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Ralstonia spp. in a dialysis unit: an experience in the identification and control of an outbreak

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Abstract

Objective: to describe an experience in identification and control of an outbreak of *Ralstonia spp.* in a renal unit.
Material and Method: an epidemiological investigation of a hospital outbreak in 2 sites and extramural service of a renal unit. The investigation included patients who presented fever or chills, during or after dialysis, and who had positive blood culture for *Ralstonia spp*.
Results: Of 769 hemodialysis patients, 124 were identified with bacteremia by *Ralstonia spp.;* of these, 98.4% had catheter access and 1.6% had fistula. The overall attack rate was 16.1% and the case fatality rate was 0.8%. Environmental cultures were taken and drugs and devices were tracked. Several cultures were taken of the prefilled heparin following the methods described in the International Pharmacopoeia. However, it was the technique of microbial isolation recommended by experts that enabled the isolation of the microorganism and confirmed the source.
Conclusions: The outbreak described exceeded the number of patients affected documented in literature. It was caused by a contaminated batch of heparin. Evidence is provided of a recommended by expert technique used for the isolation of *Ralstonia spp.* in order to achieve control of outbreaks in a timely manner, minimizing clinical, economic, and social impact.

Key words: Ralstonia, Disease Outbreaks, Cross Infection

Ralstonia spp. en una unidad de diálisis: experiencia en la identificación y control de brote

Resumen

Objetivo: describir la experiencia en la identificación y control de un brote por *Ralstonia spp.* en una unidad renal.
Material y Método: investigación epidemiológica de brote hospitalario en 2 sedes y servicio extramural de una unidad renal. Se incluyeron pacientes que presentaron fiebre o escalofrío, durante o después de la terapia dialítica, y que tuvieran hemocultivo positivo para *Ralstonia spp*.
Resultados: De los 709 pacientes para hemodiálisis, se identificaron 124 con bacteriemia por *Ralstonia spp.,* 98,4% tenían acceso por catéter. La tasa de ataque global fue del 16,1% y la tasa de letalidad 0,8%. Se realizaron cultivos ambientales y trazabilidad de medicamentos y dispositivos, pero ante la presencia de casos extramurales la hipótesis fue redireccionada. La heparina prellenada había sido cultivada en varias oportunidades siguiendo la metodología de la farmacopea internacional. Sin embargo, la técnica de aislamiento microbiano recomendada por expertos fue la que permitió aislar el microorganismo y confirmar la fuente.
Conclusiones: El brote que se describe excedió el número de pacientes documentados en la literatura y fue causado por un lote contaminado de heparina. Se aporta evidencia de una técnica recomendada por expertos utilizada para el aislamiento de *Ralstonia spp.* a fin de lograr el control de brotes de manera oportuna, minimizando el impacto clínico, económico y social.

Palabras clave: *Ralstonia*, brotes hospitalarios, infecciones asociadas al cuidado de la salud

Introduction

The bacteria belonging to the genus *Ralstonia spp.* are gram-negative, non-fermenting, environmental bacilli and are found mainly in humid environments[1]. They are resistant to most disinfectants and have the capacity to form biofilms[2]. The main species within the genus are *R. pickettii*, *R. solanacearum*, *R. insidiosa* and *R. mannitolilytica*[3]. They are not usually pathogenic bacteria but have occasionally been found to cause infections associated with health care as an opportunistic pathogen. Most of these infections were associated with the use of contaminated solutions or products and all types of infections were reported[4]. They can produce outbreaks in selected populations, although usually with few affected cases because of the low virulence of the bacteria. However, large outbreaks may occur because it is not easy to find the source of the infection and control it adequately. Patients with chronic kidney disease undergoing dialysis are

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immunosuppressed due this condition, which make them more susceptible and vulnerable to be infected by opportunistic pathogen like *Ralstonia spp*[5,6]. The aim of the present study is to describe an experience of identification and control of an outbreak of *Ralstonia spp.* in a renal unit in the city of Cali, Colombia.

Material and method

On December 20, 2017, the Departmental Health Secretariat received notification of an outbreak in a dialysis unit. During the previous 2 weeks, 11 patients had presented mild symptoms of fever and/or chills during or after the dialysis session. Accordingly, blood cultures were taken and antibiotic therapy was begun. The cultures of all the patients tested positive for *Ralstonia pickettii/mannitolilytica*. All patients belonged to a renal unit and underwent hemodialysis for acute or chronic kidney disease.

The first visit was made on December 22, 2017, and, on reviewing the clinical histories and laboratory results of the reported patients, the outbreak was confirmed.

