# *Agrobacterium radiobacter* bacteremia in a child with acute lymphoblastic leukemia

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***Background:*** ***Agrobacteria*** **are Gram-negative tumorigenic plant pathogens that rarely cause infections in humans.**

***Methods:*** **The authors describe a 7-year-old boy with acute lymphoblastic leukemia who carried a central venous catheter and developed bacteremia due to *Agrobacterium radiobacter* (*A. radiobacter*).**

***Results:*** **Microbiological cure was achieved after administration of systemic ceftriaxone along with gentamicin lock therapy to the central venous catheter for 10 days. Catheter removal was not required, and the patient has not relapsed with bacteremia due to the same pathogen for more than 6 months.**

***Conclusions:*** ***A. radiobacter*** **is an emerging pathogen affecting immunocompromised children, particularly those with leukemia who carry central venous catheters. Although it has a low virulence, erratic susceptibility patterns, and high frequency of resistance to many antibiotics, ceftriaxone appears to be successful in treatment of most cases. Catheter removal for the clearance of bloodstream infections due to *A. radiobacter* may not be required in selected patients like the present case.**

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***Key words:*** ***Agrobacterium radiobacter*****;**
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## Introduction

*Agrobacterium radiobacter* (*A. radiobacter*) is a rare opportunistic Gram-negative bacillus associated with bacteremia caused by indwelling central venous catheters (CVCs) or other implantable devices.[1-5] We present a 7-year-old boy with acute lymphoblastic leukemia (ALL) who developed bacteremia caused by *A. radiobacter* and was successfully treated without catheter removal with intravenous ceftriaxone and antibiotic lock therapy to the catheter with local gentamicin.

## Case report

A 7-year-old boy with ALL and asthma who was receiving maintenance chemotherapy with oral methotrexate and 6-mercaptopurine and pulses of oral dexamethasone and intravenous vincristine every 10 weeks, according to one of the two arms of the medium-risk ALL-BFM95 protocol, presented with fever up to 39.2°C for the last 24 hours without any other accompanying symptoms. The boy had a functional double-lumen Hickman-type CVC for 15 months, i.e., since he was diagnosed with ALL. On admission, he was in good clinical condition with normal vital signs except for mild tachycardia, fever and wheezing necessitating administration of nebulized albuterol. A complete blood count showed leukocytes 3000/μl, with 62% neutrophils, 23% lymphocytes, 10% monocytes and 5% eosinophils, hemoglobin 9.9 g/dl, hematocrit 28.6%, and platelets 186 000/μl. After blood cultures were obtained from both lumens of the CVC and by venipuncture, and since the boy was not neutropenic and in good condition, no antibiotics were prescribed. However, since he was living far away from the hospital, we decided to watch him closely while he remained hospitalized. He defervesced quickly and was discharged after 24 hours of observation with oral clarithromycin and an inhaler of salmeterol/fluticasone for asthma. Before the discharge, a new set of blood cultures from the CVC was obtained. After the boy left for home, we were notified that bacterial growth was detected in the blood samples obtained from the white lumen of the CVC on both occasions, i.e., on

admission and at discharge, and from the peripheral vein on admission. The time for bacterial growth was 10.5 and 41.8 hours in the centrally drawn blood samples on admission and at discharge respectively, and 36.2 hours in the peripherally drawn blood on admission. Blood samples were cultured using the BacT/Alert3D blood culture automated system (bioMerieux, Mrcy Le Toille, France) and standard pediatric culture bottles (Organon Teknika Corporation, Durham, NC). Positive blood samples were subcultured at 35°C in McConkey, chocolate, and blood agar plates. The isolate was an oxidase and urease positive Gram-negative rod that was identified with the Api20NE card (bioMerieux, Mrcy Le Toille, France) for non-fermentative bacteria as *A. radiobacter*. Hence, the boy was called back for repeated blood cultures and reexamination. On readmission, blood samples from both lumens of the CVC were again positive for growth of *A. radiobacter*, while he remained afebrile and in excellent clinical condition. The time for bacterial growth was 62.4 and 117.6 hours in samples from the white and red lumens, respectively.

Antibiotic susceptibility was determined by E-test (AB Biodisk, Solna, Sweden). The NCCLS interpretative standards for breakpoints of other non-enterobacteriaceae Gram-negative bacteria were used for interpretation.[6] The MICs for all tested antibiotics and laboratory interpretation are shown in Table.

Since the patient was still receiving intravenous chemotherapy with vincristine through the CVC, we decided not to remove the catheter but treat him with ceftriaxone once a day (100 mg/kg per day) and antibiotic lock therapy with local gentamicin to both lumens for 10 days, based on an in-house protocol.

**Table.** Results of antibiotic susceptibility testing by E-test

| Antimicrobial agent | MIC (mg/L) | Interpretation |
|---|---|---|
| Ampicillin | 0.047 | Sensitive |
| Piperacillin | 2 | Sensitive |
| Piperacillin/tazobactam | <0.016 | Sensitive |
| Ceftazidime | 1 | Sensitive |
| Ceftriaxone | 1 | Sensitive |
| Cefotaxime | 0.25 | Sensitive |
| Cefoxitin | 0.25 | Sensitive |
| Cefepime | 0.75 | Sensitive |
| Imipenem | 0.032 | Sensitive |
| Meropenem | 0.032 | Sensitive |
| Amikacin | 125 | Resistant |
| Netilmicin | >256 | Resistant |
| Tobramycin | 16 | Resistant |
| Gentamicin | 2 | Sensitive |
| Ciprofloxacin | 0.023 | Sensitive |
| Levofloxacin | 0.064 | Sensitive |
| Trimethoprim/Sulfamethoxazole | >32/608 | Resistant |
| Tetracycline | 0.125 | Sensitive |
| Chloramphenicol | 12 | Intermediate |

More specifically, every catheter lumen was filled with a normal saline solution containing gentamicin 2 mg/ml.[7] The lock solution was left in place for 8 hours overnight and removed with aspiration in the morning. Repeated blood cultures were sterile after the end of the 10th day of systemic and local therapy. The patient has not relapsed with bacteremia due to the same pathogen for more than 6 months after the described events, i.e., until his most recent clinical follow-up.

