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1 **Encrusted urinary tract infections due to *Corynebacteria* species.**

2

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1 **ABSTRACT**

2 **Introduction**

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

6 **Methods**

7 We reported the clinical features and outcomes of 17 patients with encrusted pyelitis (n=15)
8 or encrusted cystitis (n=2). Diagnosis was based on CT scan and sonography including
9 thickening and calcified lesions of the urinary tract.

10 **Results**

11 Main clinical presentation was suggestive of sub-acute urinary tract infection with fever and
12 urological symptoms, mostly gross hematuria. Biological features were characterized by the
13 presence of struvite crystals and alkaline urine. Acute kidney injury (AKI) was reported in
14 70.6% of cases. Predisposing factors were mostly due to urological background (82.4%) with
15 a history of urological procedure (71%) and prior exposure to antibiotics (59%). All patients
16 received appropriate antibiotherapy and 15 were treated with topical urinary acidification. A
17 significant reduction of encrusted calcifications was observed in 88% of cases. Renal function
18 improved in 71% of patients. Nevertheless, poor tolerance of the treatment and side effects
19 were common, affecting 71% of patients with gram-negative bacilli urinary tract infections
20 (53%) being the most frequent. At last follow-up, 4 patients (23.5%) progressed to end-stage
21 renal disease and only one had a clinical relapse.

22 **Conclusion**

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

26

27 **Key Words** : Corynebacterium ; Corynebacterium urealyticum ; encrusted cystitis ; encrusted
28 pyelitis ; encrusted urinary tract infections

29

30

31 INTRODUCTION

32 Encrusted urinary tract infections are rare disorders characterized by the calcification
33 of the bladder (cystitis), the ureteral, and/or the pyelic (pyelitis) walls.¹ Similarly to
34 infectious-related nephrolithiasis, these calcifications are usually composed of struvite
35 (ammonium magnesium phosphate) and calcium carbonate-apatite crystals.²⁻⁴ Struvite
36 stones represent about 10% of nephrolithiasis, and are due to urinary infections with urea-
37 splitting bacteria.⁵ The expression of urease activity allows the conversion of urea and water
38 into ammonium and bicarbonate leading to urine alkalization (urinary pH is > 7.2).
39 Subsequent co-precipitation of ammonium with magnesium and phosphate then results in
40 struvite crystals and urinary encrustations.⁶ Urea-splitting agents include a wide range of
41 pathogens depending on the level of urease activity.⁷ Struvite stones are most often related
42 to upper urinary tract infections due to *Klebsiella sp* and *Proteus sp*. Encrusted pyelitis and
43 cystitis are almost invariably due to infections by *Corynebacterium urealyticum*, a gram
44 positive slow-growing bacillus, characterized by a major urease activity that colonizes the
45 skin.^{8,9} *C.urealyticum* is identified in up to 30% of hospitalized patients,¹⁰ and infection
46 usually develops in a nosocomial context, particularly after exposure to antibiotics.¹¹
47 Encrusted pyelitis and cystitis were initially reported in renal transplant patients.¹² However,
48 cases involving native kidneys were also reported.^{13,14} In the present retrospective study, we
49 addressed the spectrum and outcome of patients with encrusted urinary tract infections,
50 focusing more specifically on management and renal outcome.

51

52 METHODS

53 Study population

54 Patients were retrospectively identified through a French nationwide survey. The diagnosis
55 of encrusted cystitis and pyelitis was based on imaging features including thickening and
56 calcified lesions of the bladder and/or renal calyces and pelvis. Diagnosis of isolated
57 encrusted cystitis was made by ultrasonography while diagnosis of encrusted pyelitis with or
58 without cystitis was based on CT-scan. The identification of Corynebacteria in the urine was
59 a major diagnostic criterion. The presence of gram positive bacilli, struvite crystals and/or
60 alkaline urinary pH (≥ 8) was considered as an alternative criterion in the absence of
61 Corynebacteria.³

62 **Data Collection**

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

71 **Treatment modalities and outcome**

72 Treatment modalities included surgical resection of encrusted calcifications, use of topical
73 urine acidification, and nature of the antibiotics at diagnosis and in case of relapse.
74 Treatment efficacy was based on clinical assessment, kidney function improvement, imaging
75 studies, and urine culture. The regression of the calcifications was evaluated by CT-scan
76 (encrusted pyelitis) and/or ultrasonography (encrusted cystitis) performed at different time
77 points during follow-up.

