

Outbreak of *Ralstonia mannitolilytica* in immunocompromised patients associated with a contaminated drug

Abstract

Objective: *Ralstonia mannitolilytica* is a bacterium capable of contaminating various drugs and medical products, leading to healthcare-associated infections outbreaks. This study describes an outbreak caused by this microorganism that was controlled through an epidemiological investigation and the identification of contaminated dexamethasone ampoules as the source.

Methods: a retrospective descriptive analysis of *R. mannitolilytica* infections cases was conducted in as 80-bed tertiary care institution during August 2023. All affected patients were women undergoing chemotherapy treatment, either hospitalized in the general ward or attending the day hospital. All patients with positive cultures for *R. mannitolilytica* were included. An epidemiological analysis of the cases and bacteriology testing on pharmaceutical products were performed to identify possible sources of infection.

Results: Six patients presented with chemotherapy-catheter-related infections and positive cultures for *R. mannitolilytica*. These patients were undergoing different chemotherapy treatments, but they shared two common drugs: dexamethasone in ampoules and sodium heparin in ampoules. Upon analysis, growth of *R. mannitolilytica* was found in the 2 ml ampoules of a specific batch of dexamethasone.

Conclusion: *R. mannitolilytica* is a bacterium that can grow in media with few nutritional requirements, and hospital outbreaks are a reality. It is important to quickly control these events to avoid further occurrences.

Keywords: *R. mannitolilytica*, outbreak, healthcare-associated-infections

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Introduction

Ralstonia mannitolilytica belongs to the genus *Ralstonia* spp., which encompasses gram-negative, non-fermenting bacilli commonly found in the environment, particularly in humid areas. These bacteria typically resistant to disinfectants and possess the ability to form biofilms. The main species include *R. pickettii*, *R. solanacearum*, *R. insidiosa*, and *R. mannitolilytica*. While not typically pathogenic per se, they have been associated with healthcare-associated-infections as opportunistic pathogens.^{1,2}

Due to its phenotypic characteristics and biochemical profile, *R. mannitolilytica* can be confused with other bacterial species such as *R. pickettii*, *P. fluorescens*, and *B. cepacia* (Tables 1a & Table 1b). Phenotypic identification methods have certain limitations, and their discriminatory power is lower than that of genotypic methods.³ The identification through automated microbiology system as *Burkholderia* spp. / *Ralstonia* spp. highlighted the need for other technologies to identify this species. MALDI-TOF MS, for instance, has proven to be an effective tool for identifying non-fermenting Gram-negative bacilli, including species of the *Ralstonia* genus.^{4,5}

Table 1a Biochemical characteristics of *Ralstonia mannitolilytica* (89% Probability)

2	APPA	(-)	3	ADO	(-)	4	PyrA	(+)	5	IARL	(-)	7	dCEL	(+)	9	BGAL	(-)
10	H2S	(-)	11	BNAG	(-)	12	AGLTp	(-)	13	dGLU	(+)	14	GGT	(+)	15	OFF	(-)
17	BGLU	(-)	18	dMAL	(+)	19	dMAN	(-)	20	dMNE	(-)	21	BXYL	(-)	22	BAlap	(-)
23	ProA	(+)	26	LIP	(-)	27	PLE	(-)	29	TyrA	(+)	31	URE	(+)	32	dSOR	(-)
33	SAC	(-)	34	Dtag	(-)	35	dTRE	(-)	36	CIT	(+)	37	MNT	(+)	39	5KG	(-)
40	ILATk	(+)	41	AGLU	(-)	42	SUCT	(+)	43	NAGA	(-)	44	AGAL	(-)	45	PHOS	(-)
46	GlyA	(-)	47	ODC	(-)	48	LDC	(-)	53	IHISa	(+)	56	CMT	(+)	57	BGUR	(-)
58	O129R	(+)	59	GGAA	(-)	61	IMLTa	(+)	62	ELLM	(-)	64	ILATa	(-)			

Note: (+) presence or (-) absence of the enzymatic activities evaluated.