It was defined like an outbreak because the number of positive blood culture exceeded what it was expected for this renal unit and identification tests show a unusual bacteria[7].

The following confirmed case definition were made: Patient in renal unit who had a temperature of ≥38°C and/or chills, during or after dialysis therapy and had a positive blood culture for *Ralstonia spp.*

A review was made of the medical records of all the patients who had presented some type of reaction during or after the dialysis session. Active daily surveillance was maintained until February 12, 2018.

Traceability of drugs and devices

As part of the fieldwork, a review was made of the traceability of the batches of drugs and devices in use for each patient infected in the renal unit from 15 days before the onset of symptoms until the diagnosis of bacteremia.

Environmental and drug cultures

Environmental cultures were carried out on surfaces, walls, air, equipment, air conditioning systems, tap water and water from the treatment plant: rings, osmosis and permeated water from the dialysis machines. Repeated cultures were also performed on supplies, disinfectants, devices and medications.

Drug Cultures were performed following the method of the current United States Pharmacopeia (USP) which concurs with the International Pharmacopoeia of the World Health Organization[8] and is accepted in Colombia[9]. Additionally, prefilled heparin was tested using a method recommended by international expert and previously documented by the Spanish Society of Infectious Diseases and Clinical Microbiology[10].

Surveillance of the event was maintained as well as enforcing and monitoring of control and prevention measures including standard precautions, hand hygiene, cleaning and disinfection of equipment and environments, and contact precautions.

Results

Description of the cases

769 patients were treated for hemodialysis, 295 (38.4%) had a temporary central catheter and 474 (61.6%) had an arteriovenous fistula/graft. 362 were treated in the southern unit and 347 in the northern unit. Additionally, 60 patients were treated extramurally during the period of the outbreak.

124 patients were identified with bacteremia due to *Ralstonia spp.*, 122 (98.4%) with catheter access and 2 (1.6%) with fistula access. There were 67 (54.0%) affected patients in the southern unit, 54 (43.6%) in the northern unit and 3 (2.4%) extramural patients.

72 patients (58.1%) were men, and the average age was 63 years. The most frequent comorbidity was hypertension (51.6%), diabetes (50.8%) and obesity/overweight (10.5%).

Among the factors that could be related to the infection, it was found that, in the two weeks prior to the start of the outbreak, 19 (15.3%) patients had been hospitalized, 5 (4.0%) had been referred from another institution to start their dialysis therapy, 4 (3.2%) had received a transfusion of some blood product, 2 (1.6%) had received previous antibiotic therapy and 1 (0.8%) had had surgery.

78 (62%) patients were hospitalized, 6 patients with blood culture positive died but only one of these deaths was attributable to *Ralstonia spp.* Therefore, the case-fatality rate was 0.8%.

Epidemic curve and Attack rate

For this outbreak, a common origin curve with intermittent exposure was found (Figure 1). An outbreak of *Ralstonia spp.* was established on December 20, 2017, with the first case having occurred on December 12 of the same year. Attack rates are presented in Table 1. During the outbreak, patients who were on dialysis therapy were kept together and no new patients were admitted.

Lab results

Isolates was analyzed for 97 of the 124 patients. This bacterium showed high percentages of resistance to beta-lactams including carbapenems, however, it displayed very good sensitivity to fluoroquinolones (Figure 2).

A clonality test was performed to 21 isolates of *R. mannitolilytica* sent by both, south and north units, and 2 non-clinical isolates sent by INVIMA, which belonging to the suspected batch of heparin. The analysis of the patterns obtained con-

