

# Encrusted Urinary Tract Infections Due to *Corynebacteria* Species



Hamza Sakhi<sup>1</sup>, Olivier Join-Lambert<sup>2</sup>, Anna Goujon<sup>3</sup>, Thibault Culty<sup>3</sup>, Paul Loubet<sup>4</sup>, Julien Dang<sup>5</sup>, Sylvain Drouot<sup>6</sup>, Hubert de Bayser<sup>7</sup>, Christophe Michaud<sup>7</sup>, Louise Ghislain<sup>8</sup>, Thomas Stehlé<sup>9</sup>, Christophe Legendre<sup>1</sup>, Dominique Joly<sup>1</sup>, Paul Meria<sup>10</sup> and Mohamad Zaidan<sup>5,11</sup>

<sup>1</sup>Department of Nephrology–Transplantation, Hôpital Necker, APHP, Paris, France; <sup>2</sup>Department of Microbiology, Hôpital Necker, APHP, Paris, France; <sup>3</sup>Department of Urology, CHU Angers, Angers, France; <sup>4</sup>Department of Infectiology, CHU Nîmes, Nîmes, France; <sup>5</sup>Department of Nephrology–Transplantation, Hôpital Bicêtre, APHP, Le Kremlin–Bicêtre, France; <sup>6</sup>Clinical Pharmacy Department, Hôpital Bicêtre, APHP, Paris, France; <sup>7</sup>Department of Urology, Hôpital Edouard Herriot, HCL, Lyon, France; <sup>8</sup>Department of Nephrology and Dialysis, Hôpital Tenon, APHP, Paris, France; <sup>9</sup>Department of Nephrology–Transplantation, Hôpital Henri-Mondor, APHP, Créteil, France; <sup>10</sup>Department of Urology, Hôpital Saint-Louis, APHP, Paris, France; and <sup>11</sup>Paris-Saclay, Le Kremlin–Bicêtre, France

**Introduction:** Encrusted pyelitis and cystitis are peculiar disorders characterized by the calcification of the vesical, the pyelic, and/or the ureteral walls. These calcifications are composed of struvite and calcium carbonate–apatite due to the presence of *Corynebacterium urealyticum*.

**Methods:** We have identified the clinical features and outcomes of 17 patients with encrusted pyelitis (n = 15) or encrusted cystitis (n = 2). Diagnosis was based on computed tomography scan and sonography including thickening and calcified lesions of the urinary tract.

**Results:** The main clinical presentation was suggestive of subacute urinary tract infection with fever and urologic symptoms, mostly gross hematuria. Biologic features were characterized by the presence of struvite crystals and alkaline urine. Acute kidney injury was reported in 70.6% of cases. Predisposing factors were mostly due to urologic background (82.4%) with a history of urologic procedure (71%) and prior exposure to antibiotics (59%). All patients received appropriate antibiotherapy and 15 were treated with topical urinary acidification. A significant reduction of encrusted calcifications was observed in 88% of cases. Renal function improved in 71% of the patients. Nevertheless, poor tolerance of the treatment and side effects were common, affecting 71% of patients, with Gram-negative bacilli urinary tract infections (53%) being the most frequent. At last follow-up, 4 patients (23.5%) progressed to end-stage renal disease and only 1 had a clinical relapse.

**Conclusions:** Encrusted urinary tract infections are rare, characterized by a severe renal and overall prognosis in the absence of appropriate treatment. Topical urinary acidification and appropriate antibiotherapy are efficient but may be burdened by significant adverse events.

