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ORIGINAL PAPER

Clinical characteristics of *Raoultella ornithinolytica* bacteremia

S. Chun · J. W. Yun · H. J. Huh · N. Y. Lee

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Abstract
Purpose *Raoultella ornithinolytica* is not well known as a clinical pathogen. We performed a retrospective review of *R. ornithinolytica* bacteremia to investigate its clinical features, antimicrobial susceptibility, and overall patient outcomes.
Methods *R. ornithinolytica* bacteremia cases were collected from an electronic database of all cases of bacteremia over a 10-year period. Medical records were retrospectively reviewed. Demographic data, clinical information, the presence of underlying comorbidities, the results of antimicrobial susceptibility testing, and the antimicrobial regimen administered were investigated.
Results *R. ornithinolytica* was isolated from blood culture specimens in 16 cases. The majority of these patients had an underlying malignant condition of advanced stage (15 patients, 94 %). Seven of these patients had a solid tumor with lesions or metastases that extended to the bile duct or biliary tract. Neutropenic fever following hematologic stem cell transplantation was found in three cases. No resistance to piperacillin/tazobactam or imipenem was found. Four cases showed resistance to cefoxitin, while one of these cases showed resistance to multiple cephalosporins. In overall outcomes, seven patients (44 %) did not recover from the infection and subsequently expired.
Conclusions *R. ornithinolytica* bacteremia occurs mainly in patients with underlying malignancies. The overall outcome was not favorable, despite favorable antimicrobial susceptibility test results. The findings of this study contradict those of other studies that demonstrated that infection from *Raoultella* species have good prognoses.

Keywords *Raoultella ornithinolytica* · Bacteremia · Microbial sensitivity test · Antibacterial agents · *Klebsiella*

Introduction

The genus *Raoultella* is composed of Gram-negative, oxidase-negative, aerobic, non-motile, capsulated, facultatively anaerobic bacilli within the Enterobacteriaceae family [1]. It was initially classified within the *Klebsiella* genus, but the current taxonomy was later established based on comparative analysis of the 16S rRNA and *rpoB* genes, resulting in the creation of the new genus *Raoultella.* Members of the *Raoultella* genus include *Raoultella electrica, R. terrigena, R. planticola,* and *R. ornithinolytica*. The latter two species have been well documented as a human pathogen in many occasions. Human bloodstream infections from members of this genus have a low prevalence, but cases of bacteremia due to *R. terrigena* [2], *R. planticola* [3–5] and *R. ornithinolytica* [6–8] can be found in the literature. Thus, it seems well established that members of the *Raoultella* genus act as a pathogen; however, their virulence and susceptibility to antimicrobial agents are largely unknown.

The authors have previously reviewed the clinical characteristics of *R. planticola* [3] and have suggested that it has low virulence. We accumulated cases of bacteremia that were caused by *R. ornithinolytica* and reviewed the antimicrobial susceptibility of the isolates and their clinical outcomes. This study demonstrates the clinical characteristics of *R. ornithinolytica* as a blood-borne pathogen, and

S. Chun · J. W. Yun · H. J. Huh · N. Y. Lee (✉)
Department of Laboratory Medicine & Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-Dong, Kangnam-Gu, Seoul 135-710, Korea
e-mail: micro.lee@samsung.com; mrmicro@skku.edu

notes that the clinical outcomes may not be as favorable as those of other *Raoultella* bacteremia.

Methods

The Samsung Medical Center is a 1,983 bed tertiary care teaching hospital located in the southern area of Seoul, Korea. Of the 1,983 beds, 652 are assigned specifically to a separate cancer center, and an additional 80 beds are reserved for gynecologic cancer patients. A separate ward with 45 beds is specifically assigned for pediatric cancer patients. Thus, the proportion of patients with malignancies is around 40 % of all in patients in our institute. We reviewed all clinical microbiology reports from our hospital for a 10 year period spanning from January 2002 to December 2011.

All blood isolates that were identified as *R. ornithinolytica* were selected and the medical records of these patients were reviewed. The clinical features of these infections were examined, and cases that showed documentation of symptoms indicative of bacteremia were included in the study. Data on patient gender and age, underlying disease, symptoms indicating infection, number of blood culture sets that yielded *R. ornithinolytica,* the antimicrobial regimen administered for the infection, microbes other than *R. ornithinolytica* that were isolated, and the outcome of the infection were gathered from patient medical records.