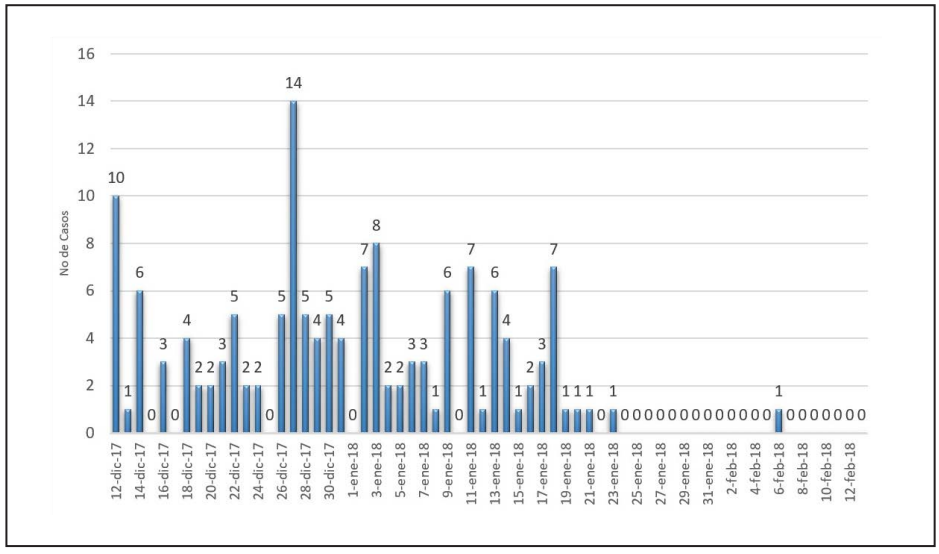

Figure 1. Epidemic curve *Ralstonia spp.* outbreak. Dialysis unit. December 2017 – February 2018

firms that all the isolates were related with a 97.68% of genetic similarity.

The results of the drugs and environmental cultures are shown in Table 2.

Traceability of drugs, devices

Six drugs were found to be from a batch shared between the 2 sites at the time of the start of the outbreak: amikacin sulfate 100 mg, amikacin sulfate 500 mg, iron (III)-hydroxide in sucrose 100 mg, erythropoietin 4000 UI, prefilled heparin 1000 units/mL and heparin sodium 5000 IU/mL. 4 medical supplies with shared batches were identified: 1mL disposable syringes, 20 mL disposable syringes, No. 16 disposable needles, and macrodrip infusion sets.

Confirmation of hypothesis

On January 11, 2018, the first extramural case was confirmed. This strengthened the hypothesis that the source was a medicine, as the extramural patients had no association with the others, the dialysis water used was independent, the care personnel and protocols were different, and, since they were hospitalized patients, the only medication administered during the procedure was prefilled heparin. The batch of this drug had been changed at the start of the outbreak as part of the control measures, however, on requesting additional information from the supplier, it was found that the preparation batch had been changed, but the batch of raw material was the same.

The prefilled heparin had already been cultured several times with negative results, so recommendations were requested from international experts in microbial isolation techniques. The recommended protocol was the following:

1. Combine several units of prefilled heparin to a total volume of 100 mL.
2. Pass the 100 mL of the medication through a 2-micron filter.
3. Grow a culture of the resulting concentrate on tryptone glucose extract agar (TGEA) and Reasoner Number 2 (R2A) between 17-23°C for 7 days.
4. If these culture media are not available, trypticase soy agar (TSA) can be used, although the results may not be as good.

   Using this method, the microorganism was isolated and, consequently, the source of the outbreak was identified.

Table 1. Attack rates by type of service and venous access.

Outpatient Service	Total Hemodialysis			Catheter Hemodialysis			Fistula/graft Hemodialysis		
	Cases	Total	Attack Rate	Cases	Total	Attack Rate	Cases	Total	Attack Rate
Southern Unit	67	362	18.5	65	123	52.8	2	239	0.8
Northern Unit	54	347	15.6	54	112	48.2	0	235	0
Total Units	121	709	1.1	119	235	50.6	2	474	0.4
Extramural Service	**Cases**	**Total**	**Attack Rate**	**Cases**	**Total**	**Attack Rate**	**Cases**	**Total**	**Attack Rate**
Hospital Institution1	2	38	5.3	2	38	5.3	-	0	-
Hospital Institution2	1	22	4.5	1	22	4.5	-	0	-
Total Extramural	3	60	5	3	60	5	-	0	-
TOTAL OUTBREAK	**124**	**769**	**16.1**	**122**	**295**	**41.4**	**2**	474	0.4

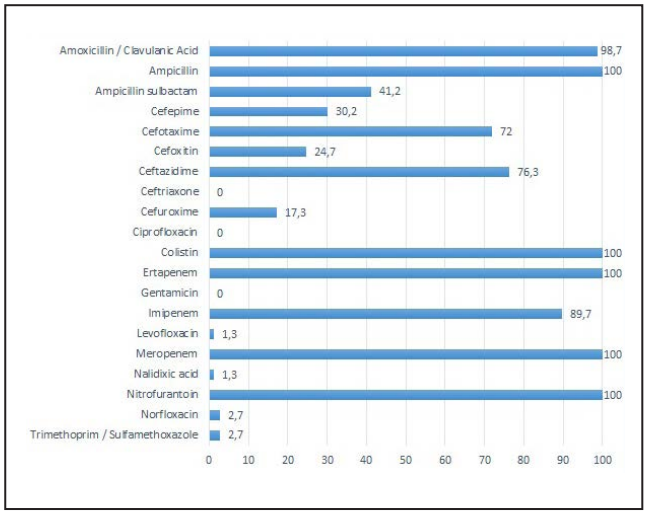

Figure 2. Antimicrobial resistance profile of *Ralstonia spp.*

Discussion

In the literature, the few reports of *Ralstonia spp.* outbreaks have a maximum of 34 affected patients, making this outbreak the largest reported in the literature, and none of them occurred in Latin America[3].

