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Outbreak of healthcare-associated bacteremia caused by *Burkholderia gladioli* due to contaminated multidose vials with saline solutions in three Croatian hospitals ☆

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ABSTRACT

Objectives: *Burkholderia gladioli* has been associated with infections in patients with cystic fibrosis, chronic granulomatous disease, and other immunocompromising conditions. The aim of this study was to better depict the outbreak of healthcare-associated bacteremia caused by *B. gladioli* due to exposure to contaminated multidose vials with saline solutions.

Methods: An environmental and epidemiologic investigation was conducted by the Infection Prevention and Control Team (IPCT) to identify the source of the outbreak in three Croatian hospitals.

Results: During a 3-month period, 13 *B. gladioli* bacteremia episodes were identified in 10 patients in three Croatian hospitals. At the time of the outbreak, all three hospitals used saline products from the same manufacturer. Two 100-ml multidose vials with saline solutions and needleless dispensing pins were positive for *B. gladioli*. All 13 bacteremia isolates and two isolates from the saline showed the same antimicrobial susceptibility patterns and pulsed-field gel electrophoresis profile, demonstrating clonal relatedness.

Conclusion: When an environmental pathogen causes an outbreak, contamination of intravenous products must be considered. Close communication between the local IPCT and the National Hospital Infection Control Advisory Committee is essential to conduct a prompt and thorough investigation and find the source of the outbreak.

Introduction

Burkholderia spp. is a genus of aerobic, rod-shaped, oxidase-negative, gram-negative bacteria found in diverse habitats such as water, soil, and plants. Members of the genus *Burkholderia* were formerly classified as *Pseudomonas*, but due to ribosomal RNA differences, the genus was divided. The genus *Burkholderia* currently consists of more than 60 species. One of them, *Burkholderia glad-*

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Table 1
Patient demographic and clinical characteristics.

Patient	Age (years)	Hospital	Sex	Ward	Clinical diagnoses	Use of IV line from the same manufacturer	Use of the saline from the same manufacturer
1	2	H1	F	Gastroenterology	Feeding disorder	Yes	Yes
2	1	H1	M	Pulmonology	ARI	Yes	Yes
3	70	H2	F	Cardiology	Atrial fibrillation, UTI	Yes	Yes
4	36	H2	M	Endocrinology	Pancreatitis, type 1 DM	Yes	Yes
5	36	H2	F	Nephrology	Nephrotic syndrome, type 1 DM	Yes	Yes
6	76	H3	M	Oncology	Rectal cancer	Yes	Yes
7	70	H3	M	Oncology	Metastatic rectal cancer	Yes	Yes
8	54	H3	F	Oncology	Breast cancer	Yes	Yes
9	65	H3	F	Oncology	Breast cancer	Yes	Yes
10	61	H3	M	Oncology	Metastatic malignant disease	Yes	Yes

ARI, acute respiratory infection; DM, diabetes mellitus; F, female; H1, Children's Hospital Zagreb, Zagreb, Croatia; H2, Clinical Hospital Dubrava, Zagreb, Croatia; H3, Čakovec County Hospital, Čakovec, Croatia; IV, intravenous line; M, male; UTI, urinary tract infection.

ioli, formerly known as *Pseudomonas marginata*, was considered a plant pathogen for many years, known for causing flower rot in gladiolus and other plants (Jorgensen et al., 2015; Winn and Koneman, 2006). Although it has a low pathogenic potential and rarely causes human infections, it has been recently recognized as a possible opportunistic pathogen associated with infections in patients with cystic fibrosis, especially after lung transplantation (Graves et al., 1997; Jorgensen et al., 2015; Kennedy et al., 2007; Segonds et al., 2009), chronic granulomatous disease, and other immunocompromising conditions (Boyanton et al., 2005; Graves et al., 1997; Imataki et al., 2014; Jorgensen et al., 2015). Few cases were also described in patients without immunodeficiencies but who were on mechanical ventilation and in a 2-year immunocompetent child with a cervical abscesses (Graves et al., 1997; Kennedy et al., 2007). Lately, outbreaks of *B. gladioli* sepsis in newborns, with a high mortality rate of 7%, have been described. Particularly vulnerable are those who are severely immunocompromised and premature newborns (Dursun et al., 2012; Zhou et al., 2015).