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**KEYWORDS:** *Corynebacterium*; *Corynebacterium urealyticum*; encrusted cystitis; encrusted pyelitis; encrusted urinary tract infections

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Encrusted urinary tract infections are rare disorders characterized by the calcification of the bladder (cystitis), the ureteral, and/or the pyelic (pyelitis) walls.<sup>1</sup> Similarly to infection-related nephrolithiasis, these calcifications are usually composed of struvite (ammonium magnesium phosphate) and calcium

carbonate–apatite crystals.<sup>2–4</sup> Struvite stones represent about 10% of nephrolithiasis, and are due to urinary infections with urea-splitting bacteria.<sup>5</sup> The expression of urease activity allows the conversion of urea and water into ammonium and bicarbonate, leading to urine alkalization (urinary pH > 7.2). Subsequent coprecipitation of ammonium with magnesium and phosphate then results in struvite crystals and urinary encrustations.<sup>6</sup> Urea-splitting agents include a wide range of pathogens depending on the level of urease activity.<sup>7</sup> Struvite stones are most often related to upper urinary tract infections due to *Klebsiella* sp and *Proteus* sp. Encrusted pyelitis and cystitis are almost

**Correspondence:** Hamza Sakhi or Mohamad Zaidan, Department of Nephrology–Transplantation, Hôpital Necker, APHP, 149 Rue de Sèvres, 75015 Paris, France. E-mail: [sakhi.hamza@gmail.com](mailto:sakhi.hamza@gmail.com) or [mohamad.zaidan@aphp.fr](mailto:mohamad.zaidan@aphp.fr)

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invariably due to infections by *Corynebacterium urealyticum*, a Gram-positive slow-growing bacillus, characterized by a major urease activity that colonizes the skin.<sup>8,9</sup> *C urealyticum* is identified in up to 30% of hospitalized patients,<sup>10</sup> and infection usually develops in a nosocomial context, particularly after exposure to antibiotics.<sup>11</sup> Encrusted pyelitis and cystitis were initially reported in renal transplant patients.<sup>12</sup> However, cases involving native kidneys were also reported.<sup>13,14</sup> In the present retrospective study, we addressed the spectrum and outcome of patients with encrusted urinary tract infections, focusing more specifically on management and renal outcome.

## METHODS

### Study Population

Patients were retrospectively identified through a French nationwide survey. The diagnosis of encrusted cystitis and pyelitis was based on imaging features including thickening and calcified lesions of the bladder and/or renal calyces and pelvis. Diagnosis of isolated encrusted cystitis was made by ultrasonography while diagnosis of encrusted pyelitis with or without cystitis was based on computed tomography (CT) scan. The identification of corynebacteria in the urine was a major diagnostic criterion. The presence of Gram-positive bacilli, struvite crystals, and/or alkaline urinary pH ( $\geq 8$ ) was considered as an alternative criterion in the absence of corynebacteria.<sup>3</sup>

### Data Collection

Demographic, clinical, and biologic data were recorded retrospectively at diagnosis, during and at the end of follow-up for all patients. Systemic symptoms, signs of cystitis or pyelonephritis, serum creatinine level, urine culture, urine pH, and crystalluria were collected. Acute kidney injury (AKI) was defined according to clinical practice guidelines.<sup>15</sup> Estimated glomerular filtration rate was determined using the simplified Modification of Diet in Renal Disease equation, and chronic kidney disease (CKD) was defined according to the Kidney Disease Outcomes Quality Initiative classification.<sup>16</sup> Patients were evaluated by ultrasonography and/or CT scan at diagnosis and during follow-up.

### Treatment Modalities and Outcome

Treatment modalities included surgical resection of encrusted calcifications, use of topical urine acidification, and nature of the antibiotics at diagnosis and in case of relapse. Treatment efficacy was based on clinical assessment, kidney function improvement, imaging studies, and urine culture. The regression of the calcifications was evaluated by CT scan (encrusted

pyelitis) and/or ultrasonography (encrusted cystitis) performed at different time-points during follow-up.

## Statistical Analysis

Descriptive statistics were used to summarize the data using STATA version 11.2 (StataCorp, College Station, TX). Continuous variables were expressed using median values with interquartile range, as appropriate for nonparametric data. Categorical variables were expressed as count and percent for categorical variables.

