

4th Edition of the Clinical Cases Competition related to the non-surgical clinical management of non-surgical clinical management of renal lithiasis

Official template

Title: Recurrent infective lithiasis in patients with chronic kidney disease, a challenge for the urologist

Keywords (between 3 and 6): chronic kidney disease, infective lithiasis, l-methionine, acetoacetic acid, struvite.

1. Abstract

In the last few years, a considerable increase in the incidence of nephrolithiasis in the general population has been detected. The high rate of associated recurrence is surprising, being around 35-50% at 5 years and 80% at 10 years of follow-up. Special attention should be paid to population groups with a higher risk of recurrence, including both infective lithiasis and patients with chronic kidney disease. The urologist's performance when both situations come together is usually a challenge, both because of the need for early removal of lithiasic material, as well as the limitations that arise both in the performance of certain surgical procedures due to their implications in morbimortality, and in medical treatment, where the dispensation of certain compounds can favor renal damage if they are not correctly prescribed considering the patient's residual renal function.

2. Introduction

The prevalence of lithiasis in the general population ranges between 4 and 20%. In recent years an increase in incidence has been detected, especially in developed countries, where it is associated with an increase in the frequency of cardiovascular factors as well as the presence of unhealthy lifestyles and diets. A relevant aspect in the epidemiology of this disease is its high recurrence rate, around 35-50% at 5 years and 80% at 10 years of follow-up.

Struvite calculi represent between 2 and 15% of all urinary calculi. Their incidence increases in the presence of risk factors such as female sex, presence of urinary shunts or neurogenic bladder, as well as recurrent lithiasis of long evolution. Its origin may be de novo or on pre-existing calculi infected by urea splitting bacteria, *Proteus mirabilis* being the pathogen isolated in more than half of all urinary tract infections with urease-positive bacteria. The usual mineral composition is usually struvite and/or apatite carbonate and/or ammonium urate, usually with coral-like calculus morphology. Urine culture is considered essential to demonstrate the presence of urease-producing bacteria, whose activity causes an increase in ammonium ions resulting in the development of an alkaline urine that favors crystallization and precipitation of the aforementioned minerals.

All infectious stone-forming patients are considered to have a high risk of recurrence. Therefore, the management of lithiasis is frankly complex and challenging, since it does not only involve surgery, but rather a holistic approach where active medical treatment and treatment of recurrences as well as hygienic-dietary habits are highly considered.

Specific measures to consider in the treatment of infective lithiasis include complete surgical removal of the stones, short- or long-term antibiotic treatment, and urine acidification. Among the compounds that can currently be employed for urine acidification that are in use and documented in European guidelines (EAU) are L-methionine and ammonium chloride.

The use of acetohydroxamic acid is proposed as a urease inhibitor, preventing the generation of an alkaline medium. Its indications are limited, currently its use is limited to urinary tract infections caused by urease-producing germs (*Proteus*, *Klebsiella* and *Pseudomonas*) as an adjuvant during the eradication treatment of calculus in recurrent infectious lithiasis or as a palliative treatment in those residual lithiasis in which therapeutic maneuvers have been exhausted, with the aim of avoiding the continuous growth of the calculus. It has important adverse effects, which occur in up to 50% of patients, such as venous thrombosis, hemolytic anemia (with obligatory hemogram monitoring), digestive intolerance and headache, most of them being dose-dependent. Its use is contraindicated in pregnancy due to its teratogenicity and its use is limited in renal insufficiency, as it can worsen renal damage.

There is increasing evidence linking nephrolithiasis with the risk of developing chronic kidney disease (CKD) and vice versa. Therefore, the evaluation of the lithiasic patient should include the risk of developing CKD, since the presence of urolithiasis can compromise renal function due to the stone itself due to obstruction or infection of the stone, due to renal damage due to the primary disease causing the stone, or due to renal damage due to the primary disease causing the stone or infection of the stone itself, renal damage due to the primary disease causing stone formation or due to the urological treatments used. Surgical removal of urolithiasis is considered a priority in patients with renal insufficiency, whether due to CKD, bilateral obstruction or because the patient is anatomically or functionally monorenal.

