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REVIEW

Raoultella ornithinolytica: Emergence and Resistance

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Roy Hajjar[1,*]
Georges Ambaraghassi[2,*]
Herawaty Sebajang[1]
Frank Schwenter[1]
Shih-Hann Su[2]

[1]Digestive Surgery Service, Department of Surgery, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada; [2]Department of Medical Microbiology and Infectious Diseases, Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada

*These authors contributed equally to this work

Abstract: *Raoultella ornithinolytica* is an encapsulated Gram-negative, oxidase-negative, catalase-positive, aerobic, non-motile rod that belongs to the *Enterobacteriaceae* family. This bacterium was initially classified in the genus *Klebsiella* as *Klebsiella ornithinolytica*, until the creation of the genus *Raoultella* in 2001. *R. ornithinolytica* is usually found in water environments and soil, and due to its ability to convert histidine to histamine, it has been associated with histamine poisoning in humans. *R. ornithinolytica* is an emerging entity in human infections, with several reports of virulent infections in comorbid at-risk patients. Increasing reports are potentially due to better and more precise identification tools. The objective of this article is to provide a comprehensive review of reported cases of *R. ornithinolytica* infections, the emergent virulence of described multiresistant strains, and an overview of currently used identification methods.

Keywords: *Raoultella ornithinolytica*, *Raoultella spp*., infection, resistance

Background

Raoultella ornithinolytica is an encapsulated Gram-negative, oxidase-negative, catalase-positive, aerobic, non-motile rod that belongs to the *Enterobacteriaceae* family.[1–5] It was initially classified in cluster II of the genus *Klebsiella* as *Klebsiella ornithinolytica* along with other environmental organisms comprising *Klebsiella terrigena, Klebsiella planticola* and *Klebsiella trevisanii*.[2,3] With advanced phylogenetic testing including 16S rRNA and rpoB sequence analysis, the genus *Klebsiella* was further divided into two genera.[3] Thus, in 2001, the genus *Raoultella* was created and species included in the cluster II of the genus *Klebsiella* were transferred and renamed to the new genus.[3,6] The *Raoultella* genus is named after Didier Raoult, a French bacteriologist from the Université de la Méditerranée in Marseille, France.[3]

R. ornithinolytica has been found in water environments, soil, insects, fish, ticks and termites.[3,5,7–11] This bacterium converts histidine to histamine causing histamine poisoning with cutaneous flushing, better known as the scombroid syndrome associated with fish poisoning.[7,9] In addition to skin flushing, this syndrome may cause vomiting, diarrhea, headache or pruritus depending on the quantity of ingested histamine.[11,12] This syndrome is mainly associated with "scombroid" fish belonging to the *Scombridae* and *Scomberesocidae* families where exogenous microbial decarboxylation of histidine occurs.[12–14]

The incidence of human disease associated with *R. ornithinolytica* is low with few previously reported cases of clinical infections requiring treatment. The low prevalence of *R. ornithinolytica* related infections in the literature might be explained by the challenges and difficulty to properly identify this species with conventional

Correspondence: Roy Hajjar; Georges Ambaraghassi
Centre Hospitalier de l'Université de Montréal, 1000, Rue Saint-Denis, Montréal, Québec H2X 0C1, Canada
Tel +1 514 890 8000
Email Roy.hajjar@umontreal.ca; Georges.ambaraghassi@umontreal.ca

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biochemical and phenotypic tests. Similarly to other members of the *Enterobacterales* order, such as *Aeromonas, Plesiomonas* and *Leclercia* and non-fermenting Gram-negative bacteria, such as *Stenotrophomonas maltophilia, Burkholderia cepacia complex* and *Alcaligenes faecalis*, due to the scarcity of reported cases, the associated pathogenicity and antibiotic susceptibility testing remain overlooked.[15–18] Nonetheless, there is a rapidly emerging role for *R. ornithinolytica* in human infections, with some multi-drug resistant strains being increasingly reported.[4,11,19]

Objective

The objective of this paper is to provide a comprehensive review of available current knowledge on the emerging role of *R. ornithinolytica* in human infections, its virulence and resistance to antibiotic treatment.

Data Sources

A literature review was performed in Medline, Pubmed and Embase, using the expressions "*Raoultella ornithinolytica"* and "*Raoultella* spp.", to identify reported cases of infections with *Raoultella ornithinolytica*. The references of identified publications were also reviewed for the identification of relevant cases.

