

3rd Edition of the Clinical Cases Contest related to the non-surgical clinical management of renal lithiasis

Title: New lines of treatment for the prevention of recurrences in infective lithiasis

Keywords: struvite, urinary ph, phytate, L-methionine

1. Summary

Infective lithiasis or struvite stones are a potentially serious pathology due to their ability to affect the kidney severely and quickly despite representing 2-15% of all lithiasis. Clinical case report of a 19-year-old female patient with left staghorn lithiasis who required surgical treatment, as well as antibiotics to achieve total resolution of the lithiasis. The severity of the stone, the age of the patient and the type of lithiasis are serious factors that must be treated first and then prevented to avoid recurrences. That is why pharmacological preventive measures that acidify urine after lithiasis initial resolution are so important. In this case Lit-Control pH Down[®] was used, it is composed of phytate and L-methionine, which can reduce the development of pathological calcifications such as lithiasis and prevent infective lithiasis.

2. Introduction

Nephrolithiasis is a high prevalence disease that can result in significant morbidity and economic cost. Its incidence has increased in Western countries since 1970 being the prevalence between 5-9% in Europe and 13% in North America⁹. Struvite stones account for 2 to 15% of all lithiasis, but their medical and economic burden is disproportionately higher, since they represent a quarter of staghorn lithiasis and are associated with serious renal and infectious complications.

These stones may originate de novo or grow on pre-existing stones that are infected with urease-producing microorganisms^{1,2}. The bacteria's urease breaks down urea into ammonia and carbon dioxide. Ammonia reacts with water forming ammonium and hydroxide ions, which generate an alkaline medium that favors crystallization. The most common urease-producing bacterial pathogens are *Proteus spp*, *Klebsiella spp*, *Providencia spp*, *Morganella morganni* and *Staphylococcus aureus*.

There are risk factors associated with the formation of this type of stones, such as female gender and urinary tract disorders such as neurogenic bladder urinary derivations¹.

Regarding the clinical features, patients may be asymptomatic or suffer recurrent infections, low back or flank pain, hematuria and less often sepsis or kidney failure. The treatment for these stones, as well as their prevention, is considered mandatory; due to the possible potential complications if left untreated, such as severe infections or kidney function loss that can occur in up to 50% of cases³.

Treatment of choice for infective stones is surgical treatment that ensures the eradication of lithiasis, since, otherwise, bacteria create a biofilm that inhibits the entry of antimicrobials and perpetuate an alkaline pH that allows the growth of new

stones⁴.

Since the stones have an infectious etiology, antibiotic therapy is essential for the management of this pathology. There are multiple antibiotic regimens that must be adjusted according to the antibiogram of the urine culture selectively collected during surgery ⁴. In addition to surgical treatment and antibiotic treatment, pharmacological preventive measures should also be considered by inhibiting urease, antibiotic therapy and acidification of urine, maintaining a pH below 6.5. To attain this, in addition to hygienic-nutritional measures, such as abundant liquids intake, urinary acidifiers such as brown rice or food supplements such as Lit-Control pH Down[®] are recommended, which is composed of rice bran extract (phytate), L-methionine, vitamin A and Zinc. There are studies that have shown that phytate can reduce the development of pathological calcifications such as kidney stones, cardiovascular calcifications and soft tissue calcifications. On the other hand, L-methionine is an oral medication with excellent ability to dissolve infective stones and its use is recommended by the UAE guidelines ^{3,5}.

3. Description of the clinical case

a. Relevant medical history

Clinical case report of a 19-year-old female patient with a two-year history of left lower-back pain, as well as a previous diagnosis of acute pyelonephritis.

