

Original Article

An outbreak of *Ralstonia pickettii* bloodstream infection and clinical outcomesŞirin Menekşe¹, Demet Haciseyitoğlu², Serap Süzük Yıldız³, Fatma Bayrakdar³¹ Department of Infectious Diseases, Koşuyolu Kartal Heart Training and Research Hospital, İstanbul, Turkey² Bulent Ecevit University Faculty of Medicine, Department of Medical Microbiology, Zonguldak, Turkey³ National Molecular Microbiology Reference Laboratory, Public Health General Directorate, Ministry of Health, Ankara, Turkey**Abstract**

Introduction: *Ralstonia pickettii* infections are rare and may be mistaken for other bacteria. This study aims to report a hospital outbreak of *R. pickettii* at a tertiary hospital, which was initially misidentified as *Ralstonia insidiosa*, along with its clinical consequences.

Methodology: A bacteraemia outbreak occurred between August 14 and October 4, 2019, infecting 22 patients admitted to diverse intensive care units. All isolates were identified with the use of the automated VITEK 2 Compact system and were then subjected to a microbial identification system, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Bacterial identification and genomic DNA typing was made using pulsed-field gel electrophoresis. Investigation covered all potential sources of the outbreak.

Results: An index patient and five additional patients developed fever while receiving care. Blood cultures of these patients yielded *R. insidiosa* by the VITEK 2 Compact system. Culture isolates were then submitted to a reference centre for confirmation by the MALDI-TOF MS system, where the bacterium turned out to be *R. pickettii*. No pathogen was isolated in the commercial products except for three samples of unopened sterile distilled water. Despite its discontinuation, 16 new cases were identified, in which blood cultures grew *R. pickettii* by the MALDI-TOF MS system. Attempts to uncover the source of the outbreak failed. Clinical manifestation was confined to fever in all the patients.

Conclusions: During this outbreak, *R. pickettii* infections ran a relatively mild course without clinical deterioration or mortality, possibly due to low virulence.

Key words: *Ralstonia pickettii*; hospital outbreak; low virulence.

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Introduction

Ralstonia pickettii is an aerobic, Gram-negative, non-fermentative bacillus of the *Ralstonia* genus having 16 species and three subspecies [1]. Previously named as *Pseudomonas pickettii* and *Burkholderia pickettii*, *R. pickettii* is the first identified and most common species of the genus. It is a water-borne bacterium that can grow at very low concentrations of nutrients [2]. In addition, it can survive at a wide range of temperatures (15-42 °C) and even pass through 0.2 µm filters, leading to outbreaks of infections via therapeutic fluids used in hospital settings [3]. Reportedly, outbreaks have often been associated with contamination of various therapeutic fluids and materials, such as sterile water, intravenous ranitidine, saline solution, narcotics, and magnesium vials by *R. pickettii* during the manufacturing of these products [2]. This bacterium has also been reported to cause pseudo-outbreaks by contamination of skin disinfectants and blood-culture bottles [1,2]. It has low virulence, but may result in

severe infections such as meningitis, endocarditis, osteomyelitis in immunocompromised patients [1]. It may develop resistance to ciprofloxacin, trimethoprim-sulphamethoxazole, piperacillin-tazobactam, imipenem/cilastatin, and ceftazidime and has the ability to form biofilms, posing challenges to treatment [1]. We aimed to report a hospital outbreak of *R. pickettii* with its clinical consequences at a tertiary hospital.

Methodology*Hospital settings*

This prospective study was performed at Kartal Koşuyolu Training and Research Hospital, a 465-bed tertiary referral center in İstanbul, Turkey, with three intensive care units (ICU) (adult cardiovascular surgical ICU, pediatric cardiovascular surgical ICU, and coronary ICU) as well as cardiovascular surgery clinics (one for pediatric cardiovascular surgery), gastroenterology surgery clinic, transplantation clinic, and cardiology clinics. The study was approved by the

institutional review board and all study protocol conformed to the Declaration of Helsinki.