Identification

Adequate identification of *Raoultella* species remains a challenge with conventional identification methods.[1] It is suggested that *R. planticola* can represent up to 19% of misidentifications of *Klebsiella* and *Raoultella* species with conventional testing.[20–22]

R. ornithinolytica and *R. planticola* are two closely related species and differentiating them with phenotypic methods is difficult. Data collected from studies with 16S rDNA sequencing did show high DNA homology between *R. ornithinolytica* and *R. planticola*, with these bacteria bound in a tight cluster. Few phenotypic tests are available to differentiate these two species. Ornithine decarboxylase (ODC) was proposed for instance to provide a potential separation tool.[23] While *R. planticola* has been reported as ODC negative, *R. ornithinolytica* is ODC positive.[24,25] However, ODC-negative *R. ornithinolytica* has nonetheless been described and such isolates can be misidentified as *R. planticola* and *Klebsiella oxytoca*.[24] Indole production is another biochemical test that can be helpful in distinguishing between *R. ornithinolytica* and *R. planticola*. While *R. ornithinolytica* is indole-positive, *R. planticola* is indole variable.[24,25] Moreover, previous studies have reported cases of incorrect identification of *R. ornithinolytica* as *K. oxytoca*. Park et al (2011) conducted a study comparing three identification systems (VITEK®2, MicroScan and API 20E) for the identification of *R. ornithinolytica* and *K. oxytoca*.[24] Among *R. ornithinolytica* isolates identified with sequence-specific primer PCR, VITEK®2 provided 100% correct identification of *R. ornithinolytica*, while Microscan and API 20E identified 92.6% and 88.9% of the isolates as *Klebsiella oxytoca*.[24] Novel techniques, such as lateral-flow test strips, have been developed for rapid detection of *R. ornithinolytica* and closely related species and have showed favorable results. To our knowledge, this technology has been mainly applied to the food industry.[26]

While phenotypic-based identification systems yielded conflicting results for distinguishing *K. oxytoca* from *R. ornitholytica*, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has allowed better characterization and detection with improved differentiation between *Klebsiella* and *Raoultella* spp.[1,27] This technology was used in our previous work to properly identify *R. ornithinolytica* in a patient with gut-derived sepsis.[28] However, because mass spectra from *R. ornithinolytica* and *R. planticola* are highly similar, difficulty in differentiating between these two species has been reported with MALDI-TOF technology.[29,30] Misidentification as *Enterobacter aerogenes* (now *Klebsiella aerogenes*) has also been reported with the use of MALDI-TOF.[29] This could be potentially explained by the fact that *K. aerogenes* is closely related to *Raoultella* species (formerly environmental *Klebsiella* species) in the phylogenetic tree derived from 16S rDNA sequencing.[3,23,31]

Virulence and Resistance

As stated by Haruki et al (2014), *R. ornithinolytica* was thought to be highly virulent due its occurrence in fragile patients with significant comorbidities and its initial association with the *Klebsiella* genus, which comprises several virulent strains.[33] However, according to previously reported cases, prognosis in highly variable and depends on the patient's overall health status and the type of infection, and outcomes are not necessarily poor when proper treatment is promptly initiated.[33]

Most species in the genus *Raoultella* are usually broadly sensitive to antibiotics based on the isolates from case series in the literature.[34] Similarly to some *Klebsiella* species, *Raoultella spp*. exhibit intrinsic resistance to ampicillin and ticarcillin which are the result of

chromosomally encoded beta-lactamases.[34–37] Chun et al (2015) reported a series of 16 patients with isolates showing antibiotic susceptibility to cephalosporins ranging from 69% to 100%, 93% susceptibility to amoxicillin/clavulanic acid, 88% to trimethoprim/sulfamethoxazole (TMP-SMX) and 100% to meropenem, imipenem and piperacillin/tazobactam.[4] Seng et al (2016) reported, in the largest series published, that resistance to amoxicillin/clavulanic acid, ceftriaxone, quinolones, TMP-SMX and aminoglycosides were 16%, 4%, 6%, 10 and 1% respectively.[1] No resistance to imipenem-cilastatin was reported.[1] Multidrug resistant *R. ornithinolytica*, with acquired antibiotic resistance genes, has nonetheless been isolated in clinical specimens. Production of beta-lactamases remains the most frequently described mechanism of resistance. Strains exhibiting beta-lactamases from Ambler class A, B and D have been reported. Several case reports have described isolates producing extended-spectrum beta-lactamases belonging to the SHV, TEM and CTX-M.[34,38,39] AmpC beta-lactamases producing strains were also isolated from clinical specimens in Iraq.[40]

