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Raoultella Infections from Clinical to Laboratory- Update & Literature review

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ABSTRACT

The genus Raoultella is yet understudied in comparison with other Enterobacteriales members. However, there are various distributed case reports on Raoultella infections. The genetic similarity among Raoultella spp. and Klebsiella spp. perhaps cause to misidentification using conventional microbiology methods. The prevalence of this bacterium in clinical service can shift geographically. Our knowledge of its resistome evolution contributing to Raoultella antibiotic resistance is restricted to a scanty characterized genetic determinates, too. This review summarizes the current understanding on Raoultella genetic and microbiology aspects, its identification methods, virulence factors, clinical manifestations, and so on. This combined data significant the crevices in our understanding of Raoultella pathogenesis, resistome, and vaccine recommending for future investigating purposes. The diversity and plasticity of the antibiotic resistance plane of Raoultella species have determined the early and accurate identification of Raoultella infection is exceptionally necessary to progress the guess of the clinical infections and to control the spread of this bacterium. According to our literature review results, patients with multiple congenital abnormalities are susceptible to Raoultella infection. Some risks prone to infection include tumors, human immune system disorders, and invasive surgeries.

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1. Introduction

Raoultella genus is a gram-negative, rod-shape, encapsulated, biofilm forming, non-motile, facultative anaerobic bacterium that currently comprise within *Enterobacteriales* (1). The Klebsiellae tribe, subfamily "*Klebsiella* clade" includes the genera *Klebsiella, Raoultella, Kluyvera, Pluralibacter, Trabulsiella,* and *Yokenella* (2,3).

It being found in plants, water and soil, and are known to colonize humans and animals. *Raoultella* is a histamine-producer that causes fish poisoning (4). *Raoultella* changes histidine to histamine as the etiology of histamine poisoning via cutaneous flushing, or as the "scombroid syndrome" related due to fish poisoning (5).

Two species R. *ornithinolytica* and R. *planticola* are mainly isolated from human specimens. But R. *terrigena* and R. *electrica* are rarely isolated from clinical human specimens. *Raoultella planticola* can exist in animal mucus membranes (https://lpsn.dsmz.de/genus/*Raoultella*). The typical reservoirs of R. *planticola* are the upper respiratory tract and the gastrointestinal tract (6,7).

Raoultella spp. are opportunistic bacteria that generally begin infections. The first report of *Raoultella* human infection [1984, France] was in a patient with sepsis (8).

As the late 2000s there has been an excess in case reports of human *Raoultella* infections. Some authors are suggesting that *Raoultella*

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species are rare and/or emerging pathogens rather than underdiagnosed (9-11).

Most strains of Raoultella on solid media grow in the form of mucous colonies, which is related to forming polysaccharide capsules (12) (Fig1).

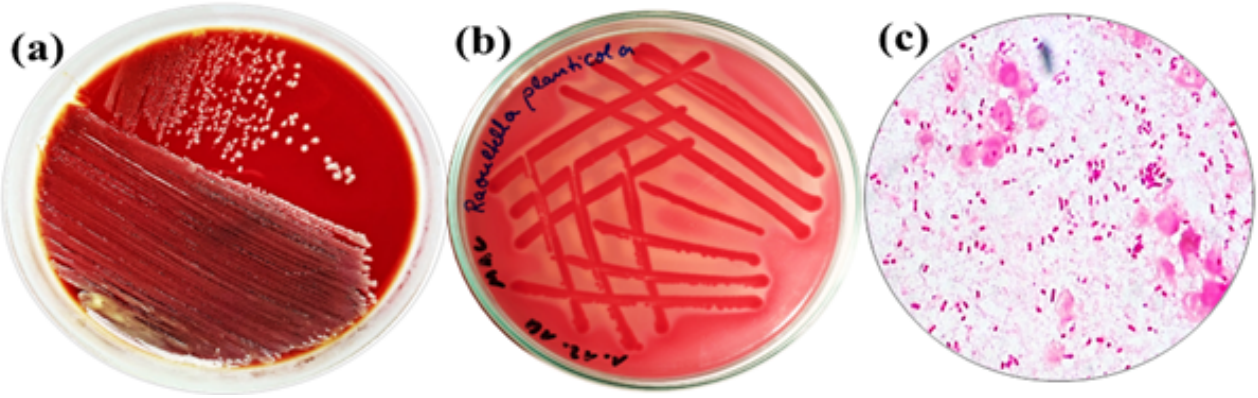

Figure1. (a) R. terrigena circular, smooth, glistening, light yellow, and non-hemolysis colonies on sheep blood agar (13). (b) Mucoid, lactose-fermenting colonies of R. planticola on Mac Conkey agar (Wikimedia, commons.wikimedia.org/wiki/File:Raoultella_planticola_MacConkey_colonies). (c) Gram-negative bacilli of R. ornithinolytica (Gram staining, 10 × 100 magnification

The purpose of this review is to summarize the literature about microbiology aspect, clinical manifestations, diagnostic methods, biotechnology applications, and antibiotic therapy aspects of Raoultella species based on published reports until now.