The aim of this study was to better depict the outbreak of healthcare-associated bacteremia caused by *B. gladioli* due to exposure to contaminated multidose vials with saline solutions occurring in three Croatian hospitals during a 3-month period.

Materials and methods

A retrospective description and analysis of a case series of healthcare-associated *B. gladioli* bacteremia was performed.

Outbreak detection

In three Croatian hospitals, two located in the capital city of Zagreb and one in Čakovec, 13 *B. gladioli* bacteremia episodes were identified in 10 patients during a 3-month period.

The Children's Hospital Zagreb (H1) is a central and unique care institution for children and adolescents in Zagreb, Croatia. The Clinical Hospital Dubrava (H2) is a 650-bed university hospital in Zagreb, Croatia, and Čakovec County Hospital (H3) is a main hospital in Međimurska County in the northern part of Croatia.

All patients were hospitalized in the period from March to May 2016 on different wards and with various diagnoses (Table 1).

Although separate epidemiologic investigations had been conducted in H2 and H3 by local Infection Prevention and Control Teams (IPCTs), the true magnitude of the problem was identified after all three hospitals sent isolates for confirmation to the Department of Clinical and Molecular Microbiology, University Hospital Center Zagreb, acting as the National Reference Center for Healthcare-Associated Infections, where it is possible to conduct matrix-assisted LASER desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) identification (MALDI Biotyper; Bruker Daltonics, Bremen, Germany). Thereafter, the National Hospital Infection Control Advisory Committee was consulted.

Environmental sampling

As a part of environmental and epidemiologic investigation, local IPCTs in H2 and H3 interviewed healthcare workers who were involved in the treatment of the patients and reviewed their medical records. In H2, medical devices (including intravenous catheters, needleless dispensing pins), heparin and saline solutions (unopened and opened on the day of environmental sampling) used for catheter flushing of catheters, humidifier water from respiratory devices, oxygen water, sink drains, tap water, and antiseptic products were microbiologically analyzed. Samples were taken from different locations in the emergency department, observation room, reanimation room, infirmary, and storage cabinet.

In H3, samples from the inanimate environment were analyzed, but samples of heparin and saline were not investigated.

Environmental sampling was not conducted in H1 because there were just two cases of bacteremia with this pathogen at that moment, and the IPCT was not aware of the same problem in two other hospitals.

Bacterial cultures, species identification, and genotyping

Blood cultures were obtained from patients who were febrile and processed using BacT/Alert 3D (bioMerieux; Marcy l'Etoile, France) and BACTEC 9120 (BD, Sparks, MD) and incubated for 7 days at 35°C. Identification of the isolates was performed by MALDI-TOF MS (MALDI Biotyper; Bruker Daltonics). The antimicrobial susceptibility, minimal inhibitory concentration (MIC), was determined by the VITEK 2 System, using AST-N222 cards for aerobic gram-negative bacilli (bioMerieux) according to CLSI break points. Eight patient isolates and one saline solution were available for pulsed-field gel electrophoresis (PFGE) typing. Genotyping of *B. gladioli* isolates was performed by PFGE (CHEF-DRIII; Bio-Rad, Ivry sur Seine, France), with chromosomal digestion, using restriction endonuclease Xbal. GelCompar software (Applied Math, Kortrijk, Belgium) was used to establish a similarity between PFGE patterns. *B. gladioli* isolated from the blood culture of the patient with Wegener's granulomatosis from the University Hospital Center Zagreb (H4) that was isolated independently from the outbreak was used as a control strain.

Table 2
Minimal inhibitory concentrations of 13 isolates from blood culture and two isolates from saline solutions from all three Croatian Hospitals.