In the last decade, several emerging cases of carbapenem resistance were described.[41] The first case of the bla_{KPC} carbapenemase-encoding gene in *R. ornithinolytica* was reported by Castanheira et al (2009) in a postoperative infection after a valve replacement surgery.[42] The authors reported the presence of this resistance factor in several *Raoultella* spp. including *R. planticola* and *R. ornithinolytica*, with fatal outcomes in all 3 patients.[42] Other carbapenemase-harboring strains were reported in the following years.[34,43] The first case of bla_{NDM-1} in *R. ornithinolytica* was described in 2013 by Khajuria et al in an adult male patient with postoperative perineal infection, who recovered well with an appropriate antibiotic treatment.[44] Other cases of metallo-beta-lactamase -producing *R. ornithinolytica* harboring NDM or VIM genes were reported since then.[41,45–48] An IMI-producing *R. ornithinolytica* strain acquired by a transposon was also isolated from a clinical sample in China.[49] Isolated cases of carbapenemase bla_{OXA-48}-harboring *R. ornithinolytica* harvested from a surgical site infection in South America and the fecal sample of a patient with Hodgkin lymphoma in Lebanon were also reported.[50,51] Other *Raoultella* species were also described as exhibiting OXA-48 carbapenemase.[52–55] Nonetheless, a few strains of *R. ornithinolytica* generating simultaneously different types of beta-lactamase (TEM, SHV, KPC and OXA) were described.[42,56] The first case of co-existence of bla_{KPC-2} and bla_{IMP-4} carbapenemase genes in the genus *Raoultella* was reported by Zheng et al (2015) in a 13-year-old male patient with postoperative infection after an orthopedic surgery.[57] The *R. ornithinolytica* strain was identified in this report by 16S rRNA sequencing and antimicrobial susceptibility was determined with VITEK®2 and Etest strips (Biomérieux, France) on 7 samples collected from the wound fluid and necrotic tissue.[57] The isolated strains were reported as resistant to all antimicrobials except ciprofloxacin. All but one strain were also susceptible to TMP-SMX.[57]

Since the emergence of plasmid-mediated polymyxin resistance by the *mcr-1* gene, the latter, along with other *mcr* resistance genes, have been isolated in many *Enterobacteriaceae* in different continents.[58,59] The *mcr* gene has rarely been isolated in *R. ornithinolytica* strains, with the first cases being found in retail vegetables in China.[60] Furthermore, emergence of *mcr-8* gene and variant was also identified in *R. ornithinolytica* which raised concern about its co-transferability with other beta-lactamase genes.[58,61]

Gastrointestinal and Hepatobiliary Infections

Gastrointestinal and hepatobiliary infections are among the most frequently reported infections with *R. ornithinolytica* in the literature. Fully detailed cases are depicted in Table 1.

Bhatt et al reported in 2015 a case of postoperative intra-abdominal infection with *R. ornithinolytica* after a Whipple's pancreaticoduodenectomy.[19] The author identified a multiresistant strain harboring the New Delhi metallo-b-lactamase gene (bla_{NDM}) in sub-hepatic peritoneal fluid.[19] The presence of bla_{NDM} gene was reported only once before, by Khajuria et al (2013) in a patient with a *R. ornithinolytica* soft tissue infection.[44]

Seng et al (2016) described, in a series of 112 cases of *R. ornithinolytica* infections in 4 French university hospitals, 16 cases of gastrointestinal infections with 6 being hospital-acquired.[1] The majority of these cases consisted of hepatobiliary and pancreatic infections.[1] *R. ornithinolytica* was also isolated, among other bacteria, in fish fillets potentially involved in an incident of foodborne poisoning in southern Taiwan.[12]

Chun et al (2015) reported 7 patients with biliary infection in a review of 16 cases of *R. ornithinolytica* bacteremia.[4] All patients had a malignancy except one who suffered from end-stage renal disease on peritoneal dialysis.[4] The latter

Table 1 Reported Cases of Gastrointestinal Infections with *Raoultella ornithinolytica*

