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Original Article

Central line-associated bloodstream infection outbreak related to *Ralstonia pickettii*-contaminated saline in a pediatric hematopoietic stem cell transplant center

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ABSTRACT

Background. *Ralstonia pickettii* is an aerobic Gram-negative non-fermentative bacillus. It is an opportunistic pathogen that has recently prompted nosocomial outbreaks. Although it has low virulence, it can cause a wide range of invasive diseases in immunosuppressive patients. The characteristics of *R. pickettii*-related central line-associated bloodstream infection (CLABSI) outbreak in pediatric hematopoietic stem cell transplant (HSCT) recipients are presented in this study.

Materials and Methods. This was a single-center, retrospective analysis conducted at Bahcesehir University Goztepe Medicalpark Hospital . The clinical and laboratory characteristics of twelve children with Ralstonia-related CLABSIs were analyzed.

Results. Of the twelve patients with *R. pickettii* growth, seven were female. The median age was 12.1 (2-17) years. Autologous HSCT was performed in two of the patients and allogeneic HSCT was performed in ten patients for both malignant and non-malignant diseases. In the conditioning regimens, all patients were given myeloablative therapy. Clinical sepsis was the most common presentation. As a result of the investigations, *R. pickettii* growth was observed in saline solutions. All cases were successfully treated with the appropriate antibiotic regimen and the bacteria was not found in repeat cultures. Catheter removal was required in two patients. Mortality was not observed in any patient as the outcome of the infection episode.

Conclusion. The detection and control of the infectious source are critical in pediatric HSCT patients with severe immunosuppression, as medical equipment-related outbreaks can be life-threatening.

Key words: *Ralstonia pickettii*, stem cell transplantation, child, outbreak, infectious disease.

Ralstonia pickettii is a Gram-negative, aerobic, oxidase-positive, non-fermentative bacterium from the *Ralstonia* genus that has recently come to light due to its ability to cause nosocomial outbreaks.[1] It was previously described in the formation of biofilms in plastic industrial water pipes and has since been detected in a variety of water sources, including bottled water, standard purified water, laboratory-based high-purity water systems, and hospital water supplies.[2-5] It has the ability to reproduce in intravenous treatment solutions, posing a serious risk of bacteremia. *R. pickettii*-related central nervous infections and osteomyelitis have previously been reported.[6,7] Because of its low virulent nature, clinical infections almost exclusively occur in immunocompromised individuals, such as neonates, cancer patients, and patients in intensive care units.[1,8,9]

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Hematopoietic stem cell transplantation (HSCT) is a well-established treatment option for patients with a wide range of malignant and nonmalignant diseases. Patients undergoing HSCT require a central line (CL) for the administration of chemotherapy, blood products, and total parenteral nutrition during their long and tedious treatment.[10] Due to prolonged periods of immunosuppression, myeloablation, and indwelling catheter days, these patients are at a high risk of developing central line-associated bloodstream infections (CLABSIs).[11] Furthermore, since *R. pickettii* can form a biofilm layer, CLABSI is more likely to occur in the course of bacteremia. Although its mortality was found to be low due to its low virulence, the results of the outbreak can be disastrous if appropriate treatment is not promptly administered and precautions are not taken in HSCT patients who are severely immunosuppressed.[1,12] The purpose of this study is to present our experience with a *R. pickettii*-associated CLABSI outbreak in a pediatric HSCT unit.

Materials and methods

This was a retrospective analysis of an outbreak that occurred between May 2019 and August 2019 at the Pediatric HSCT Units of Bahcesehir University Goztepe Medicalpark Hospital.

Clinical setting & HSCT protocol

Our facility features a pediatric and hematology-oncology unit with 26 beds that serves as Türkiye's reference for auto and allo-HSCT. Every year, about 100 transplants are carried out. Each allogeneic HSCT recipient is housed in a single room equipped with high-efficiency (>99%) particulate air (HEPA) filters that can remove particles larger than 0.3 µm in diameter and more than 12 air exchanges per hour.

All patients have double-lumen tunneled central venous catheters (CVCs) named Broviac and Hickman catheters placed before HSCT. Needleless connectors and closed infusion systems are attached to the CVC. Central line care is provided by the nursing staff with hematology-oncology experience and trained in handling chemotherapy and infection control. The nurse-to-patient ratio is one for every three transplant beds. Standard practices for CVC care includes bathing every other day and cleaning the insertion site with chlorhexidine after every shower.

Closed infusion systems are changed every 72 hours. Access ports are scrubbed with chlorhexidine and accessed only with sterile devices. All lumens are covered with disinfecting hub caps.

