Raoultella Species Associated Sepsis in Children: A Case Series at a Tertiary Hospital, Karachi

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ABSTRACT

Objective: To determine the clinical outcome and management options of gram-negative *Raoultella species* reported at a tertiary care pediatric Hospital in Karachi.

Study Design: Descriptive study.

Place and Duration of Study: Pediatric and child Health department of The Aga Khan University Hospital from January 2017 to June 2020.

Methodology: A retrospective chart review was done. Data was extracted for 20 patients with culture-positive *Raoultella species.* Study variables included demographic features, infection site, antibiotic sensitivities, Hospital duration, clinical outcome, and management options. Data were summarised using descriptive statistics and Kaplan–Meier plots using SPSS version 22.

Results: *A total of twenty-three site cultures positive with Raoultella species were isolated among 20 children with a wide array of clinical symptoms and disease severity. Predominantly the organism was isolated in blood with 12 positive cultures (60%). Eleven (55%) of the patients were females having a median age of 9.5 months.* Multidrug-resistant (MDR) and extensively drug-resistant species (XDR) were isolated from eleven (47.8%) and ten (43.5%) culture sites respectively. Combination therapy of colistin or fosfomycin with carbapenem and tigecycline (triple regimen) was used in seven (35%) patients with severe sepsis. Microbiological clearance (sterility) was achieved in twelve (60%) children. Eight children (40%) died of MDR/XDR *Raoultella* associated sepsis.

Conclusion: Highly resistant *Raoultella species* were associated with high mortality among reported cases, with a limited choice of antibiotics and combination therapy. The management of *Raoultella species* is required with a multi-specialty approach. Furthermore, strict antimicrobial stewardship measures are required to control an outbreak of MDR and XDR infections in Pakistan.

Key Words: *Raoultella species, Enterobacteriaceae, Children, Multidrug-resistant, Antimicrobial resistance.*

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INTRODUCTION

Gram-negative sepsis is the leading cause of inpatient and nosocomial pediatric mortality. It's a continuous threat because of increasing resistance to almost all possible known antibacterial drugs, leading to an alarming situation with minimal choices.[1] *Raoultella species* are gram-negative bacilli that belong to the family *Enterobacteriaceae*, with a clinical spectrum of diseases including septicemia, meningitis, and disseminated infection. They are found in environmental sources like surface and drinking water, sewage, vegetation, soils, and industrial effluents.[2]

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It is a relatively new known pathogen with an emerging threat to modern medicine. It has been recognised as an important pathogen in recent years due to the occurrence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. The pathogen is associated with high-risk global multi-resistant genetic lineages, procuring multi-resistant plasmids, and acquiring resistance genes located on transposons.[3] The possibility of pan-drug resistance (Pan-DR) is not unpredictable in plasmids-mediated resistance.

Raoultella XDR sepsis is complicated with higher mortality rates. There are risks of prolonged hospital stay, prolonged antibiotics use, and the need for intensive care and mechanical ventilation. The concern of achieving sterility on therapy, particularly in younger children, is essential. Identification of *Raoultella species* is difficult and requiring specialised microbiological skills and the availability of specialized assays.[4] Molecular testing is an important tool; however, availability and cost limit its use in low-middle-income countries. Early identification is the key to starting targeted therapy, as most of the conventional empiric therapies would not cover the *Raoultella* infection.[5] Therefore, this study

was conducted to determine the clinical outcome of *Raoultella* sepsis in children and its management options.

METHODOLOGY

A retrospective observational study was conducted at Aga Khan University Hospital (AKUH) after ERC (Ethics Review Committee) approval. Twenty cases of children with culture-positive *Raoultella species* were retrieved from the hospital medical record and the health information management system. All pediatric patients (aged 0–18 years) were included if admitted to either neonatal intensive care unit (NICU), pediatric intensive care unit (PICU), or pediatric ward from January 2017 to July 2020 with the presence of *Raoultella* species in blood, cerebrospinal fluid, urine, tracheal, peritoneal, and pleural culture or in any line or tube or drain cultures. Children with culture-positive *Raoultella species* in out-patient were excluded. Patient-related data on variables like age, gender, year of admission, previous history of hospitalization, co-morbid, length of stay in the hospital, sterility, use of antibiotics, and mortality were recorded in a structured proforma.