3. Description of the clinical case

We present the case of a patient with a history of infective choriform lithiasis recurrences requiring concomitant surgical and medical treatment. During the course of time she progressively develops chronic kidney disease, being currently in stage IV, being right functional monorenal, which favors the precocity of surgical treatment in the kidney of higher functionality as well as limits the dispensation of a concomitant acidificant or urease inhibitor treatment given the remaining glomerular filtrate.

a. Relevant background

Female 52 years old

Medical history: hypertension Urological history:

- Recurrent urinary tract infections since May 2020.
- Grade IV chronic kidney disease developed since December 2020 in the context of bilateral renal lithiasis and obstructive uropathy.
- Right functional monorrhea

The patient's follow-up requires the performance of several surgical procedures:

- Sept/2021 : Right retrograde intrarenal surgery (RIRS).
 - Left pseudocoraliform lithiasis is found occupying the pelvis and lower calyx.
 - Right subpyloric lithiasis of 16 mm that migrates to the lower calyx. Anatomically difficult access by infundibulopelvic angle parallel to ureter. With high difficult access that does not allow complete fragmentation of the lithiasis. (IMAGE 1).
 - Intraoperative urine culture positive for proteus mirabilis. Positive lithiasis fragment analysis for magnesium ammonium phosphate infectious lithiasis.

Since then, the patient has presented endoscopically unapproachable lithiasis fragments in the right lower calyx.

- March /2022: Left RIRS: Left pseudocoraliform lithiasis is approached.
 - Removal of difficult urinary stent due to calcification of the distal end. She was admitted in June 2022 for complicated right renal colic associated with acute renal failure, with urgent urinary diversion. Right pseudocoraliform lithiasis affecting the lower and middle calyx and renal pelvis was found in CT and echo (IMAGE 2). The patient was scheduled for bilateral URS.
- August /2022: Bilateral URS
 - Right URS: No lithiasis is observed, abundant fibrin of rubbery appearance that occupies the entire renal pelvis and renal calyces. A repletion defect is observed in pyelography (IMAGE 3). The fibrin is taken for microbiological analysis with a positive result for proteus mirabilis.
 - URS of left ureter: no lithiasis is observed.

Given the persistence of fibrin without clear evidence of approachable lithiasis in the right kidney, it was decided to start concomitant treatment with acetohydroxamic acid. The patient had to discontinue treatment due to progressive worsening of renal function and associated digestive discomfort. She presented again with symptomatic cramps that required urgent urinary admission and referral in November. Urgent CT scan showed persistent right chorioriform lithiasis, so percutaneous nephrolithotomy was considered (IMAGE 4).

- January/2023 Right percutaneous nephrolithotomy due to persistence of floci in the right kidney.
 - Persistent positive urine culture for proteus.

Treatment with Lit-Control® pH Down 1 capsule every 12 hours for at least 6 months.

b. Diagnostic support studies and results



IMAGE 1. Elevated right lower calyx angulation



IMAGE 2. Coralliform lithiasis in the right kidney.

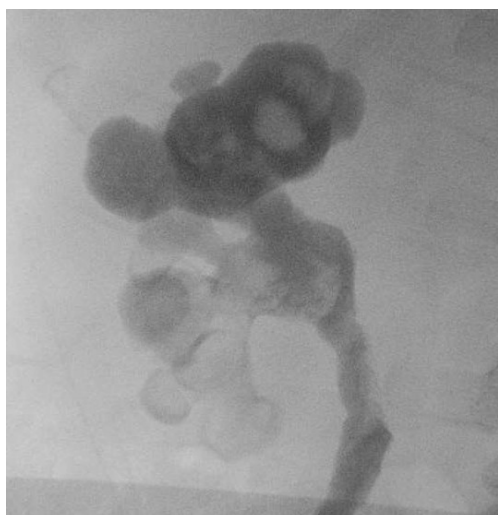


IMAGE 3: Repletion defects of fibrinoid material.



IMAGE 4: Persistence of right chorioriform lithiasis.

c. Diagnosis

Recurrent infective lithiasis in patient with advanced stage chronic kidney disease.

d. Treatment

The study of the lithiasis and fibrin samples obtained during the patient's surgical interventions concluded the presence of infective lithiasis. Concomitant treatment with acetohydroxamic acid was proposed, but after weeks of use it was rejected due to its adverse effects as well as the progressive worsening of the patient's renal function. Given the advanced stage of CKD, the use of the urinary acidifier Lit-Control® pH Down was agreed upon, prescribing the use of 1 capsule every 12 hours, and urinary pH control with Lit-Control® pH Meter was recommended.

e. Evolution and follow-up

During the following 9 months the patient was totally asymptomatic. Thus achieving the highest stone-free rate since the beginning of her follow-up.

f. Clinical results

Currently, after 6 months of medical treatment with Lit-Control® pH Down and urinary pH control, a Stone-Free Rate of approximately 9 months has been achieved, previously considered a maximum of 4-5 months without requiring admission for urgent urinary diversion or surgery. In addition, after switching to Lit-Control® pH Down, renal function has remained stable. Finally, after several rounds of antibiotic treatment, negative urine culture was achieved.