Patients

We identified a bacteraemia outbreak due to *R. pickettii* at Kartal Koşuyolu Training and Research Hospital between 14th August and 4th October 2019. The study included 22 patients whose blood cultures were positive for *R. pickettii* (Table 1).

Data collection

Data included patients' demographic features, symptoms, physical examination findings, laboratory results, comorbidities, treatments, daily visit records, and outcomes.

Microbiological characterization and antimicrobial susceptibility

All isolates were identified with the use of the automated VITEK 2 Compact system that utilize GNI cards (bioMérieux Vitek Hazelwood, Missouri, USA). Culture isolates were then submitted to Kartal Dr. Lütfi Kırdar Training and Research Hospital for confirmation by a microbial identification system, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (VITEK MS; bioMérieux, France). Susceptibility testing was conducted by the Etest (bioMérieux, France). As the

breakpoints for the *Ralstonia* spp. have not been specified by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), antimicrobial susceptibility testing was performed using breakpoints for similar species, including *Pseudomonas* spp., *Burkholderia cepacia* and *Acinetobacter* spp. (EUCAST, Clinical breakpoints - breakpoints and guidance, 25th January 2020). The MICs were read after incubation overnight at 35 °C. The MICs for the bactericidal drugs (ertapenem, meropenem, ceftazidime, ciprofloxacin, levofloxacin, ceftriaxone, amikacin, and piperacillin-tazobactam) were defined as the point of intersection between the ellipse edge and the Etest strip, where there was complete inhibition of growth. The MIC for the bacteriostatic drug (trimethoprim-sulfamethoxazole and tigecycline) was read at 80% inhibition.

Bacterial identification and genomic DNA typing by pulsed-field gel electrophoresis

Pulsed-field gel electrophoresis (PFGE) was performed as previously described by Durmaz et al. [4]. Briefly, bacterial cells embedded in 1% low-melting-point agarose (Bio-Rad Lab, Hercules, CA, USA) plugs were lysed with lysozyme and proteinase K, and then chromosomal DNA was digested with 40U SmaI (Thermo Scientific-Fermentas Corporation, Vilnius, Lithuania). Fragmented DNA samples were

Table 1. Characteristics of patients affected by the *R. pickettii* outbreak.

Case no.	Wards	Age / Sex	Baseline disease	MV/ECMO	Comorbidities	Date of specimen collection in 2019	CVC removal day	Antibiotic Treatment	APACHE score	Days of fever	Outcome
1	CS-ICU	72 F	Mitral, tricuspid valve insufficiency	MV	COPD	14 th Aug	6	Ceftazidim	12	3	Died-23
2	CS-ICU	72 F	Mitral valve insufficiency	MV	DM	22 nd Aug	10	Ceftazidim	10	1	Alive
3	CD	87 F	Acute limb ischemia	None	COPD, HT	21 st Aug		Ertapenem	8	1	Alive
4	CS-ICU	69 F	Colon cancer	MV	HT	26 th Aug	1	Imipenem	8	1	Alive
5	CS-ICU	69 M	Coronary artery disease	MV	COPD	27 th Aug	15	Piperacillin/Tazobactam	7	2	Alive
6	CICU	23 M	Myocarditis-pulse steroid	MV, ECMO	None	26 th Aug	7	Meropenem	5	2	Alive
7	CS-ICU	61 F	Aortic aneurysm	MV	Acromegaly, Hypothyroidism	3 rd Sep	0	Meropenem	19	1	Died-62
8	CS-ICU	70 M	Coronary artery disease	None	DM HT	3 rd Sep		Piperacillin/Tazobactam	6	3	Alive
9	CICU	27 F	Pulmonary hypertension	None	Postpartum period	3rd-15th Sep		Meropenem	5	1	Alive
10	CD	63 M	Coronary artery disease	None	HT	4 th Sep		None	6	1	Alive
11	CD	26 F	Pulmonary hypertension	None	Scleroderma	10 th - 21 st Sep		Piperacillin/Tazobactam	12		Alive
12	CICU	49 F	Coronary artery disease	None	COPD	14 th Sep		None	5	1	Alive
13	CS-ICU	77 F	Coronary artery disease	MV	DM, HT, COPD	1 st Sep	15	Meropenem	13	3	Died-56
14	CS-ICU	34 M	Atrial septal defect	None	None	21 st Sep	1	None	7	2	Alive
15	CD	69 M	Coronary artery disease	None	DM	23 rd Sep		None	8	1	Alive
16	PCICU	17 M	Pulmonary valve insufficiency	MV	None	1st Oct	10	Meropenem	10	2	Alive
17	CS-ICU	60 M	Coronary artery disease	None	DM, HT	4 th Oct	2	None	6	3	Alive
18	CS-ICU	20 M	Aortic valve stenosis	None	None	4 th Oct	2	None	6	1	Alive
19	CICU	31 F	Pulmonary hypertension	MV	None	3 rd Oct	3	Meropenem	18	3	Died-13
20	CICU	56 M	Coronary artery disease	None	None	3 rd Oct	1	Meropenem	7	2	Alive
21	PCICU	3 F	Atrial septal defect	None	Hypothyroidism	1 st Oct	1	Piperacillin/Tazobactam	9	3	Alive
22	CS-ICU	44 M	Aortic dissection-Brain dead	MV	DM	3 rd Sep	0	None	27	3	Died-5