The process of *Raoultella species* identification was performed in the microbiology department at Aga Khan University Hospital, Karachi. The disk diffusion method was used according to Clinical and Laboratory Institute (CLSI M100) guidelines for 2020, for the determination of drug susceptibility.[6] Colistin minimum inhibitory concentration (MIC) was determined by broth micro-dilution (BMD). *Enterobacterales* that were Colistin-resistant underwent extended identification. Lactose fermenting gram-negative rods that were non-motile, indole, and urease negative were tested by setting up an extended panel of biochemical tests, API 20E (Biomerieux, France). *Raoultella species* were identified when the biochemical profile matched with the organism on the Analytic Profile Index database and gave an acceptable or greater confidence of identification.

Pan-sensitive *Raoultella* was defined as sensitive to the first-line drug class. Multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (supplementary Table I). Extensive-Drug resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories), and Pan-Drug resistance (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories. Sterility (Microbiological clearance) was defined as two or more consecutive negative cultures from all sites sampled, with no subsequent positive cultures.

Descriptive analysis was performed for demographic features with median and interquartile range (IQR) reported for quantitative variables such as age and length of hospital stay (LOS) and frequencies (percentage) for qualitative variables such as gender, co-morbid conditions, and mortality. Kaplan–Meier survival curves were calculated. SPSS version 22.0 was used for data analysis.

Table I: Demographic and clinical characteristics of the children with Raoultella species infection.

Variables	N (%)
Age (months)	
Median (IQR)	9.5 (1-367.5)
Gender	
Female	11 (55)
Male	9 (45)
Year of admission	
2017	4 (20)
2018	6 (30)
2019	7 (35)
2020	3 (15)
Antibiotic history	12 (60)
Comorbid	14 (70)
Previous hospitalization	10 (50)
Ventilated	9 (45)
Central line	13 (65)
Abdomen drain/tube	2 (10)
Length of stay in days; Median (IQR)	
PICU stay	1.5 (0-9.5)
Hospital stay	17 (10-27)
Discharge disposition	
Recovered	12 (60)
Died	8 (40)
Sterility achieved	12 (60)
Duration of Raoultella treatment in days; (Median (IQR)	9 (6-14)
Multi-organ involvement	12 (60)

PICU: Pediatric intensive care unit, IQR: Inter quartile range.

RESULTS

Between January 2017 to July 2020, a total of 23 *Raoultella* isolates from twenty children were identified, with the lowest n=4 (20%) in 2017 and the highest n=11 (55%) isolated in 2019, the majority of the patients identified were female 11 (55%). The median age in months was 9.5 (1-367.5). Twelve (60%) children were already on antibiotics at the time of admission. Approximately 10 (50%) children required intensive care due to severe illness on admission. Eight children (40%) died of MDR/XDR *Raoultella* associated sepsis (Table I).

Raoultella species were isolated from the following sample types: Blood culture 12 (60%), urine (catheterised and midstream) 6 (10%), trachea 1 (5%), CSF 1 (5%), skin and soft tissue 1 (5%), Peritoneal fluid 2 (10%). The median length of hospital stay was 17 days. The antibiotic analysis showed high resistance to commonly used antibiotics, 11 (47.8%) patients had MDR, while 10 (43.5%) had XDR susceptibility pattern (Table II). The most frequent combination was colistin and carbapenem in 13 (65%) children. Seven (35%) children received a triple regimen of colistin or fosfomycin with tigecycline and carbapenem, three of whom survived. Twelve (60%) had multi-organ involvement and 9 (45%) required vasopressor support.

The sample isolates were resistant to penicillin 19 (83%), cephalosporins 21 (91%), aminoglycosides 20 (87%), and carbapenems 19 (83%, Figure 1). The median duration of antibiotic treatment of *Raoultella species* was 9 (6-14) days due to the delayed starting of appropriate antibiotics.

Table I: Supplementary.

Summarised proposed antibiotics options of *Raoultella* sepsis in children.		
***Raoultella* spp. infection**	**First-line antibiotic options**	**Second-line antibiotic options**
Pan-sensitive	Third or fourth-generation Cephalosporin	aminoglycoside, fluoroquinolones and Carbapenems, piperacillin-tazobactam, trimethoprim-sulfamethoxazole
MDR	Tigecycline/aminoglycoside/fluoroquinolone Alone.	combination of an aminoglycoside with fluoroquinolones or aminoglycosides with Tigecycline Or a combination of Carbapenems with Fosfomycin
XDR	Tigecycline with polymixin B/Colistin	Fosfomycin or rifampicin with polymixin B /Colistin
Pan-DR	Triple regimen Polymixin B/Colistin), Tigecycline with amikacin or Carbapenems.	