## RESULTS

### Demographics

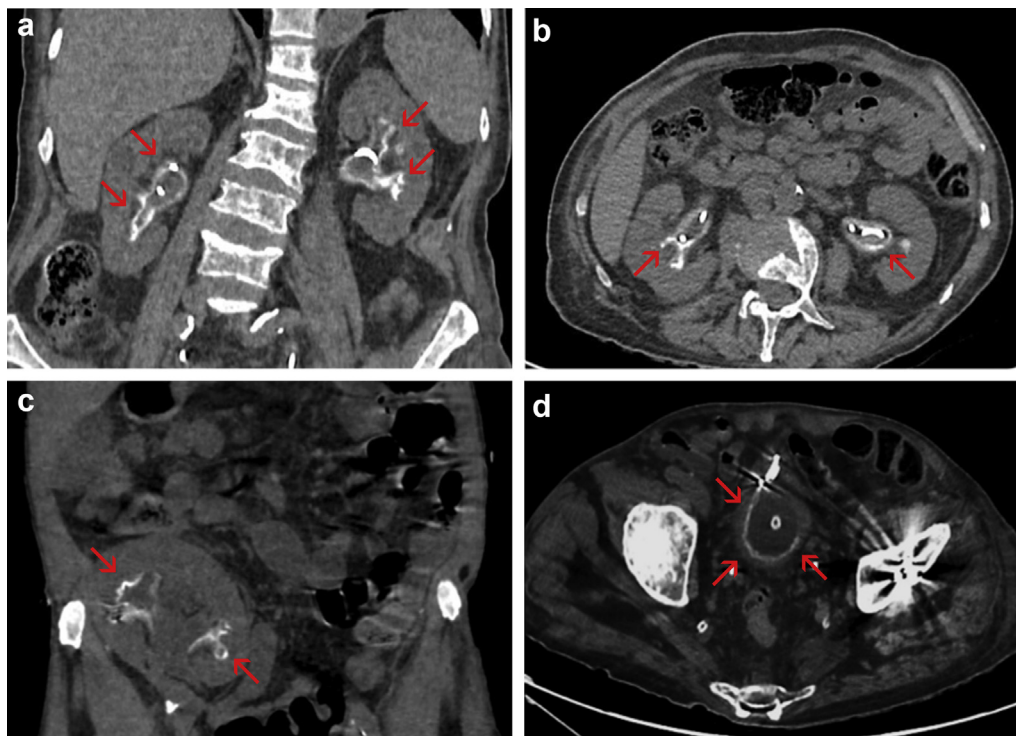
Over the last 2 decades, 17 patients with encrusted pyelitis and/or cystitis, including 7 males and 10 females, were identified from 7 different French hospitals. Two patients had isolated encrusted cystitis based on ultrasonography findings, and 15 displayed encrusted pyelitis, associated with encrusted cystitis in 3, as assessed by CT scan. Four patients had bilateral encrusted pyelitis, and 4 had encrusted pyelitis on the renal allograft (Table 1 and Figure 1).

Past medical history included type 2 diabetes mellitus (23.5%), untreated HIV infection (1 patient), and autoimmune hepatitis in 4 (1 patient). Ten (58.9%)

**Table 1.** Patients' characteristics at diagnosis

Characteristics	All patients (N = 17)
<b>Demographics</b>	
Age, yr	67.5 (56–68)
Female	10 (58.8)
<b>Presenting symptoms</b>	
Delay between first symptoms and diagnosis, mo	2 (1–6)
Weight loss	6 (35.3)
Fever	7 (41.2)
Dysuria	2 (11.8)
Flank or suprapubic pain	4 (23.5)
Gross hematuria	11 (64.7)
<b>Biologic parameters</b>	
Inflammatory syndrome	10 (58.8)
<b>Renal function</b>	
SCr, $\mu\text{mol/L}$	315 (209.8–395)
Underlying CKD	10 (58.9)
AKI	12 (70.6)
Hydronephrosis	11 (64.7)
Urine pH > 8	11 of 11 (100)
Struvite crystals	11 of 11 (100)
<b>Radiologic findings (CT scan, sonography)</b>	
Isolated cystitis	2
Encrusted pyelitis	15
Unilateral pyelitis	7 (46.7)
Bilateral pyelitis	4 (26.7)
Kidney graft pyelitis	4 (26.7)
With encrusted cystitis	3 (20)

AKI, acute kidney injury; CKD, chronic kidney disease; CT computed tomography; IQR, interquartile range; SCr, serum creatinine. Data are n (%) or median (IQR), unless otherwise noted.



