Clinical Features and Outcomes of Raoultella Terrigena Infections. A Single-center Experience from Karachi, Pakistan: A Retrospective Study

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Abstract

Objectives:

Raoultella terrigena (formerly *Klebsiella terrigena*) is an environmental gram-negative rod. It may cause infections in humans, especially in the elderly and immunosuppressed patients. Moreover, this organism tends to be multi-drug resistant, limiting treatment options. Evidence on clinical presentation and outcomes of this infection is limited. We conducted this study to see its various clinical features, available treatment options, and associated clinical impacts of the *R.terrigena* infections.

Methodology:

We conducted a cross-sectional study on all adult patients with clinical specimens positive for *Raoultella terrigena* at a 700-bedded tertiary care hospital in Karachi, Pakistan, between January 2013 to December 2018.

Results:

There were 58 patients with *R.terrigena* in different cultures specimens identified. Amongst them n=12 (22.6%) were colonizers. The median age was 61.5 years (IQR=28), and most were male (60.9%). The most common infection site was the respiratory tract in 28.3%, followed by urinary tract infections, 26%, and central line-associated infections at 26.1%. Amongst infected cases, 37% were in septic shock, and of which 76.5% required vasopressors. 45.7% had respiratory failure requiring non-invasive ventilation in 47.6%, and mechanical ventilation in 52.4%. The previous history of multidrug-resistant organisms was present in 67.4% of patients and the history of prior antibiotics use within the last six months was present in 78.3%. 91.3% of isolates were resistant to piperacillin-tazobactam and meropenem, 65.2% were resistant to colisthemethate. Eight patients lost to follow up. The majority of patients treated with combination therapy (n=31, 81.6%) and meropenem plus colisthemethate was the most commonly used combination (n=11, 44%). The overall mortality rate was 44.7%.

Conclusion:

R.terrigena is a highly drug-resistant organism with a high mortality rate and causes hospital-acquired respiratory tract infections in most patients.

Background

Raoultella Terrigena, initially known as "*Klebsiella Terrigenna*," was discovered in 1981 and is a rare gram-negative organism, mostly found in soil and water¹. It was separated from *Klebsiella* species in 2001 based on molecular analysis². These organisms are oxidase negative, capsulated, immotile, facultatively anaerobic, and aerobic bacilli². However, many microbiology laboratories continue to identify this organism as a "*Klebsiella species*," making the true incidence and pathogenesis uncertain³. The first

reported case as a human pathogen was in 2007 in a middle-aged post-liver transplant patient with endocarditis⁴. Another case report was published on sepsis secondary to *R. terrigena* in 2011⁵. A literature search reveals that most of the reported cases caused by genus *Raoultella* consist of *R. orinithinolytica* and *R. planticola*^{6,7}, and are associated with diseases of the biliary tract and surgical interventions^{6,8} as well as necrotizing fasciitis⁹, cellulitis¹⁰, cystitis¹¹, cholangitis¹², cholecystitis¹³, and pancreatitis¹⁴. However, despite reviewing the literature, we could not find a sizeable descriptive study on clinical presentations and outcomes on *Raoultella terrigena*.

Ethical review:

The study started after receiving approval for exemption from the Aga Khan University Ethics review committee. (ERC Reference No:2019-1232-3287). Patient confidentiality was maintained by not taking personal identifiers such as names or medical record numbers. As this was a retrospective study, the committee waived the requirement of informed consent.

Methodology

We conducted a cross-sectional study on all adults above 18 years of age, admitted to Aga Khan University Hospital (AKUH) between (January 2013 to December 2018), who had *Raoultella terrigena* in cultures. We excluded patients with recurrent *Raoultella* infections and colonizers. Patients who fulfilled the eligibility criteria were consecutively included in the study. Data on patient-related variables such as age, sex, co-morbid, prior history of hospitalizations, invasive procedures, and use of antibiotics, etc., were collected from the Health care information and management system (HIMS) on a pre-tested structured proforma. Microbiological culture specimens related data extracted from Integrated Laboratory Management Services records.