2. Clinical Manifestations & Epidemiology

Raoultella is considered as an opportunistic pathogen for human (13). *Raoultella planticola* is involved in severe infections e.g., bloodstream, upper gastrointestinal (GI), pancreatitis, peritonitis, cholangitis, cellulitis, pneumonia and lung abscesses, meningitis, cerebral abscess, mediastinitis, pericarditis, conjunctivitis, mandibular osteomyelitis, otitis, surgical site infections, urinary tract infections, and sepsis following the consumption of seafood (14-16).

Raoultella ornithinolytica can cause pneumonia, biliary or urinary tract infections and bacteremia and similar episodes are being increasingly reported (17,18).

Literature review data that presented at Table1 indicate the high rate and extended wide infections for *Raoultella* species. One reason/hypothesis for this issue has been supported by Yokota et al. [Japan, 2012] report that R. *planticola* colonizes the gastrointestinal tract and converts a potential origin of infection (19). Atici S et al. [Turkey, 2017] were isolated *Raoultella terrigena* as causative agent of subungual abscess in an infant (20).

Although R *planticola* is mainly an aquatic and soil bacterium, it has been clinically isolated from human sputum, stool, wound, blood, discharges, and urine (21). The epidemiology of *Raoultella*-infections incidence might be underestimated (22). The actual incidence of R. *planticola* infections is complex to approximate because of misidentification and underreported cases (23).

The infection via R. *planticola* is correlated with either immunosuppression conditions, for example neoplasia, cancer, chronic renal disease, and diabetes mellitus, or invasive procedures and trauma (24,25).

For example, UTIs by *Raoultella* species occur in immunocompromised, oncological, instrumented or basic urological patients (26). There were 363 cases of R. *terrigena* contamination between 1988 and 2021. The mortality of this disease is approximately 44%, and in 38.6% of cases, R. terrigena, has an MDR anti-microbial affectability profile (13).

The species *Raoultella ornithinolytica* determined in 2011 is an emerging bacterium in urogenital tract infections (27).

Raoultella ornithinolytica, have been suggested as opportunistic pathogen that usually infect elderly patients with immunosuppression or co-morbidities, especially solid tumors (28).

Raoultella planticola is considered to have more virulencity than the other species, and it is related to with a higher attribute mortality rate (22).

Table 1. Examples of Raoultella spp. associated with human infections

Species	Human infections	Location / Time/ Numbers of cases	Underlying diseases	Ref
R. planticola	• Cardiac implantable device infection	France (2017) / A case	Immunocompromised	(14)
	• Pneumonia	Korea (2015) / A case	Smoking history	(29)
	• Cholangitis & Sepsis	Italy (2014) / A case	COPD & bronchiectasis	(30)
	• Pancreatitis	Brazil (2007) / A case	----------	(31)
	• Pancreatic pseudocyst	Brazil (2016) / A case	Alcoholic pancreatitis	(32)
	• Gastroenteritis	Spain (2013) / A case	Hypercholesterolemia, Pituitary adenoma	(33)
	• Urinary tract infection	USA (2018) / A case	IgA Nephropathy	(34)
	• Soft-Tissue Infection	Ireland (2010) /A case	----------	(35)
	• Necrotizing fasciitis	Korea (2012) / A case	Cardiovascular disease, DM	(36)
	• Conjunctivitis	Malta (2016) / 4 cases	Cataract surgery, scratching with twig	(37)
	• Prostatitis	Greece(2014) / A case	Renal allograft recipient	(38)
	• Osteomyelitis & Epidural abscess	USA (2017) / A case	DM, Hypertension, Hyper- lipidemia	(39)
	• Pelvic cellulitis	Germany (2018) / A case	Neutropenic patient	(40)
	• Bacteremia & Sepsis	Florida (2017) /A case	Cirrhosis	(41)
R. ornithinolytica	• Catheter-related bacteremia	Spain (2017) / A case	Pancreatic cystic neoplasm	(42)
	• Conjunctivitis	France (2016) / 4 cases	----------	(43)
	• Enteric fever-like syndrome	Spain (2009) / A case	Arterial hypertension & DA	(44)
	• Skin/wound infection	France (2016) / 2 cases	----------	(43)
	• Pericarditis	France (2016) / A case	----------	(43)
	• Pneumonia	Turkey (2011) / A case	A 16-month-old female child	(45)
	• Diabetic foot infection	USA (2017) / A case	DM, Hypertension, CKD	(46)
	• Prosthetic joint infection	France (2018) / A case	----------	(47)
	• Pansinusitis	USA (2017) A case	Hypertension, poor hygiene life style	(48)
	• Urinary tract infection	France (2016) / 6 cases	----------	(43)
	• Post-ERCP acute cholangitis, Sepsis	UK (2007) / A case	AHT, obesity	(49)
	• Gastrointestinal infection	France (2016) / 15 cases	----------	(43)
R. terrigena	• Fatal Endocarditis	USA (2007) / A case	Liver transplantation, HCV	(50)
	• Urinary tract infection	Turkey (2015) /A case	Premature newborn	(51)
	• Endocarditis & Sepsis	UK (2011) / A case	Pancreatic cancer	(52)
	• Skin (n=4) & UTI (n=4)	Tunisia (2021) / 8 cases	HSCT recipients	(53)
	• Subungual Abscess	China (2016) / A case	Washing the thumb wound by river water	(54)
	• Fulminant sepsis	Pakistan (2019) / A case	Uncontrolled diabetes	(55)
R. electrica	Not founded any report of human infection due to R. electrica			(56, 57)

Abbreviations: COPD; Chronic Obstructive Pulmonary Disease, DA; degenerative arthropathy, IgA; Immunoglobulin A, DM; Diabetes Mellitus, HSCT recipients; Hematopoietic Stem Cell Transplant recipients, CKD; Chronic Kidney Disease, ERCP; endoscopic retrograde cholangiopancreato-graphy, AHT; arterial hypertension.