No.	Isolate	MIC value (mg/l)										
		TZP	CAZ	FEP	AN	GN	TOB	CIP	MIN	IMI	MEM	COL
1	H1-1	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
2	H1-2	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
3	H2-1	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
4	H2-2	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
5	H2-3	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
6	H2-4[a]	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
7	H2-5[a]	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
8	H3-1	≤4 (S)	8 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	2 (S)	≤0.25 (S)	1 (S)	≥16 (R)
9	H3-2	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
10	H3-3	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
11	H3-4	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
12	H3-5	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
13	H3-6	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
14	H3-7	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)
15	H3-8	≤4 (S)	4 (S)	16 (I)	≤2 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤1 (S)	≤0.25 (S)	1 (S)	≥16 (R)

AN, amikacin; CAZ, ceftazidime; CIP, ciprofloxacin; COL, colistin; FEP, cefepime; GN, gentamicin; H1, Children's Hospital Zagreb, Zagreb, Croatia; H2, Clinical Hospital Dubrava, Zagreb, Croatia; H3, Čakovec County Hospital, Čakovec, Croatia; I, intermediate; IMI, imipenem; MEM, meropenem; MIC, minimal inhibitory concentration; MIN, minocycline; R, resistant; S, sensitive; TOB, tobramycin; TZP, piperacillin/tazobactam.
[a] Isolate from saline solution.

Results

A total of 13 *B. gladioli* isolates from blood cultures were isolated during the study period in 10 patients from three Croatian hospitals (Table 1).

In hospital H1, *B. gladioli* was isolated from the blood culture of two healthy children without previously documented immunodeficiency or cystic fibrosis. As these patients were neither on mechanical ventilation nor had a central line catheter placed, the pathogen portal of entry was speculated to be through venipuncture, as previously described by Matijasic et al. (2016).

Three patients from H2 were admitted to the hospital through the emergency department from April to May 2016. At admission, both patients had had an intravenous catheter placed, and afterward, they were sent to three different wards (cardiology, endocrinology, and nephrology). On the second day of hospitalization, all three patients became febrile (>38°C), and blood cultures were obtained. The incidence of a rare *B. gladioli* bacteremia in a short period raised suspicion that the source of infection could be a piece of contaminated medical equipment or the environment.

In H3, *B. gladioli* was isolated in five patients with malignant diseases admitted to the Hemato-oncology ward at the Department of Internal Diseases. Four of five patients had an implanted port by which the therapy was administered. The patency of the port was maintained by injecting heparin. During the procedure, sterile saline solutions from multidose vials were used.

At the time of the outbreak, all three hospitals used saline products from the same manufacturer.

Antimicrobial susceptibility patterns of all 13 bacteremia isolates of *B. gladioli* were equal for all tested antibiotics (Table 2). All isolates were susceptible to imipenem, meropenem, ceftazidime, piperacillin/tazobactam, gentamicin, amikacin, tobramycin, minocycline, and ciprofloxacin and resistant to colistin. Eight patients were treated with antimicrobials according to *in vitro* susceptibility testing results; the condition of seven patients improved and one patient died. Two patients did not receive any antimicrobial treatment and despite that, their condition improved. The antimicrobial treatment used was meropenem or ceftriaxone (H1), ciprofloxacin (H2), and meropenem (H3).

Two 100-ml saline solutions with needleless dispensing pins (opened on the day of environment sampling) that had been obtained from the emergency department in H2 were positive for *B. gladioli*. Antimicrobial susceptibility patterns of these two isolates were the same as of isolates from blood cultures. Although all three hospitals used saline products from the same manufacturer, microbiological analysis of saline solutions in H1 and H3 were not conducted. None of the other tested environmental samples grew *B. gladioli*.

The PGFE profile of all analyzed isolates demonstrated clonal relatedness (Figure 1).

Outbreak control measures

Reinforcement of aseptic procedures when using multidose vials, sufficient contact time of antiseptic solution used for cap decontamination, and reinforcement of regular hospital infection and prevention control measures stopped the outbreak. Because the complete lot of saline solution was already used up, the planned withdrawal of the rest of the saline from the same lot was not carried out.

Discussion

During a 3-month outbreak described in this paper, 13 *B. gladioli* isolates from blood cultures were isolated in 10 patients from three Croatian hospitals due to the exposure to contaminated multidose vials with saline solutions. Furthermore, two 100-ml saline with needleless dispensing pins (opened on the day of environmental sampling) that were obtained from the emergency department in H2 were positive for *B. gladioli*. These products from the same manufacturer were in use in all three hospitals at the time of the outbreak but were not analyzed in H1 and H3. Antimicrobial susceptibility profiles of these two isolates were identical to the isolates from blood cultures, whereas the PFGE profiles of all analyzed isolates demonstrated clonal relatedness.

