Urinary Tract Infection due to Corynebacterium urealyticum in Kidney Transplant Recipients: An Underdiagnosed Etiology for Obstructive Uropathy and Graft Dysfunction—Results of a Prospective Cohort Study

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Background. Corynebacterium urealyticum is a cause of urinary tract infection and encrusting cystitis or pyelitis. Information about this infection in renal transplant recipients is based on case reports. We communicate the first prospective epidemiological study for this population.

Methods. We selected a cohort of 163 renal transplant recipients who were screened for urinary tract infection due to C. urealyticum. Long-term incubation and special media were used for culture of C. urealyticum. The cohort was observed for a mean of 26.2 months (standard deviation, 8.7; range, 1–36 months). Risk factors and outcomes were assessed.

Results. At baseline, 16 (9.8%) of 163 patients had C. urealyticum bacteriuria (6 were asymptomatic, 9 had acute cystitis, and 1 had encrusting pyelitis). Independent risk factors (assessed by multivariate analysis) for urinary tract C. urealyticum infection were: antibiotic administration during the previous month (odds ratio, 8.04; 95% confidence interval, 1.57–41.06; \( P = .012 \)), history of nephrostomy (odds ratio, 51.59; 95% confidence interval, 3.62–736.06; \( P = .004 \)), and skin colonization (odds ratio, 208.35; 95% confidence interval, 21.54–2015.22; \( P < .001 \)). Presence of urinary tract infection symptoms for >1 month (odds ratio, 27.7; 95% confidence interval, 2.55–300.5; \( P = .006 \)) and obstructive uropathy (odds ratio 25.9; 95% confidence interval, 4.43–152.31; \( P < .001 \)) were more frequent during follow-up in patients with C. urealyticum bacteriuria.

Conclusions. When specifically tested for, C. urealyticum bacteriuria is more prevalent than previously thought in renal transplant recipients, and it is closely related to obstructive uropathy. Future studies are necessary to establish the relevance of treating the infection during follow-up after renal transplantation.
de Octubre, Madrid, Spain). During a period of 13 months, we prospectively recruited 163 renal transplant recipients: 100 who consecutively attended the Renal Transplant Unit office and 63 who were consecutively admitted to the hospital ward of the Department of Nephrology for ≥2 days (with or without urinary tract infection symptoms at the time of recruitment). Twenty-five of 63 patients admitted to the hospital had received renal transplant in the preceding 7 days. All the recipients received prophylactic cotrimoxazole for the first 6 months after transplantation.

Management and follow-up. The following patient data were collected at recruitment: age, sex, date of transplantation, urinary tract infection in the previous month (yes or no), number of episodes of acute rejection, antibiotic use in the preceding month, type of immunosuppression, presence of obstructive uropathy, and history of urological manipulation (urological surgery after transplantation, cystoscopy, nephrostomy, ureteral catheterization, or insertion of urethral catheter for >1 month). On the first day of recruitment, urine culture and inguinal skin culture were performed for all patients.

Case patients whose urine and/or skin cultures were positive for \textit{C. urealyticum} were evaluated monthly. At each visit, the patient was asked about the presence of urinary tract symptoms (lower urinary tract symptoms, abdominal pain over the graft, or presence of blood or lithiasis in urine), and urine pH and sediment were assessed. New urine and inguinal skin cultures were performed at each visit. During long-term follow-up, the following outcome items were collected: number of days of hospitalization, renal function, number of episodes of acute rejection, graft loss and mortality, need for derivative procedures of the urinary tract, and number of urinary tract infections.

Microbiological studies. Urine samples were obtained by the clean-catch method or through urinary catheter. A measured volume of urine (5 μL) was inoculated by streaking it over the entire surface of 2 standard media (5% sheep blood agar and MacConkey agar) and 1 selective medium for \textit{C. urealyticum}. Selective medium contained heart infusion agar (40 g/L), l-cysteine (0.128 g/L), urea (20 g/L), phenol red (0.01 g/L), glucose (10 g/L), Tween-80 (10 g/L), polymyxin B (2500 U/L), aztreonam (16 mg/L), fosfomycin (50 mg/L), and amphotericin B (2 mg/L). Definitive pH of the medium was 6.8. Urine sediment was microscopically assessed for every specimen. Significant hematuria or pyuria was defined by the presence of ≥5 RBCs or WBCs per high-power field.