All blood culture sets issued contained a secondary and/or a tertiary blood culture at different venous sites. 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 performed on the first specimen.

Isolation of microbes from the 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) along with the VITEK 2 GN ID card, accompanied by routine bacteriologic methods. The software version of the VITEK 2 system was 4.01 prior to 2005, 4.03 from 2005 to 2007, 5.01 until the end of 2008, 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 [9].

Results

Overall, 16 patients were diagnosed with *R. ornithinolytica* bacteremia during the 10-year period of our study. Over the same period, a total of 32,745 tests showed positive blood culture results, while *R. ornithinolytica* was isolated 31 times. Consequently, *R. ornithinolytica* bacteremia occurred in less than 0.1 % of positive blood culture test results. 10,642 patients' blood samples showed positive blood culture results in the same period, showing that *R. ornithinolytica* bacteremia accounted for about 0.15 % of all bacteremia cases.

The number of *R. ornithinolytica* bacteremia cases ranged from 0 to 3 cases per year, with an average of 1.6 cases annually. The gender distribution of the patients was eleven males and five females. Patient age ranged from 20 to 73 years, with a mean of 55.7 years. All but one patient had an underlying malignant condition. Of the patients with underlying cancer, seven had infections associated with the bile duct or the biliary tract. There were five patients with neutropenia that had underlying hematologic malignancies. The patient without an underlying malignancy had end-stage renal disease and was on continuous ambulatory peritoneal dialysis; blood culture results and the culture for dialysate demonstrated the growth of *R. ornithinolytica.* Overall, seven patients (44 %) expired due to the infection. Five cases showed polymicrobial infection. While the clinical outcome of cases 11, 14 and 15 was favorable, cases 9 and 13 had bacteremia with isolates of the *Enterococcus* species along with *R. ornithinolytica*. Both cases resulted in the patients expiring from septic shock. All cases are described in chronological order in Table 1.

Cases 1, 2, 4, 6 and 16 showed bacteremia with *R. ornithinolytica* as the sole isolate with a poor outcome. All cases had underlying malignancies of advanced stage. Excluding case 13, the selected antimicrobial therapy of choice was sufficient regarding in vitro susceptibility and dosage. In case 13, *R. ornithinolytica* showed resistance to amoxicillin/clavulanic acid, aztreonam, all tested cephalosporins including cefepime, cefotaxime and ceftazidime, but remained susceptible to imipenem and meropenem, along with showing susceptibility to piperacillin/tazobactam. Screening tests for extended-spectrum beta-lactamase (ESBL) were not performed on this strain. The regimen applied was ceftriaxone and metronidazole, implicating that this may not have been the effective antimicrobial agent for the infection.

Seven cases showed malignant lesions or metastasis than anatomically extended to the bile duct or biliary tract (cases no. 1, 4, 10 and 13–16). Clinical outcome was mixed in this group with four cases (cases no. 1, 4, 13 and 16) that failed recover from sepsis. On the other hand, cases 3, 7 and 8 involved patients with pancytopenia following hematopoietic stem cell transplantation. All three patients showed isolates of only *R. ornithinolytica* and subsequently recovered from the infection.

Table 1 Patient characteristics of 16 cases with *Raoultella ornithinolytica* bacteremia

