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Low virulence? Clinical characteristics of *Raoultella planticola* bacteremia

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Abstract
Purpose Numerous case reports regarding *Raoultella planticola* infection have accumulated in the literature; however, its significance as a clinical pathogen remains unknown. We performed a retrospective review of *R. planticola* bacteremia to characterize its clinical features, antimicrobial susceptibility, and patient outcome.
Methods *Raoultella planticola* bacteremia cases were culled from an electronic database of all bacteremia cases occurring over a 4-year-period. Medical records were retrospectively reviewed and demographic data, clinical findings, presence of underlying disease, results of antimicrobial susceptibility testing, and the antibiotic regimens administered during the treatment were evaluated.
Results *Raoultella planticola* was isolated from blood culture specimens in 20 cases. The majority of these patients had underlying malignant conditions (17 patients, 85 %). The most prevalent causes of malignancy were adenocarcinoma involving the gallbladder or bile duct (7 patients) and hematologic malignancies (6 patients). No cases with resistance to carbapenem or third generation cephalosporins were found. All 14 patients with *R. planticola* as the sole microbial isolate recovered with the use of empirical antibiotics. Of the six patients with polymicrobial infection, three did not recover and subsequently expired.
Conclusions *Raoultella planticola* bacteremia seemed to occur mainly in immunocompromised patients, and was also frequently found in patients with lesions involving the gallbladder or bile duct. The overall outcome was favorable when *R. planticola* was treated with administration of empirical antibiotics. Mixed outcomes were found when blood cultures yielded multiple species of microbes.

Keywords *Raoultella planticola* · Bacteremia · Microbial sensitivity test · Antibacterial agents · Polymicrobial infection

Introduction

Raoultella planticola is an aerobic, non-motile, encapsulated, Gram-negative bacterium within the Enterobacteriaceae family [1]. It was initially classified as a member of the *Klebsiella* genus as *Klebsiella planticola* or as *Klebsiella trevisanii*. The current taxonomy was established based on comparative analysis of the 16S rRNA and *rpoB* genes, resulting in the creation of the new genus *Raoultella*. There have been sporadic case reports suggesting that *R. planticola* is a pathogen, with recent reports describing its role in urinary tract infections [2] and in bacteremia following gastroenteritis [3]. Although it may be a well-established potential pathogen, its virulence and susceptibility to antimicrobial agents have yet to be thoroughly investigated. We performed a 4 year retrospective review of *R. planticola* bacteremia isolates to demonstrate its clinical characteristics as a pathogen.

Methods

We retrospectively reviewed the clinical microbiology reports from our institute for the period spanning October 2008 to September 2012.

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All blood isolates that were reported as *R. planticola* were selected and the medical records of these patients were reviewed. The clinical features of these infections were reviewed, and cases with symptoms indicative of bacteremia were included in the study. The medical record investigation included the patient's gender and age, any underlying disease, symptoms indicating infection, the number of blood culture sets that yielded *R. planticola,* the antimicrobial regimen administered for the infection, any microbes other than *R. planticola* that were isolated, and the outcome of the infection.

All blood culture sets issued contained a secondary and/or a tertiary blood culture at different venous site. When all blood vials yielded positive results on a single blood culture set, and when the isolates from each vial showed identical bacteriologic characteristics, identification and antimicrobial susceptibility testing was done on the first specimen.

Isolation of microbes from blood culture samples was performed using the BacT/ALERT Culture Media system (bioMérieux, Marcy l'Étoile, France). Microbe identification and antibiotic susceptibility tests were performed using the automated VITEK 2 system (bioMérieux, Marcy l'Étoile, France) accompanied by routine bacteriologic methods. Version of the VITEK 2 system was 5.01 prior to 2009, and 5.02 after that. All isolates were identified with a probability score exceeding 96 %. Antimicrobial susceptibility testing was conducted according to the standards established by the Clinical and Laboratory Standards Institute [4].

Results

Overall, 20 inpatients were identified with *R. planticola* bacteremia during the 4 year period of the study. Over the same period, a total of 26,208 patients were evaluated with blood cultures, and 13,764 tests showed positive blood culture results, while *R. planticola* was isolated 41 times. Consequently, *R. planticola* bacteremia occurred in less than 0.3 % of positive blood culture test results. The number of *R. planticola* bacteremia cases ranged from 2 to 6 cases per year, with an average of five cases annually. The majority of patients (17/20, 85 %) survived the infection. In the three cases in which the patient did not survive, blood cultures revealed evidence of polymicrobial infection.

