**Citrobacter amalonaticus** human urinary tract infections, Marseille, France

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**Abstract**

*Citrobacter amalonaticus* is a bacterium that has rarely been reported as a human pathogen. Here we report four cases of *C. amalonaticus* infections occurring in patients hospitalized in Marseille, France, and review all cases described in the published literature.

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**Keywords:** Bacteria, *Citrobacter*, epidemiology, infection, MALDI-TOF, urine

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**Introduction**

*Citrobacter amalonaticus*, formerly called *Levinea amalonatica*, was first studied and described in 1971 after being isolated from various human samples from hospitalized patients, especially faeces [1]. Since then this bacterial species has been isolated from the environment [2,3] as well as sporadically isolated from humans, mainly in faecal, urine, wound and respiratory samples [1,4–9]. Recently our syndromic clinical laboratory-based surveillance system, called BALYSES (the BActerial real-time LaboratorY-based Surveillance System) [10], detected two consecutive *C. amalonaticus* kidney infections in two renal transplant recipients hospitalized in the same nephrology unit of Conception Hospital, Marseille, France. An additional two cases of *C. amalonaticus* infection were then detected over the following few weeks at other university hospitals in Marseille. We report here all cases from the literature to date.

**Case Reports**

**Case 1**

A 75-year-old woman with chronic renal failure due to membranoproliferative glomerulonephritis who had received a transplant in December 2010 was admitted to the nephrology unit of Conception Hospital for a regular check of her renal transplant. Since her transplantation the patient had developed membranoproliferative glomerulonephritis in the kidney transplant, urinary tract infections (UTIs) and diabetes as a result of immunosuppressive therapy. At admission in December 2014 analysis of a urine sample revealed leukocyturia (29.8 elements/mm3) and bacteriuria (10⁴/mL *C. amalonaticus*, identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF; Bruker Daltonics, Leipzig, Germany)). Antimicrobial susceptibility testing revealed that the isolate was resistant to amoxicillin and susceptible to third-generation cephalosporins, carbapenem, cotrimoxazole, ciprofloxacin and amoxicillin/clavulanate. The patient was treated with amoxicillin/clavulanate during 7 days and was considered cured.

**Case 2**

A 61-year-old man who had received a renal transplant in November 2014 visited the nephrology unit at Conception Hospital for his weekly checkup in December 2014. In the urine samples collected, leukocyturia was 25.2 elements/mm³, and bacteriuria was 10⁴/mL *C. amalonaticus*, identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF; Bruker Daltonics, Leipzig, Germany)). Antimicrobial susceptibility testing revealed that the isolate was resistant to amoxicillin and susceptible to third-generation cephalosporins, carbapenem, cotrimoxazole, ciprofloxacin and amoxicillin/clavulanate. The patient was treated with amoxicillin/clavulanate during 7 days and was considered cured.
Case 3
A 4-year-old child with Leigh syndrome, which is a mitochondrial cytopathy due to a heterozygote mutation on the SURF1 gene, was admitted to the intensive care unit at Timone Hospital for cardiogenic shock due to Epstein-Barr virus infection on 16 February 2015. On 6 April 2015 a urine sample was collected; analysis revealed that leukocyturia was 35 elements/mm³, hematuria 8 elements/mm³ and bacteriuria 10⁷/mL. The bacterium C. amalonaticus, identified by MALDI-TOF, was resistant to amoxicillin, amoxicillin/clavulanate, ticarcillin and ticarcillin/clavulanate and susceptible to carbapenems, third-generation cephalosporins, carbapenems and third-generation cephalosporins but resistant to amoxicillin and ticarcillin. The patient was symptomatically treated with paracetamol for fever; no antibiotic treatment was provided for asymptomatic urinary colonization.

Epidemiologic features
Because the two initial cases were reported in the nephrology unit in renal transplant recipients, we looked at our updated 13-year historical database [11] and retrospectively found that 36 patients had experienced C. amalonaticus infections before 2015 (Fig. 1). Most of the infections occurred in male subjects (21 male and 15 female patients), were hospital-acquired infections (22 infections, 62%) and were UTIs (29/36, 80%) (Fig. 2). We also identified a peak in the number of infected patients in 2012: a total of 12 patients were infected that year (Fig. 1). When we

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FIG. 1. Annual evolution of number of patients with *Citrobacter amalonaticus* infections at our hospital from January 2002 to December 2014.

**Case 4**
A 27-day-old newborn girl was brought into the paediatric unit in North Hospital on 4 March 2015 for rhinitis and fever (temperature 38.3°C). A urine sample was collected; analysis revealed leukocyturia at 13.2 elements/mm³ and bacteriuria 10⁴/mL. The strain was susceptible to amoxicillin/clavulanate, ticarcillin/clavulanate, ciprofloxacin, cotrimoxazole, nitrofurantoin, carbapenems and third-generation cephalosporins but resistant to amoxicillin and ticarcillin. The patient was symptomatically treated with paracetamol for fever; no antibiotic treatment was provided for asymptomatic urinary colonization.

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FIG. 2. Main features of 36 patients with *Citrobacter amalonaticus* infections. (A) Age distribution of patients infected with *C. amalonaticus*. (B) Different kinds of samples from which bacterium was isolated.