Crystalloid fluids are continuously infused into central lines routinely. Central lines are flushed with saline solutions after every antibiotic infusion.

Systemic antimicrobials prophylaxis are not administered routinely before or after HSCT. Antifungal prophylaxis is routinely started on the date of CVC insertion and continued for 100 days after HSCT.

Surveillance data

Active surveillance of hospital-acquired infections is carried out by infection control nurses from the Hospital Infection Control Committee (HICC) in collaboration with infectious disease specialists in the HSCT unit of our hospital. The CDC and NHSN criteria are used to establish the diagnosis of CLABSI.[13]

As soon as an outbreak was suspected, HICC staff launched an investigation to determine the pathogen's source and transmission path. First, the newly purchased materials at the hospital were examined. Culture samples were taken from unsealed catheters, newly changed serum sale ampoules, distilled water, batticon, and any type of intravenous fluids and total parenteral nutrition (TPN) solutions. Samples were also taken from tap water and liquid soaps.

Identification of the bacteria

The culture samples were directly collected from the CVC and peripheral blood without saline flush. Determined samples were cultivated on blood agar, chocolate agar, and MacConkey agar by reduction method. If growth was observed after 24 hours of incubation in an oven at 35-37 °C for 24 hours, the identification phase was started (If no growth is observed, incubation is extended for up to 72 hours). Colony samples were taken and stained in a Gram staining device and the colonies were evaluated under the microscope, then suspended for delivery to the Vitek device where the McFarland ratio was adjusted. It was given to the device as the non-fermentative Gram negative group.

It was kept in incubation for 24 hours and turbidity was observed in liquid medium (If there was no change, it was extended for another 72 hours). As the image was blurred, the passage was performed on blood and MacConkey media. Following that, Gram-negative/positive separation on the medium was observed, and the colony was stained with Gram and examined under the microscope. After passage, the growths were placed in the device with the appropriate group to be identified based on colony morphology.

Statistical analysis

The statistical package for social science (SPSS) for Windows version 21.0 was used to analyze the data (SPSS 21.0, SPSS Inc. USA). Histogram graphics and Shapiro-Wilk tests were used to evaluate normality. The median, minimum, maximum, frequency, and percentage of the data are given. When the expected cell size was five, categorical variables between groups were compared using the two test or Fisher exact test. The student t-test was used to compare continuous variables that were normally distributed. Continuous variables that are not normally distributed were subjected to the Mann-Whitney U test. All p values are based on 2-tailed statistical analyses, and statistical significance was set at $p<0.05$. Univariate analysis and multivariate logistic regression analysis were performed to identify risk factors for mortality.

Ethical committee and informed consent

This study was performed with the permission of the Clinical Research Ethical Committee. Since it was a retrospective case-control study, no informed consent was taken.

Results

There were 12 patients diagnosed with *R. pickettii*-related CLABSI in this outbreak. Auto-HSCT was performed in two of the patients and allo-HSCT was performed in ten patients with both malignant and non-malignant disorders. In the conditioning regimen, all patients were given myeloablative therapy. The clinical and laboratory characteristics of the patients are detailed in Table I.

Antiviral (acyclovir 30 mg/kg/d IV or 100 mg/kg/d PO), antifungal (fluconazole 5 mg/kg/d PO or IV), and anti-*Pneumocystis jirovecii* pneumonia prophylaxis (trimethoprim - sulfamethoxazole 5 mg/kg/d PO 3 days/week) were given to all patients.

Of the 12 patients with *R. pickettii* growth, seven were female and five were male. The median age was 12.1 (2-17 years). All of the patients had a fever and a degree of clinical sepsis findings. Two patients required inotrope infusion for hypotension. The median absolute neutrophile count (ANC) was 22 (0-3690) / mm^3 and the median serum C-reactive protein (CRP) level was 93 (0.2-195) mg/L.

At the time of infectious episode, four patients had graft versus host disease (GvHD). All patients received meropenem, although some received combination therapy. The mean duration of treatment was fourteen days (7-30 days). The catheters of two patients were removed due to prolonged fever and hypotension. Mortality was not observed in any patient as an outcome of the infection episode.

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Table I. The clinical and laboratory characteristics of the patients.

