

Outbreak of Ralstonia Mannitolilytica Infection at a Tertiary Care Oncology Center in South India: A Case Series

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Abstract

Introduction: Ralstonia Mannitolilytica (RM) is a rare opportunistic pathogen capable of causing a serious infection in immunocompromised patients. It is ubiquitous in nature and a frequent contaminant of water supplies. RM infection in cancer patients may have serious implications as they are already susceptible due to underlying malignancy, treatment related immunosuppression, malnutrition and prolonged presence of indwelling central catheters. In this study, we report a case series of RM infection with focus on clinical characteristics, management and patterns of antibiotic sensitivity. **Methods:** This case series includes 17 cancer patients admitted at Healthcare Global oncology hospital, Bangalore, presenting with fever and/or chills between 22nd February 2020 to 5th May 2020, who had a positive blood culture and/or a chemoport/PICC/central venous catheter (CVC) tip culture positive for RM species. **Results:** Among all patients, RM was grown from the blood sample of 12 patients having an indwelling chemo-port, 4 patients with PICC line and 1 patient with a central venous line. All patients had a positive blood culture for RM, and two patients had a positive tip culture in their chemo-port and PICC line respectively. Antibiotic treatment includes cefoperazone-sulbactam for 10 patients, ceftazidime for 4 patients, meropenem for 2 patients and ceftriaxone for 1 patient. All 17 patients recovered from the infection without any complications. After 48 hours of incubation, no growth of Ralstonia was reported from any of the current environmental or pharmaceutical water samples. **Conclusion:** RM may be capable of causing serious infections in cancer patients as they are already immuno-compromised. Furthermore, RM may serve as an effective quality indicator of water and therapeutic supplies. Healthcare professionals should adhere to infection control policies, monitor outbreaks of unusual pathogens and study the emergence of pattern for antibiotic resistance.

Keywords: Ralstonia mannitolilytica- Outbreak- Oncology- Saline water flush- CLABSI

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Introduction

There is increased susceptibility for blood stream infections among cancer patients due to the underlying malignancy, treatment related immunosuppression, steroid use and malnutrition, which could all contribute to increased morbidity and mortality. Central venous catheters (CVC) whether implanted or non-implanted, are frequently used for administration of therapy among patients with solid tumors or hematological malignancies. CVCs can be a source for central line- associated bloodstream infections (CLABSI). Besides these clinical implications, CLABSI may increase costs for both the patient and healthcare system by adding to the financial burden. The main

etiological agents attributed to CLABSI among the Western Countries are gram positive organisms, which contribute to 73% of all catheter related infections [1]. On the contrary, in India there is predominance of gram negative CLABSI and some studies report the prevalence in the range of 60%. The common microbes isolated include Klebsiella pneumoniae, Pseudomonas aeruginosa, E.coli and Acinetobacter species [2-3].

The three main pathogenic species of the novel genus Ralstonia include: R.pickettii, R.insidiosa, R.mannitolilytica (RM). Ralstonia pickettii biovar 3/'thomassii' was recently shown to represent a separate

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species 'RM' [4]. This genus comprises a group of non-fermentative, gram-negative (NFGN) bacteria found in moist environments such as water, soil and plants [5]. RM is recognized as an opportunistic pathogen among immunocompromised patients [4]. It is widely distributed in the nature and a frequent contaminant of water supplies. It could be an aetiological agent among common source nosocomial outbreaks, due to contamination of parenteral fluid and medical equipment which are considered to be sterile [4]. *Ralstonia* have the ability to survive in disinfectants and pass through 0.2 µm filters normally used to sterilize solutions. It is frequently misidentified as *Burkholderia* or *Pseudomonas*.

Ralstonia are causative agents of bacteremia, haemoperitoneum, renal transplant infection, meningitis and sepsis among immunocompromised patients and central venous catheter (CVC) associated bacteremia among oncology patients [5]. Hospital outbreaks which have been reported were associated with contamination of water for injection, saline solution, disinfectants and antiseptics. Such NFGN, particularly those found in hospital settings are commonly reported as multidrug resistant organisms. They also act as potential reservoirs of antibiotic resistant genes.