78 **Statistical analysis**

79 Descriptive statistics were used to summarize the data using STATA 11.2 software
80 (StataCorp). Continuous variables were expressed using median values with interquartile
81 range, as appropriate for non-parametric data. Categorical variables were expressed as
82 counts and percentages for categorical variables.

83

84 **RESULTS**

85 **Demographic characteristics**

86 Over the last two decades, 17 patients with encrusted pyelitis and/or cystitis, including 7
87 males and 10 females, were identified from seven different French Hospitals. Two patients
88 had isolated encrusted cystitis based on ultrasonography findings, and 15 displayed
89 encrusted pyelitis, associated with encrusted cystitis in three, as assessed by CT-scan. Four
90 patients had bilateral encrusted pyelitis, and four had encrusted pyelitis on the renal
91 allograft (**Table 1** and **Figure 1**).

92 Past medical history included type 2 diabetes mellitus (23.5%), untreated HIV infection (one
93 patient), and autoimmune hepatitis in 4 (one patient). Ten (58.9%) patients had preexisting
94 CKD with a median eGFR at baseline of 39 [30.5-71.5] ml/min/1.73m² (**Table 2** and
95 **Supplementary Table S1**), but none had been previously referred to a Nephrologist. Four
96 patients had undergone a renal transplantation. Overall, 14 patients (82.4%) had a
97 “urological background”, including urological cancer (n=4), former neurogenic bladder (n=3),
98 urological complication after renal transplantation (n=2) which were lymphocele and
99 ureteral anastomosis necrosis, extrinsic chronic ureteral obstruction (n=2), and other causes
100 (n=3). Interestingly, 12 patients (70.6 %) had undergone some kind of urological procedure,
101 including continent skin diversion or cutaneous ureterostomy in five patients, endoscopic

102 procedures in three cases, and post-transplantation re-intervention in two renal transplant
103 patients. Two patients had non urological cancer with non-Hodgkin B-cell lymphoma and
104 colonic cancer with peritoneal carcinomatosis. Finally, 10 patients (59%) had been exposed
105 to antibiotics prior to diagnosis, most often (n=9) due to urinary tract infections with gram-
106 negative bacilli (**Table 2** and **Supplementary table S1**).

107 **Diagnosis**

108 Presenting features are summarized in **Table 1** and detailed in **Supplementary Table S1**. The
109 delay between initial symptoms and diagnosis was variable with a median of 2 months
110 IQR[1-6]. Median age at diagnosis was 67.5 years IQR[56-68]. Eleven patients (64.7%) had
111 systemic manifestations including weight loss and fever. Urological signs were reported in
112 more than 70% of cases, including dysuria in two patients with encrusted cystitis. Flank pain
113 was observed in three cases (20%). Hematuria was present in all but one patient, with gross
114 hematuria in 64.7% of cases. Inflammatory syndrome was reported in 10 patients, all with
115 encrusted pyelitis. *Corynebacterium* was identified in 14 patients, but initially missed in 4
116 cases. *C. urealyticum* was involved in 13 cases and *C. striatum* in one patient. Three patients
117 had a negative urine culture on standard media, albeit gram positive bacilli were initially
118 detected on direct urine examination. Alkali urinary pH ≥ 8 was a constant finding.
119 Crystalluria showed struvite crystals in all cases. Acute kidney injury was observed in 12
120 (70.6%) patients, all with encrusted pyelitis, and dilatation of the collecting duct system was
121 observed in 11 patients (64.7%). At diagnosis, median serum creatinine was 315 $\mu\text{mol/L}$
122 IQR[209.8-395].

123 **Treatment and outcome**

124 All patients were treated with appropriate antibiotherapy for a median period of 9 weeks
125 IQR[4.5-12.5]. Intra-venous glycopeptides (Vancomycin or Teicoplanin) were administered in
126 15 patients, and Linezolid in one.

