



Bug in a Bottle – Report of an Outbreak Response in a Pediatric Oncology Unit

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Abstract

Healthcare-associated infection (HAI) outbreaks can result in significant morbidity and require prompt, coordinated responses to contain them. Immunocompromised children undergoing chemotherapy are particularly vulnerable to bloodstream infections (BSIs) caused by opportunistic pathogens. This report describes the investigation and management of an outbreak of BSI caused by an unusual organism, *Ralstonia pickettii*, in a Pediatric Oncology Department of a tertiary care hospital in India between May and June 2024. Nine children developed BSI at a median of 5 days following chemotherapy. A systematic epidemiological investigation, guided by national infection prevention and control guidelines, was undertaken, including root cause analysis and targeted environmental sampling. Six suspected medical products were cultured, of which sterile water for injection was identified as the source of contamination. Further testing of additional samples from the same batch confirmed contamination. Immediate withdrawal and recall of the implicated product effectively halted the outbreak. All affected patients responded to appropriate antibiotic therapy, although two experienced recurrent infections that required chemoport removal. No infection-related mortality was observed. This outbreak highlights the risk posed by contaminated liquid medical products in vulnerable populations. Vigilant surveillance, rapid identification of the source, and timely intervention are essential to control transmission and ensure patient safety.

Keywords

- healthcare-associated infections
- bloodstream infection
- liquid medical product
- antibiotic susceptibility testing
- *Ralstonia pickettii*

Introduction

Healthcare-associated infections (HAI) are the most common complications associated with the delivery of healthcare services, leading to increased treatment costs, prolonged hospital stay, the emergence of antimicrobial resistance, morbidity, and mortality.¹ A recent meta-analysis estimated

the prevalence of HAI in low- and middle-income countries, including India, to be 22%.²

An HAI outbreak is defined as the occurrence of infection above the background rate at a healthcare facility, or as the recognition of an unusual microbe or adverse event.³ Managing HAI outbreaks is often challenging as it demands rapid, coordinated, multi-disciplinary action despite information

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gaps. Timely investigation and action are critical not only because they limit the size of an outbreak, but also because the availability and quality of microbial evidence and epidemiological data deteriorate quickly with time.³

In this report, the authors describe the management of an outbreak caused by an unusual organism, originating from an unsuspected source in children receiving cancer chemotherapy at a pediatric oncology unit in India.

Methods

This epidemiological study for source identification and control of an HAI outbreak was conducted at the Department of Pediatric Hematology Oncology, St. John's Medical College Hospital, Bangalore, between May and June 2024, in accordance with the National Guidelines for Infection Prevention and Control in Healthcare Facilities, India – 2020.³ The outbreak investigation proceeded through the following systematic steps:

Step 1: Diagnosis of HAI

During this period, nine children receiving cancer chemotherapy at the center developed fever at a median duration of 5 days (range: 8 hours to 16 days) following chemotherapy administration in the Pediatric Hematology Oncology ward. Clinical examination did not reveal an obvious focus of infection. Investigations included complete blood counts, blood cultures, C-reactive protein, and procalcitonin. Empirical first-line antibiotics, viz, ceftazidime and amikacin were initiated as per departmental protocol in all children pending test results. Defervescence was noted within 12 to 24 hours of antibiotic administration in all children. Blood cultures from all nine patients revealed growth of an unusual pathogen, namely *Ralstonia pickettii* (RP), a rare cause of primary bloodstream infections (BSIs), establishing a diagnosis of *Ralstonia pickettii* bloodstream infection (RP-BSI). Other results are summarized in ►Table 1.

Step 2: Confirmation of Outbreak

The clustering of multiple RP-BSI cases over a short duration, combined with the absence of any cases in the preceding 5 years, confirmed the occurrence of an HAI outbreak.

Step 3: Case Definition

Any child on cancer chemotherapy evaluated for fever and whose blood culture yielded growth of RP was considered a “confirmed case” of RP-BSI.

Step 4: Line-Listing of Cases and Process Analysis

Line-listing of cases was performed to describe epidemiological features (►Table 1) to characterize the outbreak, identify common exposures, obtain clues regarding the probable source, and guide further investigations. A process flow chart (►Fig. 1A) mapping patient care activities was created and updated as new cases emerged to analyze potential points of contamination. Root cause analysis was done using the fishbone diagram (►Fig. 1B).