**Figure 1.** Abdominal computed tomography scan findings at diagnosis showing bilateral encrusted pyelitis of the native kidney (a,b) (red arrows), the kidney graft (c; red arrows), and encrusted cystitis (d; red arrows).

patients had pre-existing CKD with a median estimated glomerular filtration rate at baseline of 39 (30.5–71.5) ml/min per 1.73 m<sup>2</sup> (Table 2 and Supplementary Table S1), but none had been previously referred to a nephrologist. Four patients had undergone a renal transplantation. Overall, 14 patients (82.4%) had a

“urologic background,” including urologic cancer (n = 4), former neurogenic bladder (n = 3), and urologic complications after renal transplantation (n = 2), which included lymphocele and ureteral anastomosis necrosis, extrinsic chronic ureteral obstruction (n = 2), and other causes (n = 3). Interestingly, 12 patients (70.6%) had undergone some kind of urologic procedure, including continent skin diversion or cutaneous ureterostomy in 5 patients, endoscopic procedures in 3 cases, and post-transplant reintervention in 2 renal transplant patients. Two patients had nonurologic cancer with non-Hodgkin B-cell lymphoma and colonic cancer with peritoneal carcinomatosis. Finally, 10 patients (59%) had been exposed to antibiotics before diagnosis, most often (n = 9) due to urinary tract infections with Gram-negative bacilli (Table 2 and Supplementary Table S1).

**Table 2.** Patients’ past medical history

	All patients (N = 17)
General history	
Renal transplantation	4 (23.5)
Type 2 diabetes mellitus	4 (23.5)
Chronic kidney disease	10 (58.9)
Baseline eGFR, ml/min per 1.73 m <sup>2</sup>	39 (30.5–71.5)
HIV/autoimmune hepatitis	2 (13.3)
Nonurologic cancer	2 (13.3)
Urologic history	
Prior urinary tract infection	9 (52.9)
Urologic disease	14 (82.4)
Urologic cancer	4 (23.5)
Post-transplant complications	2 (11.8)
Neurogenic bladder	3 (17.6)
Extrinsic chronic ureteral obstruction	2 (11.8)
Other	3 (17.6)
Urologic procedures	12 (70.6)
Continent skin diversion/cutaneous ureterostomy	5 (29.4)
Post-transplant reintervention	2 (11.8)
Endoscopic procedure without further surgery	3 (17.6)
Other (scrotal fistula surgery/unilateral nephrectomy)	2 (11.8)

eGFR, estimated glomerular filtration rate; IQR, interquartile range. Data expressed as n (%) or median (IQR), unless otherwise noted.

## Diagnosis

Presenting features are summarized in Table 1 and detailed in Supplementary Table S1. The delay between initial symptoms and diagnosis was variable, with a median of 2 (interquartile range [IQR] 1–6) months. Median age at diagnosis was 67.5 (IQR 56–68) years. Eleven patients (64.7%) had systemic manifestations, including weight loss and fever. Urologic signs were reported in >70% of cases, including dysuria in 2 patients with encrusted cystitis. Flank pain was observed in 3 cases (20%).

Hematuria was present in all but 1 patient, with gross hematuria in 64.7% of cases. Inflammatory syndrome was reported in 10 patients, all with encrusted pyelitis. *Corynebacterium* was identified in 14 patients, but initially missed in 4 cases. *C urealyticum* was involved in 13 cases and *C striatum* in 1 patient. Three patients had a negative urine culture on standard media, albeit Gram-positive bacilli were initially detected on direct urine examination. Alkali urinary pH  $\geq 8$  was a constant finding. Crystalluria showed struvite crystals in all cases. AKI was observed in 12 (70.6%) patients, all with encrusted pyelitis, and dilation of the collecting duct system was observed in 11 patients (64.7%). At diagnosis, median serum creatinine was 315 (IQR 209.8–395)  $\mu\text{mol/L}$ .