127 Conservative therapy consisted in topical urine acidification using Thomas' solution (27 g
128 each of sodium gluconate, citric acid and malic acid, in 1 L of distilled water) or Suby's
129 solution (citric acid 32.3 g, sodium carbonate 4.4 g, magnesium oxide 3.8 g, distilled water
130 1 L). Recommended parameters of irrigation were a flow rate of 10-20 ml/h increasing to 50-
131 100 ml/h with an intrarenal or pelvic pressure < 25 cmH₂O, but treatment was tailored under
132 patient's doctor supervision. Treatment was administered through a percutaneous
133 nephrostomy placed at the initiation of the treatment. All the patients, except two, received
134 topical acidification, which was administered for a median time of 3 weeks IQR[2-6]. When
135 available, urine pH acidification (urinary pH < 4) was obtained in all treated patients.
136 Acetohydroxamic acid was given for one month after topical acidification in two patients,
137 but was well-tolerated in only one case (**Supplementary Table S2**). Among the two patients
138 who did not receive acidification therapy, one underwent a surgical resection of the
139 encrusted material and the other was given Linezolid for only two weeks. The availability of
140 the topical acidification at the time of management in these two cases was unknown.
141 Another patient with encrusted pyelitis and struvite stones also underwent a pyelotomy to
142 extract the stones (**Supplementary Table S2**).

143 All the patients had a favorable clinical and biological response, including the two patients
144 with isolated encrusted cystitis (**Supplementary table S3**). Nevertheless, poor clinical
145 tolerance of the topical acidification was reported in four (23.5%) patients due to pain and
146 malnutrition. Metabolic acidosis was observed in five (29.4%) patients (**Table 3**), whereas
147 infections were observed in 11 (73.3%) patients. Nine patients developed urinary tract

148 infection with a septic shock in two, one had a cutaneous fistula near the nephrostomy, and
149 seven displayed urinary candidosis in the course of topical acidification.

150 Urine cultures finally returned negative for *Corynebacteria* in all cases. Complete or partial
151 regression of encrusted calcifications was observed in 15 patients, including 14 who were
152 treated by acidification (**Figure 2**). Persistent calcifications were described in 10 (67%)
153 patients treated by acidification. The non-responder patient was actually treated for only
154 five days, and before kidney function worsened, leading to treatment discontinuation (**Table**
155 **3**). At the end of the treatment, renal function improved in almost all cases, whereas it
156 remains stable in 5 patients, 3 with initially normal baseline value, and 2 with CKD.
157 Nevertheless, return to baseline value was observed in only 6 patients (35.3%), and median
158 serum creatinine was 165 $\mu\text{mol/L}$ IQR[105-210] (**Table 3**).

159 Only one of the treated patients with acidification presented a new symptomatic flare. The
160 patient had been treated less than one week and rapidly progressed to end-stage renal
161 disease requiring hemodialysis. He finally died from a septic shock. One patient presented a
162 progression of the encrustations one month after treatment discontinuation, and finally
163 underwent a surgical resection. Two patients had recurrence of struvite crystals in the urine,
164 including one with a positive urine culture for *C. urealyticum*, but none displayed *de novo*
165 renal calcifications or symptomatic encrusted pyelitis. Finally, two patients presented new
166 struvite stones one of which resulted in obstructive AKI (**Table 3**).

167 At last follow-up, and after a median follow-up time of 15 [10-30] months, median eGFR was
168 34 mL/min/1.73m² IQR[16-70], eight (47%) patients had severe CKD, and four (23.5%) had
169 reached end-stage renal disease. Four patients died (23.5%) because of urothelial carcinoma
170 (n=1), progressive lymphoma (n=1), septic shock (n=2) (**Table 3** and **Supplementary table S4**).

171

172

173

174 **DISCUSSION**

175 The present study illustrates the diagnostic challenge, management modalities, and
176 renal outcome of patients with encrusted pyelitis and/or cystitis. So far, only a few series
177 have characterized the spectrum of encrusted urinary tract infections due to *Corynebacteria*
178 species (**Supplementary table S5**).^{11–14,17–26}

179 Despite suggestive imaging features, the diagnosis of encrusted urinary tract infections is
180 challenging given the need for specific culture media to identify *Corynebacteria* species and
181 the important delay between first symptoms and established diagnosis.²⁷ Of note, most
182 patients present with obstructive renal failure, and most have preexisting chronic kidney
183 disease at the time of diagnosis, suggesting a chronic unrecognized process. Although
184 urinary tract obstruction is likely the main cause of chronic kidney disease, local
185 inflammation due to encrustations, and pyelonephritis may also contribute to renal function
186 deterioration. Recent studies indicate an increase in the incidence of *Corynebacterium*
187 urinary infections,²⁵ suggesting a potential underestimation of encrusted pyelitis and cystitis.
188 *Corynebacterium* urinary colonization is observed in less than 1% of patients, mostly in those
189 who had been hospitalized and had previous antibiotic treatment and urological gestures, as
190 observed in our study.²⁸ At-risk patients include immunocompromised subjects,^{12,18} and
191 those with a heavy urological background, including malignancy and other urological
192 disorders.