Laboratory Identification

The identification process was performed in the microbiology laboratory at Aga Khan University Hospital Karachi. This involved culture inoculation on MacConkey, chocolate, and 5% sheep blood agar at 37 degrees Celsius for up to 48 hours. The blood agar was made by phlebotomizing sheep in the animal house at AKUH. Upon growth of lactose fermenter mucoid colonies on MacConkey agar, further biochemical tests involve the utilization of citrate, hydrogen sulfide, urease, indole, and motility tests negative within acidic/acidic reaction on Tripe Sugar Test.

Further identification was carried out by API 20 E, which detects 91% to 95% of cases correctly. Antibiotic susceptibility testing was initially carried out by Mueller-Hinton agar with Kirby-Bauer disk diffusion test or Vitek-2 MS automated system. Colistin minimum inhibitory concentrations were confirmed by colistin broth microdilution, which is currently the most reliable method. Results were interpreted as per Clinical and Laboratory Standards Institute antibiotic guidelines.

Statistical Methods

Descriptive analysis was performed for all patient-related variables with frequencies and proportions reported for categorical variables like sex, comorbid, clinical features, etc. And median with interquartile range reported for continuous variables like age, hospital stay. Chi-square test or Fisher exact test were used as appropriate to determine the association between two categorical variables, e.g., chronic kidney disease and death. SPSS software (version 25.0) was used for data analysis. A P-value of less than 0.05 is supposed to be statistically significant.

Results

There were 58 patients with *R.terrigena* isolated from different culture specimens. Out of those, 12 patients were identified as colonizers, remaining included in the study (see Figure-1). The median age was 61.5 years (IQR=28), with more males than females (60.9 % vs. 39.1%). The most frequent co-morbid conditions were diabetes mellitus in n=18 (39.1%), followed by chronic kidney disease in n=16 (34.7%) and malignancy in n=11 (23.9) (see table-1). Most patients n= 34 (73.9%) had a previous history of hospitalization (within the past six months), and in the majority, n=24 (52.17%) had at least one hospital admission. 78% patients (n=36) reported antibiotic use in last 6 months. The most commonly used antibiotics were carbapenems in n=26 (56.5%). Also beta-lactam, beta-lactamase inhibitors in n=23 (50%) and glycopeptides in n=20 (43.5).

Almost n=31 (67.4%) of the patients had had a prior culture growing a multidrug-resistant organism in the last six months. The most commonly found organism was carbapenem-resistant *Klebsiella pneumonia* in n=13 (28.2%), followed by multidrug-resistant *Acinetobacter* and *Pseudomonas aeruginosa* n=11 (23.9%) of patients. Approximately n=35 (76.1%), had a urinary catheter in place, and central lines were present in n=22 (47.8%), surgical drains in n=14 (30.4%) , and VP shunt in n=1 (2.2%) of patients. There were 29 patients (63%) with this infection who had a recent history (past six months) of invasive procedures. Of those, n=9 (31%) had undergone skin soft tissue procedures, genitourinary surgeries in n=8 (27.6) cases, n=7 (24.1%) had abdominal procedures, and n=7 (24.1%) had central nervous system interventions.

The most common site of infection was the respiratory tract in n=13 (28.3%), followed by Urinary tract infections n=12 (26%), and bloodstream infections n=12 (26.1%). (Table 1). Approximately n=21 (45.7%) had respiratory failure, that required mechanical ventilation in n=11 (52.4%), and non-invasive ventilation in n=10 (47.6%). N=17 patients, (37%) were in septic shock due to *R.terrigena*. Of them n=13, (76.5%) required vasopressors and n=4 (23.5%) treated with fluid resuscitation

Monomicrobial growth of Raoultella terrigena was identified from n=26 (56.5%) of culture specimens, and polymicrobial growth was identified from n=20 (43.5%) culture specimens. The most common sources were blood in 32.6%, sputum in 28.3%, and urine in 21.7%. The organism was highly resistant to most of the commonly used antibiotics. Carbapenem resistance was present in 91.3%, colistimethate

resistance 65.2%. Tigecycline resistance present in 10.9% (checked in 31 strains) and fosfomycin resistance in 28.3% (checked in 29 strains) (Table-2). In most cases, sensitivities were checked for tigecycline and fosfomycin after they were resistant to colistimethate.