Case 1. The index patient. CS-ICU: Cardiac Surgery Intensive Care Unit; CD: Cardiology Department; PCICU: Paediatric Cardiac Intensive Care Unit; CICU: Cardiac Intensive Care Unit; F: Female; M: Male; COPD: Chronic obstructive pulmonary disease; HT: Hypertension; DM: Diabetes mellitus; CVC: Central venous catheter; MV: Mechanical ventilation; UF: Ultrafiltration; ABP: Intra-aortic balloon pump; ECMO: Extracorporeal membrane oxygenation; HD: Haemodialysis; PEG: Percutaneous endoscopic gastrostomy.

electrophoresed in 1% pulsed-field certified agarose (Bio-Rad Lab, Hercules, CA, USA) using a CHEF-DR III system (Bio-Rad Lab, Nazareth, Belgium) with 5-30 seconds pulse time, for 18 hours at 14 °C at 6 V/cm². The gel was stained with ethidium bromide (5 µg/mL), visualized under UV light, and photographed using ChemiDoc MP Imaging System (BIO RAD Company, United Kingdom). Analysis of PFGE patterns was made using BioNumerics software version 7.5 (Applied Maths, Saint-Matins-Latem, Belgium) and compared using a Dice coefficient with a tolerance of 1.5% and an optimization of 1%. Isolates with identical patterns were considered to be genotypically ‘indistinguishable’, while those that differed by 1-3 bands were defined as ‘closely related’ and 4-6 bands as ‘possibly related’. ‘Unrelated’ or ‘different’ strains indicated those that differed by ≥ 7 bands [4].

Both antimicrobial susceptibility testing and PFGE identification were performed in 13 isolates recovered from the patients and in three isolates recovered from unused sterile distilled water.

Investigation covered all potential sources of the outbreak. The first six cases of *R. pickettii* were detected in the mid-August, when the weather was quite hot and dry. In accordance with institutional infection control measures, there was no evidence for the infection source, such as plants, organic matter, leakages of any kind, moisture, ventilation/heating problems. Eighty commercial samples from different wards and from commercial products commonly used in infected patients were taken for culture and tested for *R. pickettii*, including distilled water (10 samples), chlorhexidine and alcohol-solutions (10 samples), povidone-iodine (10 samples), magnesium (10 samples), heparin (10 samples), and saline solution (30 samples, of which, after the outbreak 10 isolates were documented). Although the study patients had fever, 10 unused blood-culture bottles were examined to exclude a pseudo-outbreak.

Table 2. Therapeutic solutions and agents used in patients affected by the *R. pickettii* outbreak.