Most of the them are due to the use of contaminated solutions, blood products, chlorhexidine, saline, sterile water and colonization of medical devices. In addition, there are cases of outbreaks due to contamination of blisters such as heparins, fluconazole or another commonly used injectable drug contaminated with the bacteria[1-3,11]. In this outbreak, prefilled heparin was found to be the source of infection. As this was one of the first hypotheses that emerged during field research, it was cultured several times following the method of the current United States Pharmacopeia (USP) which concurs with the International Pharmacopoeia of the World Health Organization[8] and is accepted in Colombia[9]. However, the microbiological cultures and sterility tests were always negative for the growth of microorganisms, so the opinion of international experts was requested. They suggested another method previously recommended by the Spanish Society of Infectious Diseases and Clinical Microbiology[10].

This confirms the importance of the microbiology laboratory in the investigation of an outbreak associated with health care, since in addition to identifying the microorganism involved, it provides its resistance profile and helps with patient follow-up, as well as assisting in the identification of potential sources of infection and transmission mechanisms when hypotheses have been derived from the analysis of the epidemiological investigation[12,13].

The literature has clearly described the ability of *Ralstonia spp.* to penetrate the 0.2 and 0.22 µm filters used in sterility tests, in conditions of poor nutrient availability such as drug solutions, where they can survive by decreasing in size. For

Table 2. Number of drugs and environmental cultures

Specimen type	Specimen	Not acceptable	Acceptable	Total
Environmental	Air	1	10	11
	Surfaces	0	11	11
	Machine surfaces	0	63	63
	Water from the Air-Conditioner	1	16	17
	Tap water	0	10	10
	Air conditioner	0	2	2
Drugs	Prefilled heparin	0*	4	4
	Sodium chloride	0	19	19
	Erythropoietin	0	6	6
	Heparin	0	3	3
	Sodium heparin	0	2	2
	Ca–Mg–K Chloride	0	4	4
	Citric acid	0	10	10
	Sodium bicarbonate	0	17	17
	Dextrose	1	9	10
	Bicarbonate prepared	2	3	5
	Amikacin sulfate	0	2	2
Water plant	Permeated water - rings	2	25	27
	Permeated water - osmosis	1	10	11
	Tank water	0	5	5
	Port. MiniRev. Osmosis Water Sys.	0	6	6
	Acid	0	3	3
	Bicarbonate	0	12	12
Dialysis machines	Permeated water	0	34	34
	Dialysis fluid	1	10	11
Supplies	Syringes	0	11	11
	Needles	0	2	2
	Surgical soap	0	2	2
	TOTAL	9	311	320

*Results with the conventional technique

this reason, several authors suggest using filters of 0.1 µm,[14,15] however, this recommendation has not been included in the current pharmacopeias.

Despite the low virulence of *Ralstonia spp.* the literature has described cases resulting in death. In the present outbreak investigation, the fatality rate was 0.8%. Other investigations have shown low fatality rates consistent with those reported in our case[3,4].

Regarding treatment, there are no standardized recommendations for the treatment of *Ralstonia spp.* Differences in sensitivity to antibiotics are found, particularly carbapenems and aminoglycosides[16]. However, most reported infections have been treated with piperacillin-tazobactam, meropenem, ciprofloxacin, amikacin, and a combination of cephalosporins and aminoglycosides with good results[3,17]. In this outbreak, most patients received treatment with ciprofloxacin with adequate results.

Emphasis was placed on changing the catheters of all patients in whom the infection was confirmed, given that Ralstonia spp. is able to produce biofilms and cause persistence of infection and rise values suggested internationally[18,19].

We suggest for outbreak study to know in detail the medicines received, the coincidences between them and we carry out deeper methods for the study of each one, without forgetting other possible causes of infection such as water, devices or frequently used elements.

Ethical disclosures

Protection of human and animal subjects. No experiments were performed in animal nor humans.

Confidentiality of data. Patient´s data were anonymized

Competing interests. None declared.

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Ethical approval. This research was approved by the Ethics Committee of the University.

Conflict of interest. The authors have no conflicts of interest to declare.

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