193 Urological gestures associated with a mucosal breach, particularly transurethral prostate
194 interventions or percutaneous stone surgery, may favor bacterial inoculation within the

195 urinary tract leading to infection in 1-5% of cases.²⁹ Thus, *Corynebacterium*, which usually
196 colonizes the skin,¹⁰ may be inoculated within the urinary tract during such procedures.

197 Given the risk of incomplete recovery of renal function after urine diversion and septic shock
198 with pyelocaliceal microabscesses,¹⁹ an earlier diagnosis would improve renal and overall
199 outcome. The detection of alkali urine (especially pH \geq 8), and struvite crystals in at-risk
200 patients may thus be helpful and cost-effective to make an early diagnosis of *Corynebacteria*
201 infections. CT-scan may also show typical encrusted calcifications. Differential diagnosis
202 includes other infectious diseases such as schistosomiasis and tuberculosis, cytotoxic
203 chemotherapy, and underlying neoplastic lesions. Nevertheless, it should be stressed that
204 the presence of linear calcifications along the pyelic wall is strongly evocative²², and the
205 presence of *Corynebacteria* in urine culture make the diagnosis. However because
206 *Corynebacteria* are slow-growing germs, and the gram positive rods initially identified on
207 direct examination may be missed by standard urine culture, the diagnosis should not be
208 ruled out on the basis of negative standard cultures, and the bacteriologist should be aware
209 of the suspicion of *Corynebacterium* infection to adapt the medium culture and the
210 diagnostic procedure.³⁰ The broader use of modern techniques, such as MaldiTOF, will
211 certainly allow a more accurate recognition of such species³⁰ and should be carried out in
212 these cases.

213 Although *Corynebacterium* seem to be less virulent than other urinary tract bacteria,⁴ the
214 germs are resistant to most of the commonly used antibiotics for urinary tract infections.¹¹
215 Because ineffective treatment is associated with poor outcome,¹² it should be underscored
216 that glycopeptides with vancomycin represent the most commonly used antibiotics for the
217 treatment of *Corynebacteria*. Given the risk of nephrotoxicity associated with glycopetids,

218 particularly when prescribed for a prolonged period, the use of linezolid, as reported in one
219 of our patients, may represent an interesting alternative, but require further investigations.
220 The present series also illustrates the different options to treat encrusted urinary tract
221 infections due to *Corynebacteria* species. The management was historically based on the
222 surgical resection of the encrusted material, which is burdened by a significant risk of
223 hemorrhage.^{1,12,13} Oral acetohydroxamic acid was also proposed as a complementary
224 treatment, albeit its use was limited because of a poor tolerance³¹ and important delay
225 before significant improvement.¹ As suggested by our study, the combination of topical
226 urine acidification and antibiotherapy represent a good alternative to control the infection
227 and improve immediate renal function.

228 Nevertheless, a prolonged hospitalization is most often necessary, exposing to iatrogenic
229 complications in elderly and frail patients. Acidification may be poorly tolerated and may
230 require reducing the flow rate of instillation. Patients are also exposed to a high risk of *de*
231 *novo* urinary tract infections and candiduria, which may convert into septic shock.

232 Altogether, such adverse events may prompt the interruption of the treatment before the
233 initially defined duration of 4 weeks. Surprisingly, the rate of recurrence seems to be very
234 low, despite the potential persistence of calcifications in some cases. Indeed, complete
235 regression of encrustations was observed in only 7 (41.2%) patients. The eradication of
236 calcifications at any cost should thus be discussed in the light of treatment tolerance and
237 overall prognosis.

238

239 In conclusion, encrusted pyelitis and cystitis affect frail patients with a long-standing
240 urological history and comorbid conditions. Early diagnosis is mandatory to initiate
241 appropriate treatment. The therapeutic strategy is unique compared to other urinary tract

242 infections. The combination of topical urine acidification and antibiotherapy represents an
243 alternative to surgery. Nevertheless, treatment tolerance and potential complications should
244 also be considered. Further studies would help to better clarify treatment modalities,
245 including the duration of urine acidification and antibiotherapy. A better monitoring of at-
246 risk patients would also improve renal and overall outcomes.