To our knowledge, contaminated intravenous fluids or intravascular catheters with *B. gladioli* have not been described in the literature as a source of bacteremia and potential sepsis yet. Phenotypic methods used with commercial identification systems are unreliable to differentiate *B. gladioli* from the bacteria of the *B. cepacia* complex, and misidentification is common. Therefore, the use of molecular-based methods or MALDI-TOF MS is recommended to identify *B. gladioli* and discriminate it from similar species (Jorgensen et al., 2015; Winn and Koneman, 2006).

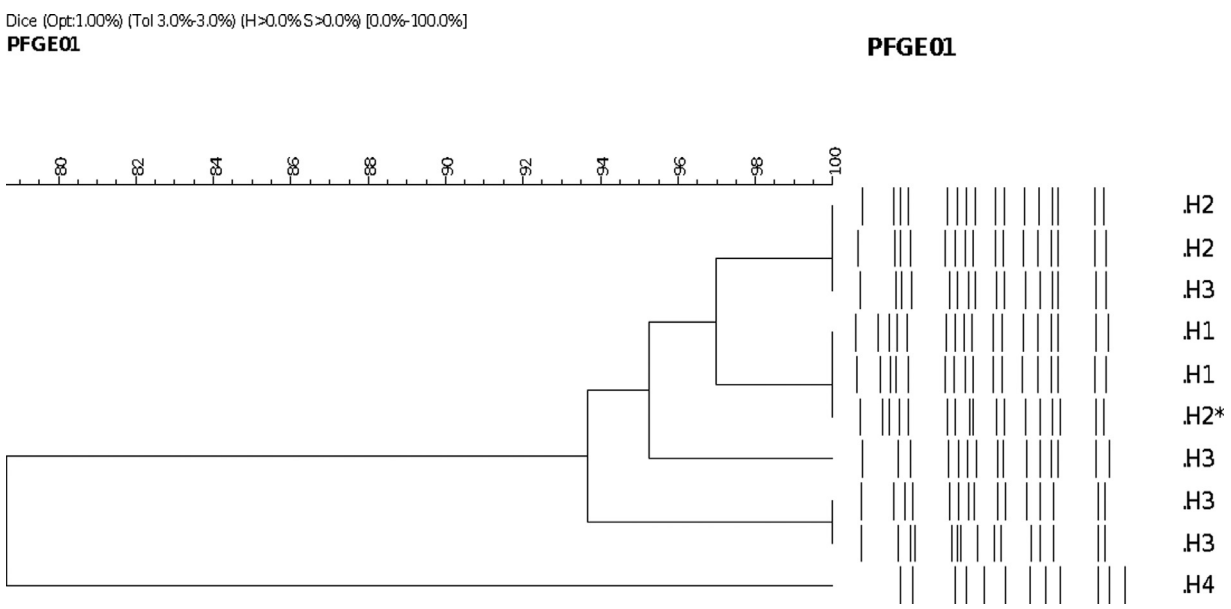

Figure 1. Dendrogram of pulsed-field gel electrophoresis (PFGE) of the *B. gladioli* isolates from blood culture and saline solutions.
H1, Children's Hospital Zagreb, Zagreb, Croatia; H2, Clinical Hospital Dubrava, Zagreb, Croatia; H3, Čakovec County Hospital, Čakovec, Croatia; H4, control strain from the University Hospital Center Zagreb.
*Isolate from the saline solutions.

However, in recent decades, other microorganisms were documented as causative agents of healthcare-associated bacteremia resulting from exposure to contaminated intravenous fluids. In 1971, *Enterobacter cloacae* and *Enterobacter agglomerans* septicemia developed in 378 patients in 25 American hospitals while receiving intravenous products from the same manufacturer (Mackel et al., 1975). Furthermore, Matsaniotis et al. (1984) described 63 cases of Enterobacter spp. sepsis in a pediatric hospital due to exposure to contaminated intravenous fluid. Bacteremia with the same microorganism found in infusion fluid was reported in Mexico in 2010 (Macias et al., 2010). The growth of several microorganisms is supported by nutrient-poor intravenous fluids such as 5% dextrose or 0.9% saline solution, with even better multiplication of microorganisms in nutrient-poor 0.9% saline solution than in 5% dextrose solution (Infante et al., 2012). A group of authors in Nigeria described a high contamination rate of unopened intravenous fluids (Atata et al., 2007). In resource-rich countries, the contamination rate of unopened parenteral medications in the pharmacy environment is low and varies between 0.00% and 0.66%. Those prepared by medical staff in clinical wards have a much higher contamination rate (7.85%), suggesting that contamination occurs after manipulation with intravenous fluids and therapeutics (Larmené-Beld et al., 2019).