The production of biofilm by RM is incriminated in their ability to cause CLABSI leading to localized and systemic infections which is key to their survival in the environment, evasion of the host's immune response and frequent antibiotic resistance [1]. RM has also been isolated from contaminated oxygen delivery devices [6].

Objectives

- i) To assess the clinical characteristics of RM infection
- ii) To list the drug susceptibility of the bacterial strain,
- iii) To analyze its impact on an immunocompromised group at an oncology setting.

Materials and Methods

This case series includes 17 patients and their clinical information was analyzed. The cases include patients attending the infusion center at the Healthcare Global Oncology hospital between 22nd March 2020 and 5th May 2020, presenting with symptoms of fever and/or chills, and a positive blood culture and/or a chemoport/PICC/central venous catheter (CVC) tip culture for *Ralstonia* species. The authors assisted by an infection control nurse reviewed the medical records of all cases identifying any common medical procedure or factors which might have posed a risk for acquiring *Ralstonia* infection.

Most of the cases were from a common tower in the hospital. Blood culture samples from the peripheral lines along with port/PICC line were sent for microbiological investigation. The demographic characteristics of the patient were also noted.

Surveillance swabs were taken from the following areas in the hospital:

Drug mixing box, hand rub solution, hand rub can, samples from both hands of 3 nurse practitioners, dressing trolley, nursing station, floor of one room, biomedical

area, heparin injection, sterile water and cleaning solution.

Isolation & identification

Blood cultures were taken from both the peripheral vein and chemoport or CVC line. These were tested on Biomerieux automated blood culture system. After growth was detected, they were plated on Mac Conkey & Sheep Blood (5-7%) agar plates. Subsequently, it was incubated aerobically at 37±1 °C for 24-48 hrs. Colonies were then put on Vitek 2 Compact System (Biomerieux) using Vitek 2GN card. The software version used was 8.01. The system was not able to report the sensitivity pattern to the desired antibiotics. Hence, manual sensitivity was put up for all the isolates. Mueller Hinton agar was used for testing of antibiotic discs. Discs were procured from Hi-Media. Discs were put up as per Clinical and Laboratory Standards Institute (CLSI) guidelines. As there were no CLSI breakpoints or zones available for *Ralstonia*, results were interpreted using CLSI criteria for *Pseudomonas* and *Burkholderia cepaciae* complex. *P aeruginosa* ATCC 27853 and *E.coli* ATCC 25922 were put up as controls.

Results

A total of 17 cases were reported from the oncology wards of Healthcare Global, Bangalore. All the cases presented with fever either at the time or within 48 hours of admission. As per the in-patient (IP) records, patients originated from varied residential areas. After 48 hours of incubation, no *Ralstonia* growth was reported from any of the current environmental or pharmaceutical water samples. The complete baseline characteristics are listed in Table 1.

Table 1 shows that among all patients, RM was grown from the blood sample of 12 (70.5%) patients having an indwelling chemo-port, 4 (23.5%) patients with PICC line and 1 (6%) patient with a central venous line. 8 (47%) patients had no co-morbidities while the remaining 9 (53%) had hypertension, type 2 diabetes, ischaemic heart disease and/or hypothyroidism. All patients had a positive blood culture for RM and two patients had a positive tip culture in their chemo-port and PICC line respectively. 9 (53%) patients were being treated for advanced malignancy while remaining 8 (47%) had localized disease.

The results of biochemical assessment as depicted in Table 2 shows that 7 (41%) patients had neutropenia, out of which only 2 (12%) patients had grade 4 neutropenia. Only 3 (18%) patients had elevated serum procalcitonin levels. Hypoalbuminemia was noted among 5 (29%) patients, which could possibly be contributed by advanced malignancy and the nutritional status. Growth factor support was given to 7 (41%) patients who had grade 1 or higher neutropenia with symptomatic infection. For RM infection, the following treatment were given: cefoperazone-sulbactam to 10 (59%) patients, ceftazidime to 4 (23.5%) patients, meropenem to 2 (12%) patients and ceftriaxone to 1 (5.5%) patient. All 17 patients recovered without any infection related complications.