Table 1b Biochemical characteristics of *Ralstonia mannitolilytica*

2	APPA	(-)	3	ADO	(-)	4	PyrA	(+)	5	IARL	(-)	7	dCEL	(+)	9	BGAL	(-)
10	H2S	(-)	11	BNAG	(-)	12	AGLTp	(-)	13	dGLU	(+)	14	GGT	(+)	15	OFF	(-)
17	BGLU	(-)	18	dMAL	(+)	19	dMAN	(-)	20	dMNE	(-)	21	BXYL	(-)	22	BAlap	(-)
23	ProA	(+)	26	LIP	(-)	27	PLE	(-)	29	TyrA	(+)	31	URE	(+)	32	dSOR	(-)
33	SAC	(-)	34	Dtag	(-)	35	dTRE	(-)	36	CIT	(+)	37	MNT	(+)	39	5KG	(-)
40	ILATk	(+)	41	AGLU	(-)	42	SUCT	(+)	43	NAGA	(-)	44	AGAL	(-)	45	PHOS	(-)
46	GlyA	(-)	47	ODC	(-)	48	LDC	(-)	53	IHISa	(+)	56	CMT	(+)	57	BGUR	(-)
58	O129R	(+)	59	GGAA	(-)	61	IMLTa	(+)	62	ELLM	(-)	64	ILATa	(-)			

Note: (+) presence or (-) absence of the enzymatic activities evaluated.

Infections linked to contaminated pharmaceutical products are uncommon and typically arise during the production process. Several cases describing contaminated products and various associated infections types have been documented.¹⁻³ These infections tend to cause outbreaks in specific populations, usually involving few cases, as they are often caused by bacteria of low virulence. However, they can lead to outbreaks of significant concern due to the difficulty in locating and controlling the source.⁴ This bacterium has been identified in a range of products used in the treatment of hospitalized patients, including sterile distilled water, saline solution, intravenous ranitidine, narcotics, skin disinfectants, blood culture bottles, and magnesium ampoules. When administered intravenously, through drip infusion, or used in wound care, these contaminated products can lead to serious infections.

Patients undergoing chemotherapy, such as those described in this outbreak, are considered immunosuppressed, rendering them more susceptible and vulnerable to opportunistic infections.⁵ This study describes the experience with an outbreak of *R. mannitolilytica* in 6 patients undergoing chemotherapy treatment with implanted catheters, the epidemiological investigation conducted, and the microbiological evaluation to identify potential sources and halt the outbreak.

Material and methods

Between July and August 2023, several episodes of fever were identified in oncology patients with implanted catheters, who were undergoing chemotherapy for breast cancer. Cultures from these patients' retrocatheter samples (from chemotherapy catheters) or peripheral blood cultures tested positive for *Ralstonia* species. These patients were treated at the Oncology Department of a high-complexity private institution in Concordia, Argentina. All patients received care either in the day hospital infusion room or the general ward during the aforementioned period. As a result of this finding, an epidemiological investigation was initiated for all patients receiving chemotherapy treatment with implanted catheters.

Epidemiological surveillance and data collection

The initial finding was that only female oncology patients had been affected, and all had an implanted catheter for chemotherapy. While all patients had breast cancer as their underlying condition, they were not all undergoing the same chemotherapy regimen. Consequently, there were differences in the pre-chemotherapy medications administered to prevent adverse effects related to the oncological drugs. Therefore, the investigation focused on the pharmaceutical products used in common across all patients. In this regard, the only drugs they all received in common were sodium heparin in 10 ml ampoules and dexamethasone 8 mg in 2 ml ampoules.

Two criteria were adopted to define a case: 1) positive *Ralstonia* culture from peripheral blood cultures and/or retrocatheter samples

from the chemotherapy catheter, and 2) common use of drugs among the oncology patients (sodium heparin, dexamethasone ampoules).

In the hospital pharmacy, there were two different brands of 2 ml dexamethasone ampoules, and two distinct batches from one of these brands. Conversely, all sodium heparin ampoules were from the same laboratory and batch.

The closed, unused ampoules of dexamethasone in circulation (from 2 different laboratories) and the closed, unused ampoules of sodium heparin (from a single laboratory and batch) were sent to the microbiology laboratory for cultivation. *Ralstonia* was found only in the dexamethasone ampoules from the laboratory with two different batches in circulation, and only in one of the dexamethasone batches.