Raoultella terrigena is an opportunistic pathogen with a high level of mortality (44%), which may lead to an infection handle with the endogenic source (fecal and bile) as well as an exogenic source (water, drain, and soil) additionally may be related with healthcare-associated infections. However, it is not clear might the R. *terrigena* be a portion of the typical microbiota of the human digestive system or its asymptomatic carriers of the pathogen (13).

The gastrointestinal infections with *Raoultella* are often occurred in individuals with an altered immune system either by a malignant condition, endoscopic procedure, enteral feeding tubes, or a chronic disease(18).

According to some studies, *Raoultella* is able to survive in a domain of hospital environments through developing resistance to disinfectants (58). In study of Zadoks R and et al, [New York, 2011] on dairy farms has been showed that R. planticola was the most frequent species among isolates from soil and feed crops (59).

So, these environmental resources are involved in the epidemiology of *Raoultella* species infections. According to the molecular epidemiology studies by 16s-rRNA analysis, it is confirmed that the prevalence of these organisms in clinical settings can vary geographically (60).

3. Genome structure

It is noteworthy that *Raoultella* was initially part of the genus *Klebsiella*, in 1981(61), but later re-classified based on the 16s-rDNA sequence and the *rpo* B, *gyr* A, and gyr B genes , in 2001 (62).

Although, the phylogenetic evidence was weak; the genus *Raoultella* did not seem monophyletic in the phylogeny of the partial *rpo*B sequence. Recently, several studies have been performed on *Raoultella* genome structure. Huang YT and et al, [Taiwan-USA, 2018] were sequenced the complete genome of a human clinical isolate *Raoultella planticola* GODA strain (63).

This isolate the genome size, G+ C content, and CDSs was possessed 5,592,163 bp, 55.4%, and 5,461, respectively. The genome of *Raoultella ornithinolytica* strain Marseille-P1025 comprises the chromosome size, G + C %, and CDS content were 5,644,584 bp, 55.6% and 5,260, respectively. In this strain no putative plasmid sequence was detected (47).

In study of Xu S and et al, [China, 2019] the whole genome of Raoultella sp. strain X13 has been sequenced (64). The circular chromosome comprises 5,404,711 bps, which correspond to 4375 protein-coding genes, 1 microsatellite sequence, 74 minisatellite sequences, 25 rRNA genes, and 85 tRNA genes with an average G + C content of 55.94%. Also, the plasmid of *Raoultella* sp. strain X13, possesses 43,768 bps with an average G + C content of 34.90 %.

In another research Fazal MA and et al, [UK, 2019] sequenced the chromosome of R. *terrigena* strain NCTC 13097. This strain has two contigs of 5,574,669 bp, with a GC content of 57.3%. There were 5,386 CDS genes, 84 tRNA genes, and 25 rRNA genes (65).

The genomic diversity and mechanisms of pathogenesis underlying the molecular evolution of this bacterium have not yet been thoroughly investigated (66).

A whole-genome sequencing by Schicklberger M and et al [USA, 2015] on R. *terrigena* R1Gly was performed.

In their study, they found that the draft genome sequence revealed a 5.7-Mb genome with 57.84 mol% GC content, which is comparable to those of the diazotrophs R. *planticola* (5.8 Mb; 55.4 mol%) and R. *ornithinolytica* S12 (5.5 Mb; 57.47 mol%) as well as the non-diazotrophs R. *ornithinolytica* B6 (5.3 Mb; 55.75 mol%) and R. *ornithinolytica* TNT (5.6 Mb; 55.5 mol%) (67).

4. Pathogenicity, Virulencity

Raoultella is not a highly virulent pathogen. This bacterium can colonize in gastrointestinal and oropharyngeal tracts of adults and newborns (68). The virulence factors of *Raoultella* are thought to be similar to the ones of Klebsiella species due to their phylogenic similarities, however, no such correlation was found in-vivo (69).

Multiple factors can involve in the pathogenesis of diseases arising from the genus of *Raoultella*. These factors include lipopolysaccharide (LPS) (O-antigen), polysaccharide capsule (CPS) (K-antigen), fimbriae, siderophores, toxin, hydrolytic enzymes and bacteriocins (70, 71).

The hemagglutinins, type 1 & type 3 fimbriae, siderophores, enterobactin and occasionally aerobactin are shared between R. *planticola*, R. *terrigena*, and even K. *pneumoniae* (72).

Mannose-sensitive haemagglutination (MSHA) and type 3 pili (MR/K-HA) were observed in some of R. *terrigena* isolates similar to K. *pneumoniae* (73). The polysaccharide capsule is considered a major virulence factor of R. *planticola* (Fig 2) (74).