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In 2009, a Chinese woman who had received a kidney transplantation developed wound infection caused by *C. amalonaticus*. Another case concerned a 75-year-old man with pancreatic cancer who contracted a biliary tract infection and bacteremia due to *C. amalonaticus*. In Italy, it was recovered from a urine sample in one patient who had received a renal graft 10 months earlier. In the United States, between 1972 and 1978, at the Seattle Veterans Administration Medical Center, *C. amalonaticus* was identified in urine and fluid samples from five patients. Among these patients, two had UTIs. In Thailand, a man contracted enteric fever, and *C. amalonaticus* was incriminated.

In our study, we identified four cases of *C. amalonaticus* infection by MALDI-TOF. The four spectra were then included in a dendrogram built with Bruker MALDI Biotyper 3.0 software (Fig. 3). Among all cases reported, including ours, we observed five patients who had undergone kidney transplantation or who had a urinary tract abnormality (case 6) [7]. Also, we observed that patients were mainly immunocompromised, including a patient with a renal graft [9,12], a newborn patient (case 4) and patients with leukaemia and pancreatic cancer (cases 2 and 3) [4,6]. Taken together, our observations and those in previously published reports (Table 1) lead us to think that this bacterium is an opportunistic pathogen, especially in patients with urinary tract failure. The fact that *C. amalonaticus* infection was rarely reported in the past may be explained by the fact that this bacterium is difficult to identify (Table 1). Thus, conventional methods such as the API system and RapID onE may underestimate their prevalence by misidentifying the strains [7,13–16]. The fact we statistically identified more *C. amalonaticus* infections after we instituted the routine use of the MALDI-TOF may have resulted in an improvement in the identification of this bacterium.

**Discussion**

*C. amalonaticus* has only rarely been isolated in humans (Table 1). In 2009, a Chinese woman who had received a kidney transplant contracted peritonitis due to *C. amalonaticus*. In another study, a 63-year-old woman who had undergone bone marrow transplantation developed wound infection caused by *C. amalonaticus*. Another case concerned a 75-year-old man with pancreatic cancer who contracted a biliary tract infection and bacteremia due to *C. amalonaticus*. In Italy, it was recovered from a urine sample in one patient who had received a renal graft 10 months earlier. In the United States, between 1972 and 1978, at the Seattle Veterans Administration Medical Center, *C. amalonaticus* was identified in urine and fluid samples from five patients. Among these patients, two had UTIs. In Thailand, a man contracted enteric fever, and *C. amalonaticus* was incriminated.

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### Table 1. Characteristics of patients with *Citrobacter amalonaticus* infections reported in our studies and elsewhere

| Case, no. of patient (country) | Age (years)/sex | Infection type | Underlying condition | Sampling date | Identification method | Antibiotic therapy | Issue | Reference |
|--------------------------------|-----------------|----------------|----------------------|---------------|-----------------------|-------------------|-------|-----------|
| 1, 1 (China)                   | 47/F            | Peritonitis    | IgA nephropathy, renal graft, intermittent peritoneal dialysis | NA            | Biochemical tests and 16S rRNA | CAZ AK | Cure   | [9]       |
| 2, 1 (Italy)                   | 63/F            | Wound infection| ABMT, AML, intracranial haemorrhage | NA            | Vitel 2 system Phoenix automated system | TG | Cure | [4]       |
| 3, 1 (Taiwan)                  | 75/M            | Bacteraemia    | Ampullary vater cancer | NA            | Biochemical tests | NA | CRO SXT | Cure [8] |
| 4, 1 (Italy)                   | 53/M            | Enteric fever  | Urinary tract abnormality, diabetes, malignancy | NA            | Biochemical tests | NA | CRO SXT | Cure [8] |
| 5, 1 (Thailand)                | NA              | Renal allograft 10 months earlier | Fever, water diarrhoea, headache, travel to Asia | NA            | Biochemical tests | NA | CRO SXT | Cure [8] |
| 6, 5 (USA)                     | 2 patients      | NA             | Renal graft, chronic nephropathy, diabetes mellitus | 02/03/15      | MALDI-TOF | NA | AMC | Our study |
| 1, 1 (France)                  | 77/F            | Urinary tract infection | Urinary tract infection | NA            | MALDI-TOF | NA | SXT | Cure [8] |
| 2, 1 (France)                  | 61/M            | Renal graft, lymphatic cyst of graft, ureteral stenosis, diabetes | Renal graft, chronic nephropathy, diabetes mellitus | 10/12/14      | MALDI-TOF | CIP | Cure | Our study |
| 3, 1 (France)                  | 4/M             | Le Monch syndrome | Le Monch syndrome | 04/03/15      | MALDI-TOF | SXT | Cure | Our study |
| 4, 1 (France)                  | 0/F             | Fever, rhinitis | 04/03/15 | MALDI-TOF | No | Cure | Our study |

*ABMT*, allogenic bone marrow transplantation; *AMC*, amoxicillin/clavulanate; *AML*, acute myelogenous leukaemia; *CAZ*, cefazidine; *CIP*, ciprofloxacin; *CMZ*, cefmetazole; *CRO*, ceftriaxone; *lg*, immunoglobulin; *MALDI-TOF*, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; *NA*, data not available; *SXT*, cotrimoxazole; *TG*, tigecycline.

*Case* = number of cases previously described in the literature; *no* of *patient* = number of patients infected in the case report.

*Only studies reporting fully described infections with well-identified *C. amalonaticus* are included.*
bacterial species. However, we found a statistically higher prevalence of the number of UTIs due to this bacterium even after routine use of MALDI-TOF (after 2012), suggesting that it is likely that this bacteria could be an emerging pathogen responsible for UTIs in immunocompromised patients.

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Conflict of Interest

None declared.

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