Table 1 Diagnostic and treatment characteristics of children with *Ralstonia pickettii* sepsis

Laboratory profile of children evaluated for fever					Treatment characteristics of children with <i>Ralstonia pickettii</i> sepsis						
Case no	Diagnosis	Absolute neutrophil count (per μ L)	CRP (mg/dL)	Procalcitonin (ng/mL)	Type of chemotherapy received in the last hospital visit	Date of systemic chemotherapy administration	Date of chemoport handling	Date of intrathecal chemotherapy	Date of fever onset	Location at the time of fever onset	Duration (in days) between last chemotherapy exposure and fever onset
1	ALCL	9,860	<0.02	0.6	S + IT	26/04/24–27/04/24	26/04/24–27/04/24	27/04/24	02/05/24	Home	5
2	ALL	130	6.73	2.89	S + IT	27/04/24–02/05/24	27/04/24	27/04/24	03/05/24	Home	1
3	BL	1,000	–	–	S + IT	15/04/24–22/04/24	15/4/24–22/4/24	20/04/24	01/05/24	Home	9
4	ALL	4,410	1.4	0.19	IT only	–	18/05/24	18/05/24	23/05/24	Home	5
5	ALL	5,900	12.98	149.74	IT only	–	17/05/24	17/05/24	27/05/24	Home	10
6	ALL	3,080	–	0.24	S + IT	31/05/24	31/05/24	31/05/24	16/06/24	Home	16
7	ALL	3,690	9.95	10.42	IT only	–	28/05/24	28/05/24	04/06/24	Home	7
8	ALL	1,000	<0.02	0.18	IT only	–	05/06/24	05/06/24	05/06/24	Home	0.33
9	AML	11,120	0.03	0.19	IT only	–	05/06/24	05/06/24	05/06/24	Home	0.33

Abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BL, Burkitt lymphoma; IT, intrathecal chemotherapy; S, systemic chemotherapy.