Table 1. Baseline Characteristics of the Patients

Patient	Age	Gender	Co-morbidities	Type of IV line	Date of sample collection	Type of cancer	Localized/ Metastatic	Line of Chemo	No. of cycles
A	63	M	DM, HTN	Port	22.02.2020	Carcinoma GE junction	Metastatic	Second	2
B	52	F	HTN	PICC	25.02.2020	Carcinoma Breast	Localized	First	3
C	43	F	Nil	Port	25.02.2020	Carcinoma Breast	Localized	First	4
D	56	M	Nil	Port	07.03.2020	Carcinoma Colon	Localized	First	5
E	57	F	HTN, Hypothyroidism	PICC	24.03.2020	Carcinoma Breast	Localized	First	4
F	40	F	DM	PICC	27.03.2020	Carcinoma Breast	Localized	First	4
G	53	M	DM	Central	14.04.2020	GBM	-	Third	6
H	50	F	Nil	Port	16.04.2020	Carcinoma Breast	Metastatic	First	3
I	51	M	IHD	PICC	18.04.2020	Carcinoma Oral cavity	Metastatic	First	2
J	43	F	HTN, Hypothyroidism	Port	23.04.2020	Carcinoma Breast	Localized	First	4
K	30	F	Nil	Port	02.05.2020	Carcinoma Breast	Localized	First	1
L	65	M	Nil	Port	03.05.2020	Carcinoma Rectosigmoid	Metastatic	First	7
M	47	F	Nil	Port	05.05.2020	Carcinoma Breast	Localized	First	1
N	52	F	Nil	Port	09.04.2020	Carcinoma Rectum	Metastatic	First	6
O	50	F	Nil	Port	16.04.2020	NHL	Metastatic	First	3
P	52	F	Nil	Port	25.04.2020	Carcinoma Breast	Metastatic	Fifth	4
Q	65	F	DM	Port	25.04.2020	Carcinoma Breast	Metastatic	Second	2

DM, diabetes mellitus; HTN, hypertension; IHD, ischaemic heart disease; GE, gastroesophageal junction; PICC, peripherally inserted central catheter; GBM, glioblastoma multiforme; NHL, Non- Hodgkins lymphoma.

Table 3 depicts the proportion of cases who were resistant to each of the antibiotics. Antibiotic sensitivity panel shows maximum resistance to cotrimoxazole & least resistance pattern to cephalosporins. The antibiotics used and percentage of resistance is depicted in Table 3.

Discussion

Ralstonia are waterborne bacilli implicated in hospital acquired infections [7]. It is a non-pathogenic environmental microbe and clinical infection with this species is rare [8]. However with the development of modern day

Table 2. Laboratory Investigations, Treatment Received and Outcome of the Patients

Patient	ANC ^a (10 ⁹ /L) [Grade]	Procalcitonin ^b (ng/mL)	Albumin ^c (g/dL)	Growth factor administration	Treatment received	Outcome
A	1.66 [1]	0.2	3.7	Yes	Cefoperazone-Sulbactam	Recovered
B	1.82 [1]	0.1	3.6	Yes	Cefoperazone-Sulbactam	Recovered
C	1.16 [2]	0.33	3.8	Yes	Ceftriaxone	Recovered
D	2.63 [0]	0.24	3.9	No	Cefoperazone-Sulbactam	Recovered
E*	6.05 [0]	19.42	3.9	No	Meropenem + Colistin	Recovered
F	1.18 [2]	0.3	4.2	Yes	Cefoperazone-Sulbactam	Recovered
G*	5.05 [0]	0.1	2.3	No	Cefoperazone-Sulbactam	Recovered
H	3.04 [0]	0.1	3.5	No	Cefoperazone-Sulbactam	Recovered
I*	0.02 [4]	0.2	3.2	Yes	Meropenem + Metronidazole	Recovered
J	2.43 [0]	0.1	3.7	No	Cefoperazone-Sulbactam	Recovered
K*	1.00 [2]	0.31	4	Yes	Meropenem	Recovered
L	12.07 [0]	0.38	3.4	No	Cefoperazone-Sulbactam	Recovered
M	7.64 [0]	>50	3.3	No	Cefoperazone-Sulbactam	Recovered
N	7.10 [0]	0.1	3.9	No	Ceftazidime + Amikacin	Recovered
O	17.88 [0]	0.1	4.1	No	Ceftazidime + Amikacin	Recovered
P	4.15 [0]	35.8	3.6	No	Ceftazidime + Amikacin	Recovered
Q	0.01 [4]	0.2	3	Yes	Ceftazidime + Amikacin	Recovered