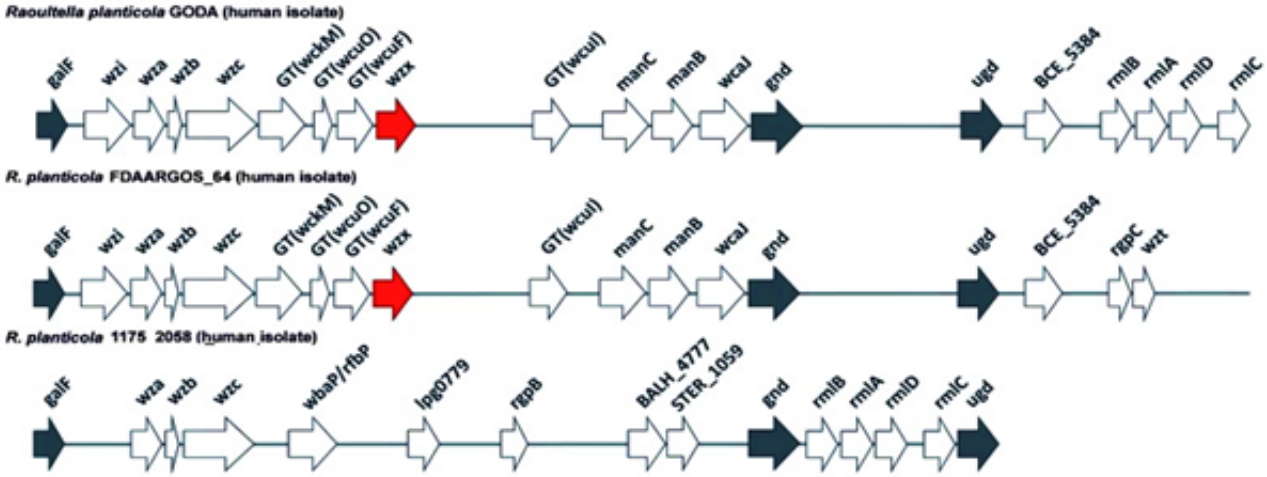

Figure 2. The genetic diversity in the cps gene cluster of several Raoultella planticola strains. Gene clusters are shown in gray. Strain specific wzx genes are marked in red color. GT: glycosyltransferase. [Huang YT & et al, Taiwan-USA; 2018]63

LPS fatty acids profiles of K. *oxytoca*, R. *terrigena*, R. *planticola*, and "K. *trevisanii*" strains were very identical and differed from that of the K. *pneumoniae* strain by higher levels of dodecanoic acid (approximately 5-6 times) and absence of 2-hydroxytetradecanoic acid (75). This obtained data indicated more close relatedness of K. *oxytoca*, R. *terrigena*, and R. *planticola* and some their remoteness from K. *pneumoniae*. In particular, R. terrigena expresses a smooth-LPS (S-LPS), Two major factors of virulence, capsular polysaccharide and LPS-O antigen, are involved in mucosal colonization and the development of infections by *Raoultella* (76).

Also, these species can form biofilm (77). The ability to form biofilms, will help us better understand the relationship of *Raoultella* species human infections (e.g., R. *ornithinolytica*) with invasive procedures e.g., implantation of venous catheters, intra-vascular prostheses or orthopedic devices. R. planticola pathogenicity and occurrence should be known by clinicians and a high level of awareness is necessary to precisely identify it provide the correct antibiotic regimen (14).

The ability of R. *ornithinolytica* to adhere to human tissues and to form biofilms in urinary catheters is an important issue (78). These two mechanisms could exhibit a role in the pathogenesis of bone and joint infections caused by R. *ornithinolytica*.

The strain R. *ornithinolytica* WM1 encoding the type I fimbriae, *Escherichia coli* common pilus, type II & VI secretion systems, yersiniabactin, enterobactin, and surface polysaccharide (66). A genomic island (RoGI) was determined in *Raoultella ornithinolytica* strain Marseille-P1025 that isolated from chronic prosthetic joint infection in an immunocompetent illness. This genetic island was specific for R. *ornithinolytica* strains (47). RoGI was presumably obtained via lateral gene transfer from a member of the *Pectobacterium* genus and harbored for a type-IVa SS. It is detected in other pathogenic bacteria and maybe has a role in the virulence and pathogenicity of R. *ornithinolytica* strains. According to several research studies, it is noteworthy that numerous similarities via K. *pneumoniae* and R. *planticola* bacteremia; the biliary tract was a route of entrance in a large portion of cases, and was usual in elderly patients via malignancies (79).

5. Laboratory diagnostic methods

According to the remarkable increase in the frequency of *Raoultella* spp. isolating from clinical samples, it perhaps be related to introduction of methods, which allow for reliable identification of these bacteria assigning them to particular genus and species (80, 81). A retrospective research on 240 blood samples from the collection of the Ramón y Cajal University Hospital laboratory in Madrid [Spain, 2015], via bacteria of the *Klebsiella* genus seen, appeared that 11 of them really included of *Raoultella* genus (28).