247

248

249 **FIGURE LEGENDS**

250 **Figure 1. Abdominal CT-scan findings at diagnosis** showing bilateral encrusted pyelitis of
251 the native kidney (**A and B, red arrows**), the kidney graft (**C, red arrows**), and encrusted
252 cystitis (**D, red arrows**).

253

254 **Figure 2. Comparison of CT-Scan findings** before (left panels) and after (right panels)
255 treatment by topical acidification and antibiotics in case of encrusted pyelitis on native (**A**
256 **and B**) or kidney graft (**C**) showing a significant reduction of encrusted calcifications (red
257 arrows) at the end of treatment.

258

259 **AUTHOR CONTRIBUTIONS**

260 H.S. : Conceptualization, Investigation, Writing- Original draft preparation, O.J-L. :
261 Resources. A.G. : Resources ; T.C. : Resources ; P.L. : Resources, Writing - Review & Editing ;
262 J.D. : Resources ; S.D. : Resources ; H.d.B. : Resources; C.M. : Resources ; L.G. : Resources ;
263 T.S. : Resources, Writing - Review & Editing ; C.L. : Resources D.J. : Resources ;
264 P.M. : Resources, Supervision, Writing - Review & Editing ; M.Z. : Writing - Review & Editing,
265 Supervision.

266

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269

270 **DISCLOSURES**

271 The authors have nothing to disclose

272

273

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

	All Patients (n =17)
Demographic data	
Age, median (IQR)	67.5 (56-68)
Female, n (%)	10 (58.8)
Presenting symptoms	
Delay between 1 st symptoms and diagnosis (months), median (IQR)	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)
Biological parameters	
Inflammatory syndrome	10 (58.8)
Renal function	
- SCr ($\mu\text{mol/L}$), median (IQR)	315 (209.8-395)
- Underlying CKD, n (%)	10 (58.9)
- AKI, n (%)	12 (70.6)
- Hydronephrosis, n (%)	11 (64.7)
Urine pH >8, n (%)	11/11 (100)
Struvite crystals, n (%)	11/11 (100)
Radiological findings (CT scan, sonography)	
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)

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372 **Table 2. Patients' past medical history.**

	All Patients (n =17)
General history	
Renal transplantation, n (%)	4(23.5)
Type 2 Diabetes mellitus, n (%)	4 (23.5)
Chronic kidney disease, n (%)	10 (58.9)
- Baseline eGFR (ml/min/1.73m ² , median (IQR)	39 (30.5-71.5)
HIV/Auto immune hepatitis, n (%)	2 (13.3)
Non urological cancer, n (%)	2(13.3)
Urological history	
Prior urinary tract infection, n (%)	9 (52.9)
Urological disease, n (%)	14 (82.4)
- Urological cancer, n (%)	4 (23.5)
- Post transplantation complications, n (%)	2 (11.8)
- Neurogenic bladder, n (%)	3 (17.6)
- Extrinsic chronic ureteral obstruction, n (%)	2 (11.8)
- Other, n (%)	3 (17,6)
Urological procedures	12 (70.6)
- Continent skin diversion/cutaneous ureterostomy, n (%)	5 (29.4)
- Post-transplantation reintervention, n (%)	2 (11.8)
- Endoscopic procedure without further surgery, n (%)	3 (17.6)
- Other (scrotal fistula surgery/unilateral nephrectomy, n (%)	2 (11.8)

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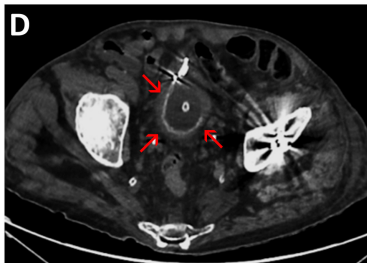
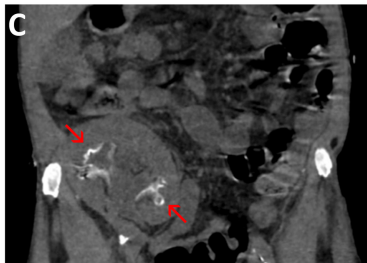
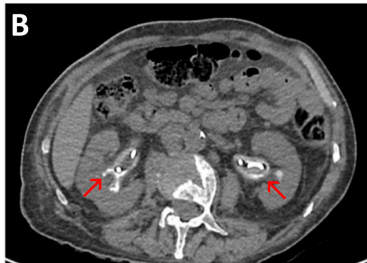
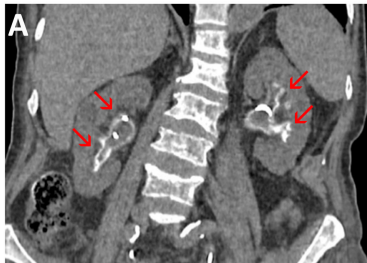
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383 **Table 3. Patients' outcome at the end of treatment and at last follow-up**