Out of 46 cases, eight patients lost to follow up, and treatment information was not available. The remaining 38 patients, n=31 patients (81.6%) received combination therapy, and n=6 (15.8%) received monotherapy. One patient died before starting treatment. The most frequent combination was carbapenem and colistimethate in n=11 (28.9%), followed by a combination of carbapenem with colistimethate and tigecycline in n=8 (21.1%) (Table-3). In 71.1% cases, the treatment was inappropriate for *R. terrigena* while the remaining 28.9%, given appropriately. Mortality association with monotherapy was ($p=0.672$), and with combination therapy ($p=0.70$). Out of n=14 (36.84%) cases in whom repeat cultures for clearance needed, bacteriological clearance was achieved in n=9 (64.2%) cases. There were 23 cases that needed source control of underlying infection. It was achieved in n=12 (52.1%). Two cases (5.3%) relapsed.

The average hospital stay was a median of 11.50 days (IQR=17), with a median of 3 days before positive culture. Approximately n=23 (60.52%) of patients were seriously ill, requiring intensive care unit care with a median ICU stay of 6 days (IQR=7). In-hospital mortality recorded in n=17 (44.7%) patients.

In the subgroup analysis of factors associated with death in *R. terrigena* infections, it was found that chronic kidney disease (CKD) ($p=.029$) and septic shock ($p=.005$) were significantly associated with mortality. Also, persons with a high (greater or equal to three) Charlson- comorbidity index had increased mortality ($p=0.002$).

Discussion

In our study, most patients had hospital-acquired respiratory tract infections, followed by urinary tract infections. Clinical symptoms identified in the vast majority were respiratory failure, septic shock, and altered mental status. The grown isolates were highly resistant to beta-lactams, carbapenems, and colistimethate.

Its clinical impact remained mostly unknown until 2007 when a middle-aged liver transplant person suffered infective endocarditis with *R. terrigena* (Table-4). Before his surgery for liver transplantation, he was found to be a colonizer with ESBL *R. terrigena* and was given piperacillin-tazobactam as a prophylactic agent. The organism identified after the death of the patient in tissue (aortic valve)⁴. Previously stated that infections caused by the genus *Raoultella* are common in older-aged groups who were suffering from malignancy or underwent surgical interventions. Many of them developed infections of the biliary tract and had different mortality rates.¹⁵ In our study group, most patients were male in the middle and older aged group, who were diabetics in the vast majority, followed by CKD and cancer patients. Around two-thirds of them had recent surgical interventions. We had only one patient with biliary

tract involvement, and we found a higher rate of nosocomial pneumonia and urinary tract infections in our patients. (table-1).

Another case published in 2011 was about a monomicrobial *R.terrigena* infection. It was causing post-laparotomy intrabdominal sepsis with fluid encasement⁵ (Table-4). The organism identified in blood and drain cultures was sensitive to amoxicillin-clavulanic acid, cephalosporins, ciprofloxacin, and imipenem. The patient was treated successfully with imipenem piperacillin-tazobactam. In 2016, a case of subungual abscess caused by *R.terrigena* reported, resulting from working in a field. It was pan sensitive and treated with imipenim¹⁶ (Table-4). However, in most of our patient population, the grown isolates were highly resistant to many drugs, including carbapenems and colisthemethate. These findings also present in a recent small case series of three patients published from Pakistan in 2019 (Table-4). In that all three patients were female, two of them had diabetes and one had CKD. All patients had a complicated hospital course; they were already on treatment for other hospital-acquired infections. Two patients had complicated urinary tract infections; they grew highly drug-resistant *R.terrigena* in urine and blood cultures. One died and the other was critically ill and transferred to another hospital. The remaining one patient suffered nosocomial respiratory tract infection by *R.terrigena* sensitive to colisthemethate and tigecycline in both respiratory and blood samples. This patient also died despite appropriate treatment¹⁷. In comparison, we found a higher frequency of nosocomial pneumonia in our patients. Similarly, we also found increased mortality among our infected cases.