For the study of inguinal skin colonization, the specimen was obtained from a 2 cm² skin area at the groin. Skin was rubbed for 30 s with a cotton swab moistened in wash fluid, as described elsewhere [8]. The swab was introduced into a tube with 2 mL of wash fluid and was expressed by pressing and rotating it against the side of the tube for 30 s. This solution was diluted (1:100) in wash fluid, and 2 plates containing the selective medium were inoculated with 10 μL of both fluids (diluted and undiluted solutions).

All agar plates were inoculated at 35°C for 72 h. The isolation of any number of colonies from urine was considered to be a positive result. Colonies suspected to be \textit{C. urealyticum} were examined by Gram stain. The coryneform bacteria were streaked onto Christensen urea agar and onto 5% sheep blood agar. Definitive identification of a urealytic microorganism as being \textit{C. urealyticum} was performed using the API Coryne system [9]. Antimicrobial susceptibility was performed on all \textit{C. urealyticum} strains by the agar dilution method by use of Mueller Hinton agar with 5% sheep blood.

Clinical definitions. A patient was considered to be experiencing cystitis caused by \textit{C. urealyticum} if he or she had lower urinary tract infection symptoms plus leukocyturia and ≥2 urine samples positive for \textit{C. urealyticum}. A patient was considered to be experiencing urinary colonization with \textit{C. urealyticum} if he or she was asymptomatic but if urine culture was positive for this bacteria. Cystitis was arbitrarily classified as acute (symptoms present for <4 weeks) or chronic (symptoms present for >1 month). Pyelonephritis was defined as the presence of fever (>38°C), flank pain or abdominal pain over the renal graft, and detection of \textit{C. urealyticum} in urine and/or blood. Encrusted cystitis was diagnosed cystoscopically by the presence of chronic inflammation of the bladder mucosa with ulcerative lesions and by the presence of struvite stones [10]. Encrusting pyelitis was defined as the presence of struvite incrustations on the pelvis during surgical inspection.

Statistical analysis. Continuous variables were expressed as mean ± SD for those with normal distribution of test results. Categorical variables were expressed as percentages. Student's unpaired \textit{t} test was used to compare continuous variables, and the \textit{χ²} or Fisher's exact test was used to compare proportions. All statistical tests were 2-tailed, and the threshold of statistical significance was \textit{P} < .05.

Statistically significant variables (\textit{P} < .05) in the univariate analysis were introduced into a multivariate model by use of forward stepwise logistic regression (SPSS software, version 12.0 [SPSS]) to identify the independent risk factors for \textit{C. urealyticum} infection and the independent outcome events.

RESULTS

One hundred sixty-three renal transplant recipients were included in the study (107 males and 56 females). Mean age was 44.8 ± 12.9 years (range, 18–70 years). Culture results at baseline revealed \textit{C. urealyticum} in the urine of 16 patients (9.8%) and \textit{C. urealyticum} colonization of the skin of 22 patients (13.5%).

Study of risk factors. Risk factors for bacteriuria due to \textit{C. urealyticum} at baseline are summarized in table 1. Risk factors
as determined by univariate analysis were age (mean age, 50.8 years for those with bacteriuria vs. 44.1 years for those without bacteriuria; \( P < .05 \)), female sex (\( P < .05 \)), urinary tract infection of any etiology in the previous month (\( P < .001 \)), antibiotic administration in the previous month (\( P < .01 \)), presence of a urethral catheter for >1 month (\( P < .05 \)), previous nephrostomy (\( P < .05 \)), and skin colonization by \( C. \) urealyticum (\( P < .001 \)). In the multivariate analysis, the following independent risk factors were detected: antibiotic administration in the previous month (OR, 8.04; 95% CI, 1.57–41.06; \( P < .01 \)), presence of a urethral catheter for >1 month (\( P < .05 \)), previous nephrostomy (\( P < .05 \)), and skin colonization by \( C. \) urealyticum (\( P < .001 \)).