The gender distribution of the patients was 11 males and 9 females. Patient ages ranged from 18 to 81 years, with a mean of 65 years. The major underlying disease was found to be malignancy (17 patients). Among these patients, nine were diagnosed with solid tumors within or with metastasis to the gallbladder or bile duct. Of these nine cases, seven had adenocarcinoma involving the gallbladder or bile duct. Six cases had hematologic malignancies with pancytopenia after having received allogeneic or autologous hematologic stem cell transplants. In 14 cases, *R. planticola* was the sole microbial isolate, while in 6 cases, additional microbes were also isolated. All cases are described in chronological order in Table 1.

Antimicrobial susceptibility testing revealed a universal resistance to both ampicillin and piperacillin, while all strains were susceptible to these antibiotics when combined with β-lactamases inhibitors. Most strains showed susceptibility to cephalosporins; however, occasional resistance to cephalothin (6 %) or intermediate susceptibility to cefoxitin (10 %) was observed. Isolated stains were also susceptible to all third generation cephalosporins, as well as to carbapenems. No resistance to fluoroquinolone agents was observed (Table 2).A total of seven cases (case nos. 1, 4, 9, 12, 18, and 20) were patients with pancytopenia following hematopoietic stem cell transplantation. In ten patients (case nos. 2, 3, 6, 7, 10, 13, 14, 15, 16, and 19) cytotoxic anti-neoplastic agents had been administered, resulting in some degree of myelosuppression. With the exception of case no. 10, all patients recovered with the use of various antimicrobial agents ranging from ciprofloxacin to the combination of vancomycin and cefepime. Case no. 10 was a patient with polymicrobial infection whose blood culture results showed growth of both *Pseudomonas aeruginosa* and *R. planticola.* Despite the administration of meropenem, the last blood culture obtained revealed the presence of both pathogens, and the patient died. Case no. 8 was a patient with hepatocellular carcinoma with multiple metastases who refused all forms of treatment.

Among the three cases without underlying malignant diseases, case nos. 11 and 17 had positive outcomes. Case no. 5 was a patient who experienced cardiac arrest with the return of spontaneous circulation after cardiopulmonary resuscitation. Despite the use of cutaneous cardiopulmonary support and vigorous administration of norepinephrine, the patient failed to maintain a mean blood pressure of 60 mmHg. We were unable to determine whether the low blood pressure was of cardiogenic origin or sepsis-related; nonetheless the patient's blood culture results showed growth of both *Morganella morganii* and *R. planticola.*

Discussion

Raoultella sp. is known to be a Gram-negative aerobic bacillus that is a member of the Enterobacteriaceae family. First described by Ferragut et al. [5], it was subsequently reported by Freney et al. to be a cause of sepsis in three patients [6, 7]. Additional reports of *R. planticola* as a pathogen include cases with acute pancreatitis and

Table 1 Patient characteristics of the 20 cases with *Raoultell aplanticola* bacteremia