Author	Year	Age (Yr)	Sex	Comorbidities	Diagnosis	Positive Sample	Identification Technique	Antimicrobial Susceptibility	Treatment	Clinical Outcome
Morais et al[62]	2009	82	Female	Hypertension Degenerative arthropathy	Enteric fever-like syndrome	Blood Stool	API	-	Ciprofloxacin (10 days) then amoxicillin/clavulanate (10 days)	Improvement
Mau et al[63]	2010	0 (<1 month)	Male	Visceral heterotaxy Functional asplenia Congenital heart block Double outlet single ventricle	NEC and septicemia	Blood	-	S: Aminoglycosides, cefepime, carbapenems, quinolones, trimethoprim/sulfamethoxazole	Empirical cefepime, metronidazole, amikacin and fluconazole, then amikacin and meropenem	Improvement
Hadano et al[64]	2012	92	Male	Hypertension Advanced-stage cholangiocarcinoma	Cholangitis	Blood	MicroScan	S: Piperacillin, amoxicillin/clavulanate, piperacillin/tazobactam, ceftriaxone, cefepime, meropenem, gentamicin, levofloxacin, minocycline, trimethoprim/sulfamethoxazole, ceftazidime	Piperacillin/tazobactam (2 weeks)	Improvement then transfer to palliative care
		52	Female	Advanced-stage pancreatic cancer	Cholangitis	Blood		S: Piperacillin, amoxicillin/clavulanate, piperacillin/tazobactam, ceftriaxone, ceftazidime, cefepime, meropenem, gentamicin, levofloxacin, minocycline, trimethoprim/sulfamethoxazole	Imipenem/cilastatin then cefmetazole	Improvement
		59	Male	Early-stage gastric cancer (5 days post-distal gastrectomy)	Cholangitis	Blood		S: Piperacillin, amoxicillin/clavulanate, piperacillin/tazobactam, ceftriaxone, ceftazidime, cefepime, meropenem, gentamicin, levofloxacin, minocycline, trimethoprim/sulfamethoxazole	Piperacillin/tazobactam then cefmetazole, followed by amoxicillin/clavulanate	Improvement

Haruki et al[33]	2014	73	Female	Cerebral infarction	Cholangitis	Blood	Microscan	S: Ceftriaxone, levofloxacin R: piperacillin	Piperacillin then ceftazidime	Improvement
		75	Male	Cholecystolithiasis				S: Ceftriaxone, levofloxacin, piperacillin	Cefepime and amikacin	Improvement
		92	Female	Cholangitis; pancreatitis; choledocholithiasis					Cefoperazone/ sulbactam then ciprofloxacin	Improvement
		44	Male	Sigmoid colon cancer, liver metastasis					Cefoperazone/ sulbactam then amoxicillin/ clavulanate	Improvement
		77	Female	Cholangiocarcinoma				S: Ceftriaxone, levofloxacin R: piperacillin	Piperacillin/ tazobactam then cefazolin	Improvement
Bhatt et al[19]	2015	75	Male	Hypertension Diabetes Whipple's pancreaticoduodenectomy	Sub-hepatic space infection	Peritoneal fluid (sub-hepatic drain)	VITEK®2	S: Colistin, tigecycline R: Aminoglycosides, fluoroquinolones, cephalosporins, carbapenems	-	-
Hajjar et al[28]	2018	54	Male	None	Appendicitis	Blood	MALDI-TOF MS	S: Amoxicillin/clavulanate, ciprofloxacin	Appendectomy	Improvement
					Septic shock	Peritoneal fluid			Ciprofloxacin and metronidazole then amoxicillin/ clavulanate	

Abbreviations: Yr, year; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; S, susceptible; R, resistant.

presented with peritoneal dialysis-related peritonitis and *R. ornithinolytica* was isolated in the dialysate.[4]

Reported cases of gastrointestinal, and specifically biliary, infections with *R. ornithinolytica* are often depicted as affecting mainly individuals with an altered immune system either by a malignant condition or a chronic disease. Nonetheless, rare cases involving healthy patients with no identifiable risk factors exist, and usually present as food poisoning and acute gastroenteritis.[12,28]

Urological Infections

Cases of urinary tract infection (UTI) with *R. ornithinolytica* are very scarce. Table 2 summarizes the previously detailed cases of UTIs with this pathogen. Among other reported cases, Vos et Laureys (2009) described a case of an infected giant renal cyst causing colonic obstruction and an inflammatory syndrome.[65] Chun et al (2015) reported in his case series 2 cases of urosepsis in patients with diffuse large B cell lymphoma and bladder cancer respectively.[4] One patient was treated with piperacillin/tazobactam and azithromycin, and the second with imipenem/cilastatin and vancomycin.[4] In the latter, a coinfection with *Enterococcus faecalis* was found.[4] The outcome was death in both cases.[4] In non-English literature, reported cases include urinary tract infections with *R. ornithinolytica* in patients with malignancies.[66]

Seng et al (2016) reported in his series of 112 cases 36 urinary infections with *R. ornithinolytica*, including 20 cases of cystitis, 8 cases of pyelonephritis, 5 cases of prostatitis and 3 cases of renal cyst infection.[1] Furthermore, Boattini et al (2016) reported 9 cases of cystitis due to *R. ornithinolytica*.[67]

It is worth noting that many of the reported cases were diagnosed in patients with either immunodeficiency, malignant conditions or anatomical abnormalities, thus making them complicated rather than simple community-acquired infections.