### Clinical and microbiological data.
There were 16 patients with \( C. \) urealyticum bacteriuria (6 who were asymptomatic, 9 with acute cystitis, and 1 with encrusting pyelitis). Symptoms of cystitis were similar to those produced by other bacteria. Nine of 10 patients were symptomatic the first time \( C. \) urealyticum was isolated in urine, whereas the remaining became symptomatic 1 month after the first isolation of the bacteria in urine. Table 2 includes laboratory data for the patients with bacteriuria. Symptomatic patients presented alkaline urine (pH >7), hematuria, and struvite stones more frequently than did asymptomatic subjects. Because of the small number of cases in each group, differences are not statistically significant.

Nine of 10 symptomatic subjects presented \( >2.5 \times 10^4 \) colony-forming units (cfu) per mL of \( C. \) urealyticum in urine. In contrast, all asymptomatic subjects had \( <2.5 \times 10^4 \) cfu/mL of the bacteria. Fifteen (93%) of 16 strains of \( C. \) urealyticum grew on selective medium, but only 3 (18%) of 16 strains grew on sheep blood agar. Therefore, selective medium permitted a 5-fold increase in recovery of \( C. \) urealyticum in urine (\( P < .001 \)). Moreover, in the 3 cases of isolation in conventional medium, the presence of the bacteria was not detected before 48 h of incubation. All isolated \( C. \) urealyticum strains were susceptible to vancomycin and teicoplanin and showed different levels of resistance to other antibiotics (table 3).

### Treatment and follow-up.
Eight symptomatic subjects with bacteriuria due to \( C. \) urealyticum were treated with teicoplanin (100–400 mg intramuscularly per day for 14 days), and 2 were treated with vancomycin (20–40 mg/kg per day for 14 days). Two asymptomatic patients received teicoplanin as prophylaxis. Surgical resection of lithiasis was necessary for the patient with encrusting pyelitis.

The cohort had a mean follow-up time of 26.2 months (SD, 8.7; range, 1–36 months). Evolution of subjects with bacteriuria, skin colonization by \( C. \) urealyticum, or both was as follows: 3 of 10 symptomatic patients who were initially treated experienced relapses of symptomatic bacteriuria in the following 3 months. Five of 9 subjects who presented only skin colonization at recruitment developed bacteriuria in the following months (all of them asymptomatic).

### Table 1. Risk factors at recruitment for bacteriuria due to \( Corynebacterium urealyticum \) in renal transplant recipients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without bacteriuria ((n = 147))</th>
<th>With bacteriuria ((n = 16))</th>
<th>(P)</th>
<th>OR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>44.1 (13.2)</td>
<td>50.8 (8.6)</td>
<td>&lt;.05</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>31.3</td>
<td>62.5</td>
<td>&lt;.05</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Hospitalization at baseline</td>
<td>36.1</td>
<td>62.5</td>
<td>.07</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>UTI in previous month</td>
<td>4.1</td>
<td>43.8</td>
<td>&lt;.001</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Antibiotic therapy in previous month</td>
<td>31.3</td>
<td>75</td>
<td>&lt;.01</td>
<td>8.04 (1.57–41.06)</td>
<td>&lt;.012</td>
</tr>
<tr>
<td>Serum creatinine level &gt;1.5 mg/dL</td>
<td>59.2</td>
<td>62.5</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Acute rejection</td>
<td>37.4</td>
<td>43.8</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression with 3 drugs</td>
<td>51.7</td>
<td>43.8</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Urologic manipulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urethral catheterization &gt;1 month</td>
<td>2.7</td>
<td>18.8</td>
<td>&lt;.05</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Ureteral catheter</td>
<td>2</td>
<td>6.3</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Cystoscopy</td>
<td>2</td>
<td>6.3</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Nephrostomy</td>
<td>4.1</td>
<td>18.8</td>
<td>&lt;.05</td>
<td>51.59 (3.62–736.06)</td>
<td>.004</td>
</tr>
<tr>
<td>Urological surgery</td>
<td>6.8</td>
<td>12.5</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Lymphocele</td>
<td>2.7</td>
<td>12.5</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>6.8</td>
<td>12.5</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Perirenal hematoma</td>
<td>2.7</td>
<td>12.5</td>
<td>NS</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Skin colonization with ( C. ) urealyticum</td>
<td>6.1</td>
<td>81.3</td>
<td>&lt;.01</td>
<td>208.3 (21.54–2015.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**NOTE.** Data are percentage of patients, unless otherwise indicated. NS, not significant; UTI, urinary tract infection.