A few reports indeed propose that about 20% of *Raoultella* species are misdiagnosis as *Klebsiella* (usually K. *oxytoca*) (82). Also, R. *ornithinolytica* infections in humans perhaps underestimated because that this microorganism is hard to distinguish utilizing phenotypic detection tests. An extended range of different clinical samples have been used for culture and isolation of *Raoultella* species such as bronchoalveolar and lavage fluid samples,

urine, stool, wound, discharges, sputum, blood, and so on.

5. 1 Biochemical tests

The three species belong to the Raoultella genus maybe be distinguished based on their characteristic biochemical profiles¬(71) (Table2). However, no distinct morphological, physiological, or biochemical phenotype between *Klebsiella* and *Raoultella* has been proved yet (1). Drancourt M and et al. [France, 2001] characterized that growth at 10°C can be the hallmark of the genus *Raoultella* (62).

Raoultella planticola and R. *terrigena* are regularly misidentified as K. *pneumoniae* or K. *oxytoca*; as a result, knowledge on their clinical importance stays poor (note that the validity of genus *Raoultella* that was suggested for the two pervious species, has been challenged).

Table 2. Metabolic characteristics of Raoultella & Klebsiella

Reaction	Raoultella	Klebsiella
Catalase	+	+
Oxidase	-	-
Ferment glucose	+	+
Ferment lactose	+	
Ferment lactose at 44.5 °C	+(Without gas)	
Ferment L-sorbose	+	
Nitrate reduction	+	+
Pigment production δ	+	
Lysine decarboxylase	+	+
Ornithine decarboxylase	-a	-
Histamine production	+	-
Indole	-/+b	-/+c
2, 3-butanediol	+	-/+ d
Malonate	+	
Growth at 10 °C	+	-e

Symbols: (+) positive, (-) negative, (-/+) variable reactions, respectively. € K. oxytoca indole Positive. a Except with R. ornithinolytica (72, 83). b R. planticola indole variable. δ Pigment Production on gluconate-ferric citrate agar.d K. pneumoniae subsp. pneumoniae & K. oxytoca Are VP (+).e K.

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5.1.1 API® (analytical profile index) test strip

The API20E system (bioMérieux) may be a standardized distinguishing system for *Enterobacteriales* and other non-fastidious, gram-negative rods which utilizes 21 miniaturized biochemical tests and a database (84). It is named a modified way for same-day enterobacterial identification.

In the study of Appelbaum P and et al. [Maryland, 1982] two usual methods, API 20E & Micro-ID, have been evaluated for Enterobacterales members (85). API during 5 hours distinguished 78.5% of strains to species, 9.5% to genus just, 10.1% as a portion of a range of identifications (SI), and 1.9% incorrect. Micro-ID at 4 hours resulted 90.0% accurate identification to species and 3.3% to genus only, 4.0% SI, and 2.7% incorrect.

API identification of many *Serratia*, *Citrobacter* and *Providencia* strains was to genus only; most incorrect outcomes happened in *Serratia marcescens*. Park J and et al. [2011] appraised the potential of three phenotypic systems (VITEK 2 GN ID card, MicroScan Neg Combo 32 panel,& API 20E) to determine R. *ornithinolytica* in comparison via the genotypic methods on 114 clinical isolates (86).

Their outcomes appeared that VITEK 2 determined all of them as R. *ornithinolytica* (26 isolates). MicroScan and API identified 25 isolates (92.6%) and 24 isolates (88.9%) as K. *oxytoca*, respectively. These isolates were ornithine decarboxylase (ODC) negative in all three phenotypic systems. MicroSeq 500 identified 24 isolates (88.9%) as R. *ornithinolytica*. As the final result, MicroScan & API requires extra biochemical tests to distinguish among ODC-negative R. *ornithinolytica* with K. *oxytoca*.

5. 2 Molecular Genetics Methods

The evaluating of 16s rRNA (16s ribosomal RNA), *rpo*B gene (RNA polymerase subunit B) or *hdc* gene (histidine decarboxylase), also the attendance of *blaORN, blaPLA*, and *blaTER* genes may be a substitute to the biochemical identification of *Raoultella* species in the laboratory (28,62,87).

Also, sequencing three housekeeping genes include rpoB, *gyr*A (DNA gyrase subunit A), and *par*C (DNA topoisomerase 4 subunit A) with phylogenetic analysis can be useful for accurately taxonomic identifying and species-level discriminating the *Klebsiella*/*Raoultella* complex (66). In study of Granier S and et al, [France, 2003] R. *ornithinolytica* strains can be distinguished from K. *oxytoca* bacteria via ERIC-1R PCR method (Enterobacterial Repetitive Intergenic Consensus1R PCR) (88).

Kovtunovych G and et al, [Ukraine, 2003] used a PCR way for *pehX gene* of K. *oxytoca* strains, to differentiate this species from *Raoultella* bacterial genus (89).

Enterobacterial isolates of *Raoultella* spp. present a penicillinase-related β-lactam resistance pattern proposing the presence of a chromosomal *bla* gene. PCR and gene sequencing of highly-specific chromosomal class A β-lactamase genes (bla¬PLA;1123bp, *bla*¬ORN;1128bp)as the reference identification methods have been stablished by Ponce-Alonso M and et al (28,90).