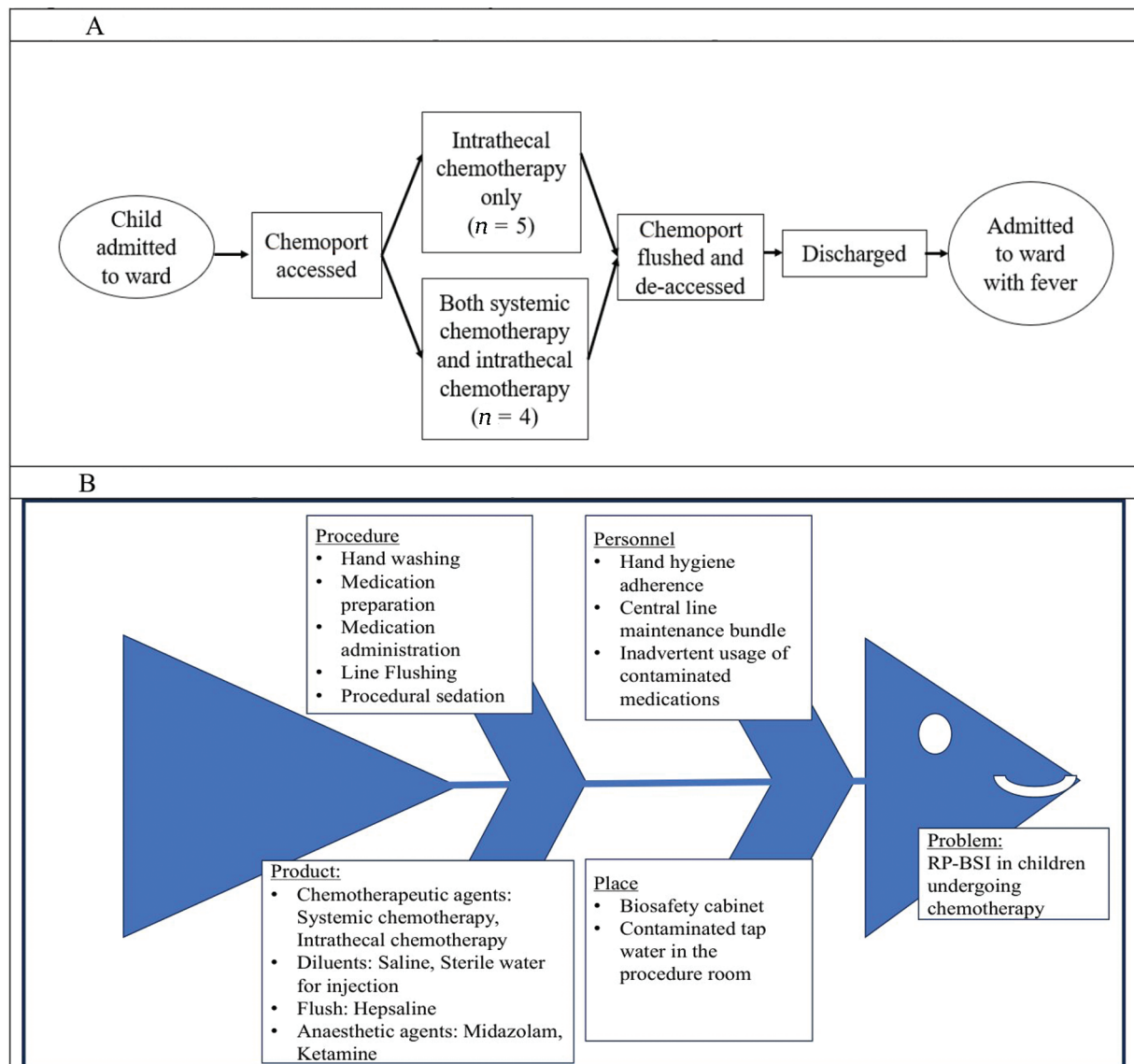


Fig. 1 Process flow chart and fishbone analysis. (A) Process flow chart describing events before the development of febrile illness. (B) Fishbone diagram for root cause analysis.

Step 5: Stakeholder Communication

Details regarding the outbreak and epidemiological profile of cases were promptly shared with the Department's clinicians and nurses, the infection-control nurse, and the hospital infection-control committee and microbiologists, to ensure coordinated action.

Step 6: Hypothesis Generation and Testing

A literature review highlighted that RP commonly causes nosocomial infections in immunocompromised patients through contamination of liquid medical products (LMP), especially saline and sterile water. Based on the data gathered from the line-listing of cases and process flow chart, the following hypotheses were generated and tested sequentially.

Hypothesis 1: The first hypothesis was formulated after the first three cases (case numbers 1, 2, 3) were diagnosed. At this

point, it was noted that all three children had received both systemic and intrathecal chemotherapy. Since administration of intrathecal chemotherapy would likely result in meningitis, which was not observed, systemic chemotherapy-related solutions were suspected as the source of contamination. While the chemotherapeutic agents used in the three children were different, all three received drugs reconstituted using normal saline from 100 mL NS bottles of the same batch. Hence, multiple samples from this saline batch were cultured.

Hypothesis 2: With the identification of two additional cases of RP-BSI (case numbers 4 and 5), it became evident that not all affected children had received systemic chemotherapy, though all had undergone intrathecal methotrexate administration approximately 1 week (range 5–10 days) before fever onset. This shifted suspicion to agents

used during intrathecal chemotherapy and procedural sedation.

Hence, the following agents used for intrathecal chemotherapy administration were implicated as a possible source of infection and cultured:

- Methotrexate ampoules: agent administered intrathecally
- Ketamine vials: used for the purpose of intravenous (IV) sedation
- Midazolam vials: used for the purpose of IV sedation
- Sterile water for injection: used for diluting ketamine and midazolam
- Heparinized saline ampoules: used for chemoport flush after administering IV sedation.

All samples were cultured on 5% sheep blood agar and MacConkey agar and incubated at 37°C. On prolonged incubation, none of the samples (ketamine, methotrexate, midazolam, and heparinized saline) yielded any growth. But the sterile water sample yielded growth on both MacConkey and Blood agar, which was identified as RP by MALDI-ToF method.

Results

Six different samples were cultured for source identification across two time points. Of these, only SWI yielded growth of RP. To confirm contamination, 10 additional SWI tubes from the same batch and manufacturer were cultured; seven demonstrated growth of RP. To confirm the presence of this organism,

ten other 10 mL tubes of SWI of the same company and batch were cultured, of which seven showed growth of RP. This conclusively identified contaminated SWI as the outbreak source.

Species Identification, Antibiotic Susceptibility Testing, and Molecular Typing

Colonies isolated from both patient blood cultures and contaminated SWI were identified as RP (→ Fig. 2). Antibiotic susceptibility testing of the RP isolated from blood samples showed uniform resistance to beta-lactams like ampicillin, aminoglycosides like amikacin, and gentamicin, but were sensitive to cephalosporins, ciprofloxacin, and carbapenems. A similar pattern was also observed among the sterile water isolates.