To increase the possibility of detection, the context of five dexamethasone ampoules (from both laboratories, processed separately) were centrifuged prior to plating. A portion of the remaining sediment after centrifugation was plated on a tryptic soy agar plate (Figure 1), and another part of the pellet was placed into a Bact/ALERT 3D blood culture bottle (bioMerieux). The same procedure was performed with two sodium heparin ampoules. All cultures were processed under strict aseptic and safety standards.

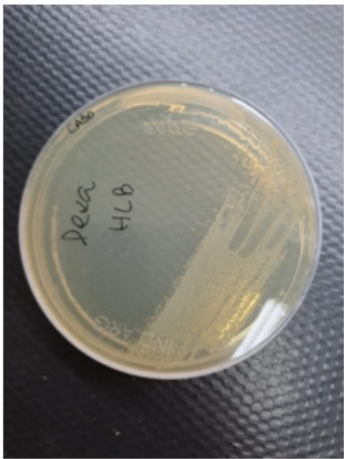


Figure 1 Colony Development of *Ralstonia* on Tryptic Soy Agar.

Although the methodology used to investigate the presence of this bacterium in the dexamethasone ampoules is not the recommended one for microbiological testing of pharmaceutical products, we were able to identify the bacterium using this method consistent with the work discussed by Saldarriaga-Quintero et al.⁶ In their study, these authors utilized several unopened heparin and passed their contents through a 2-micron filter to increase yield.⁶ In our case, lacking this filter, the entire content of the ampoules was subjected to prior centrifugation to work with the sediment and enhance the chances of bacterial recovery.

Results

Between July and August 2023, cultures from six oncology patients tested positive for *Ralstonia mannitolilytica* (Table 2), identifying this bacterium as the cause of their implanted-catheter- associated

infection. All patients were female, with breast cancer, averaging 58 years of age. Four of them had previously visited emergency departments at different hospitals due to fever, where antibiotics were prescribed without microbiological follow-up. Blood cultures or retrocatheter samples were not taken on any of these occasions.

Table 2 Clinical characteristics of the six patients with *Ralstonia*-associated infections

	Case 1	Case 2	Case 3		Case 4		Case 5	Case 6
Gender	Female	Female	Female		Female		Female	Female
Age	61	60	81		38		54	60
Underlying disease	Breast cancer	Breast cancer	Breast cancer		Breast cancer		Breast cancer	Breast cancer
Comorbidities	Pulmonary metastases	Pulmonary metastases	No		Pulmonary metastases		No	Cutaneous metastases
Chemotherapy Treatment	Paclitaxel	Paclitaxel	Doxorubicine Ciclofosfamida		Paclitaxel Atezolizumab		Doxorubicine Ciclofosfamida	Gemcitabine
Retroculture Hemocultures	Positive Negative	Positive Negative	Positive	Negative	Positive	Positive	Positive Negative	Positive Negative
Antibiotic Treatment	Initial PTZ - then TMS	Initial PTZ - then TMS	Initial PTZ - then TMS		Initial PTZ - then TMS		TMS	TMS
Evolution	Favorable	Favorable	Favorable		Favorable		Favorable	Favorable

Note: PTZ (Piperaciline-Tazobactam) TMS (Trimetoprim-Sulfametoxazole)

Due to persistent fever despite antibiotic therapy, the patients were admitted to our clinic for further studies. Blood cultures and retrocatheter samples were collected from all six patients; *Ralstonia mannitolilytica* was recovered from all retrocatheter samples, and only one patient also had growth in peripheral blood cultures. All patients had received chemotherapy infusions at the same institution, with different drugs according to the chemotherapy regimen prescribed by the oncologist for each specific case. All patients were attended by the same nurse, who also cared for other oncology patients during the same period.

All cases required hospitalization and the initiation of empirical

intravenous antibiotic treatment with Piperacillin-Tazobactam 4.5 g every 6 hours until culture results were obtained. Once available, antibiotic treatment was adjusted based on antibiotic sensitivity, de-escalating to Trimethoprim-Sulfamethoxazole 8-10 mg/kg/day of the Trimethoprim component, administered in two doses (every 12 hours). This adjustment aligned with published scientific evidence regarding the sensitivity of this microorganism and the antibiogram obtained in our laboratories from Bact/ALERT 3D (Table 3). The implanted catheters were removed from all patients. The patients had a favorable progression and were discharged after a few days of intravenous antibiotic treatment to continue with oral antibiotic therapy.