They displayed, the 16s-rRNA sequencing provides no certain outcomes, as this method is not capable to differentiate among *Klebsiella* and *Raoultella* genera. The bla gene amplification technique can be utilized to distinguish these species from together.

Also, the *rpo*β-sequencing analysis can correctly identify *Raoultella* isolates with high specificity (28). But, the 16s-rRNA has not the suitable selectivity because of the high homology among the correspondent sequences of both *Klebsiella* and *Raoultella* genera (86).

5.3 Semi-automated/Automated identification systems

Nowadays, the clinical microbiology laboratories are strongly required for the quick and valid detection of microorganisms due to the importance of timely corrected chemotherapy. But, routine strategies are in some cases questionable and appear doubtful results. Nowadays, the automated and semi-automated identification sets (e.g., VITEK®2 systems, BD Phoenix™, VITEK®MS, Bruker Biotyper, Sensititre ArIS 2X) can provide the capability to upgrade sick care, shorten length of stay and decrease health care costs (91).

A) VITEK®-2 compact system

The Vitek® 2 (bioMérieux, Marcyl'Etoile, France) system is a fully automated system that does bacterial identification and antibiotic susceptibility plan. A fluorogenic technique for organism identification and a turbidimetric methodology for susceptibility testing has been applied (92).

The Vitek2 ID-GN card (gram-negative bacillus identification card) identifies 154 species of *Enterobacteriaceae* and a select group of glucose non-fermenting gram-negative bacteria during 10 hours. Vassallo J and et al.,[Malta, 2015] reported four cases of R. *planticola* conjunctivitis from the conjunctival swabs that were obtained in their institution from patients with purulent discharge from one or bilateral eyes (37). A comparative study by Alegría Puig C and et al., [Spain, 2019] has been done on 97 clinical isolates of *Raoultella* species. They have done identification of R. *ornithinolytica* and R. *planticola* by MALDI-TOF MS systems (Vitek MS and Bruker Biotyper) with Vitek2 and API20E systems (93).

The clinical collection isolates of *Raoultella* species were identified with Vitek MS, in parallel via Vitek2 and API, and finally with Bruker Biotyper. Among the two most widely used MALDI-TOF MS platforms, results obtained with Vitek MS were slightly superior to those acquired with the Bruker Biotyper system, with sensitivities and specificities of 98.9/57.9% and 98.8/37.0%, respectively. Also, API galleries permitted genus identification for about 18 (19.7%) isolates.

The MALDI-TOF based Vitek-MSTM system is faster and more efficient than the Vitek2 system or API20E galleries for reliable identification of R. *ornithinolytica* and R. *planticola*. However, Vitek 2 is almost as reliable as Vitek-MS for identification of genus *Raoultella*, it needs 24 hours until results are available. Finally, API galleries do not assign correct identification at the species level of most clinical isolates of R. *ornithinolytica* and R. *planticola*.

The Vitek 2 system (BioMérieux) had five biochemical discriminating tests that can identify ODC-negative R. *ornithinolytica* isolates, but this technique had to be confirmed by molecular identification by 16s-rRNA gene sequencing due to the lack of specificity (43).

B) BacT/ALERT® culture system

BacT/Alert (bioMe´rieux,Marcyl'Etoile, France) is a fully automated continuously monitored blood culture system for detecting bacteria and fungi from all of the sterile body fluids. The colourimetric technology and sophisticated algorithms minimize false-negative results for it (94).

The specialized liquid emulsion sensors (LES) at the bottom of each culture bottle visibly change colour when the pH changes due to the increase in CO2 gas as it is made with microorganisms. Chun S and et al., [2014, Korea] diagnosed 20 cases of R.*planticola* bacteremia (22).

They isolated microbes from blood culture-positive specimens by utilizing the BacT/ALERT culture media system. However, microbe identification and antibiotic susceptibility tests were done applying the automated VITEK 2 system accompanied via conventional bacteriologic techniques. All isolates were

determined via a probability score exceeding 96% with VITEK 2 system.

C)Phoenix automated microbiology system

The BD-Phoenix™automated identification and susceptibility testing system (BD Diagnostic Systems, Sparks, MD) for the identification (ID) & antimicrobial susceptibility testing (AST). It can analyze up to 100 combination ID and AST panels simultaneously. The time required to get a perfect set of ID & AST results varies around 8 to 12 h and is dependent on the bacteria tested (95).

Both growth-based and enzymatic substrates are applied to support the various kinds of reactivity in the range of taxa. The Phoenix AST technique is a broth based microdilution test. Yan Y and et al. [China, 2011] found 2 Raoultella species that were determined as K.

oxytoca by BD-Phoenix ID system, have been identified as *Raoultella* species by MALDI-TOF MS (96). The BD-Phoenix system exhibits complex issues, e.g., that of R. *planticola* not being included in its database. To date, MicroScan and BD Phoenix systems are able to identify R. *ornithinolytica*, but not R. *planticola* or R. *terrigena* (97).