a With use of the regression logistic model.

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Table 2. Laboratory characteristics of renal transplant recipients with bacteriuria due to *Corynebacterium urealyticum* at recruitment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With acute cystitis (n = 9)</th>
<th>With encrusted pyelitis (n = 1)</th>
<th>With asymptomatic infection (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline pH urine</td>
<td>7</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pyuria</td>
<td>9</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Microhematuria</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Struvite crystals</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Simultaneous UTI by other bacteria</td>
<td>1a</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2.5×10^5 cfu/mL of <em>C. urealyticum</em></td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin colonization with <em>C. urealyticum</em></td>
<td>7</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

**NOTE.** cfu, Colony-forming units; UTI, urinary tract infection.

a *Escherichia coli* (10^5 cfu/mL) also present—impossible to assess which bacteria produced symptoms.

The outcomes of those with and those without *C. urealyticum* bacteriuria were compared. The following events were more frequent in those with bacteriuria (table 4): hospitalization for >30 days (P < .05), need for surgical derivative procedures or nephrostomy (P < .001), >3 episodes of urinary tract infection (P < .05), and presence of urinary tract infection symptoms for >1 month (P < .001). In multivariate analysis, 2 events were independently associated with *C. urealyticum* bacteriuria during long-term follow-up: presence of urinary tract infection symptoms for >1 month (OR, 27.7; 95% CI, 2.55–300.5) and obstructive uropathy (OR, 25.9; 95% CI, 4.43–152.31).

**DISCUSSION**

Previous reports have described *C. urealyticum* infections and their complications among renal transplant recipients [5–7, 11], but to our knowledge, this is the first study that has prospectively searched for the presence of this infection in a cohort of renal transplant recipients. This strategy allowed calculation of the frequency of this urinary tract infection—that is, 9.8%. This frequency is much higher than that detected in the general population admitted to hospital (0.1% in 1 study [12] and 0.33% in another [13]). It should be pointed out that, in the present study, any bacteria count in urine was considered to be positive. But even if only cultures with detection of >10^5 cfu/mL of *C. urealyticum* are considered (5 of 163), the frequency is 3%, higher than in the unselected population [12, 13]. Renal transplant recipients should be considered to be a very high-risk population for this type of infection.

Skin colonization by this bacteria was an independent risk factor for urinary tract infection, but we consider that incidence to be not high enough to introduce this screening technique into clinical routine. Systematic screening for this bacteria in