Osteoarticular Infections

Very few reports of osteoarticular infections with *R. ornithinolytica* have been published in the literature. Table 3 describes the reported detailed cases of such infections. Seng et al (2016) reported 4 cases of bone and joint infection, including 3 cases of chronic osteitis without orthopedic device and 1 case of tibia pandiaphysitis.[1] These cases were community-acquired.[1]

Although several patients in the previously reported cases had multiples comorbidities, none of them appeared to have an active immunosuppressive condition. The clinical presentation and symptoms did not significantly differ from, nor were they more severe than, the cases of osteoarticular infections caused by other pathogens. Furthermore, the majority of cases responded adequately to treatment, the latter consisting usually of debridement and lavage of the affected joint and subsequent prolonged antimicrobial therapy.[69] Although response to standard treatment was frequently reported as satisfactory, amputation was previously required to control the infection.[69]

While some cases may suggest that a prior intervention may have led to infection, other cases were described in immunocompetent patients with no identifiable entry points. Nonetheless, osteoarticular manifestations account for a minority of infectious events with *Raoultella ornithinolytica* in the literature.

Ear, Nose and Throat Infections

Singh et al (2017) reported a case of ENT infection in a 70-year old female patient with history of tobacco chewing, presenting as pain in the throat and ear, postnasal discharge and voice change.[71] The bacterium was identified on throat swab cultures, and antimicrobial susceptibility was determined using the VITEK®2 system.[71] The cultured strain was susceptible to piperacillin/tazobactam, ertapenem, amikacin, gentamicin, nalidixic acid, ciprofloxacin, norfloxacin, cefixime, ceftazidime, ceftriaxone and TMP-SMX, and resistant to amoxicillin/clavulanic acid, fosfomycin and cefoxitin.[71] The patient received an initial empirical treatment of amoxicillin/clavulanic that was changed to piperacillin/tazobactam and subsequently ciprofloxacin, with clinical improvement.[71]

In a study aiming at identifying pathogenic bacteria in the saliva of individuals wearing dentures, Derafshi et al (2017) reported 2 cases where *R. ornithinolytica* was isolated.[72] No clinical repercussions or related infections with this pathogen were however described in this cohort.[72] In another study aiming at identifying sulphate-reducing bacteria in saliva samples, *R. ornithinolytica* was isolated in one smoker patient with no local or systemic infection.[73]

To the best of our knowledge, the only described cases of *R ornithinolytica* ENT infections include the one reported by Singh et al (2017), and 2 cases of external otitis (one of which hospital-acquired) reported by Seng et al (2016).[1,71] The presence *R. ornithinolytica* in human saliva samples points to its potential role in infection pathogenicity. More cases are however required to better

Table 2 Reported Cases of Urinary Tract Infections with *Raoultella ornithinolytica*

Author	Year	Age (Yr)	Sex	Comorbidities	Diagnosis	Positive Sample	Identification Technique/ Antimicrobial Susceptibility Assessment	Antimicrobial Susceptibility	Treatment	Clinical Outcome
Haruki et al[33]	2014	65	Male	-	Acute prostatis	Blood	Microscan	S: Cefotaxime, levofloxacin R: Piperacillin	Cefixime then levofloxacin	Recovery
Nakasone et al[11]	2015	73	Female	Rheumatoid arthritis (methotrexate) Previous urosepsis due to CA-ESBL Escherichia coli	UTI	Urine	Not specified	S: Ampicillin-sulbactam, amikacin, ceftriaxone, gentamycin, tobramycin, cefepime, ciprofloxacin, nitrofurantoin, ertapenem, piperacillin-tazobactam, trimethoprim/sulfamethoxazole	Empirical oral trimethoprim-sulfamethoxazole for 3 days then oral ciprofloxacin for 5 days	Recovery
De Petris et al[68]	2018	0 (8 months)	Female	Previous UTI due to *E. coli* Bilateral vesicoureteral reflux	UTI	Urine	MicroScan	Not specified	Empirical ceftriaxone (60 mg/kg/day) for 3 days then oral cefpodoxime proxetil (5 mg/kg) for a total of 10 days	Recovery
Büyükcam et al[10]	2018	6	Female	Hydronephrosis and recurrent UTI	UTI	Urine	MALDI-TOF MS and VITEK®2 (Biomérieux, France)	S: Gentamycin, amoxicillin/clavulanate, piperacillin/tazobactam, cefuroxime, amikacin, ciprofloxacin, ertapenem, imipenem, meropenem, trimethoprim/ sulfamethoxazole, ceftazidime, cefixime, cefuroxime axetil, fosfomycin, nitrofurantoin, cefoxitin, ceftriaxone	Cefixime (8 mg/kg/ day) for 14 days	Recovery