Case no.	Gender/age	Date of isolation	Underlying disease	Presentation of infection	Other source of isolation	No. positive/total no. of cultures	Antibiotic regimen	Other microbes isolated	Outcome
1	M/73	Apr. 2, 2002	AGC with liver metastasis	Biliary septic shock	–	2/2	Ceftriaxone	None	Expired
2	M/68	May 15, 2002	NSCLC	Septic shock	Central line	2/2	Meropenem	None	Expired
3	M/40	Nov. 28, 2002	AML, post-allogenic BMT	Neutropenic fever	Central line	4/6	Cefepime, metronidazole	None	Recovered
4	M/57	Jan. 1, 2003	HCC	Biliary septic shock	–	2/2	Ceftriaxone, metronidazole, tobramycin	None	Expired
5	F/38	Apr. 25, 2003	DLBCL	Neutropenic fever	Central line	3/3	Ceftazidime, tobramycin	None	Recovered
6	M/69	Jul. 5, 2005	Bladder cancer	Urosepsis	Urine	2/2	Piperacillin/tazobactam, azithromycin	None	Expired
7	M/29	May 17, 2006	AML, post-allogenic PBSCT	Neutropenic fever	Central line	1/2	Cefepime	None	Recovered
8	F/38	May 28, 2006	AML, post-allogenic PBSCT	Neutropenic fever	Central line	2/3	Imipenem/cilastatin	None	Recovered
9	M/73	Jun. 2, 2006	DLBCL	Urosepsis	Urine	2/3	Imipenem/cilastatin, vancomycin	*Enterococcus faecalis*	Expired
10	M/72	Aug. 3, 2007	Cholangiocarcinoma	Fever, acute cholangitis	Bile	2/2	Ceftriaxone	None	Recovered
11	M/68	Nov. 2, 2007	ESRD on CAPD	Peritonitis	Dialysate	1/2	Ceftazidime	*Enterococcus faecalis*	Recovered
12	M/20	Nov. 22, 2007	Relapsed ABL	Neutropenic fever	–	4/4	Cefepime	None	Recovered
13	M/73	Apr. 7, 2008	AGC with liver metastasis	Biliary septic shock	Bile	1/2	Ceftriaxone, metronidazole	*Enterococcus casseliflavus, Enterococcus gallinarum*	Expired
14	F/70	Jun. 16, 2008	Pancreatic cancer	Cholecystitis, septic shock	–	1/2	Meropenem, vancomycin	*Enterococcus faecalis*	Recovered
15	F/57	Dec. 31, 2010	Cholangiocarcinoma	Fever, acute cholangitis	Bile	1/2	Meropenem	*Escherichia coli*	Recovered
16	F/46	Feb. 15, 2011	Colon cancer with liver metastasis	Fever, septic shock	Peritoneal fluid	1/2	Piperacillin/tazobactam	None	Expired

AGC advanced gastric cancer, *NSCLC* non-small cell lung cancer, *AML* acute myeloid leukemia, *BMT* bone marrow transplantation, *HCC* hepatocellular carcinoma, *DLBCL* diffuse large B cell lymphoma, *PBSCT* peripheral blood stem cell transplantation, *ESRD* end-stage renal disease, *CAPD* continuous ambulatory peritoneal dialysis, *ABL* acute biphenotypic leukemia

Table 2 Antibody susceptibility of 16 cases with *Raoultella ornithinolytica*

Antimicrobial agent	No. (%) of cases			No. (%) of strains		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Amikacin	16 (100 %)			31 (100 %)		
Ampicillin		2 (12 %)	14 (88 %)		2 (6 %)	29 (94 %)
Cefazolin	12 (86 %)		2 (14 %)	23 (86 %)		4 (14 %)
Ceftriaxone	5 (100 %)			10 (100 %)		
Cefoxitin	11 (69 %)	1 (6 %)	4 (25 %)	23 (74 %)	1 (3 %)	7 (23 %)
Ciprofloxacin	13 (93 %)		1 (7 %)	24 (89 %)		3 (11 %)
Gentamycin	14 (88 %)		2 (12 %)	26 (84 %)		5 (16 %)
Imipenem	16 (100 %)			31 (100 %)		
Meropenem	6 (100 %)			11 (100 %)		
Trimethoprim/sulfamethoxazole	14 (88 %)		2 (12 %)	26 (84 %)		5 (16 %)
Cefepime	15 (94 %)		1 (6 %)	29 (94 %)		2 (6 %)
Piperacillin/tazobactam	16 (100 %)			31 (100 %)		
Cefotaxime	13 (93 %)		1 (7 %)	26 (93 %)		2 (7 %)
Ceftazidime	13 (93 %)		1 (7 %)	26 (93 %)		2 (7 %)
Amoxicillin/clavulanic acid	13 (93 %)		1 (7 %)	26 (93 %)		2 (7 %)
Tetracycline	8 (89 %)		1 (11 %)	15 (88 %)		2 (12 %)
Aztreonam	10 (91 %)		1 (9 %)	19 (90 %)		2 (10 %)