Case no.	Gender/ age	Date of isolation	Underlying disease	Presentation of infection	Other source of isolation	Positive/total no. of cultures	Antibiotic regimen	Other microbes isolated from blood	Outcome	Version of VITEK2
1	F/51	Sep. 24 and Oct. 17, 2008	MM, post autologous PBSCT	Neutropenic fever	–	5/6	Ciprofloxacin	None	Recovered	5.01
2	F/69	Dec. 22, 2008	Cervical cancer with multiple metastasis including liver/bile duct	Fever, UTI	Urine	2/2	Ceftriaxone, ciprofloxacin	None	Recovered	5.01
3	M/64	Apr. 9, 2009	Cholangiocarcinoma	Fever	–	1/2	Tazocin	*Streptococcus anginosus*	Recovered	5.02
4	M/64	Jun. 13, 2009	AML, post allogeneic PBSCT	Neutropenic fever	Central line	4/4	Cefepime	None	Recovered	5.02
5	M/59	Sep. 9, 2009	AMI, ROSC after cardiac arrest	Septic shock	Central line	4/6	Vancomycin, imipenem	*Morganella morganii*	Expired	5.02
6	F/66	Nov. 24, 2009	Gallbladder adenocarcinoma	Fever	–	2/2	Tazocin	None	Recovered	5.02
7	M/81	Jan. 26, 2010	Cholangiocarcinoma	Fever	–	2/2	Tazocin, levofloxacin	None	Recovered	5.02
8	M/72	Mar. 18, 2010	HCC with multiple metastasis	Septic shock	Peritoneal fluid	1/2	No treatment	*Streptococcus viridans*	Expired	5.02
9	M/59	Jun. 1, 2010	MM, post autologous PBSCT	Neutropenic fever	–	3/4	Cefepime, metronidazole	None	Recovered	5.02
10	F/54	Jun. 24, 2010	Cervical cancer, recurrent cholangitis due to metastasis	Fever, acute cholangitis	–	2/3	Meropenem, tobramycin	*Pseodomonas aeruginosa*	Expired	5.02
11	F/69	Jul. 9, 2010	Diabetes mellitus	Bacteremia due to UTI	–	2/3	Ciprofloxacin	None	Recovered	5.02
12	F/60	Nov. 29, 2010	DLBCL, post autologous PBSCT	Neutropenic fever, forearm swelling	–	3/3	Vancomycin, cefepime	*Enterobacter cloacae*	Recovered	5.02
13	F/75	Apr. 19, 2011	Gallbladder adenocarcinoma	Fever, acute cholangitis	–	2/4	Ceftriaxone, metronidazole	*Escherichia coli*	Recovered	5.02
14	F/78	May 6, 2011	Cholangiocarcinoma	Fever	–	1/2	Ceftriaxone, metronidazole	None	Recovered	5.02
15	F/53	Jun. 4, 2011	Gallbladder adenocarcinoma	Fever	PTBD	2/2	Ceftriaxone, metronidazole	None	Recovered	5.02
16	M/65	Jun. 29, 2011	Pancreatic adenocarcinoma	Acute cholangitis	–	1/2	Ceftriaxone, metronidazole	None	Recovered	5.02
17	M/69	Sep. 20, 2011	Nonspecific	Acute cholecystitis	–	2/3	Ceftriaxone, metronidazole	None	Recovered	5.02
18	M/18	Dec. 29, 2012	B-LBL, post allogeneic PBSCT	Neutropenic fever	Central line	2/4	Cefepime, teicoplanin	None	Recovered	5.02
19	M/75	Feb. 29, 2012	Cholangiocarcinoma	Biliary septic shock	–	2/3	Tazocin	None	Recovered	5.02

Table 1 continued

Case no.	Gender/age	Date of isolation	Underlying disease	Presentation of infection	Other source of isolation	Positive/total no. of cultures	Antibiotic regimen	Other microbes isolated from blood	Outcome	Version of VITEK2
20	M/21	May 12, 2012	AML, post allogeneic PBSCT	Neutropenic fever	Central line	1/3	Meropenem, cefepime	None	Recovered	5.02

MM multiple myeloma, *PBSCT* peripheral blood stem cell transplantation, *AML* acute myeloid leukemia, *ROSC* return of spontaneous circulation, *HCC* hepatocellular carcinoma, *DLBCL* diffuse large B cell lymphoma, *B-LBL* B cell lymphoblastic lymphoma, *UTI* urinary tract infection, *PTBD* Percutaneous transhepatic biliary drainage

retroperitoneal abscess [8], cellulitis [9], cholangitis [10], cholecystitis [11], necrotizing fasciitis [12], and cystitis [2]. All described cases were resolved with fair clinical outcomes. Our current observations, in conjunction with these findings, demonstrate that patients with *R. planticola* infections generally have a good clinical outcome when first line empirical antimicrobial agents are administered. The majority of the patients in our study had underlying malignancies resulting in low blood neutrophil counts, making bacteremia an imminent issue.

The narrow characteristics of the underlying disorders seen in our 20 patients are of note. Despite the fact that malignancies involving the gallbladder or bile duct are of low prevalence in Korea [13], seven patients in our study had gallbladder adenocarcinoma or cholangiocarcinoma as an underlying disease. In addition, all six cases with hematologic malignancies were in the post-transplantation phase of hematopoietic stem cell transplantation, a condition well known to be prone to infection [14].

Despite the immunosuppressive state of many of our patients, the clinical outcome was fair when proper therapy was administered and *R. planticola* was the only microbe isolated. In our study, no patients with *R. planticola* as the sole microbial isolate died. However, in cases with polymicrobial infection, the outcomes differed. Our data revealed that in the six cases with polymicrobial infection, half failed to recover. On the other hand, all of the 14 patients with *R. planticola* as the sole isolate recovered.

