ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 4, 2025

Online - 2455-3891
Print - 0974-2441

Case Study

CEPHALOSPORINS AS A POTENTIAL RISK FACTOR FOR UROLITHIASIS: A CASE-CONTROL STUDY

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Received: 22 January 2015, Revised and Accepted: 10 March 2025

ABSTRACT

The study aimed to explore the impact of *Oxalobacter formigenes* colonization and cephalosporin antibiotic treatment on urinary oxalate, calcium, and citrate levels, with a focus on evaluating the bacterium's role in mitigating the risk of calcium oxalate kidney stone formation. An observational, case–control study was conducted involving 350 controls and 280 kidney stone patients. Participants were stratified based on recent cephalosporin use and *O. formigenes* colonization. Results demonstrated that *O. formigenes* colonized individuals consistently exhibited lower urinary oxalate and calcium levels and higher citrate levels than noncolonized counterparts. Cephalosporin treatment exacerbated urinary biochemical imbalances, further increasing oxalate and calcium excretion while reducing citrate levels, particularly in non-colonized individuals. This highlights the protective role of *O. formigenes* in maintaining urinary biochemical homeostasis and reducing kidney stone risk. The findings underscore the need for strategies to preserve gut microbiota, especially *O. formigenes*, during antibiotic therapy to mitigate metabolic consequences and prevent urolithiasis.

Keywords: Cephalosporins, Gut microbiota, Kidney stones, *Oxalobacter formigenes*, Urinary oxalate.

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i4.53944. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Antibiotic therapy has revolutionized modern medicine, saving countless lives by effectively treating bacterial infections. However, the unexpected consequence of these life-saving treatments is their profound impact on the gut microbiota, a complex ecosystem of microorganisms that play critical roles in maintaining human health. The disruption of this microbial community, often referred to as symbiosis, can lead to a cascade of metabolic and immunological consequences [1].

Cephalosporins are one of the most commonly prescribed classes of antibiotics due to their broad-spectrum activity against a wide range of Gram-positive and Gram-negative bacteria. These antibiotics are widely used in treating infections of the respiratory tract, urinary tract, skin, and other tissues [2]. Despite their effectiveness, cephalosporins can inadvertently eliminate beneficial gut microbes along with pathogenic ones. This collateral damage is particularly concerning for bacteria like *Oxalobacter formigenes*, which are known to provide significant health benefits [3].

O. formigenes is an obligate anaerobic bacterium that resides in the colon and plays a unique role in human oxalate metabolism. It degrades oxalate, a metabolic byproduct found in many foods, into formate and carbon dioxide, preventing its absorption into the bloodstream [4,5]. By reducing the intestinal oxalate pool, *O. formigenes* decreases the renal excretion of oxalate, which is a major component of calcium oxalate in urine, and can lead to calcium oxalate stone formation. The incidence of urinary stones continues to rise, and current therapeutic interventions remain limited. Urolithiasis affects approximately 12% of the global population [6].

The absence of significant reduction of *O. formigenes* in the gut microbiota has been strongly correlated with an increased risk of developing calcium oxalate kidney stones [7]. The bacterium's dependence on the anaerobic environment of the colon and its susceptibility to broad-spectrum antibiotics further exacerbate the risk of its depletion during antibiotic treatment [8,9].

Understanding the relationship between cephalosporin use and *O. formigenes* prevalence is essential for evaluating the broader implications of antibiotic therapy on kidney stones and gut health. Despite its importance, there is limited data on how recent antibiotic exposure affects *O. formigenes* colonization [10,11]. We carried out this investigation to determine whether cephalosporins have an impact on *O. formigenes* colonization in the human gastrointestinal system and to examine potential relationships between kidney stones and *O. formigenes* colonization.

This study aims to provide insights into whether the presence of *O. formigenes* affects urinary oxalate, citrate, and calcium levels and how cephalosporins use influences this relationship, into the unintended metabolic consequences of antibiotic therapy, and to inform strategies for preserving gut microbiota health to reduce urolithiasis risk. The objective of the investigation is to determine the availability of *O. formigenes* in individuals administered with 5–7 days of cephalosporins 3 months before the index date and individuals who had not taken cephalosporins for at least 3 months.

METHODS

An observational, case–control study was conducted after getting the study protocol approval from the Subham Ethics Committee of Chennai (ECR/323/Indt/TN/2020). In the case of independent sample t-tests, we assumed a mean difference of 8.5%, a standard deviation of 0.05, and a power of 80%. Our sample size was then calculated using the PS power and sample size calculator [12].