Abbreviations: Yr, year; CA-ESBL, community-acquired extended-spectrum ß-lactamase; UTI, urinary tract infection; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; S, susceptible; R, resistant.

Table 3 Reported Cases of Osteoarticular Infections with *Raoultella ornithinolytica*

Authors	Year	Age (Yr)	Sex	Comorbidities	Diagnosis	Positive Sample	Identification Technique	Antimicrobial Susceptibility	Treatment	
Zheng et al[57]	2015	13	M	–	Wound infection (post-ORIF)	Wound fluid	16S rRNA gene sequencing	S: Ciprofloxacin, piperacillin/tazobactam R: Amikacin, ceftriaxone, imipenem, ertapenem, aztreonam, tobramycin, ceftazidime, gentamicin, ampicillin/sulbactam, cefepime	Debridement/drainage, trimethoprim/sulfamethoxazole	
Venus et al[70]	2016	68	F	Sickle cell disease Treated breast cancer	Septic arthritis of the knee	Articular fluid	MALDI-TOF	S: Amoxicillin/clavulanate, cefazolin, ceftriaxone, ciprofloxacin, gentamicin, trimethoprim/sulfamethoxazole	Knee irrigation and debridement	IV cefazolin (2 weeks) then oral ciprofloxacin (2 weeks)
Seng et al[69]	2016	67	M	COPD Peripheral artery disease Hypertension Bilateral hip prosthesis Plate osteosynthesis of a periprosthetic femur fracture	Prosthetic joint infection	Periprosthetic effusion	MALDI-TOF 16s rRNA gene sequencing	S: Amoxicillin/clavulanate, ticarcillin/clavulanate, ceftriaxone, ciprofloxacin, doxycycline, aminoglycosides, cotrimoxazole R: Amoxicillin, rifampin	Prosthetic exchange	IV ceftriaxone (1 month) and oral ciprofloxacin, then oral doxycycline and ciprofloxacin
Levorova et al[5]	2017	38	F	-	Septic arthritis of the temporomandibular joint	Articular fluid	Not specified	S: Amoxicillin/clavulanate, ampicillin/sulbactam, sulbactam, ciprofloxacin, cotrimoxazole, cefuroxime	Arthrocentesis	Amoxicillin and amoxicillin/clavulanate
Lam et al[6]	2018	85	M	Emphysema Hypertension Dyslipidemia Molar extraction	Mandibular osteomyelitis	Aspirate of the abscess	MALDI-TOF	S: Ciprofloxacin, trimethoprim/sulfamethoxazole, cefotaxime, piperacillin/tazobactam I: Cefazolin	Piperacillin/tazobactam (4 days) then amoxicillin/clavulanate (total of 1 month) then trimethoprim/sulfamethoxazole (2 months)	

Abbreviations: Yr, years; M, male; F, female; COPD, chronic obstructive pulmonary disease; ORIF, open reduction and internal fixation; rRNA, ribosomal RNA; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; S, susceptible; R, resistant; I, intermediate.

understand the clinical characteristics and risk factors of such infections in the ENT sphere.

Soft Tissue Infections

The first case of cutaneous soft tissue infection with *R. ornithinolytica* was reported by Solak et al (2011) in a patient with diabetic foot infection that presented with fever, weakness and a maculopapular rash.[9] The pathogen was isolated from a wound specimen and identification was done with the VITEK®2 system (Biomérieux, France).[9] The patient, who had diabetes, hypertension and chronic kidney disease (CKD), improved after being treated initially with piperacillin/tazobactam then tigecycline after antibiotic susceptibility testing reported that the strain was susceptible only to ertapenem, levofloxacin, and tigecycline.[9]