b. Diagnostic support studies and results

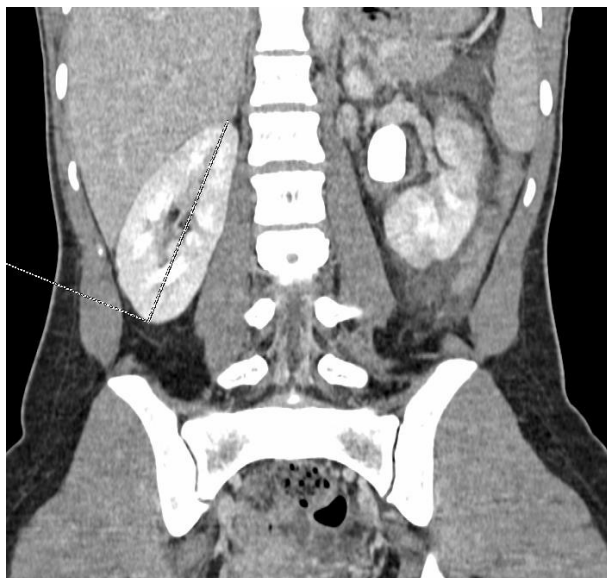
The patient arrives at the emergency room again after being asymptomatic for a couple of months, with a fever of up to 39°C and pain in her left flank. Lab tests showed inflammatory and infectious parameters with no deterioration of kidney function. In urine sediment showed pH 9.0, leukocyturia, microscopic hematuria and positive nitrites. An abdominal X-ray was performed, identifying staghorn lithiasis occupying the renal pelvis and middle and lower calyceal groups.



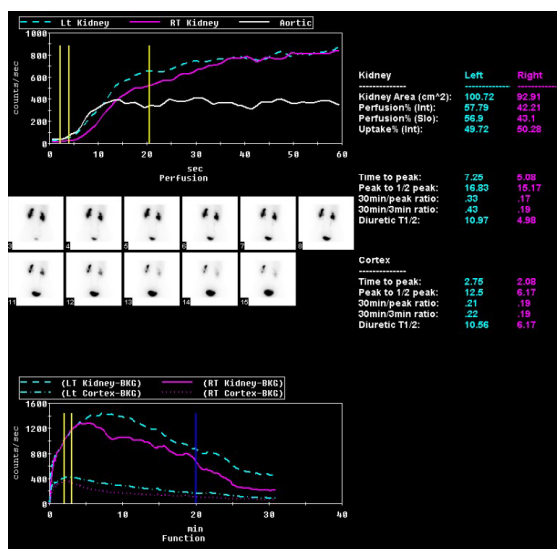
c. Diagnosis

It was decided to request an abdominal/pelvic CT scan, observing a staghorn lithiasis that occupied the renal pelvis and both middle and lower calyceal groups, with small focal, patched hypodense

areas in the cortex of the upper pole, interpolar region and lower pole (nephritis) and enhancement of the associated urothelium (findings suggestive of acute pyelonephritis). The patient was admitted and treated with broad-spectrum antibiotics. The urine culture was positive for *Klebsiella pneumoniae* being treated subsequently and at discharge with guided antibiotic therapy.



At discharge, a renogram with diuretics was performed for surgical planning. It showed that the right kidney provided 50.13% of the overall kidney function and the left kidney 49.87%. Likewise, the right kidney showed normal vascularization and renal function, and altered elimination with pyelocaliceal ectasia pattern. The left kidney showed normal vascularization and function and altered elimination with partial obstructive pattern, responding to diuretics.



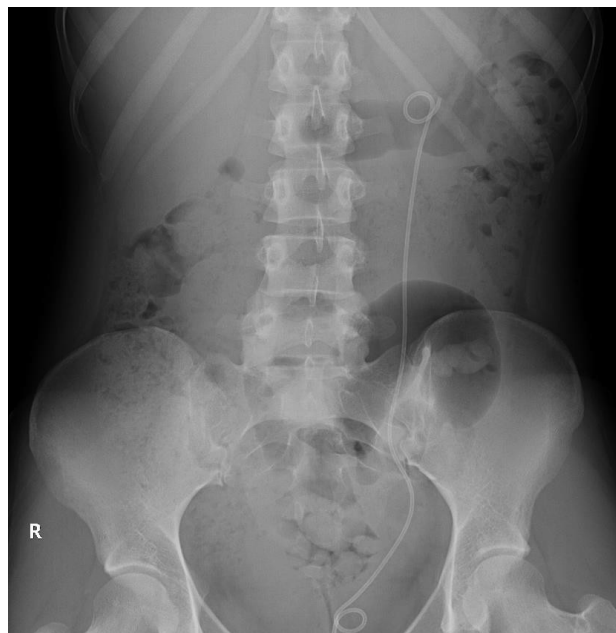
d. Treatment

Given the previous findings, it was decided to perform a left percutaneous nephrolithotomy, approaching through the lower calyx of the left kidney. Subsequent laser lithotripsy and extraction of the stone fragments, and placement of a double-J stent. The patient was treated with antibiotics based on previous urine cultures. During the postoperative period the patient

recovered without relevant incidents.

e. **Outcome**

Follow-up abdominal X-ray in consultations showed resolution of the lithiasis, the double-J stent was subsequently removed. The patient has been asymptomatic during follow-ups and remains without new recurrences.



f. **Clinical results**

After analyzing the stone fragments, it was found that its composition was 100% struvite, starting treatment with Lit-Control pH Down[®], antibiotic therapy and hygienic-nutritional measures.