### Treatment and Outcome

All patients were treated with appropriate anti-biotherapy for a median period of 9 (IQR 4.5–12.5) weeks. Intravenous glycopeptides (vancomycin or teicoplanin) were administered in 15 patients, and linezolid in 1 patient.

Conservative therapy consisted in topical urine acidification using Thomas solution (27 g each of sodium gluconate, citric acid, and malic acid, in 1 L of distilled water) or Suby solution (32.3 g citric acid, 4.4 g sodium carbonate, 3.8 g magnesium oxide, 1 L distilled water). Recommended parameters of irrigation included a flow rate of 10 to 20 ml/h, increasing to 50 to 100 ml/h with an intrarenal or pelvic pressure  $<25$  cm  $\text{H}_2\text{O}$ , but treatment was tailored under patient's doctor supervision. Treatment was administered through a percutaneous nephrostomy placed at the initiation of the treatment. All patients, except 2, received topical acidification, which was administered for a median time of 3 (IQR 2–6) weeks. When available, urine pH acidification (urinary pH  $<4$ ) was obtained in all treated patients. Acetohydroxamic acid was given for 1 month after topical acidification in 2 patients but was well tolerated in only 1 case (Supplementary Table S2). Among the 2 patients who did not receive acidification therapy, 1 underwent a surgical resection of the encrusted material and the other was given linezolid for only 2 weeks. The availability of the topical acidification at the time of management in these 2 cases was unknown. Another patient with encrusted pyelitis and struvite stones also underwent a pyelotomy to extract the stones (Supplementary Table S2).

All the patients had a favorable clinical and biologic response, including the 2 patients with isolated encrusted cystitis (Supplementary Table S3). Nevertheless, poor clinical tolerance of the topical acidification was reported in 4 (23.5%) patients due to pain and