5. 4 MALDI-TOF Mass Spectrometry

Matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS) method has been utilized for identification of bacterial isolates, illustrated in general great execution within the recognizable of gram-negative bacilli (98), and can correctly identify and differentiate *Klebsiella* from *Raoultella* spp. Initial reports displayed some misidentifications, but supplementation of databases should improve efficiency (99). Therefore, MALDI-TOF mass spectrometry is reliable in identifying the genus *Raoultella* (100).

In research of Jong E et al., [the Netherlands,2013] 99 clinical isolates formerly determined as *Klebsiella oxytoca* that identified

again with MALDI-TOF MS. According to their results, eight isolates were identified as *Raoultella* spp. (8.08%) (101).

In the study of Jong E and et al., a minimum difference of 10% among the top score with next closest scores was needed for individual isolates (referred to as the 10% differential rule in MALDI-TOF). Martiny D and et al. [Belgium, 2012] found one R. ornithinolytica isolate and also one R. *planticola* isolate that could not be detected via VITEK or the Saramis (Axima Assurance-Saramis database; bioMérieux) MALDI-TOF-MS system, but were correctly determined via the Bruker MALDI-TOF MS system to the species and genus levels, respectively (102).

6.Antibiotic therapy & Resistome

The notification of the clinicians with respect to the study of disease transmission and susceptibility levels of *Raoultella* is of the most extreme significance. *Raoultella* species presented intrinsic resistance to ampicillin (similarly to some *Klebsiella* spp.) because of chromosomally encoded beta-lactamase enzymes (18).

Species from both *Raoultella* and *Klebsiella* genera are intrinsically resistant to penicillins because of the expression of an Ambler class A β-lactamase: LEN-1 or SHV-1 in K. *pneumoniae*, K1 in K. *oxytoca*, and PLA-1, ORN-1, and TER-1 in R. *planticola*, R. *ornithinolytica*, and R. *terrigena*, respectively (103).

In addition to the intrinsic resistance determinants, the acquisition and circulating of the antibiotic resistance genes (ARGs) among all of the bacteria help to the development of the "resistome" of bacteria (Table3).

Table 3. The antibiotic-resistance determinants have been published by studies in our literature review

R. planticola	R. ornithinolytica	R. terrigena	ESBL	Ref
blaCTX-M-9 group			+	(105)
	blaIMP-4 + blaKPC-2		blaTEM-1 , blaSHV-12 , blaOXA-1	(110)
	blaOXA-48 α		-	(111)
	blaNDM-1 + blaCTX-M-3, bla TX-M-14		+	(112)
blaIMP-8 *			-	(113)
blaKPC-3, blaKPC-2 (2 isolates)	blaKPC-3 (1 isolate)		blaTEM-1 , blaSHV-7	(114)
	blaOXA-162, blaOXA-1		blaTEM-1 , blaSHV-5	(115)
	blaNDM-1 + blaKPC-2 µ		ND	(116)
blaOXA-48			-	(106)
		**		

Symbols:* Plasmidic carbapenemase, αThe blaOXA-48-like gene has been found related via Tn1999 in Enterobacteriales. µ Both of these genes were harbored on a different plasmid. **Any molecular genetic epidemiology study of the Antibiotic resistance genes has not been published for R. terrigena until October 2021. ND; not determined.

This resistance evolution occurs among *Raoultella* species, too. *Raoultella planticola*, similar with other *Raoultella* species, carries a chromosomal b-lactamase that makes this agent naturally resistant to multiple antimicrobial agents (31). However, until now, antimicrobial resistance (AMR) of *Raoultella* that causing human infections has not been analyzed systematically. In study of Chen X and et al, [China, 2020] all of the four cases of neonatal septicemia that caused by R. *planticola* strains were only sensitive to amikacin, but resistant to other groups of drugs: cephalosporins (e.g., cefazolin, cefotetan, etc.) and penicillins (e.g., ampicillin-sulbactam, piperacillin, etc.), and even developed resistance to carbapenem (104).

Most, not all, of the case reports include of *Raoultella* species that encoding extended spectrum β-lactamases (ESBLs) and carbapenemase genes have been from Europe and the USA regions (105).

The antibiotic susceptibility of R. *planticola* has not been completely explored, however. Most researches have displayed that R. *planticola* strains are frequently susceptible to third or fourth generation cephalosporin, β-lactamase inhibitor combinations (e.g., amoxicillin-clavulanic & piperacillin-tazobactam), aminoglycosides (AGs), netilmicin, ciprofloxacin, levofloxacin, tigecycline and carbapenems. Although, R. *planticola* can acquire plasmid-mediated antibiotic resistance (9). Also, several studies have reported isolates of R. *ornithinolytica* and R. *planticola*, which are resistant to carbapenem and carry different carbapenemases, including *blaKPC*, *blaOXA*-48, and *blaOXA*-162 genes (106). In the report of Castanheira M et al, has been displayed that all patients with infections due to KPC-producing *Raoultella* infections have been received antimicrobial therapy with carbapenems that could have facilitated selection of *Raoultella* strains resistant to these agents (107).

Eminently, broad utilization of third-generation cephalosporins and other β-lactam antibiotics in the past decades has led the appearance of third-generation cephalosporin-resistant bacteria (e.g., *Raoultella*) that generate ESBLs and AmpC β-lactamases that are, respectively, harbored via plasmids and chromosomes (108, 109).