Deoxyribonucleic acid (DNA) extracted from both blood and SWI isolates was subjected to Gel electrophoresis, where we found that the DNA in both the samples, i.e., saline and blood isolate samples, showed similar electrophoretic patterns, and the amplified product was also similar when compared with the ladder base ranging from 100 to 1,000 base pairs. We conducted a BLAST (basic local alignment search tool) analysis on the FASTA (Fast Sequence Alignment Tool-All) files obtained from Sanger sequencing. Sequence 1 (SWI sample) showed 100% similarity to *Ralstonia* species sequences uploaded in the National Center for Biotechnology Information (NCBI), while Sequence 2 (blood sample) exhibited 99% similarity to *Ralstonia* species sequences uploaded in NCBI. The similarity between the two sequences was

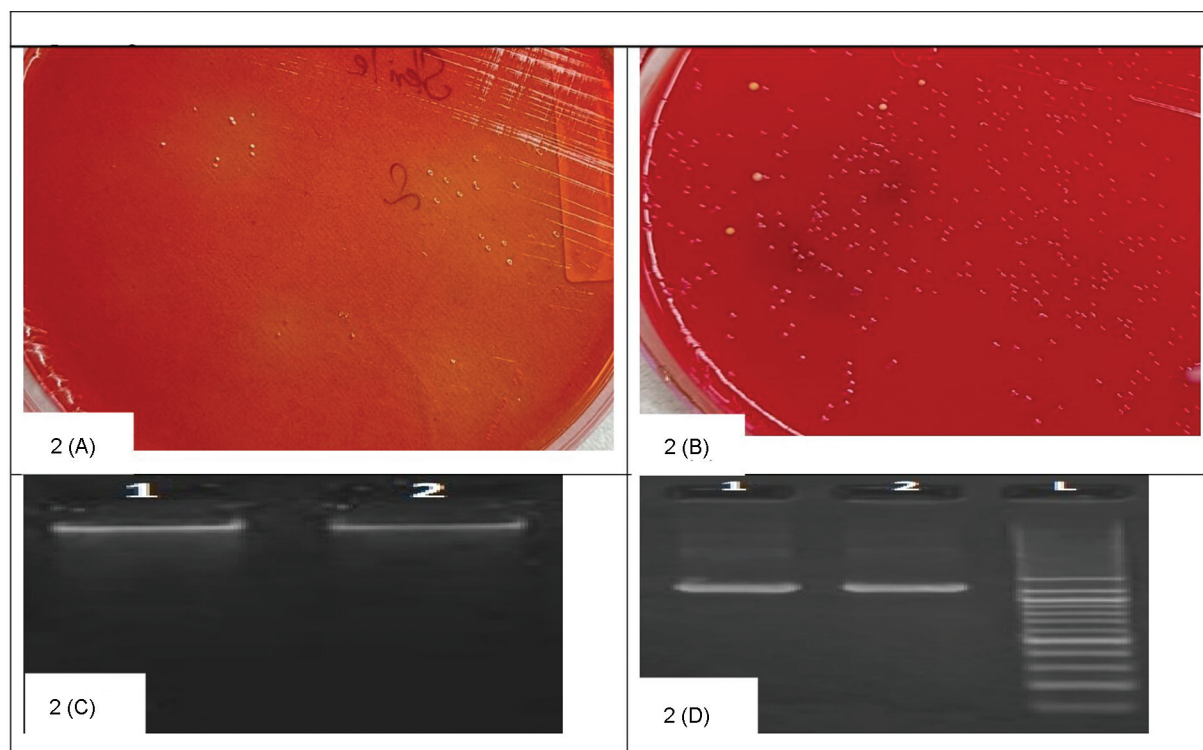


Fig. 2 Species identification. 2(A) Growth showing non-lactose fermenting colonies on MacConkey media. 2(B) Growth of *Ralstonia pickettii* on blood agar. 2(C) Gel electrophoresis showing genetic deoxyribonucleic acid (DNA) from blood and sterile water samples passing quality control. 2(D) Gel electrophoresis after polymerase chain reaction, showing amplification of genetic DNA, which is similar in both blood and sterile water samples. DNA, deoxyribonucleic acid.

calculated to be 99.5%. While Sanger sequencing lacked sufficient resolution to fully differentiate strains, the findings supported a common source (–Fig. 2).

Step 7: Control and Prevention

To control the suspected HAI outbreak, all infected children were cohorted in a designated clinical bay to facilitate cohort nursing and eliminate cross-transmission. Upon confirmation of the source, results were immediately communicated to the hospital administration and pharmacy services. Dispensing of the implicated sterile water was stopped, and all available samples, regardless of batch number, were recalled from all wards within 6 hours. This prompt action effectively halted further transmission.

