratory studies as recommended by IDSA guidelines.

### Compliance with ethical standards

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**Informed consent** Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent may be requested for review from the corresponding author.

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