^a Reference value: Normal 1.5- 8*10⁹/L; ^b Reference value: Normal < 0.15 ng/ml; ^c Reference value: Normal 3.5-5 g/L; *Patient 'G' was detected with pan-drug resistant *Klebsiella pneumoniae*, after recovering from RM infection. The patient died due to advanced glioblastoma multiforme after recovering from the above infection. *Patients 'E', 'I', and 'K' were treated with upfront meropenem as they presented with hemodynamic instability and signs of sepsis.

pharmaceuticals, larger use of immunosuppressive drugs like chemotherapy, steroids, biological therapy etc. in oncology settings and rampant use of broad-spectrum antibiotics has resulted in increased rates of this infection [8]. RM has been implicated in few clinical infections, often resulting in subsequent severe conditions such as septicemia, recurrent meningitis, myelitis and peritonitis [8]. This study investigates the source of the outbreak and suggests measures for implementing infection control and prevention.

RM has the ability to pass through 0.2 µm filters which are used for sterilization of many medical products, such as saline solution. This ability enables it to potentially pass through the dialysis reverse osmosis membrane or even a dialyzer. Chlorhexidine with 0.05% aqueous solution is used as a topical antiseptic in venous catheter related procedures [9]. Dotis J et al report that RM can form a biofilm on plastic catheters [10]. Basso M et al report that members of the genera *Ralstonia* are the significant taxa identified in atherosclerotic plaques removed during surgery [1]. Regardless of the source of infection, a combination of arterial thrombosis and biofilm related chronic contamination could be the key factors for the persistence and relapse of the *Ralstonia* species bacteraemia, which occurred despite an appropriate and long-term antibiotic therapy [1].

There is limited evidence regarding serious non-outbreak related RM infections, but it is essential not to misidentify RM as *Pseudomonas fluorescens*, *Burkholderia multivorans* and/or *Ralstonia pickettii*, which are often treated as contaminants [1]. Similar to our study, Mukhopadhyay et al's study also report no growth of RM from environmental samples [4]. Their study reports that RM was unlikely to be a contaminant from saline solution or deionized water used for parenteral fluids as three consecutive isolates had the same antibiotic sensitivity pattern [4]. In our case series as well, RM could be not detected either through microbiological or epidemiological investigations. From an epidemiologist and health worker point of view, the possible source of contamination of the RM outbreak in our study was contaminated saline or pharmaceutical supply used in

the recent past.

In Mukhopadhyay et al's study, the probable source of infection include hemodialysis machines and catheters used to dialyze the patient or the peritoneal dialysis catheter which was used later on [4]. The results from this study show that the graft and renal transplant patients were saved because of prompt microbiological identification, sensitivity testing and administration of appropriate antibiotics. All 17 patients in our study successfully recovered from the RM infection [4]. These results are similar to studies done by Claudia et al [5] and Liu et al [8], which report that RM did not cause life threatening infections and all their patients showed full recovery. Results from Coman et al's study shows that RM infection was associated with dramatic outcomes in terms of disease acceleration and raised mortality rates [11].