**Table 3.** Patients' outcome at end of treatment and at last follow-up

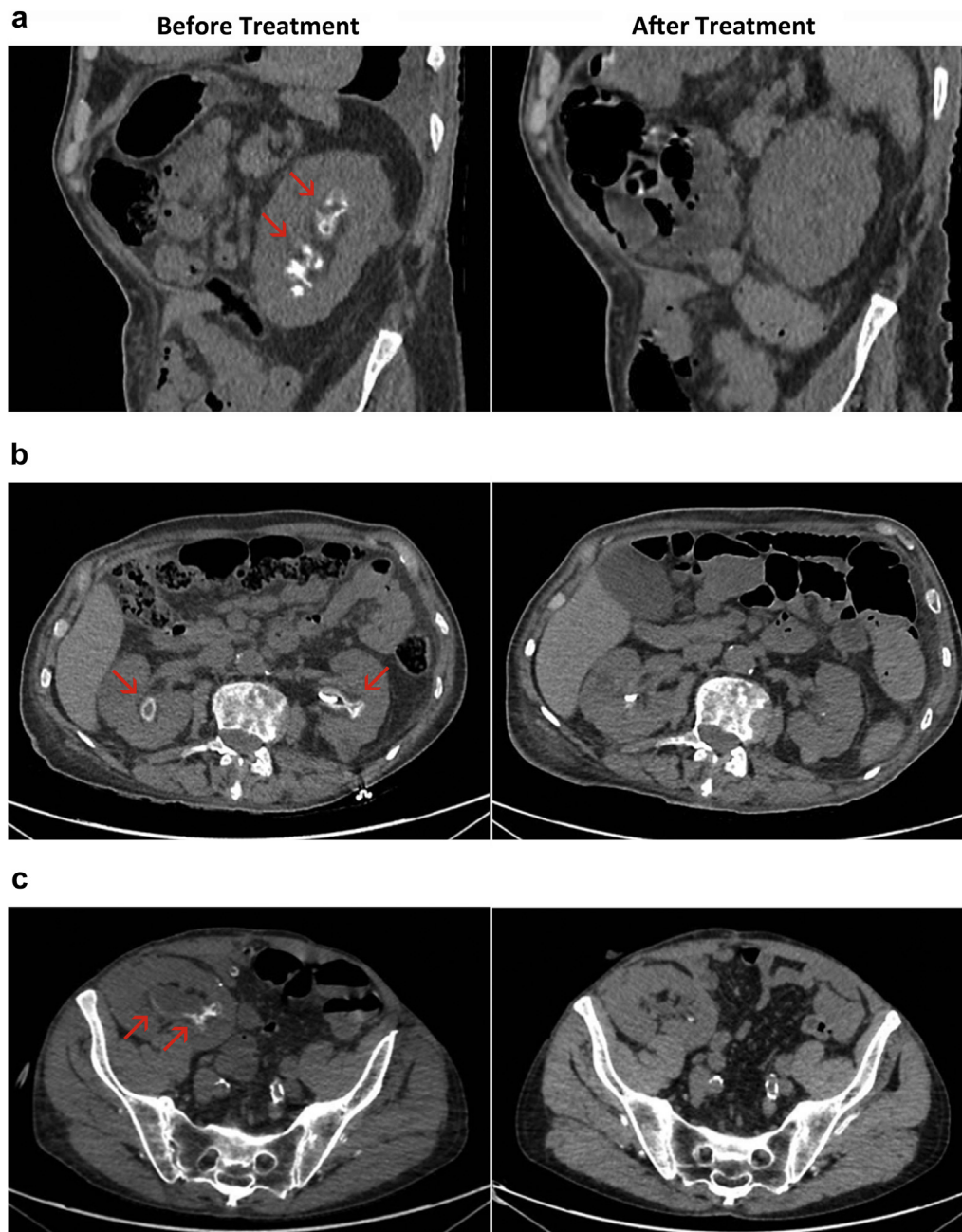
All patients (N = 17)	
At end of treatment	
Response evaluation	
Negative urine culture for corynebacteria	17 (100)
Urine pH	6.5 (6.3–6.7)
Renal calcification reduction observed	15 (88.2)
Persistent residual calcifications	10 (58.8)
Renal function assessment	
Normal renal function	3 (17.6)
Improvement of kidney function	11 (64.7)
Return to baseline function	6 (35.3)
No improvement	1 (5.9)
Stable renal function	2 (11.8)
Creatinine	165 (105–210.5)
Side effects	
Infections	
Urinary tract infection	9 (52.9)
Candiduria	7 (41.2)
Metabolic acidosis	5 (29.4)
Poor clinical tolerance (pain, fistula, other)	4 (23.5)
At last follow-up	
Follow-up, mo	15 (10–30)
Kidney assessment	
eGFR, ml/min per 1.73 $\text{m}^2$	34 (16–70)
eGFR $<30$ ml/min per 1.73 $\text{m}^2$	8 (47.1)
ESRD	4 (23.5)
Relapse	
Clinical relapse	1 (5.9)
Asymptomatic relapse suspected	3 (17.6)
Crystal struvite	2 (11.8)
Positive culture	1 (5.9)
Encrustation progression	1 (5.9)
Renal calculi	2 (11.8)

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IQR, interquartile range.

Data expressed as n Data are n (%) or median (IQR), unless otherwise noted.

malnutrition. Metabolic acidosis was observed in 5 (29.4%) patients (Table 3), whereas infections were observed in 11 (73.3%) patients. Nine patients developed urinary tract infection with a septic shock in 2, 1 had a cutaneous fistula near the nephrostomy, and 7 displayed urinary candidosis in the course of topical acidification.