Table 3 Antibiotic sensitivity of *Ralstonia mannitolilytica*.

Antibiotic	MIC	Result	Antibiotic	MIC	Result
ESBL			Meropenem	≥16	R
Ampiciline			Amikacine	≥64	R
Ampiciline/Sulbactam	16	I	Gentamicine	≥16	R
Piperaciline/Tazobactam	≥128	R	Nalidixic Acid		
Cefalexine			Ciprofloxacine	≥4	R
Cefotaxime	8	S	Nitrofurantoine		
Ceftazidime	≥64	R	Colistin	≥16	R
Cefepime	8	S	Trimetoprim/Sulfametoxazole	<+20	S
Imipenem	8	R			

Microbiologic research

Samples of dexamethasone (from 2 different laboratories) and sodium heparin (from a single laboratory and batch) in circulation at the institution were sent to the bacteriology laboratory for culture. All analyzed samples were unopened ampoules or vials. *Ralstonia* was detected only in the dexamethasone ampoules from the manufacturer that had two different batches in circulation, and only one of those batches tested positive for the microorganism.

Subsequently, the strains were sent to the bacteriology laboratory of the Department of Clinical Microbiology at the José de San Martín Clinical Hospital in Buenos Aires. Mass spectrometry was

performed after an ethanol/formic acid extraction using the MALDI-TOF MS (BrukerDaltonik®, Bremen, Germany). The result obtained was the recovery of *Ralstonia mannitolilytica* in all three submitted samples, with an identification score > 2.00. Unfortunately, genomic sequencing studies could not be performed to confirm the outbreak through this method.

The dexamethasone ampoules from the affected batch were removed from use and reported to the competent authorities of the National Administration of Drugs, Foods, and Medical Technology (ANMAT) via the corresponding reporting form. Since their removal from use in the institution, no further infectious complications associated with this pathogen have occurred.

Discussion

An outbreak of *Ralstonia mannitolilytica* is described, associated with the contamination of a batch of dexamethasone that led to infections in six oncology patients. The epidemiological and microbiological investigation successfully identified the source and controlled the outbreak. Most *Ralstonia spp.* outbreaks are typically linked to contaminated solutions, blood derivatives, chlorhexidine, sterile distilled water, or colonization of medical devices. Contamination of heparin ampoules and other injectable substances has also been reported. In our study, we were able to demonstrate that the source of infection was indeed the unopened ampoules from a specific batch of dexamethasone.

This microorganism can pose a significant challenge. The ability of *Ralstonia spp.* to penetrate 0.2 to 0.22 µm filters, commonly used in sterility testing, has been described in conditions of low nutrient availability, such as in pharmaceutical solutions. In such environments, they can survive by reducing their bacterial size.^{6,7} The presence of the bacterium inside unopened dexamethasone ampoules suggests contamination during the production process or ineffective sterilization, as noted in other studies.⁷

Ralstonia spp. is considered a low-virulence bacterium; however, cases of patient's mortality have been reported. In our patient series, all individual had a favorable outcome following hospitalization, antibiotic treatment, and catheter removal, with no subsequent complications, despite being immunosuppressed. Only one of the six patients showed bacterial growth in blood cultures, which may have been due to the antibiotic treatment they were receiving prior to hospitalization. Given the characteristics of this bacterium, including its ability to persist in very small filters, we believe it was recovered from all implanted catheters due to its capacity to produce biofilm and survive under adverse conditions.

The epidemiological and microbiological investigation, led by the institution's Infection Control Committee, identified of the source of the infection and the cause of the contamination within seven days. This intervention once again highlights the value of Infection Control Committees, which are multidisciplinary and include trained microbiology team members, in identifying, investigating, and controlling outbreaks.

Conclusion

Ralstonia spp. is a difficult-to-characterize bacterium that can cause outbreaks through the contamination of medications or other medical supplies. Therefore, it is essential to remain alert to these complex situations and initiate a rapid response for outbreak control.

The swift epidemiological investigation by the Infection Control Committee and the microbiological work of the laboratory allowed for the control of this outbreak. It is important to emphasize the role of microbiological vigilance and inter-laboratory cooperation to respond rapidly to these kind of situations. Additionally, national authorities were alerted to prevent this event through adequate surveillance and batch traceability in other hospital pharmacies.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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