Patient number	Age, gender	Primary diagnosis	HSCT characteristics	GVHD prophylaxis	Time of growth, day	Clinical & laboratory characteristics	Presence of GVHD	Resistance	Treatment, duration	Infection Outcome
1	7 yrs Female	ALL	Allogenic 1st HSCT Source: BM Donor: MUD	MTX, tacrolimus	-77 d	Clinic sepsis ANC: 0 CRP: 177 mg/L	No	Colistin	Colisitn+ meropenem + G-CSF 10 d	Cured
2	16 yrs Male	ALL	Allogenic 1st HSCT Source: PBSC Donor: MUD	MMF MTX tacrolimus	4	Clinic sepsis, hypotension (inotrope support) ANC: 0 CRP: 91 mg/L	No	Gentamycin, Levofloxacin	Meropenem + amikacin 21 d	Cured
3	9 yrs Male	Fucosidosis	Allogenic 1st HSCT Source: BM Donor: MFD	MTX tacrolimus	-1	Fever+ tachycardia ANC: 3200/mm^3 CRP: 106 mg/L	No	None	Meropenem 20 d	
4	5 yrs Female	SCID	Allogenic 1st HSCT Source: BM Donor: MUD	MTX tacrolimus	19	Fever ANC: 230 /mm^3 CRP: 11 mg/L	No	Gentamycin, Amikacin	Meropenem 14 d	Cured
5	2 yrs Female	JMML	Allogenic 1st HSCT Source: BM Donor: MUD	MTX tacrolimus	46	Fever ANC: 1160 /mm^3 CRP: 0.2 mg/L	No	Gentamycin, Netilmicin	Meropenem 12 d	Cured (catheter is removed)
6	9 yrs Male	ALL	Allogenic 1st HSCT Source: PBSC Donor: MUD	MTX tacrolimus	4	Clinic sepsis ANC: 0 /mm^3 CRP: 188 mg/L	Grade 4 Gastrointestinal involvement	Gentamycin, Amikacin Netilmicin Ceftazidime	Meropenem 17 d	Cured

ALL; acute lymphoblastic leukemia AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; CRP, C-reactive protein; CSA, cyclosporine; SCID, Severe combined immune deficiency; JMML, juvenile myeloid monocytic leukemia; G-CSF, granulocyte colony stimulating factor; GVHD, graft versus host disease; HSCT, hematopoetic stem cell transplantation; MFD, Matched family donor; MMF, Mycophenolate mofetil; MSD, Matched sibling donor; MTX, Methotrexate; MUD, matched unrelated donor; PBSC, periphreal blood stem cell; PIP-TAZ, Piperacillin-tazobactam; Post-Cy, post transplant Cyclophosphamide.

Table I. Continued.

Patient number	Age, gender	Primary diagnosis	HSCT characteristics	GVHD prophylaxis	Time of growth, day	Clinical & laboratory characteristics	Presence of GVHD	Resistance	Treatment, duration	Infection Outcome
7	2 yrs Female	ALL	Allogenic 1st HSCT Source: BM Donor: MSD	MTX CSA	-28	Clinic sepsis, vomiting ANC: 0 /mm^3 CRP: 195 mg/L	No	Amikacin Gentamycin, PIP-TAZ	Colisitn+ meropenem + amikacin G-CSF 14 d	Cured
8	17 yrs Female	Ewing sarcoma	Autologous 1st HSCT	None	8	Fever ANC: 0 CRP: 172 mg/L	No	Netilmicin	Meropenem 9 d	Cured
9	7 yrs Female	ALL	Allogenic 1st HSCT Source: PBSC Donor: MUD	Post-CY tacrolimus Steroid	-86	Fever ANC: 420 /mm^3 CRP: 9 mg/L	Grade 2 Liver involvement	Gentamycin, Amikacin Netilmicin PIP-TAZ	Meropenem 17 d	Cured
10	10 yrs Male	AML	Allogenic 2nd HSCT Source: PBSC Donor: MUD	MTX CSA	-23	Fever, pneumonia ANC: 610 /mm^3 CRP: 95 mg/L	Grade 4 Gastrointestinal involvement	Gentamycin, PIP-TAZ	Colistin+ meropenem + amikacin 24 d	Cured (catheter is removed)
11	17 yrs Male	Hodgkin Lymphoma	Autologous 1st HSCT	None	2	Fever ANC: 44 /mm^3 CRP: 30 mg/L	No	None	Meropenem 7 d	Cured
12	17 yrs Female	Aplastic anemia	2nd HSCT Haplo Source: PBSC+BM Donor: Father	MMF Post-CY tacrolimus	2	Clinic sepsis, hypotension (inotrope support) ANC: 0 /mm^3 CRP: 55 mg/L	Grade 4 Liver involvement	None	Meropenem+ amikacin 19 d	Cured

ALL; acute lymphoblastic leukemia AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; CRP, C-reactive protein; CSA, cyclosporine; SCID, Severe combined immune deficiency; JMML, juvenile myeloid monocytic leukemia; G-CSF, granulocyte colony stimulating factor; GVHD, graft versus host disease; HSCT, hematopoetic stem cell transplantation; MFD, Matched family donor; MMF, Mycophenolate mofetil; MSD, Matched sibling donor; MTX, Methotrexate; MUD, matched unrelated donor; PBSC, periphreal blood stem cell; PIP-TAZ, Piperacillin-tazobactam; Post-Cy, post transplant Cyclophosphamide.