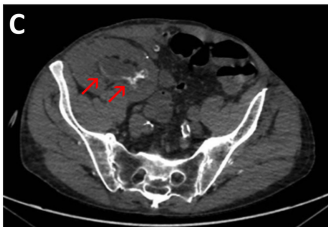
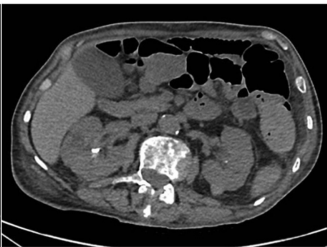
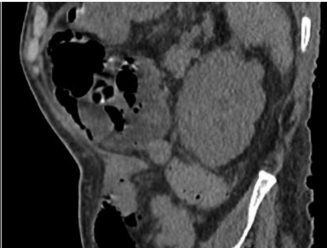
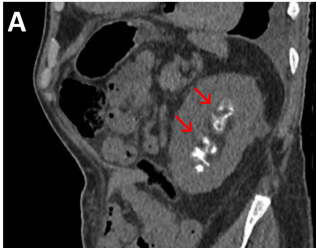
	All Patients (n =17)
At the end of treatment	
Response evaluation	
Negative urine culture for Corynebacteria, n (%)	17 (100)
Urine pH, median (IQR)	6.5 (6.3-6.7)
Renal calcification reduction observed, n (%)	15 (88.2)
Persistent residual calcifications, n (%)	10 (58.8)
Renal function assessment	
Normal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

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Before Treatment

After Treatment

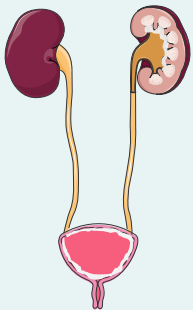


Encrusted urinary tract infections (UTI) due to *Corynebacteria* species

DIAGNOSIS

17 patients with encrusted UTI

Encrusted pyelitis
n = 15



Isolated
Encrusted Cystitis
n=2

Past medical history

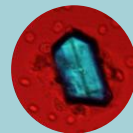
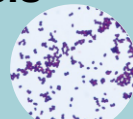
- urological background
- antibiotics exposure

Characteristics

- sub-acute UTI
- gross hematuria
- AKI

Urine analysis

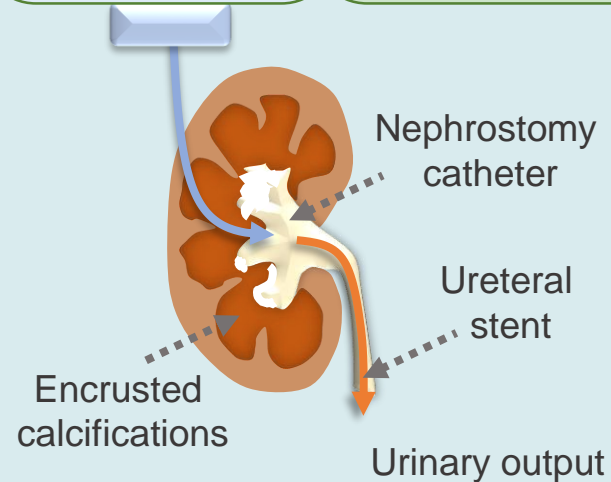
- gram (+) rods
- alkaline urine
- struvite crystals



TREATMENT

Topical
urine
acidification

Prolonged
antibiotherapy
(glycopeptides)



OUTCOME

Encrustations

Reduction
88%

Relapse
6%

Kidney function

Improvement
65%

ESRD
24%

Side effects

UTI
50%

Metabolic
acidosis
29%

CONCLUSION:

Encrusted urinary tract infections primarily affect patients with heavy urological background. Topical acidification is an effective treatment.