Doses: Meropenem: 20-40mg/kg/dose 8hourly (max: 3g/day); Amikacin: 15mg/kg OD (MAX: 1.5g/day); Piperacillin-tazobactam: 300mg/kg/day divided 8 hourly (max: 16g/day); Fosfomycin: IV 200-400mg/kg/day divided 8hourly (Max: 4g/dose); Rifampicin: IV 10-15mg/kg/day (max:600mg OD); Colistin: 125,000IU/kg/dose -30,000IUkg/dose 8hourly; Trimethoprim-sulfamethoxazole: 6-12mg/kg/day divided 12 hourly (max 160mg/dose); Levofloxacin: 6months to 5 years: IV 8mg-10mg/kg/dose BD; 5yrs onward: IV 10mg/kg/dose OD (Max: 750mg); Ciprofloxacin: IV 10mg/kg/dose every 12horly (max: 400mg/dose); Tigecycline: loading dose: 1.5-3mg/kg once, Maintenance dose: 1.2mg/kg/dose 12 hourly (Max: 50mg).

Table II: Raoultella spp. and their sensitivities in children.

Site – culture	Drug sensitivity			
	Pan-sensitive [a]	**Multi-drug Resistance [b]**	**Extensive drug Resistance [c]**	**Pan-Resistant [d]**
Blood	1	3	7	1
Urine	-	4	2	-
Tracheal	-	1	-	-
CSF	-	1	-	-
Skin & soft tissue	-	1	-	-
Peritoneal fluid	2	1	1	-

[a]Sensitive to all first-line drug classes; [b]Non-susceptibility to at least one agent in three or more antimicrobial categories; [c]Non-susceptibility to at least one agent in all but two or fewer antimicrobial categories; [d] Non-susceptibility to all agents in all antimicrobial categories.

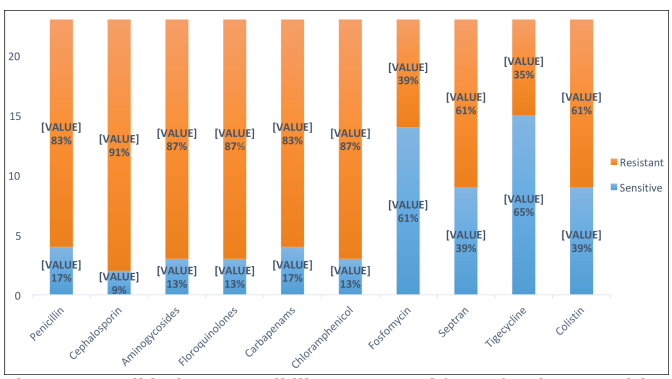

Figure 1: Antibiotic susceptibility pattern of (N=23) culture-positive *raoultella species* in children.

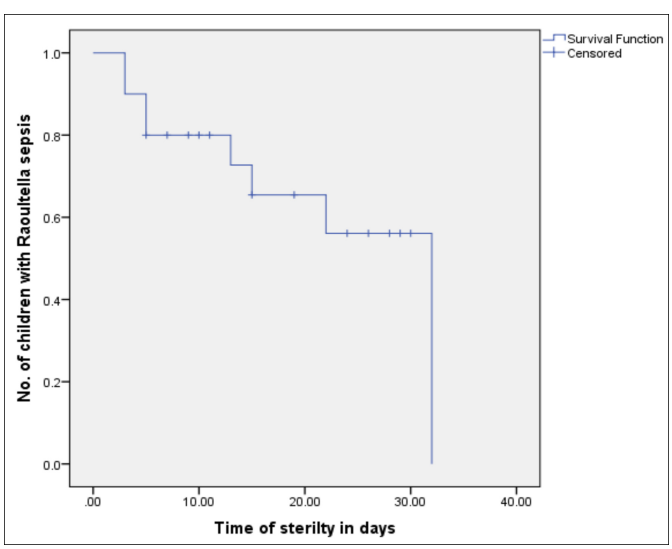

Figure 2: Cumulative survival with the time of sterility for children admitted with *raoultella* sepsis.

Microbiological clearance (sterility) was achieved in 12 (60%) of the children. According to the Kaplan Meier survival function (Figure 2), the first and last event was observed on the 3rd and 32nd day of sterility, respectively. The overall survival in children with *Raoultella* sepsis was 12 (60%).