As the result of the investigations, *R. pickettii* growth was observed in 50, 100, and 250 ml isotonic saline solutions. The use of the specific saline was immediately stopped by the Hospital Infection Control Committee.

Discussion

Ralstonia pickettii was discovered in 1973 and initially classified as *Pseudomonas* spp.[14] It was later reclassified into the genus Burkholderia, and the genus *Ralstonia* was named in 1995.[15] *R. pickettii* is the most common cause of invasive disease among *Ralstonia* species. The microorganism can survive in many water sources due to its low micronutrient requirement.[1] As it can contaminate medical treatment solutions, it causes hospital outbreaks.[1,4,9,12,16] Contamination occurs during the production line because bacteria can pass through the 0.2-micron filters used to sterilize pharmaceutical products.[17] As with saline, nosocomial infections have been reported due to magnesium vial, heparin flush, and intravitreal solutions.[18-20]

This was the first *R. pickettii* outbreak to impact our HSCT unit. When we encountered this unfamiliar microorganism, we immediately initiated surveillance screening. In accordance with the literature, we began by inspecting the newly purchased equipment, treatment solutions, and water supplies in the unit. As a result of our research, we discovered the growth of *R. pickettii* in isotonic solutions and instantly halted their use. Luckily we were able to control the outbreak without any loss. Recently, Bedir Demirdag et al.[12] from our country reported an outbreak of *R. pickettii* in pediatric oncology units. In that report, like ours, the source was determined to be the isotonic saline solution, and was taken under control without any mortality.

R. pickettii-associated pseudo-outbreaks have also been described in the literature due to the use of contaminated liquids in the laboratory process.[21] If a sample is collected by flushing with isotonic fluid during the culture collection process, it may result in false positivity. In our routine procedure, we collect culture samples directly from the CVC and peripheral blood without using a saline flush, excluding the possibility of contamination. Besides, all patients with *R. pickettii* growth exhibited fever and clinical signs of sepsis. Two patients required inotropes due to hypotension. Moreover, appropriate antibiotic treatment led to a rapid improvement in clinical findings.

The management of *R. pickettii* infections can be difficult due to the wide spectrum of antimicrobial susceptibility. Previous studies indicate a high level of β-lactam and aminoglycoside resistance in *Ralstonia* spp.[10,22] However, carbapenems and fluoroquinolones stand out as weapons in our arsenal.[23] In the present study, all of the isolates were susceptible to carbapenems. Levofloxacin resistance was detected in only one isolate. Most of the strains were resistant to aminoglycosides. During the outbreak, we used combination therapy for some patients until we obtained sensitivity results in culture antibiograms, at which point we used de-escalation. All patients responded well to the antibiotic regimen, and persistent bacteremia was not observed.

The decision to withdraw the catheter is critical in the treatment of CLABSI. Physicians hesitate to remove the catheter for a variety of reasons, particularly in pediatric patients due to the challenges of inserting a new catheter and the inadequacy and inconvenience of peripheral thin veins for continuation of treatment. However, rapid removal of the catheter is of vital importance in cases of clinical sepsis, where the appropriate antibiotic response cannot be obtained, and in the presence of microorganisms with high mortality that are difficult to eradicate.[24-26] During the infection episode, we had to remove the central catheter of two patients who had prolonged fever. No *R. pickettii* growth was observed in any cultures of removed catheters.

Although we cultivated *Ralstonia pickettii* in isotonic solutions as part of an epidemic control effort, we were unable to demonstrate the clonal relationship between the isolates from patients and the saline solution through pulse field electrophoresis. This was the limitation of this research.

In conclusion, it is crucial to identify and control the source of outbreaks, particularly in wards where critically ill patients like pediatric HSCT are admitted.

Ethical approval

This study was approved by the ethical committee of Bahcesehir University (2022-11/05).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SSC, SZ.; data collection: MS, KY; analysis and interpretation of results: MK, GK, MAY; draft manuscript preparation: MK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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