Solution/Agent	Number of Patients (n = 22) (%)
500 mL normal saline	22 (100)
1000 mL normal saline	5 (23)
100 mL normal saline	4 (18)
Magnesium	9 (41)
Heparin	5 (23)
Potassium	6 (27)
Calcium	7 (32)
Enoxaparin sodium	7 (32)
Lidocaine HCl	9 (41)
Pantoprazole	7 (32)

Results

Investigation into the source of the outbreak

A total of 22 patients were included in this study, during which time 9,419 patients were admitted to our hospital. On August 14, a female (index) patient who had been admitted 64 days earlier to the cardiovascular surgery ICU for repair of the mitral and tricuspid valves developed an increased body temperature of 38.3 °C (Table 1). Blood samples were obtained from a central venous catheter and a peripheral vein and were collected in four bottles (2 aerobic and 2 anaerobic), two of which yielded *R. insidiosa* by the VITEK 2 Compact system at our centre.

Initially, it was thought to be a contamination related to the laboratory procedures, which led to a comprehensive review thereof. However, during the same week, blood cultures of five additional patients grew *R. insidiosa*. Of these, three patients had been in the same ICU as the index patient, while the other two had been receiving care at different wards. An investigation into the outbreak was initiated.

No pathogen was isolated from the commercial products except for three samples of unopened sterile distilled water on September 4, upon which the use of sterile distilled water was terminated. Routine weekly surveillance samples of urine and respiratory secretions were collected from all patients admitted to the ICU. None of the patients with bloodstream infections (BSIs) had pulmonary involvement, nor any growth in respiratory secretions or urine.

Culture isolates were then submitted to Kartal Dr. Lütfi Kırdar Training and Research Hospital for a more specific identification and confirmation by the MALDI-TOF MS system (VITEK MS; bioMérieux, France). In the following days, despite the discontinuation of the sterile distilled water, 16 new cases were identified. Investigation was extended to different sources, but the source of the outbreak could not be identified.

We then reviewed the procedures that the affected patients had received, which pointed to the common use of 500 mL saline solutions as part of an intravenous procedure (Table 2). Subsequently, 10 samples of saline solutions of diverse lot numbers were found to be free of contamination.

Isolation of *R. pickettii*

The isolates of the index patient and the following five patients, diagnosed as *R. insidiosa* by the VITEK 2 Compact system at our centre, turned out to be *R. pickettii* as the culprit bacterium. Blood samples of the subsequent 16 patients also grew *R. pickettii* by the MALDI-TOF MS system at the reference centre.

Antimicrobial susceptibility testing was performed in 13 isolates recovered from the patients and in three isolates recovered from unused sterile distilled water. As the breakpoints have not been specified for *Ralstonia* spp., the breakpoints given for similar species were used to interpret pathogen susceptibility. Thus, one strain isolated from the distilled water No. 2 was interpreted to be resistant to ertapenem, and three others isolated from three patients (Patients no. 3, 4, 7 - Table 2) to amikacin.

All tested isolates were found to have higher MIC values than those for ciprofloxacin and levofloxacin. They were also found susceptible to the other antimicrobials that were tested (meropenem, trimethoprim-sulfamethoxazole, tigecycline, ceftazidime, ceftriaxone and piperacillin-tazobactam, Table 3).

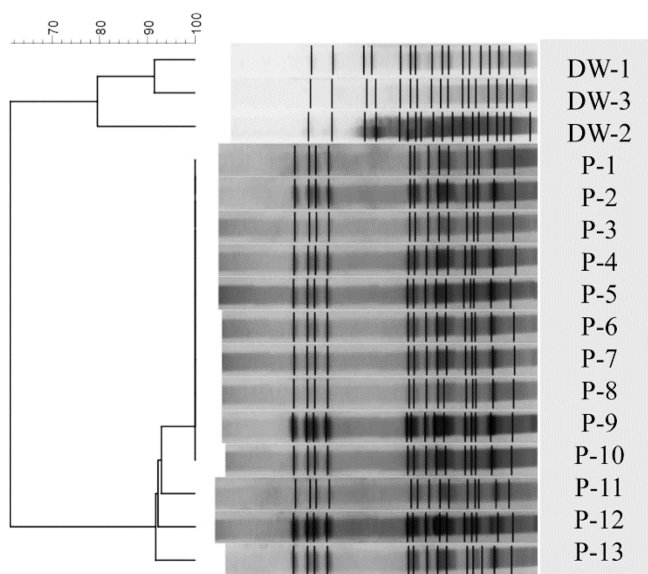
In genotypic analysis, all the 13 isolates were interpreted as "indistinguishably" similar, and three isolates from distilled water were interpreted as "different" (Figure 1).