Another diabetic foot infection with *R. ornithinolytica* was reported later by Kabbara et al (2015) in a 68-year old male patient.[7] The patient's past medical history included hypertension, diabetes and CKD.[7] The pathogen was identified in cultures from the ankle wound,[7] was susceptible to amoxicillin/clavulanate, cefepime, ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, imipenem/cilastatin, piperacillin/tazobactam and TMP-SMX, and resistant to cefazolin.[7] The patient was thus successfully treated with amoxicillin/clavulanate.[7]

Furthermore, Khajuria et al (2013) identified a multidrug resistant strain of *R. ornithinolytica* in a perineal surgical site infection that was susceptible only to tigecycline and colistin.[44] It is worth noting that the surgical procedure in this patient was performed to repair a perineal injury with urethral rupture.[44] Another case of surgical site infection was recently reported in a 64-year-old male patient after an ileocecal resection.[50] The identified strain was susceptible to third generation cephalosporins and ciprofloxacin and the patient recovered adequately with appropriate antibiotic treatment.[50]

Although most soft tissue infections were reported in patients with comorbidities increasing their risk of infectious events, such as diabetes, a first case of surgical wound infection with *R. ornithinolytica* was reported in a 24-year-old healthy female patient after a bilateral breast reduction surgery.[74] In this case, *R. ornithinolytica* was present in a polymicrobial wound culture including *Escherichia coli* and *Enterococcus faecalis* as well, and was treated with bilateral debridement and antibiotic therapy.[74] Furthermore, Seng et al (2016) reported in their series 15 cases of skin and wound infection, with 8 cases being hospital-acquired.[1]

Intrathoracic and Respiratory Infections

Detailed cases of intrathoracic and respiratory infections with *R. ornithinolytica* are shown in Table 4. Boattini et al (2016) reported in a retrospective analysis 6 cases of pneumonia due to *R. ornithinolytica*.[67] Previous cases of pneumonia or pleural effusions, both community- and hospital-acquired, have also been reported.[1] Seng et al (2016) further described 1 and 2 cases of hospital-acquired pericarditis and mediastinitis respectively.[1] Sener et al (2011) published a case of fever of unknown origin in a 16-month-old female patient presenting as fever and persistent cough, in whom *R. ornithinolytica* was identified in bronchoalveolar lavage fluid.[13] Previous detailed cases depict patients with postoperative infections or admitted to the intensive care unit (ICU) with severe systemic alterations. The presence of respiratory infections with *R. ornithinolytica* in the community seems to be extremely uncommon especially in healthy immunocompetent individuals.

Bloodstream and Other Infections

In addition to previously mentioned reports, several cases of systemic infections with *R. ornithinolytica*, presenting mainly as bacteremia with a septic status, have been reported without a source being identified. Although recovery was achievable in many of these cases, death occurred in many of them and several reported cases were described in patients with malignant conditions or immunosuppression.

Kaya et al (2015) reported a case of febrile neutropenia with *R. ornithinolytica* bacteremia in a 37-year-old male patient with acute lymphocytic leukemia.[77] The clinical outcome in this case was fatal despite aggressive antibiotic combinations using piperacillin/tazobactam, amphotericin-B, tigecycline, amoxicillin/clavulanate and ciprofloxacin.[77] Seng et al (2016) reported 6 cases of bloodstream infection in his series.[1] A case of neutropenic fever was moreover depicted by Chun et al (2015) in a patient with a relapsed acute biphenotypic leukemia, that recovered after treatment with cefepime.[4] One previous case of postoperative bloodstream infection was reported in an American 51-year-old male patient after valve replacement surgery.[42] The isolated strain was susceptible only to amikacin and gentamicin and

Table 4 Reported Cases of Intrathoracic and Respiratory Infections with *Raoultella ornithinolytica*