No cases showed susceptibility to ampicillin, while the isolates in all cases showed universal susceptibility to a combination of piperacillin and tazobactam. The isolates also generally showed good susceptibility to cephalosporins, although the susceptibility to cefoxitin was lower compared to other cephalosporins. Resistance to cefoxitin was observed in cases 4, 6, 13 and 16. All cases resulted in the patient expiring from septic shock. Resistance to the multiple cephalosporins was shown in only a single case (case 13). All cases showed universal susceptibility to imipenem and the most recent six cases were susceptible to meropenem (Table 2).

Discussion

Raoultella species are Gram-negative aerobic bacilli of the Enterobacteriaceae family. Documentation of human infection of *Raoultella* species is mostly done with *R. planticola*, with cases of bacteremia [3], urinary tract infection [10], conjunctivitis [11] and cholecystitis [4] reviewed in the literature. However, few sources show human infection with *R. ornithinolytica*. Cases of urinary tract infections caused by *R. ornithinolytica* in cancer patients have been reported [12]. *Raoultella ornithinolytica* bacteremia was reviewed by Haruki et al., and previous results have suggested fair prognoses [7]. However, our data suggested very different outcomes, with only nine patients showing favorable outcomes. Due to the small number of subjects enrolled in each study, either results may not be representative. However, it should be noted that each study applied a different biochemical identification method applied in identifying the pathogen.

In general, identification of *Raoultella* species can be problematic due to its phenotypic similarity to *Klebsiella* species. The performance of the VITEK2 system for the identification of *R. ornithinolytica* has been evaluated by multiple studies [13, 14]. Park et al. demonstrated that the VITEK2 system correctly identified all eight strains of *R. ornithinolytica*, while the MicroScan system (Dade Behring, Deerfield, Illinois, USA) failed to do so in seven cases [13]. Another evaluation of the VITEK2 GN card performed by Renaud et al. showed that the VITEK2 system identified *R. ornithinolytica* correctly in all four cases [14]. Furthermore, the MicroScan system showed a tendency to identify *R. ornithinolytica* as *Klebsiella oxytoca.* This is due to the fact that there are ornithine decarboxylase negative *R. ornithinolytica* strains that are misidentified as *K. oxytoca* by the MicroScan system. Identification of *Raoultella* from *Klebsiella* species can be done by detecting their histamine producibility. But the VITEK2 is not without fault in identifying *R. ornithinolytica*; this greater sensitivity of the VITEK2 system might have been achieved with the expense of specificity. There are reports of misidentification of *Enterobacter asburiae* as *R. ornithinolytica* [15]. Overestimation of *R. ornithinolytica* strains may be a problem with this study; thus biasing the clinical outcome. Nevertheless, the current method applied in

this study is the most sensitive method in identifying *R. ornithinolytica.*

The fair clinical outcomes of the previous reports by Haruki et al. and Hadano et al. might be due to two factors. First, their cases did not include strains that showed resistance to cefotaxime. And second, there is the possibility that the cases of *R. ornithinolytica* bacteremia with poor outcomes were incorrectly identified as *K. oxytoca* bacteremia by the MicroScan system, and thus not included in their reports. We suggest that *R. ornithinolytica* bacteremia can be a clinical threat, especially since the majority of cases was linked with underlying malignancies. The proportion of patients with underlying malignant conditions is large, considering that 6,132 (58 %) of the total of 10,642 bacteremia patients in the same period had underlying malignancies.