4. Discussion

Urolithiasis is a disease with high recurrence that affects both the morbimortality of patients and their quality of life. In the case of infective urolithiasis, where a higher recurrence rate is observed with respect to other groups of urolithiasis, it is especially important not only surgical treatment for the complete elimination of the urolithiasis but also medical treatment. Taking into account that most of our patients usually develop renal insufficiency due to the presence of recurrent lithiasis, special emphasis should be placed on making use of all available tools in order to reduce the Stone-Free Rate and their quality of life.

In these patients, as we have previously mentioned, surgery is not usually completely resolutive, especially if total fragmentation is not achieved and residual lithiasis persists. It is important to adopt a concomitant strategy that includes antibiotic treatment that acts on the urease-producing bacteria and an acidifying treatment of the urine. Currently, European clinical guidelines recommend the use of antibiotics in all patients with infective lithiasis, either short- or long-term, but the appropriate temporality has not yet been standardized. After control of the urinary tract infection, it is important to maintain an acidic environment that prevents re-growth of urease-producing bacteria as well as to avoid precipitation of the minerals that make up infective lithiasis. It is then of utmost importance the management of urine acidificant treatment in patients. There are several molecules on the market, today acetoxyhydroxamic acid (AAH) is the only urease inhibitor, its use is restricted in patients with severe renal insufficiency as well as adherence is low, only 20%, due to the presence of numerous side effects.

In the field of recurrent infectious lithiasis in patients with CKD, it is vital to experiment with all concomitant treatments that improve the patient's quality of life and lithiasis recurrence, and above all, that renal function is not affected. For this reason, special emphasis is placed on the use of urinary acidifier based on L-methionine. A product called Lit-Control® pH Down, composed mainly of L-Methionine and Phytates, is currently marketed and recommended by European clinical guidelines. Studies have shown a sustained decrease in pH values as well as a decrease in long-term recurrences. In the context of CKD, this drug has proved to be effective, presenting a lower rate of side effects and less renal involvement than AAH.

5. Conclusions and recommendations

At this point, the union of both situations, recurrent infective lithiasis with associated renal insufficiency, can be considered a complex scenario in which surgical and medical decisions must be made tailored to the patient. Not only surgical treatment is crucial, but also the application of pharmacological preventive measures through urease inhibition, antibiotherapy and urine acidification should be considered, always preserving the patient's renal function. To carry out this strategy, in addition to hygienic-dietary measures, the use of urinary acidificants should be recommended.

The use of Lit-Control® pH Down and pH control with Lit-Control® pH Meter is considered a treatment with good tolerance and few adverse effects, efficient and of safe implementation in patients with chronic kidney disease, compared to the AHA.

Therefore, it is concluded that in those patients with multiple risk factors, in this case infectious lithiasis and chronic kidney disease, a comprehensive management of the pathology should be carried out, with surgery as the central pillar, but performing an appropriate combination of medical treatments to find the best strategy for the benefit of the patient.

6. Bibliographic references (*of special interest, **of extraordinary interest).

Skolarikos A, Neisius A, Petřík A, Somani B, Gambaro TG. EAU Guidelines on Urolithiasis; 2022.**

- Siener R. Effect of L-Methionine on the Risk of Phosphate Stone Formation. *Endourology And Stones* (2016).*
- Zhe, M., et al. Nephrolithiasis as a risk factor of chronic kidney disease: a meta-analysis of cohort studies with 4,770,691 participants. *Urolithiasis*, 2017. 45: 441.**
- Jarrar K, Boedeker R.H, Weidner W. Struvite stones: long term follow up under metaphylaxis. *Ann Urol*, (1996)
- Gambaro, G., et al. The Risk of Chronic Kidney Disease Associated with Urolithiasis and its Urological Treatments: A Review. *J Urol*, 2017. 198: 268.*
- Beck, E.M., et al. The fate of residual fragments after extracorporeal shock wave lithotripsy monotherapy of infection stones. *J Urol*, 1991. 145: 6.