The susceptibility of *R. planticola* to antimicrobial agents has yet to be fully investigated. In our data, we found that, while all isolates were resistant to ampicillin and piperacillin, the addition of β-lactamases inhibitors overcame this resistance. The isolates were susceptible to most cephalosporins, and a single isolate that was resistant to cephalothin. No resistance to third generation cephalosporins or carbapenems was observed. However, there have been case reports of *R. planticola* bacteremia that resulted in poor outcomes [15]. *R. planticola* isolates in these cases were resistant to carbapenem and harbored the *bla*KPC gene. This was not the case in our study as the *R. planticola* isolated from the three patients that died showed no resistance to imipenem or meropenem. However, considering the similarities between *Raoultella* and *Klebsiella* species, resistance to carbapenem may pose a potential treat.

Suggestions have been made regarding this species as virulent as other *Klebsiella* species [16]. Serotyping of the capsular antigen, patterns in serum resistance, or the type of pili expressed on the cellular surface showed that *R. planticola* and *Klebsiella pneumoniae* share similar traits, and among these traits are some that have been proven to be factors in the microbe's virulence. In a retrospective analysis of 640 cases of *K. pneumoniae* bacteremia, it

Table 2 Antibiotic susceptibility of the isolates and cases reported as *Raoultell aplanticola*

Antimicrobial agent	No. (%) of isolates			No. (%) of cases		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Ampicillin	–	–	29 (100 %)	–	–	20 (100 %)
Amoxicillin/clavulanate	29 (100 %)	–	–	20 (100 %)	–	–
Piperacillin	–	–	29 (100 %)	–	–	20 (100 %)
Piperacillin/tazobactam	29 (100 %)	–	–	20 (100 %)	–	–
Cefazolin	15 (100 %)	–	–	5 (100 %)	–	–
Cephalothin	20 (95.2 %)	–	4 (4.8 %)	15 (94 %)	–	1 (6 %)
Cefoxitin	27 (93.1 %)	2 (6.9 %)	–	18 (90 %)	2 (10 %)	–
Cefotaxime	29 (100 %)	–	–	20 (100 %)	–	–
Ceftazidime	29 (100 %)	–	–	20 (100 %)	–	–
Cefepime	29 (100 %)	–	–	20 (100 %)	–	–
Aztreonam	29 (100 %)	–	–	20 (100 %)	–	–
Imipenem	29 (100 %)	–	–	20 (100 %)	–	–
Meropenem	29 (100 %)	–	–	20 (100 %)	–	–
Amikacin	29 (100 %)	–	–	20 (100 %)	–	–
Gentamicin	28 (96.6 %)	–	1 (3.4 %)	19 (95 %)	–	1 (5 %)
Tobramycin	29 (100 %)	–	–	20 (100 %)	–	–
Ciprofloxacin	9 (100 %)	–	–	5 (100 %)	–	–
Levofloxacin	20 (100 %)	–	–	15 (100 %)	–	–
Tetracycline	5 (62.5 %)	3 (37.5 %)	–	3 (75 %)	1 (25 %)	–
Trimethoprim/sulfamethxazole	26 (89.7 %)	–	3 (10.3 %)	18 (90 %)	–	2 (10 %)

showed to be prevalent in elderly patients in a nosocomial environment, with risk factors as solid organ transplantation, chronic liver disease, dialysis dependence, and malignancies. Primary sites of infection were the biliary and urinary tract. Overall mortality was around 20 %, yet patients with bacteremia from non-biliary or non-genitourinary sources, and patients with comorbid conditions showed worse outcome [17]. However, contrary to *K. pneumoniae* bacteremia, the virulence of *R. planticola* bacteremia has not been well demonstrated in the literature. We do notice some similarities with *K. pneumoniae* and *R. planticola* bacteremia; biliary tract was thought to be the portal of entry in a large portion of cases, and was prevalent in elderly patients with malignancies. However, excluding the three cases with polymicrobial infection that resulted in poor outcome, *R. planticola* bacteremia as a sole pathogen did not share similar outcome compared to *K. pneumoniae* bacteremia.

According to our data, *R. planticola* as a sole pathogen is of low virulence in bacteremia. Although the small number of patients recruited in our study may not be very representative, *R. planticola* does not seem to be resistant to most cephalosporins and carbapenems. Polymicrobial infection does seem to pose a threat, despite the generally low virulence of *R. planticola* as a pathogen on its own. Accrual of sufficient data would be helpful in obtaining a more complete understanding of the significance of *R. planticola* infections.

Conflict of interest The authors report no conflicts of interest relevant to this article.

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