## Discussion

*Agrobacteria* are small Gram-negative bacilli that cause tumors in plants.[3,8] Although they were once considered non-pathogenic but pure contaminants, since 1980 they have been linked with bloodstream infections in humans, especially those carrying silicone tubes with which these organisms have marked propensity for adhesion.[3] More specifically, *A. radiobacter* was initially identified as a cause of prosthetic valve endocarditis.[9] Later on, it was identified as the responsible pathogen in cases of peritonitis,[1-3,10] urinary tract infections,[11] endophthalmitis subsequent to cataract extraction,[12,13] and mainly bacteremia in debilitated and/or immunocompromised patients.[14-19]

Based on their effects in plants, *Agrobacteria* are classified into three main species: *A. tumefaciens*, *A. rhizogenes* and *A. rubi*. *A. radiobacter*, by far the most common pathogen of this genus in humans, lacks the tumorigenic Ti plasmid of *A. tumefaciens*. Curiously enough, although it is found in soil, history of direct contact with plants and soil is typically absent in cases of infection due to *A. radiobacter*, such as bacteremias in those with CVCs.

Amaya et al[18] reviewed 13 children below 14 years old with CVC-related bacteremia due to *A. radiobacter*. Since then, one more child with ALL and CVC-related bacteremia has been described by Lai et al.[19] Overall, among the 15 below 14 years old children with CVC-related bacteremia due to *A. radiobacter* described in the literature, i.e., including ours, 6 had ALL, 4 had solid tumors, and one each had AIDS, virus-associated hemophagocytic syndrome, chronic immune thrombocytopenia, severe combined immunodeficiency, and short bowel syndrome. Hence, all were immunocompromised. These 15 children constitute approximately 30% of the patients with an *A. radiobacter* infection reported in the literature. In 7 cases the CVC was retained,[5,17-20] in 7 cases it was removed,[5,18,20-22] and in 1 case no information about the catheter's fate was given.[15] The outcome was favorable irrespective of the removal of the CVC, suggesting that *A. radiobacter* is a pathogen of low virulence. Despite that, the need for catheter removal in case of infection

due to *A. radiobacter* in order to achieve a cure has been suggested. In a report of 42 cases, 33 (79%) had a foreign device in place, which was removed in 64% of these cases.[23] In other studies, microbiological and clinical cure was achieved only after removal of the device.[3,21] We found that no cases of endocarditis due to *A. radiobacter* have been described in children in contrast to adults.[9]

The antibiotic susceptibility patterns differ substantially in different isolates, with some being resistant to multiple antimicrobial agents.[24] Hence, susceptibility testing is recommended in every case of *A. radiobacter* infection in order to guide antibiotic therapy because of the varying susceptibility of the isolates, which extends even within the same class of antibiotics.[20] This was seen in our isolate as well, since it was sensitive to gentamicin but resistant to other aminoglycosides such as amikacin, tobramycin, and netilmicin. Based on data from previous reports and our case, however, ceftriaxone, imipenem, and ciprofloxacin are uniformly active against this pathogen.[3,20,23] Since ciprofloxacin is not traditionally used in children because of its effect in animal models on cartilage growth and the development of tendonitis, ceftriaxone and carbapenems remain the antibiotics of choice in children. The isolate of our patient was sensitive *in vitro* to tetracycline, but this antibiotic is not commonly used in children aged ≤8 years. Finally, it was sensitive *in vitro* to ampicillin. Despite that, we elected to use ceftriaxone, a more expensive but broader-spectrum antibiotic because our patient was immunocompromized.

Our patient who suffered from ALL in hematological remission for 14 months was in excellent clinical condition despite the fact that he remained untreated for 4 days. Since he needed more intravenous chemotherapy to complete his treatment, we decided to treat him with a combination of systemic and local antibiotic therapy. The antibiotic lock therapy was administered because the CVC was likely related to bacteremia, as the differential time to positivity of the initially drawn blood samples was in favour of CVC-related bacteremia,[25] and the patient was stable enough not requiring continuous IV hydration through the catheter overnight. Since *Agrobacteria spp*. have marked propensity for adhesion to silicone tubes, antibiotic lock therapy is an attractive treatment option that achieves high concentrations to the nidus of infection without exposing the patient to systemic antibiotics.[7] We selected gentamicin among several other potential antibiotics because it is a cheap, widely-used, old antibiotic that we have successfully used in more than a dozen cases of antibiotic lock therapy for sensitive Gram-negative pathogens with excellent results and high microbiological cure rates (data not shown). Since both systemic and local therapy were administered in our case, we can not comment on the relative contribution of each modality in the preservation of CVC and in the absence of recurrence by the same pathogen for more than 6 months after the therapy.

In conclusion, *A. radiobacter* is an emerging pathogen affecting immunocompromized children, particularly those with ALL who carry CVCs. Although it has a low virulence, erratic susceptibility patterns, and high frequency of resistance to many antibiotics, ceftriaxone and carbapenems appear to be consistently successful for treatment. Catheter removal for a cure is debatable, but should be considered in cases of persistently positive blood cultures despite seemingly appropriate antibiotic therapy. Finally, whenever non-fermentative Gram-negative bacilli are isolated from CVCs in children with leukemia and other immunocompromised patients, species identification is important to guide appropriate therapy.

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