Urine cultures finally returned negative for corynebacteria in all cases. Complete or partial regression of encrusted calcifications was observed in 15 patients, including 14 who were treated by acidification (Figure 2). Persistent calcifications were observed in 10 (67%) patients treated by acidification. The nonresponder patient was actually treated for only 5 days and before kidney function worsened, leading to treatment discontinuation (Table 3). At the end of treatment, renal function improved in almost all cases, whereas it remains stable in 5 patients, including 3 with an initially normal baseline value and 2 with CKD. Nevertheless, return to baseline value was observed in only 6 patients



**Figure 2.** Comparison of computed tomography scan findings before (left panels) and after (right panels) treatment by topical acidification and antibiotics in case of encrusted pyelitis on native (a,b) or kidney graft (c) showing a significant reduction of encrusted calcifications (red arrows) at the end of treatment.

(35.3%), and median serum creatinine was 165 (IQR 105–210)  $\mu\text{mol/L}$  (Table 3).

Only one of the treated patients with acidification presented with a new symptomatic flare. The patient had been treated for <1 week and rapidly progressed to end-stage renal disease requiring hemodialysis. He finally died from septic shock. One patient presented with progression of the encrustations 1 month after treatment discontinuation, and finally underwent a surgical resection. Two patients had recurrence of struvite crystals in the urine, including 1 with a

positive urine culture for *C urealyticum*, but none displayed *de novo* renal calcifications or symptomatic encrusted pyelitis. Finally, 2 patients presented with new struvite stones, with 1 resulting in obstructive AKI (Table 3).

At last follow-up, and after a median follow-up time of 15 (IQR 10–30) months, median estimated glomerular filtration rate was 34 (IQR 16–70) ml/min per 1.73  $\text{m}^2$ ; 8 (47%) patients had severe CKD, and 4 (23.5%) had reached end-stage renal disease. Four patients died (23.5%) because of urothelial carcinoma ( $n = 1$ ),

progressive lymphoma (n = 1), or septic shock (n = 2) (Table 3 and Supplementary Table S4).

## DISCUSSION

In this study we have illustrated the diagnostic challenge, management modalities, and renal outcome of patients with encrusted pyelitis and/or cystitis. So far, only a few series have characterized the spectrum of encrusted urinary tract infections due to corynebacteria species (Supplementary Table S5).<sup>11–14,17–26</sup>

Despite suggestive imaging features, diagnosis of encrusted urinary tract infection is challenging given the need for specific culture media to identify corynebacteria species and the important delay between first symptoms and established diagnosis.<sup>27</sup> Of note, most patients present with obstructive renal failure, and most have pre-existing chronic kidney disease at the time of diagnosis, suggesting a chronic unrecognized process. Although urinary tract obstruction is likely the main cause of CKD, local inflammation due to encrustations, and pyelonephritis may also contribute to renal function deterioration. Recent studies indicate an increase in the incidence of *Corynebacterium* urinary infections,<sup>25</sup> suggesting a potential underestimation of encrusted pyelitis and cystitis. *Corynebacterium* urinary colonization is observed in <1% of patients, mostly in those who had been hospitalized and had previous antibiotic treatment and urologic gestures, as observed in our study.<sup>28</sup> At-risk patients include immunocompromised subjects,<sup>12,18</sup> and those with a heavy urologic background, including malignancy and other urologic disorders.

Urologic gestures associated with a mucosal breach, particularly transurethral prostate interventions or percutaneous stone surgery, may favor bacterial inoculation within the urinary tract leading to infection in 1% to 5% of cases.<sup>29</sup> Thus, *Corynebacterium*, which usually colonizes the skin,<sup>10</sup> may be inoculated within the urinary tract during such procedures.