Lucarelli et al [5] in their Italian study, report the first outbreak due to RM in oncology patients bearing central venous catheter (CVC). Although a definitive source of the outbreak was not identified, the investigation suggested that contaminated saline solution used for CVC flushing may have been the source. In our study, it was interesting to note that majority of the infections occurred during the period of COVID-19 lockdown where strict hand hygiene practices and social distancing were implemented. As CVC flushing with saline is a common procedure adopted among all oncology patients, it is likely that our study subjects were exposed to one or more contaminated bottles of saline. In our study, a similar batch of sterile water which was earlier used for infusion of the port or peripheral line did not show growth of RM. We could not retrieve the ampoules of sterile water used during the time of outbreak. The sterile water is usually examined during quality check for the presence of Coliform/E. coli organisms. Subsequent to our study, the Hospital Administration informed the Supplier to henceforth test for RM contamination as well. This measure could prevent any possibility of contamination at the source.

Lim's study reports that despite the low virulence of RM, it is able to survive in harsh conditions. This could be potentially harmful to many immunocompromised patients [9]. The study focus was on RM infection among dialysis patients, which had occurred during the crisis of municipal reservoir water contamination at Serdang, Malaysia. The authors opine that RM infections at hospital settings are typically associated with contaminated medical supplies or instruments. In the hospital setting, it has been found that human RM cases are a result of contaminated solutions such as distilled water, injectable water or saline, or purified respiratory ampoules [9]. The source of RM related hospital outbreaks could also include contamination of parenteral fluids with deionised water.

De Souza et al's [12] study shows that the 15 days time duration between the first case and last case suggests that a reservoir could be the source of RM cases. This is similar to the gap of 60 days between the first and last case in our study. The molecular typing of the pathogen supports the hypothesis of a common source of contamination. Although there is some evidence regarding patients with shared strains, inter-patient transmission has not been well

Table 3. Antibiotics used in the Treatment of RM Infection and Percentage of Resistance

Drug	Resistance (%)
Amikacin	21.4
Cefepime	14.3
Cefoperazone-Sulbactam	0
Ceftazidime	14.3
Ciprofloxacin	14.3
Co-trimoxazole	42.8
Gentamicin	21.4
Imipenem	14.3
Levofloxacin	14.3
Meropenem	35.7
Piperacillin-Tazobactam	14.3

documented [12]. This suggests that a common reservoir may have caused the outbreak among multiple patients.

Shankar's study reports that in many situations the isolates of RM are overlooked as *P.aeruginosa* or *Burkholderia* species [13]. Similarly, Vanechoutte M et al report that RM strains were first misidentified as *Pseudomonas fluorescens* and *Burkholderia cepacia*. Colistin resistant 'P fluorescens' isolates and strains growing on B cepacia selective medium should be possibly considered as RM. RM can be differentiated from P fluorescens by the absence of arginine dihydrolase activity, from B cepacia and B multivorans by its pyrrolidonyl peptidase activity and from other *Ralstonia* species by the acidification of mannitol [14].

From an oncologist point of view, our study shows that variables such as the type of malignancy, stage of disease, line of chemotherapy and/or presence of comorbidities had no major influence on the incidence of infection or its outcome. Similarly the grade of neutropenia, serum albumin and procalcitonin levels did not influence the final outcome. Our study reports that the incidence of RM infection may not depend much on the patient and treatment characteristics, but could be an indirect indicator of water reservoir or quality of pharmaceutical supply. As there are no clear treatment guidelines for RM infection [8], the use of antimicrobial agents depends on the drug-susceptibility testing. In addition, cotrimoxazole, ceftriaxone and piperacillin/tazobactam could be recommended for empirical treatment [8]. Also, given the slow growth of this bacterium the microbiological growth condition should be determined after culturing for 48 hours.