The characteristics of the patients

The BSI outbreak affected 22 patients (11 males, 11 females), with 37 *R. pickettii* isolates recovered from 36 aerobic and one anaerobic blood cultures. Twenty-five blood samples were obtained from the peripheral veins, and 12 blood samples were obtained from the central catheters. The isolates of the index patient and the following five patients were initially misidentified as *R. insidiosa* by the VITEK 2 Compact system, but later were identified as *R. pickettii* by the MALDI-TOF MS system. Eleven patients were admitted to the cardiovascular intensive care unit, 10 of whom underwent cardiac surgery. The remaining 11 patients were admitted to one of the four different departments (Table 1).

The mean age of patients was 47.8 years (range 3-87 years). The mean hospital stay was 40 days (range 4-177 days). All patients exhibited fever as the main indicator of the outbreak, with no signs of sepsis.

Figure 1. Genetic relationship of *R. pickettii* isolates.



Fifteen patients had central venous catheters, which were kept in place during the BSI outbreak due to the absence of clinical deterioration. Five patients died from causes other than infection (Table 1).

A total of 15 patients received intravenous empirical antibiotic therapy due to the suspicion of BSI until culture results (Table 1). One of the seven patients (Patient no. 22- Table 1) who did not receive intravenous antibiotic therapy was diagnosed with brain-death, while the other patients survived and were discharged in good condition before obtaining the results of blood cultures. Oral amoxicillin-clavulanic acid was initiated in one of the six patients at discharge. The mean hospital stay of these six patients was 6.2 days.

During hospitalization, repeat blood cultures were obtained from 14 patients and all were tested negative. Of these, two patients with histories of both caesarean section and pulmonary hypertension had recurrent fever on days 11 and 12 of hospitalization, respectively, and had positive cultures. One of these patients underwent

Table 3. MIC values of *R. pickettii* isolates (n = 14).

Antibiotics	MIC range	MIC ₅₀	MIC ₉₀
Meropenem	0.016-0.50	0.064	0.25
Ertapenem	0.032-1	0.19	0.5
Levofloxacin	0.016-0.25	0.047	0.064
Ciprofloxacin	0.04-0.094	0.047	0.064
Trimethoprim-sulfamethoxazole	0.004-0.012	0.006	0.008
Amikacin	0.50-256	6	64
Tigecycline	0.064-0.25	0.125	0.19
Piperacillin-tazobactam	0.032-2	0.25	1
Ceftazidime	0.5-4	1	4
Ceftriaxone	0.016-1	0.032	0.125

lung transplantation 63 days after the initial positive culture and was well after transplantation (Patient no. 11- Table 1).

All patients were followed up until January 2021 without any signs of recurrent infections.

Discussion

R. pickettii infections are rare and are often mistaken for other bacteria, including *Ralstonia species*, *Burkholderia cepacia complex*, and *Pseudomonas fluorescens*. MALDI-TOF mass spectrometry provides true identification of *Ralstonia* spp. at the genus level [1,5]. Our isolates were initially misidentified as *R. insidiosa* by the VITEK 2 Compact system, but later MALDI-TOF MS enabled true identification of *R. pickettii*.

To date, there have been reports that *R. pickettii* infections are associated with contamination of fluids during the production process. Therefore, once an outbreak of *R. pickettii* is identified, contamination of solutions used for therapeutic purposes should be suspected and investigated [2,6]. Our investigation into the therapeutic solutions used at our hospital pointed to the sterile distilled water as the possible culprit. Although weekly surveillance cultures were collected from the patients in the ICU, respiratory secretions of the patients were free from *R. pickettii*. On PFGE testing, 13 outbreak-related strains were shown to be indistinguishable, while the three strains isolated from the sterile distilled water were of different genotypes. We were not able to identify the real source of the outbreak. Given that the saline solution was the sole common agent used in all patients, we considered saline solutions to be the probable source of the outbreak. Also, since the infected patients were admitted in different departments, the transmission by either health care workers or environmental contamination was less likely. So far, patient-to-patient transmission has not been reported [1].