Author	Year	Age (Yr)	Sex	Comorbidities	Diagnosis	Positive Sample	Identification Technique	Antimicrobial Susceptibility	Treatment	Clinical Outcome
Jellinge et al[75]	2017	48	Female	Subarachnoid haemorrhage Percutaneous dilatational tracheostomy	Unspecified	Tracheal culture	MALDI-TOF MS	S: Cefuroxime, gentamicin, ciprofloxacin R: Piperacillin/tazobactam	None	Recovery
Van Cleve et al[27]	2018	39	Male	Motor vehicle versus pedestrian trauma	Ventilator-associated pneumonia	BAL	Not specified	S: Amikacin, aztreonam, cefepime, ceftazidime, ceftriaxone, ciprofloxacin, gentamycin, imipenem, piperacillin/tazobactam, tobramycin, trimethoprim/sulfamethoxazole I: Ampicillin/sulbactam (LLL) R: Ampicillin/sulbactam (RLL), cefazolin	Ceftazidime and vancomycin then piperacillin/tazobactam (total of 12 days)	Recovery
		50	Male	MVC Atrial fibrillation Myocardial infarction Pacemaker COPD	Ventilator-associated pneumonia	BAL	Not specified	S: Amikacin, aztreonam, cefepime, ceftazidime, ceftriaxone, ciprofloxacin, gentamicin, imipenem, piperacillin/tazobactam, tobramycin, trimethoprim/sulfamethoxazole R: Ampicillin/sulbactam (RLL), cefazolin	Ampicillin/sulbactam then cefepime (total of 9 days)	Recovery
Papakanderaki et al[76]	2018	75	Male	NSCLC Left lower lobectomy Smoking (100 pack/years)	Pulmonary infection	Sputum	Not specified	Not specified	Meropenem then ciprofloxacin	Recovery

Abbreviations: Yr, year; MVC, motor vehicle collision; COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; BAL, bronchoalveolar lavage; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; S, susceptible; I, intermediate; R, resistant; LLL, left lower lobe; RLL, right lower lobe.

the outcome was fatal.[42] Yamakawa et al (2016) described 2 cases of *R. ornithinolytica* infection in pediatric patients in whom *R. ornithinolytica* was detected in blood culture samples.[8] Patients were 3 and 7-year-old and had IgA-nephropathy and myeloid leukemia respectively.[8] In the first case, antibiotic susceptibility testing reported susceptibility to ceftriaxone, amoxicillin/clavulanic acid and TMP-SMX, and resistance to ciprofloxacin, minocycline and fosfomycin.[8] In the second case, the isolated strain was susceptible to meropenem, minocycline and amoxicillin/clavulanic and resistant to levofloxacin, piperacillin and TMP-SMX.[8] Treatment consisted of ceftriaxone (2 weeks) and meropenem (17 days) respectively with clinical improvement in both cases.[8] Abbas et al (2018) reported a case of neonatal sepsis with a multidrug resistant strain of *R. ornithinolytica* isolated in blood cultures of a 12 hrs-old infant. The strain was susceptible only to colistin and TMP-SMX.[78] Clinical improvement was noted with colistin.[78] Moreover, *R. ornithinolytica* was isolated from blood samples of a preterm infant ventilated for hyaline membrane disease.[79] The identified strain harbored the $bla_{\text{NDM-1}}$ gene but remained susceptible to ciprofloxacin, colistin and tigecycline.[79] A first case of associated septic shock, multisystem failure and purpura fulminans was also described in a newborn female infant.[80] *R. ornithinolytica* was isolated from blood cultures and showed susceptibility to aminoglycosides, carbapenems, cefepime, quinolones and TMP-SMX.[80] Despite aggressive treatment with meropenem, netilmicin, combined hemodynamic and respiratory support, the patient died at an age of 19 days.[80] It is worth noting that the patient in this case was preterm and delivery occurred via caesarean section due to oligohydramnios.[80] The significance of these factors in the pathogenesis of *R. ornithinolytica* infections remains unclear as data with infants is scarce.

A few cases of catheter infection and catheter-related bloodstream infections have also been identified.[1,81] Among the bloodstream infection cases reported by Chun et al (2015), 5 cases had positive cultures from central lines for *R. ornithinolytica*.[4] All these patients had malignant conditions and one of them died despite treatment.[4]

Other isolated cases of vascular prosthesis infections, conjunctivitis and meningitis due to *R. ornithinolytica* were described.[1] Because of the rarity of these presentations, potential risk factors and prognosis predictors could not be identified.

Conclusion

In conclusion, *R. ornithinolytica* is an emerging bacterium in human infections. While formerly known as a relatively harmless pathogen found in aquatic environment and soil, its involvement in some severe clinical human infections we have described sheds light on a potentially increasingly virulent pathogen that affects comorbid at-risk patients. Its proper identification remains challenging and could explain why *R. ornithinolytica* infections are under-reported, although newer technologies and testing methods are allowing more accurate isolation and recognition of *Raoultella* species. Nonetheless, although the majority of reported cases are susceptible to standard antibiotic regimens, the emergence of multi-drug resistant strains may pose a serious risk to debilitated patients, and thus requires due consideration to further prevent increased virulence, especially in frail individuals.

Disclosure

The authors report no conflicts of interest in this work.

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