Step 8: Follow Up

A total of nine children were infected before the implementation of control measures. All responded well to first-line antibiotics and were discharged after completing a 7 to 10 day antibiotic course. Two children experienced recrudescence of infection (culture-proven) 70 and 75 days later, likely due to biofilm formation in central venous lines, necessitating chemoport removal. No infection-related mortality occurred.

Discussion

Ralstonia is a genus of non-fermenting, Gram-negative rods that includes three main species: *Ralstonia insidiosa*, *Ralstonia mannitolilytica*, and *RP*. These species are opportunistic human pathogens that cause nosocomial infections in immunocompromised individuals.⁴ These organisms thrive in moist habitats such as water, soil, and plant surfaces. They are frequently found in industrial and hospital settings, where they contaminate water supplies and medical products.^{4,5} Although they can produce biofilms, their virulence is thought to be low. They can cause clinical infections, mainly affecting immunosuppressed individuals and those with cystic fibrosis.^{4,5}

Few reports of HAI outbreaks due to *RP* are available in literature and have implicated saline solution, sterile water, chlorhexidine, fentanyl ampoules, enrichment broth media of blood culture bottles, and medical equipment such as central lines as sources of infection.^{6–11} Krone et al detected *RP* in blood cultures and hematopoietic stem cell products from three patients at a hospital in Germany. Genome sequencing of isolates revealed that the three isolates were closely related. Additionally, genomic comparison revealed that the patients' isolates were related to an *RP* strain from another cluster in Australia, with origins traceable to internationally distributed contaminated saline products.¹² Similarly, in our study, the outbreak was confirmed not only by culture but also through Sanger sequencing.

Clinically, *RP* infections commonly present with fever due to bloodstream sepsis. Cystic fibrosis patients also have a high risk of *RP* pneumonia.⁴ Rarely, complications of *Ralstonia* species, such as infective endocarditis, osteomyelitis, and meningitis, have been reported.^{13–15} However, no such complications were noted in our cohort. These infections usually respond to antibiotics such as cephalosporins. Multi-

drug-resistant *RP* has been reported and requires reserve antibiotics such as colistin, meropenem, etc.¹⁶

HAI outbreaks involving such unusual organisms are considered sentinel events that require immediate implementation of outbreak response strategies to prevent further events.³ Outbreak sources can be common sources or propagated sources. Line listings of cases and process flowcharts can help determine the type of outbreak source. Targeted environmental sampling must be guided by the epidemiology of the organism and known routes of transmission.³ Unusual pathogens, such as *RP*, can grow from unsuspected sources, thus widening the information gaps and making outbreak response more challenging.

Once the pathogen is identified, possible sources of the pathogen can be determined based on available epidemiological data. However, some outbreak investigations have been unable to identify the source despite extensive environmental sampling, yet have controlled infections by implementing broad control measures.¹⁷ It must be remembered that the primary goal of outbreak response is to stop transmission, not necessarily to find the source. While source identification is ideal and helps control transmission by withholding the implicated source alone, the inability to identify the source does not preclude prevention of transmission.^{3,7,17} Withholding the dispensing and circulation of all suspected sources, changing the batch of suspected LMPs, as well as disinfection of all potentially contaminated medical equipment, can contain the transmission of infection.^{3,7,17}

The national guidelines for infection prevention and control serve as an excellent template for outbreak response in health-care facilities, as demonstrated in this report. Execution of the guideline in a time-sensitive manner, with multidisciplinary support, helped successfully contain the outbreak.

Conclusion

RP-BSIs in immunocompromised children are most often associated with contaminated LMPs. Prompt recognition of an outbreak, systematic hypothesis-driven investigation, and rapid implementation of control measures are critical to limiting transmission. While source identification is valuable, preventing further spread remains the primary goal of outbreak response. This report highlights the importance of vigilance and structured outbreak management in health-care settings.

Authors' Contributions

J.M.R., A.P., and V.B. conceived and designed the study. V.G.M., H.C.A., and S.P. conducted the study. R.M. and D.M.P. collected and analyzed the data. J.M.R. and S.G. drafted the paper. S.N., S.T., A.P. and V.B. revised the manuscript for important intellectual content. All authors approved the final manuscript.

Patient Consent

A waiver of consent was approved by the Institutional Ethics Committee as the study analysed strictly anonymised medical case records.

Ethical Approval

This research project was approved by the Institutional Ethics Committee (IEC), St. John's National Academy of Health Sciences, Bangalore, Ref. No. 51/2025 and conducted in accordance with the ethical standards of the Declaration of Helsinki.

Conflict of Interest

None declared.

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