Table 3. Antibiotic sensitivity of *Corynebacterium urealyticum* isolates.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC, µg/mL</th>
<th>Percentage of resistant isolates (n = 38)</th>
<th>Cut-off value for resistance, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>0.5 1 &lt;0.06 to 2</td>
<td>0</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>0.25 0.5 &lt;0.06 to 1</td>
<td>0</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.06 2 &lt;0.06 to 4</td>
<td>5.3</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>&gt;512 &gt;512 &lt;0.06 to &gt;512</td>
<td>76.3</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;512 &gt;512 &lt;0.06 to &gt;512</td>
<td>71.1</td>
<td>&gt;64</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>216 &gt;512 2 to &gt;512</td>
<td>84.2</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>16 64 0.25 to &gt;512</td>
<td>79</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>256 &gt;512 &lt;0.06 to &gt;512</td>
<td>68.4</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>256 &gt;512 &lt;0.06 to &gt;512</td>
<td>65.8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>2 &gt;512 &lt;0.06 to &gt;512</td>
<td>44.7</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt;512 &gt;512 &lt;0.06 to &gt;512</td>
<td>86.4</td>
<td>&gt;4</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>64 128 1 to 128</td>
<td>76.3</td>
<td>&gt;32</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2 32 0.5 to 32</td>
<td>39.5</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>&gt;512 &gt;512 &lt;0.06 to &gt;512</td>
<td>57.9</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>
urine samples is probably not indicated, but it should be considered if a renal transplant recipient is experiencing any of the following: chronic urinary tract infection symptoms with negative conventional urine cultures, alkaline urine (pH > 7), pyuria or microscopic hematuria with no alternative explanation, development of struvite crystals, obstructive uropathy, and encrusting cystitis or pyelitis. It is important to remember that *C. urealyticum* was detected only in selective medium or after prolonged incubation, so clinical suspicion should be communicated to the microbiologist when urine is sent for culture.

In our study, previous manipulation of the urinary tract (including nephrostomy) was significantly associated with *C. urealyticum* infection. On the other hand, this infection was an independent risk factor for the development of obstructive uropathy. It is difficult to assess the role of *C. urealyticum* in such a vicious circle.

Because of size of the cohort, the impact of the treatment of the infection could not be determined. In the present study, patients with symptomatic infections were treated with vancomycin (intravenous administration) or teicoplanin (intramuscular administration). In the future, the clinical usefulness of oral agents, such as linezolid, for the treatment of this urinary tract infection should be tested. Linezolid has shown good in vitro activity against *C. urealyticum* [14, 15], but no clinical experience has been reported. The size of present study is not enough to assess the relevance of prophylactic treatment of asymptomatic subjects.

The study has some limitations. Patients were not systematically selected; they were consecutive renal transplant recipients attended in the office or hospital ward, regardless of time since transplantation. Patients with no urine or skin isolation of *C. urealyticum* at baseline were not followed up with new cultures. Because these subjects could have developed the infection later, we cannot be sure whether incidence of this infection is even higher than that detected in our study.

As a result of this study, we conclude that urinary tract infection due to *C. urealyticum* is an underdiagnosed infection in renal transplant recipients. It should be considered for every renal transplant recipient with obstructive uropathy, mainly in the presence of alkaline urine, struvite lithiasis, and/or "sterile" pyuria. Its treatment could be decisive for the prevention of new complications, such as encrusting cystitis or encrusting pyelitis [11].

### Acknowledgments

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### Potential conflicts of interests

All authors: no conflicts.

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**Table 4. Long-term outcome of renal transplant recipients after bacteriuria due to *Corynebacterium urealyticum***

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage of patients</th>
<th>Multivariate analysis*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without bacteriuria</td>
<td>With bacteriuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 136)</td>
<td>(n = 22)</td>
<td></td>
</tr>
<tr>
<td>&gt;90 Days of hospitalization</td>
<td>6.6</td>
<td>22.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum creatinine &gt;1.5 mg/dL</td>
<td>60.3</td>
<td>54.5</td>
<td>NS</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>18.4</td>
<td>18.2</td>
<td>NS</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>16.9</td>
<td>31.8</td>
<td>NS</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>7.4</td>
<td>4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary tract surgical derivation</td>
<td>1.5</td>
<td>36.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nephrostomy</td>
<td>4.1</td>
<td>18.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other urologic manipulation</td>
<td>1.5</td>
<td>31.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥3 Episodes of UTI</td>
<td>11.8</td>
<td>31.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| Long-term urinary tract infection symptoms    | 0.7                    | 31.8                   | 27.7  (2.55–300.58) 0.006
| Urologic sepsis                               | 1.5                    | 9.1                    | NS    |
| Obstructive uropathy                          | 1.5                    | 40.9                   | <0.001|
| Graft loss                                    | 0                      | 4.5                    |        |

**NOTE.** NS, not significant; UTI, urinary tract infection.

*With use of the regression logistic model.*