The urine cultures of subsequent follow-ups remained negative and urinary pH ranges between 6 and 7.

4. Discussion

Struvite lithiasis cannot be eliminated using medical treatment alone, requiring different surgical techniques for its elimination, which causes significant morbidity in patients and consequently, a significant economic expense.

Therefore, hygienic-nutritional measures and treatment using food supplements such as Lit-Control pH Down[®], composed of phytate and L-methionine, could help reduce morbidity in these patients.

Recent studies showed that phytate intake reduced the risk of stones significantly, as it acts as an inhibitor both in the intrapapillary tissue and in urine⁶⁻⁸, preventing lithiasis formation. Similarly, other in vitro studies have proven that L-methionine has shown an excellent ability to dissolve infective kidney stones, as well as favorable urine acidification³.

Even so, more in vivo studies are needed to support the role of both molecules, although the European urology guidelines contemplate treatment with L-methionine¹.

5. Conclusions and recommendations

Although medical treatment alone is not enough, preventing recurrences after surgery through dietary supplements such as Lit-Control pH Down® seems to reduce recurrence rate.

Recommendation is that after surgical and medical treatment, subsequent therapy with such supplements can be considered as an effort to reduce recurrence rate and morbidity in this type of patient.

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

1. A. Skolarikos (Chair), A. Neisius, A. Petřík, B. Somani, K. Thomas, G. Gambaro (Consultant nephrologist) Guidelines Associates: N.F. Davis, R. Geraghty, R. Lombardo, L. Tzelves Guidelines Office: R. Shephard. EAU Guidelines on Urolithiasis. Edn. presented at the EAU Annual Congress Amsterdam, 2022. ISBN 978-94-92671-16-5. <https://uroweb.org/guidelines/urolithiasis>
2. Nevo, A., Shahait, M., Shah, A. et al. Defining a clinically significant struvite stone: a non-randomized retrospective study. *Int Urol Nephrol* 51, 585–591 (2019). <https://doi.org/10.1007/s11255-019-02117-1>
3. Marien T, Miller NL. Treatment of the Infected Stone. *Urol Clin North Am.* 42(4):459-72 (2015). doi: 10.1016/j.ucl.2015.05.009. PMID: 26475943.
4. **Flannigan R, Choy WH, Chew B, Lange D. Renal struvite stones—pathogenesis, microbiology, and management strategies. *Nature Reviews Urology.* 11(6), 333–341 (2014). doi:10.1038/nrurol.2014.99
5. *Grases F, Costa-Bauzá A, Calvó P, Julià F, Dietrich J, Gomila RM, Martorell G, Sanchis P. Phytate Dephosphorylation Products Also Act as Potent Inhibitors of Calcium Oxalate Crystallization. *Molecules.* 27(17):5463 (2022). doi: 10.3390/molecules27175463. PMID: 36080228; PMCID: PMC9457852.
6. Grases F, Costa-Bauza A. Key Aspects of Myo-Inositol Hexaphosphate (Phytate) and Pathological Calcifications. *Molecules.* 2019 Dec 4;24(24):4434. doi: 10.3390/molecules24244434. PMID: 31817119; PMCID: PMC6943413.
7. ** Grases F, Isern B, Sanchis P, Perello J, Torres J (2007) Phytate acts as an inhibitor in formation of renal calculi. *Front Biosci* 12(1):2580–2587
8. Saw NK, Chow K, Rao PN, Kavanagh JP (2007) Effects of inositol hexaphosphate (phytate) on calcium binding, calcium oxalate crystallization and in vitro stone growth. *J Urol* 177(6):2366–2370
9. Lotan Y, Buendia Jiménez I, Lenoir-Wijnkoop I, Daudon M, Molinier L, Tack I, Nuijten MJ. Primary prevention of nephrolithiasis is cost-effective for a national healthcare system. *BJU Int.* 2012 Dec;110(11 Pt C):E1060-7. doi: 10.1111/j.1464-410X.2012.11212.x. Epub 2012 Jun 11. PMID: 22686216.