In the current study, control subjects, 350 individuals (aged 24–54 years) without kidney stone disease were recruited. In that, 240 controls had not taken antibiotics in the past 3 months, while 110 had taken antibiotics in the past 3 months.

During the study, 280 patients with kidney stones (aged 24–54 years) were enrolled. In those 188 cases had taken antibiotics in the past 3 months, while 92 had taken antibiotics in the past 3 months. The presence or absence of *O. formigenes* in both the case and control groups was assessed through urine analysis.

***O. formigenes* oxalate, citrate, and urinary calcium determination**

After getting written informed consent, patients were subjected to urine sample examination to determine the *O. formigenes* and urinary calcium and oxalate levels [13]. The study involves two main groups.

Case group

Patients who meet certain study criteria and are considered as cases.

Control group

Patients who serve as a comparison group to the cases. Each of these main groups (case and control) is further divided into two sub-groups (Group I and Group II) based on their history of cephalosporin use.

Group I

Patients who had not taken cephalosporins for a period of 3–12 months.

Group II

Patients on cephalosporins for at least 5–7 days 3 months before the index date.

Urine samples were taken from the case and control groups over 24 h. Using a commercial kit (Sigma Diagnostics, Inc., MO, USA), urinary oxalate excretion was measured [14,15]. An automated analyzer was used to measure the quantities of calcium and citrate in the urine. A comparison was made between the baseline levels of calcium and oxalate in the urine and previously published normal values (calcium 100–350 mg/24 h, oxalate <24 mg/24 h, citrate >320 mg/24 h) [16].

Statistical analysis

The data was analyzed using GraphPad Prism software, and the significance level (p-value; p≤0.05) was determined using an independent t-test (unpaired) [17,18].

RESULTS AND DISCUSSION

O. formigenes: *O. formigenes* is a gut bacterium known to degrade oxalate, which helps in reducing oxalate levels in the body. Lower mg/24 h values in *O. formigenes*-positive individuals suggest that this bacterium is actively metabolizing oxalate, reducing its excretion. Higher values in *O. formigenes*-negative individuals have less oxalate degradation, leading to higher excretion levels in urine. Cephalosporin antibiotics might be disrupting the gut microbiota, including *O. formigenes* [19].

Urinary oxalate levels in case and control groups are explained in Table 1. In the control group, individuals colonized with *O. Formigenes* had urinary oxalate levels of 25 mg/24 h, compared to 31 mg/24 h in non-colonized individuals. Among patients without cephalosporin treatment, *O. formigenes*-positive individuals had urinary oxalate levels of 31 mg/24 h, while negative individuals had levels of 47 mg/24 h. In patients treated with cephalosporins, the levels increased further, with 32 mg/24 h in colonized individuals and 45 mg/24 h in non-colonized ones. This suggests that the absence of *O. formigenes* excretes more oxalate, suggesting a higher risk for conditions like kidney stones. Cephalosporins may influence oxalate metabolism, potentially by affecting *O. Formigenes* levels.

Urinary calcium levels showed a distinct upward trend across all groups, as shown in Table 2. In the control group, the median urine calcium level in people with *O. formigenes* was 258 mg/24 h, while the median level in people without *O. formigenes* was higher at 290 mg/24 h. This implies that the presence of *O. formigenes* may be linked to decreased calcium excretion in the urine, perhaps as a result of its function in lowering intestinal oxalate absorption. In patients (no cephalosporins): urinary calcium levels in patients without *O. formigenes* are greater (387 mg/24 h) than in those with *O. formigenes* (311 mg/24 h). Compared to the control group, the difference is much more noticeable in this patient group, indicating that *O. formigenes* may be important in controlling calcium excretion, especially in those with underlying medical disorders. In patients (cephalosporins), urinary calcium levels in *O. formigenes*-positive and -negative persons are identical (432 mg/24 h). This suggests that any variations in the two groups' urine calcium excretion are eliminated by the use of cephalosporins. Given that *O. formigenes* and other gut microbiota can be disrupted by cephalosporins, antibiotic exposure may lessen or even eradicate the bacterium's capacity to affect calcium metabolism.

Lower urine calcium levels in those colonized by *O. formigenes* indicate a protective function in calcium metabolism. The risk of kidney stones may increase in those who lack *O. formigenes* because they excrete more calcium. This difference is eliminated by using cephalosporins, most likely due to disruption of gut microbiota.