Infusion-related BSIs are rarely encountered and their incidence is unknown, because routine bacteriological sampling is not performed [7]. Our major shortcoming was that we did not perform bacteriological sampling from infusates at the time the patients developed fever.

Despite its low virulence, *R. pickettii* has been shown to cause serious infections such as endocarditis, meningitis, osteomyelitis, and bacteraemia. So far, about 357 patients have been reported, of whom 121 had haematologic malignancies. The most frequently reported infection (261 patients) is bacteraemia [5,6,8-20]. In a molecular study of 15 patients with clinically

suspected intravascular catheter-related BSIs, Zhang *et al.* detected *R. pickettii* in approximately half of the intravascular catheters [21]. There are also studies emphasizing the removal of catheters due to the possibility of biofilm formation [17,21]. Kismet *et al.* reported two paediatric and severely immunosuppressed patients in whom microbiologic eradication could only be achieved after catheter removal [22]. We had two patients whose BSIs could be eradicated without catheter removal. Both patients were slightly immunosuppressed.

Six patients who did not receive antibiotic treatment during hospitalization were discharged. At their follow-up visits, they had no complaints of fever, nor any signs of infection. One patient later underwent coronary artery bypass grafting and had an uneventful recovery.

A similar and relatively favourable outcome of an outbreak with *R. pickettii* was also reported in four patients at a haemodialysis centre [11]. Of the four patients, two had catheters and both underwent catheter removal and received intravenous antibiotic therapy. The remaining two patients received oral antibiotic therapy alone.

We had two female patients who had been admitted with pulmonary hypertension in the postpartum period (Table 1). Their fever initially responded to antibiotic treatment, but later the fever recurred. Both patients had positive blood cultures for *R. pickettii* at the time of the initial and recurrent fevers.

Ralstonia spp. have been reported to cause serious respiratory tract infections such as cavitary pneumonia and lung abscesses, especially in patients with cystic fibrosis and chronic obstructive pulmonary disease [16,17,23,24]. At our centre, routine weekly surveillance samples of respiratory secretions are collected from all ICU patients. None of our patients with BSIs had pulmonary involvement, nor any growth in respiratory secretions.

Although we did not encounter any infection-related death among our infected cases, a literature search showed nine cases of mortality associated with *R. pickettii*, due to endocarditis (n = 2) [19,25], pneumonia (n = 1) [19], BSI (n = 5), and pneumosepsis (n = 1) [17].

Was the condition a real outbreak or transient bacteraemia?

During this outbreak, despite the presence of positive blood cultures in all affected patients, the infection did not result in clinical deterioration or mortality. In particular, irrespective of the presence or removal of catheters or the presence or absence of

antimicrobial treatment, the outcome did not differ with regard to mortality among affected patients. This may raise the question of whether the condition was a real outbreak or transient bacteraemia. In addition, it is likely that, had it really been an outbreak, it might have ended up with transient bacteraemia due to low virulence or relatively competent immune system of the patients.

Limitations

The main limitation to the present study is that infusion samples were not sent for microbiologic examination, which would have increased the chance to find out the source of the outbreak.

Authors' Contributions

All authors made substantial contributions to the following: (1) the conception and design of the study, (2) collection, analysis and interpretation of data, (3) drafting and revising the manuscript, (4) final approval of the manuscript before submission.

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Corresponding author

Dr. Şirin Menekşe
Department of Infectious Diseases, Koşuyolu Kartal Heart
Training and Research Hospital,
Cevizli, 2, Denizer Cad., 34865 Kartal,
İstanbul, Turkey
Tel: +90 (216) 500 15 00
Email: meneksesirin@hotmail.com

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