However, MDR strains of *Raoultella* have been explained, producing a diversity of β-lactamases (Ambler class A, B and D), including SHV-, TEM- and CTX-M-type ESBLs and these bacteria have been presented as potential sources for carbapenemase and colistin-resistance genetic determines (10). In study of Whang S and et al, [China, 2019] were report that the presence of conjugative *bla*NDM-1 and blaCTX-M plasmids in R. *ornithinolytica* isolates from healthy humans, which determine the possibility of inter-species transfer of drug resistance genes (117).

According to the diversity and plasticity of the antibiotic resistance plane of *Raoultella* species, so early and accurate identification of *Raoultella* infection is exceptionally necessary to progress the guess of the clinical infections and to control the spread of this bacterium.

7.Biotechnology applications

7. 1 R. terrigena against root-knot nematodes

Today, *Raoultella* terrigena is considered as biocontrol agents against root-knot nematodes (anti-parasitic activity). Li GJ and et al., [China, 2014] discovered the nematicidal effect of *Raoultella* terrigena (strain RN16) against *Meliodogyne incognito* as a parasite of crops (root-knot nematode - RKN) (Fig3). Several researches have confirmed that treating the cultivated herbs with just R. terrigena suspension, and in formulation via fresh wasabi extract, efficiently kills *Meliodogyne* incognito on tomatoes (118).

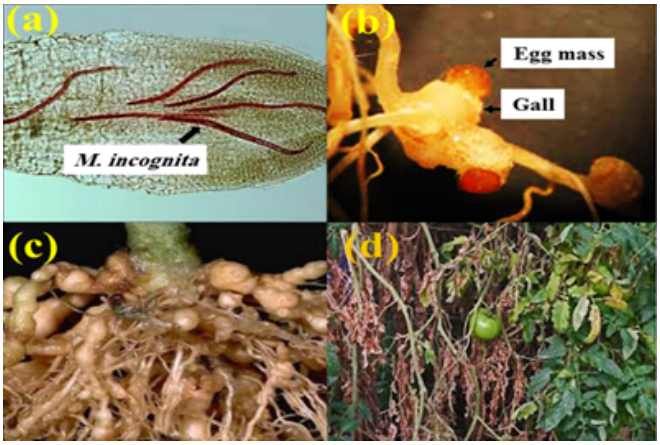

Figure3. (a) Root-knot nematode disease caused by Meliodogyne incognita nematode(119). (b) The root galls & M. incognita egg masses on cucumber root(120). (c) Close-up view of different gall sizes of tomato roots(121). (d) The patchy area due to root-knot nematode (Meloidogyne spp.) infestation on tomato (121

Raoultella terrigena may well be disconnected from the digestive system of pufferfish, milk and perhaps be utilized in biotechnology as 2,3-Butanediol producer (13).

7. 2 R. ornithinolytica against Acanthamoeba castellanii

The ability of R. *ornithinolytica* to multiply and create cytopathic effect in *Acanthamoeba castellanii* appears to be correlated with its virulence and therefore R. *ornithinolytica* has potential as biological control agent for this trophozoite (122).

Acanthamoeba castellanii is an opportunistic free-living amoeba can cause infections such as meningoencephalitis, ocular keratitis, cutaneous acanthamebiasis in human (123). The presence of a conjugative pili and the capacity of strain R. *ornithinolytica* Marseille-P1025 to invade, survive and multiply in an amoeba (*Acanthamoeba castellanii*) affirms the nearness of type IVa secretion system (47).

8.Identified Areas of Further Research

1.Awareness of Raoultella correct identification and its linked antibiotic resistance complications among clinical diagnostic laboratories.

2.Do can we develop an efficient vaccine against Raoultella species (especially for high risk patients and newborns)?

3.Do can we develop the new therapy methods for combating with MDR Raoultella infections other than antibiotic therapy?

4.Determination of molecular epidemiology of antibiotic resistance genes among R. terrigena isolates.

9.Conclusion

The genetic similarity between *Raoultella* spp. and *Klebsiella* spp. perhaps cause the misidentifications using biochemical tests such as the Vitek 2 system, the introduction of *rpo*B & 16s-rRNA genes analysis and the novel technology-based in MALDI-TOF MS permissible us a correct identification to species level of *Raoultella* spp.

Also, the diversity and plasticity of the antibiotic resistance plane of *Raoultella* species, has determined the early and accurate identification of *Raoultella* infection is exceptionally necessary to progress the guess of the clinical infections and to control the spread of this bacterium. According to our literature review results, patients that have multiple congenital disorders are more susceptible to *Raoultella* infections.

Some risks prone to infection include tumors, human immune system disorders, and invasive surgeries.

Abbreviations: NCTC; National Collection of Type Cultures, CDS; protein-coding genes, RKN; root-knot nematode, MDR; multi-drug resistance, AGs; aminoglycosides, ESBLs: Extended spectrum β-lactamases, ID; identification, AST; antimicrobial susceptibility testing, MSHA; Mannose-sensitive haemagglutination, LPS; lipopolysaccharide.

Declaration of competing interest

The authors declare that they have no known competing financial interests.

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