Manufacturers guarantee the sterility of the intravenous solution itself but not of the outside of the container. Solutions for infusion can be contaminated during manipulation using contaminated antiseptic products for cap decontamination or if the antiseptic contact time is inadequate. Doit et al. (2004) reported a 7-month outbreak of *B. cepacia* bacteremia in a pediatric hospital. *B. cepacia* strain, genotypically identical to the blood isolates, was recovered from the upper surface of capped rubber stoppers of lipid emulsion bottles used for parenteral nutrition.

Furthermore, the infusion system is vulnerable to microbial invasion through numerous routes, such as intrinsic contamination of infusion fluid during manufacturing, cracks in intravenous bottles, contamination of additives, and others (Goldmann and Pier, 1993). Another problem is the use of multidose vials. Vonberg and Gastmeier (2007) described that in 49.2% of 130 drug-related outbreaks, the use of multidose vials was reported. The introduction of even small numbers of microorganisms in intravenous fluids can have dire consequences because these products provide a surprisingly suitable environment for the growth of many pathogens. Contaminated saline used for flushing catheters is a rare source of catheter-related bacteremia.

Nevertheless, this possibility should be considered, mainly if bacteremia is caused by environmental microorganisms, such as *B. gladioli*.

Although we initially suspected contaminated saline to be the cause of the *B. gladioli* outbreak, we encountered several problems during our investigation that we would like to point out. In the early phase of the investigation, the pharmacy staff was reluctant to give us access to analyze a larger number of unopened saline fluids and IV catheters. The hurdle was a lack of protocols for such situations at hospitals and at the national level. There was also a limitation regarding saline testing in H2; it was cultured 12 days after the blood cultures came positive for *B. gladioli*, when most of the suspected products were already used and replaced with new ones. Despite that, two 100-ml saline solutions with needleless dispensing pins that had been obtained from the emergency department in H2 were positive for *B. gladioli*.

Moreover, the other reason why we could not confirm unopened saline solution contamination could be because the laboratory technician disinfected the stopper before taking a sample. We did not investigate cups and stoppers separately. At the onset of the outbreak, we were unaware of the same problem occurring in other hospitals; it was only later during the outbreak that this information became known. Thus, in addition to precious time lost, we missed the opportunity to exchange information and conduct environmental investigations simultaneously from the onset of the outbreak.

There are several lessons can be learned from this outbreak: (1) the use of multidose intravenous products should be limited, and infection control protocols should be strictly followed; (2) when an environmental pathogen causes an outbreak, contamination of intravenous products must be considered, and protocols for such events must be set in place at the national and hospital level; and (3) a system of alerting the National Hospital Infection Control Advisory Committee should also be implemented. National surveil-

lance of blood culture isolates would be beneficial for early recognition of unusual or unexpected clustering of microorganisms in different hospitals.

Conclusion

When contamination of intravenous products is suspected as a cause of the outbreak, close communication between local and the National Hospital Infection Control Advisory Committee and cooperation with the hospital pharmacy and the manufacturer is essential to conduct a prompt and thorough environmental investigation and to find the source of the outbreak.

Declaration

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere. Part of this work was presented in the ECCMID poster presentation in 2017.

All authors have seen and approved the final manuscript and have read and agreed to the terms of the International Journal of Infectious Diseases data protection notice.

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Author contributions

All authors have made substantial contributions in all the following: (1) the conception and design of the study, acquisition of data, and analysis and interpretation of data; (2) drafting the article for important intellectual content; and (3) approval of the submitted manuscript.

Ethical statement

The work described has been carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals and aims for the inclusion of representative human populations (sex, age, and ethnicity) as per those recommendations. All data derived from medical histories were fully anonymized before access. The study protocol was approved by the ethics committee of Clinical Hospital Dubrava (approval number 2021/1312-06). The ethics committee waived the need for informed consent because the information obtained for the study was collected in routine clinical practice.

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