A previous study that tested the natural antimicrobial susceptibility of 25 strains of *R. ornithinolytica* from various environmental and clinical specimens suggested that *R. ornithinolytica* is a biogroup of *R. planticola* [16]. Regarding only the antibiogram, we find this consistent with our previous study [3]. However, the clinical outcomes differed substantially, with five of the eleven cases with *R. ornithinolytica* as the sole isolate expiring from sepsis. Cases with polymicrobial infections did not show many differences; of the five cases with multiple species in blood culture isolates, two patients expired. Patients infected with *R. ornithinolytica* can be assumed to have poor prognosis, as *Raoultella* species originally were classified to be members of the *Klebsiella* genus, suggesting similar biological traits. Thus, the overall mortality of *R. ornithinolytica* bacteremia can be compared to that of other *Klebsiella* species bacteremia. Mortality is reported to be around 20–25 %, and patients with comorbid conditions show worse outcomes [11, 17]. In addition, patients with *R. ornithinolytica* infection are of older age and have an underlying comorbidity or malignancy. Our study showed that 15 of a total of 16 patients had underlying malignancies at an advanced stage. The one patient without a malignant condition was dependent on dialysis. Seven cases were associated with an infection of the bile duct or biliary tract. All of these cases were of patients with malignancies of lesions or metastasis that extended to the bile duct or biliary tract, resulting in biliary sepsis. This observation has been described before [18, 19], and the possibility of association of *Raoultella* species infection with malignant diseases that have involvement of the biliary system seems a consistent finding in multiple studies. Bile acids have previously been shown to be tumor promoters, and increased ornithine decarboxylase activity has been noted with rapid cell proliferation [18, 20]. Further research in this finding may be interesting, especially due to the fact that *R. ornithinolytica* is regularly positive for ornithine decarboxylase.

The overall mortality was 44 %, substantially higher than bacteremia involving other *Klebsiella* species. Since our study recruited only a small number of cases, this number may not reflect the true virulence of *R. ornithinolytica* bacteremia. But the observation of four strains with cefoxitin resistance leads to speculation of the possibility of the presence of AmpC beta-lactamase. All four cases resulted in poor outcome, with regimen ranging from ceftriaxone to piperacillin/tazobactam. All strains showed no resistance to imipenem, and while meropenem was not tested on all strains, cases 13 and 16 showed to be susceptible. Case no. 13 also showed resistance to cefotaxime, ceftazidime and cefepime, along with being resistant to cefoxitin. A strain with ESBL was strongly suggestive in this case, and the ceftriaxone and metronidazole regimen proved to be insufficient in this case.

There have been reports of carbapenem-resistant *R. ornithinolytica* in the literature [21]. The isolate in this reported case demonstrated the presence of the blaKPC gene, and was the only case in the literature with *R. ornithinolytica* bacteremia that resulted in a poor outcome. Although none of our cases showed resistance to imipenem or meropenem, our study also demonstrated cases with poor outcome. Interestingly, among the five patients administered carbapenem as a part of their antimicrobial regimen, two failed to respond to treatment. Since no isolates showed resistance to carbapenem, we do not suggest that the observed treatment failures were due to resistance to the regimen. However, it does bring into contrast the fact that no cases with cefepime or ceftazidime as part of the regimen showed poor responses. The number of cases may be too small to speculate. However, a systemic review regarding the volume of distribution of beta-lactams showed that in septic patients, the increase in the volume of distribution compared to healthy subjects was larger in carbapenems compared to cephalosporins, although in the case of ceftazidime, the variation of volume distribution did show a very wide range [22]. The dilution of antimicrobial agents should be considered in the treatment of septic conditions.

Another interesting finding was the contrast in the clinical outcomes of patients without ongoing malignancies (cases 3, 7, 8 and 11) and the patients with malignancies (the remainder of the cases). All cases with poor outcomes were in the latter group. While the former group included three patients with hematologic malignancies, all three were in complete remission at the time of hematopoietic stem cell transplantation and survived the infection. The presence of an ongoing malignancy can be concluded to be a risk factor for poor outcome in *R. ornithinolytica* bacteremia.

Overall, *R. ornithinolytica* is a pathogen with potent virulence. It is very rare in clinical environments, yet when isolated from blood culture samples, and should be dealt

with attention. The small number of patients recruited in our study may not seem exceptionally representative, but our results suggest a contrasting outcome as compared to previous case reports [6–8]. It appears that patients with underlying malignant conditions extending to the biliary tract are of elevated risk for *R. ornithinolytica* bacteremia. In addition, even with antibiotic therapy shown to be susceptible in vitro, the outcome may still be poor. This finding differs from previous case reports and studies. However, further study with a larger population is needed to investigate the true nature of the virulence of this organism.

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

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