Given the risk of incomplete recovery of renal function after urine diversion and septic shock with pyelocaliceal microabscesses,<sup>19</sup> an earlier diagnosis would improve renal and overall outcome. The detection of alkali urine (especially pH  $\geq$  8) and struvite crystals in at-risk patients may thus be helpful and cost-effective to make an early diagnosis of corynebacteria infections. CT scan may also show typical encrusted calcifications. Differential diagnosis includes other infectious diseases such as schistosomiasis and tuberculosis, cytotoxic chemotherapy, and underlying neoplastic lesions. Nevertheless, it should be stressed that the presence of linear calcifications along the pelvic wall is strongly evocative,<sup>22</sup> and the presence of

corynebacteria in urine culture make the diagnosis. However, because corynebacteria are slow-growing germs, and the Gram-positive rods initially identified on direct examination may be missed by standard urine culture, the diagnosis should not be ruled out on the basis of negative standard cultures, and the bacteriologist should be aware of the suspicion of *Corynebacterium* infection to adapt the medium culture and the diagnostic procedure.<sup>30</sup> The broader use of modern techniques, such as matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy, will certainly allow a more accurate recognition of such species<sup>30</sup> and should be carried out in these cases.

Although *Corynebacterium* seems to be less virulent than other urinary tract bacteria,<sup>4</sup> the germs are resistant to most of the commonly used antibiotics for urinary tract infections.<sup>11</sup> Because ineffective treatment is associated with poor outcome,<sup>12</sup> it should be underscored that glycopeptides with vancomycin represent the most commonly used antibiotics for the treatment of corynebacteria. Given the risk of nephrotoxicity associated with glycopeptides, particularly when prescribed for a prolonged period, the use of linezolid, as reported in 1 of our patients, may represent a useful alternative, but this requires further investigation.

The present series also illustrates the different options to treat encrusted urinary tract infections due to corynebacteria species. The management was historically based on the surgical resection of the encrusted material, which is burdened by a significant risk of hemorrhage.<sup>1,12,13</sup> Oral acetohydroxamic acid was also proposed as a complementary treatment, albeit its use was limited because of poor tolerance<sup>31</sup> and a major delay before significant improvement.<sup>1</sup> As suggested by our study, the combination of topical urine acidification and antibiotherapy represent a good alternative to control the infection and improve immediate renal function.

Nevertheless, a prolonged hospitalization is most often necessary, exposing to iatrogenic complications in elderly and frail patients. Acidification may be poorly tolerated and may require reducing the flow rate of instillation. Patients are also exposed to a high risk of *de novo* urinary tract infections and candiduria, which may convert into septic shock. Altogether, such adverse events may prompt interruption of the treatment before the initially defined duration of 4 weeks. Surprisingly, the rate of recurrence seems to be very low, despite the potential persistence of calcifications in some cases. Indeed, complete regression of encrustations was observed in only 7 (41.2%) patients. The eradication of calcifications at any cost should thus be discussed in the light of treatment tolerance and overall prognosis.

In conclusion, encrusted pyelitis and cystitis affect frail patients with a longstanding urologic history and comorbid conditions. Early diagnosis is mandatory to initiate appropriate treatment. The therapeutic strategy is unique compared with other urinary tract infections. The combination of topical urine acidification and antibiotherapy represents an alternative to surgery. Nevertheless, treatment tolerance and potential complications should also be considered. Further studies would help to better clarify treatment modalities, including the duration of urine acidification and antibiotherapy. A better monitoring of at-risk patients would also improve renal and overall outcomes.

## DISCLOSURE

All the authors declared no competing interests.

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## AUTHOR CONTRIBUTIONS

HS conceptualized, investigated, and wrote the original draft. OJ-L provided resources. AG provided resources. TC provided resources. PL provided resources and assisted with writing, review, and editing. JD provided resources. SD provided resources. HdB provided resources. CM provided resources. LG provided resources. TS provided resources, assisted with writing, review, and editing. CL provided resources. DJ provided resources. PM provided resources, supervision, and assisted with writing, review, and editing. MZ assisted with writing, review, editing, and supervision.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Table S1.** Detailed patients' characteristics at diagnosis.

**Table S2.** Detailed treatment modalities.

**Table S3.** Detailed outcomes at the end of treatment.

**Table S4.** Detailed outcomes at last follow-up.

**Table S5.** Main studies on encrusted urinary tract infections in adults.

**STROBE Statement.**

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