As microbiology is a cornerstone in establishing diagnosis of RM infection, we found that RM could easily be misidentified as *Burkholderia* or *Pseudomonas*. Hence, knowledge of such uncommon organisms could be useful in raising vigilance for RM infections during an outbreak of CLABSI. Polymerase chain reaction (PCR) remains the best technique to identify the species specific primers [9]. Our antibiotic susceptibility pattern showed maximum resistance to cotrimoxazole and meropenem. A study by Claudia et al, showed the presence of bla-OXA-22 and bla-OXA-60 coding for two oxacillinase, a narrow spectrum oxacillinase and an inducible carbapenemase possibly contributing to carbapenem resistance in RM [5]. Hence most of our patients were treated with third generation cephalosporins with meropenem usage only for seriously ill patients whose antibiogram showed sensitivity to meropenem. A combination of ciprofloxacin and trimethoprim-sulfamethoxazole are considered as the first-choice antibiotics in the treatment of RM infection. Other treatment recommendations include third-generation cephalosporins or carbapenems [1].

Assessing the financial impact of RM infections, patients incurred direct costs related to hospitalization which was in the range of Rs.50,000 to Rs.60,000 (USD 650 to 800). Following diagnosis of infection, the patients with positive tip culture underwent chemo port line removal (additional Rs.25,000: USD 330) and postponement of chemotherapy which further complicated

and impacted the treatment. The Indian Government's data on national income [15] states that the country's per-capita monthly income is Rs.11,254 (USD 150) during 2019-20. Since many patients seeking healthcare in India manage the related expenses through out-of-pocket payment, such opportunistic infections will be an added burden among oncology patients.

After implementing active control measures for nosocomial infections, no similar infections have been reported in our set-up. Such measures include changing the batch of water used for injection and disinfection solutions, disinfection of potential contaminant areas with chlorine containing solutions, alerting pharmaceutical companies dealing with supply of saline and sterile water, creating awareness among the medical care personnel including compliance of hand hygiene.

In conclusion, our study indicates that though RM infection was not life threatening in most cases, its incidence must immediately warrant an active search for the source of contamination. This could be an indirect indicator of the quality of water reservoir or the pharmaceutical supply. In order to prevent infections, it is imperative that parenteral treatment of cancer patients with CVC lines is done under sterile precautions using single dose solutions, and mandate the removal of CVC which is no longer necessary.

Among infections at Oncology settings in India, it has been reported that 80% are expected to be gram negative, 10% are gram positive and 10% are fungal in nature. Hence RM must also be considered when there are outbreaks of CLABSI with gram negative bacteria. Procalcitonin is an inflammatory marker especially useful in gram negative infections, though not classically elevated in RM infections, which could enable the identification of patients with sepsis and other secondary concurrent infections. The choice of antibiotic includes third generation cephalosporins, aminoglycosides and carbapenems, considering the chances of beta lactam and carbapenem resistance in RM infections.

Detection of pathogens using molecular methods which are culture independent enables the early identification of the organism. Such methods include polymerase chain reaction amplification of relevant genes especially 16S rRNA gene, cloning for purification and sequencing for identification. Such methods could be limited by their cost-effectiveness. The culture and sensitivity pattern helps in initiating appropriate treatment. For such slow-growing species, addition of specific nutrient or chemical facilitating growth and co-cultivating helper strains hastens their identification.

Healthcare professionals should adhere to infection control policies, monitor outbreaks of unusual pathogens and study the emergence of antibiotic resistance patterns. This involves teamwork involving the Physicians, Microbiologists and Laboratory technicians. Given the practice of presumptive antibiotic treatment in many healthcare settings, it is imperative to highlight the need of improved laboratory diagnosis and the potential of RM to cause sepsis when left untreated. Although RM is not recognized as a major pathogen, we should be mindful of

its ability to survive in the environment, its potential for multidrug resistance and ability to form biofilms.

Limitations of the study

1. In our case series, the source of contamination of this outbreak was not detected either through microbiological or epidemiological investigation. The samples from disinfectants, antiseptics and saline solutions used at the beginning of the outbreak were not available for microbiological investigation. These were probably removed from patient care areas during the early stages of outbreak with a safety viewpoint.

2. Farming practices and source of water consumption have definitive influence on the transmission of RM infection. However, the influence of geographic or occupational pattern could not be analyzed in our study.

3. We could not conduct molecular identification by PCR, as the machine was not available at our Center.

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Conflicts of interest

None declared.

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