DISCUSSION

Since there is a paucity of data with few cases reports on the clinical spectrum, outcome, and management options of infections with *Raoultella species* in the pediatric population all over the world,[7] hence we assume that this study is the first to be reported from Pakistan. In our study, most patients observed were female, bacteremia was the most frequent presentation followed by urinary tract and intra-abdominal sepsis. More than 75% of *Raoultella species* isolated in our study were identified as multi and extensive drug-resistant to commonly used antibiotics in treating *Enterobacteriaceae*, thus illustrating the significant adaptation in antibiotic prescribing practices and highlighting the need for greater standardization due to limited effective treatment options and the suboptimal response and high mortality despite targeted care.

Raoultella species are caused by nosocomial infection, leading to severe sepsis and poor prognosis due to prolonged hospital stay, invasive procedures, indwelling catheters, or mechanical ventilation. In uncomplicated cases, it is managed as monotherapy with the first-line cephalosporin as evident from a few case reports.[8,9] However, aminoglycoside, fluoroquinolones, and carbapenems, piperacillin-tazobactam, trimethoprim-sulfamethoxazole are the other second-line options.[10,11]

MDR gram-negative infection can be treated with an aminoglycoside, fluoroquinolones, and tigecycline alone or in a combination of an aminoglycoside with fluoroquinolones or aminoglycosides with tigecycline.[12] Fosfomycin having bactericidal activity and synergistic effect when given with carbapenem reported to significantly lower mortality rates in critically ill patients.[13]

Extensively drug-resistant species of Enterobacteriaceae class have at least five resistance determinants contributing to high resistance to β-lactam, β-lactam/inhibitor, carbapenems, aminoglycosides, quinolones, chloramphenicol, and fosfomycin. Colistin monotherapy is responsible for causing the rapid emergence of its resistance hence combination therapies have been established to enhance its synergistic effects. In our study, most of the children were treated with colistin and carbapenem empirically due to severe illness on admission. Forty percent of the children who died were critically ill, received inappropriate antibiotics before hospitalization, multidrug-resistant or extensive drug-resistant *Raoultella species*, and needed mechanical ventilation, refractory septic shock, and multi-organ involvement. Colistin resistance was evident in 61% of isolates, so targeted therapy was tailored after chasing the final culture report. Tigecycline or fosfomycin with colistin is the recent successful trial against carbapenems resistant micro-organisms as compared to colistin monotherapy.[14] Combination therapy of colistin with rifampicin is also considered beneficial against highly resistant carbapenem-resistant pathogens.[15,16]

Pan-resistant gram-negative sepsis is a serious threat to mortality and potential prolonged morbidity. Resistance to all antimicrobial agents is quite an alarming situation, not only for the patient itself but also for the healthcare facility. This may lead to an outbreak. The best management options are using triple regimen antibiotics, including colistin, tigecycline, and amikacin or carbapenems.[17,18] This will enhance the pharmacodynamics killing of pathogens. A potential concern is in critically ill children with end-organ or multi-organ failure (hepatic and renal). However, using hemodialysis or peritoneal dialysis and required adjusted creatinine clearance dosage may be a potential renal solution. This is imperative to know that these children require to prolong the stay of hospitalisation, hospital isolation, and risk of immunosuppression with a high chance of re-infection and colonisation of other potentially high-risk pathogens.

This study is limited by being a chart review of physician documentation. Follow-up of these patients in the clinic was also missing. Most children died because of sepsis, so complete knowledge on the pathogen, and its course was not defined. Organism identification was also not done based on molecular testing due to the limited resources.

CONCLUSION

Raoultella species are an emerging pathogen whose spectrum of causing disease is not well known in the pediatric population. Resistant *Raoultella species* were associated with high mortality among reported cases, with a limited choice of antibiotics and combination therapy. Therefore, to determine its clinical significance and antibiotic susceptibility, its vigilant monitoring and reporting are required.

ETHICAL APPROVAL:

Ethical approval was obtained from after ERC (Ethics Review Committee) of the Aga Khan University Hospital (AKUH) for the study.

PATIENT'S CONSENT:

Informed consent was not obtained due to the study's retrospective design.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

FA: Drafting, revision, result interpretation, writing of the manuscript.
AS, SF: An agreement, conceptualisation of the project, proofreading, and final approval of the version.
AS, FA: Data collection, data interpretation, and statistical analysis.
All authors approved the final version of the manuscript to be published.

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