Although our study has a limited sample size and is a single-center experience, it is the largest cohort of patients reported of this rare gram-negative infection to date. In this era of hard to treat hospital-acquired infections and associated antibiotic resistance, we face challenges treating these kinds of pathogens. These emerging opportunistic pathogens and associated drug resistance leave us with a limited choice of antibiotics. Interestingly, we found no outcome difference in treating patients with monotherapy against combination therapy. Patients with many comorbid conditions and immunosuppression can lead to infections with opportunistic organisms, including *R.terrigena*, leading to increased mortality if not identified and treated correctly.

Limitations

Because of the scarcity of available resources, we could not detect *R.terrigena* by molecular analysis (standard method).

Conclusion

Infections caused by *R.terrigena* are highly drug-resistant, mostly causing hospital-acquired respiratory tract infections that are difficult to treat, leading to prolonged hospital and ICU stays with a high mortality rate. Patients with underlying renal dysfunction, those on vasopressor support, and a high CCI score are at greater risk of death due to this infection.

Declarations

Authors' Contributions:

1. Ishfaq Ahmed

Data collection, Data analysis, and interpretation, Manuscript writing

2. Nosheen Nasir

Study design and methodology, Questionnaire development, editing of manuscript draft

3. Bushra Jamil

Draft editing and charts/table review

4. Syed Faisal Mahmood- Corresponding author

Study Idea, Abstract writing, and manuscript editing

Competing Interest

I declare that the authors have no competing interests (Financial or non- financial) as defined by BMC, or other interests that might be perceived to influence the results and/or discussion reported in this paper.

Ethical approval and consent to participate:

Our study was reviewed and approved as exemption by Aga Khan University (AKU) ethics review committee (Reference number: 2019-1232-3287). The study was performed in accordance with the Declaration of Helsinki and guidelines and regulations of Aga Khan University ethics review committee. The requirement for written informed consent was waived as the data was collected retrospectively from medical records and was de-identified, which had been approved by the the Aga Khan University (AKU) ethics review committee.

Consent for publication:

Not applicable

Animal Ethics:

We confirm that all experimental protocols involving animals were approved by the Aga Khan University licensing committee and all methods were carried out in accordance with ARRIVE guidelines.

Availability of data and material:

The datasets generated and/or analyzed during the current study are not publicly available due to institutional policy but are available from the corresponding author on reasonable request.

Funding:

Not applicable

Acknowledgment:

Not applicable

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Tables

Table-1

Clinical features and outcomes of R.terrigena

Age in years:	Mean: (57.72), (S.E: 2.695)	Median: (61.50) IQR = 28
Sex:	M: (n = 28), F: (n = 18)	M: (60.9%), F (39.1%)
Site of infection:		
Pneumonia	n = 9	(19.6%)
Tracheitis	n = 4	(8.7%)
Cystitis	n = 6	(13%)
Pyelonephritis	n = 6	(13%)
CLABSI	n = 7	(15.2%)
Unspecified BSI	n = 5	(10.9%)
Necrotizing fasciitis	n = 2	(4.3%)
Bed sore infection	n = 2	(4.3%)
Cellulitis	n = 1	(2.2%)
Septic arthritis	n = 1	(2.2%)
Ventriculitis	n = 1	(2.2%)
Peritonitis	n = 1	(2.2%)
Cholangitis	n = 1	(2.2%)
Clinical presentation:		
Hypotension (Systolic < 90)	n = 17	(23.6%)
Respiratory failure	n = 21	(29.2%)
Altered mental status:	n = 25	(54.34%)
Central lines:	n = 22	(47.8%)
VP shunt:	n = 1	(2.2%)
Surgical drains:	n = 14	(30.4%)
Folly's	n = 35	(76.1%)
Prior antibiotics (6, months)	n = 36	(78.3%)