Urinary citrate plays a crucial role in preventing kidney stone formation by binding to calcium and inhibiting crystallization.

Urinary citrate levels demonstrated a decline in both *O. formigenes* positive and negative individuals across groups, as shown in Table 3. In the control group, positive individuals had citrate levels of 320 mg/24 h

Table 1: Urinary oxalate levels in individuals with and without *O. formigenes* colonization. Statistical analysis performed by student's t-test for unpaired samples

Group	*O. formigenes* (+ve) mg/24 h median	*O. formigenes* (−ve) mg/24 h median	p-value
Control	25	31	0.076
Patients (No cephalosporins)	31	47	0.004
Patients (Cephalosporins)	32	45	0.002

O. formigenes: Oxalobacter formigenes

Table 2: Urinary calcium levels in individuals with and without *O. formigenes* colonization. Statistical analysis performed by student's t-test for unpaired samples

Group	*O. formigenes* (+ve) (mg/24 h) median	*O. formigenes* (−ve) (mg/24 h) median	p-value
Control	258	290	0.056
Patients (No cephalosporins)	311	387	0.032
Patients (Cephalosporins)	432	432	0.001

O. formigenes: Oxalobacter formigenes

Table 3: Urinary citrate levels in individuals with and without *O. formigenes* colonization. Statistical analysis performed by Student's t-test for unpaired samples

Group	*O. Formigenes* (+ve) (mg/24 h) median	*O. Formigenes* (−ve) (mg/24 h) median	p-value
Control	320	290	0.073
Patients (No cephalosporins)	278	269	0.041
Patients (cephalosporins)	254	212	0.032

O. formigenes: Oxalobacter formigenes

compared to 290 mg/24 h in negative individuals. This implies that colonization by *O. Formigenes* may be linked to increased amounts of citrate in the urine, which may lower the incidence of kidney stones.

In patients without cephalosporins, citrate levels decreased to 278 mg/24 h in positive individuals and 269 mg/24 h in negative individuals. The lowest levels were seen in cephalosporin-treated patients, with 254 mg/24 h in colonized individuals and 212 mg/24 h in non-colonized ones. This indicates that both the absence of *O. formigenes* and cephalosporin treatment contribute to reduced citrate excretion. Higher urinary oxalate levels were observed in individuals without *O. formigenes* colonization, especially in those treated with cephalosporins. This reinforces the protective role of *O. formigenes* in degrading oxalate and reducing its renal excretion. The absence of *O. formigenes* due to antibiotic treatment exacerbates oxalate levels, increasing the risk of kidney stone formation. Noncolonized individuals consistently exhibited higher calcium excretion across all groups, which was further amplified in cephalosporin-treated patients. This suggests that *O. formigenes* may contribute to calcium homeostasis, and its absence, coupled with antibiotic use, promotes calcium loss via urine.

Citrate levels declined in both colonized and non-colonized individuals, with the lowest levels observed in cephalosporin-treated patients without *O. formigenes*. Higher urine citrate levels in those colonized by *O. formigenes* may help lower the risk of kidney stones. Citric acid levels are lower in patients, particularly those without *O. formigenes*, and they fall most significantly in those on cephalosporins. The use of cephalosporins can deteriorate the metabolism of citrate, which raises the risk of stone formation.

CONCLUSION

This study highlights the significant role of *O. formigenes* in regulating urinary oxalate, calcium, and citrate levels, and the compounding effects of cephalosporin treatment on these parameters. The findings emphasize the importance of preserving the gut microbiota, particularly *O. formigenes*, for maintaining urinary biochemical homeostasis and reducing the risk of kidney stone formation. The results suggest that the consumption of cephalosporins could cause loss of *O. formigenes* from the GI tract in stone formers as well as normal individuals, and the individuals colonized with *O. formigenes* consistently exhibit lower urinary oxalate, and calcium levels while maintaining citrate levels, lowering kidney stone risk. It is advised that physicians only treat with antibiotics when necessary to preserve the gut microbiota and select the appropriate antibiotic category and duration. This strategy may aid in maintaining vital gut microbes. Furthermore, probiotics might be a useful strategy for preserving *O. formigenes* colonisation. To protect its presence in the gut and maintain oxalate homeostasis, more investigation is required into the antibiotic sensitivity profile of *O. formigenes.*

ACKNOWLEDGMENT

Krishnakumar Janarthanam selection of cases, compilation of data, and writing the original draft. Gandhimathi R Review, compilation of data, editing, and supervision.

AUTHOR'S CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

Nill.

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