Table-1**Clinical features and outcomes of R.terrigena**

Prior hospitalization: (6, months)	n = 34	(73.9%)
Prior MDRO's (6, months)	n = 31	(67.4%)
Recent procedures:	n = 29	(63%)
Skin, soft tissues	n = 9	(31%)
Abdomen	n = 7	(24.1%)
CNS	n = 7	(24.1%)
Genitourinary	n = 8	(27.6%)
Stent placement	n = 4	(13.8%)
Chest:	n = 4	(13.8%)
Others:	n = 6	(20.7%)
Co-morbid:		
Diabetes mellitus	n = 18	(39.1%)
Chronic kidney disease	n = 16	(34.7%)
Malignancy	n = 11	(23.9%)
Cerebrovascular accident	n = 7	(15.2%)
Chronic liver disease	n = 8	(17.3)
Steroid therapy	n = 2	(4.3%)
Connective tissue disease	n = 1	(2.1%)
Hospital stay (days)	Mean (18.47)	Median (11.50) IQR = 17
ICU stay (days)	Mean (7.70)	Median (6) IQR = 7
Alive	n = 21	(55.3%)
Dead	n = 17	(44.7%)

<p>Table-2</p> <p>Drugs susceptibility of R-terrigena</p>				
Antibiotics	Sensitivity	Resistance	Intermediate	Unchecked
Amoxi-clav	2.2%	93.5%	2.2%	2.2%
Amikacin	19.6%	76.1%	2.2%	2.2%
Imipenim	4.3%	89.1%	2.2%	4.3%
Piper-tazo	4.3%	91.3%	2.2%	2.2%
Gentamicin	8.7%	89.1%	2.2%	
Ceftriaxone	2.2%	97.8%		
Co-trimoxazole	8.7%	89.1%		2.2%
Ciprofloxacin	6.5%	91.3%		2.2%
Meropenem	8.7%	91.3%		
Colistemethate	23.9%	65.2%		10.9%
Tigecyclin	30.4%	10.9%	26.1%	32.6%
Fosfomycin	15.2%	28.3%	19.6%	37%

<p>Table-3</p> <p>Frequently used antibiotics as combination therapy</p>		
Meropenem, colistemethate	n = 11	(28.9%)
Meropenem, colistemethate, tigecycline	n = 8	(21.1%)
Meropenem, tigecycline	n = 2	(5.3%)
Meropenem, colistemethate, ciprofloxacin	n = 1	(2.6%)
Tigecycline, colistemethate	n = 1	(2.6%)
Tigecycline, fosfomycin	n = 1	(2.6%)
Imipenim, colistemethate	n = 1	(2.6%)
Meropenem, colistemethate, fosfomycin	n = 1	(2.6%)
Fosfomycin, moxifloxacin	n = 1	(2.6%)
Imipenim, colistemethate, fosfomycin	n = 1	(2.6%)
Amikacin, levofloxacin	n = 1	(2.6%)
Ceftazidime, piptaz	n = 1	(2.6%)

Table-4

Previously published case reports and case series

Authors	Case numbers	Infection Source	Treatment	Outcome
Goegele H. et. al. ⁴	1	Tissue (aortic valve)	No	Death
Oslon Ds Jr. et. al. ¹¹	1	Body fluid	Piperacillin Tazobactam, Imipenem	Recovered
Wang Y. et. al. ²⁰	1	Pus	Imipenem	Recovered
Mal PB. Et. al. ¹⁵	3 (Case 1)	Urine	Fosfomycin, Tigecycline, Co-trimoxazole	Death
	(Case 2)	Tracheal aspirate	Colisthemethate, Tigecycline, Co-trimoxazole	Death
	(Case 3)	Urine	Fosfomycin	Transferred to another hospital.

Figures

Figure 1

Flow chart showing the number of patients in the study