

# *Leclercia adecarboxylata*, An Emerging Pathogen: A Narrative Review

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## Abstract

*Leclercia adecarboxylata* is a gram negative, motile, facultative-anaerobic, oxidase-negative, mesophilic bacillus belonging to the *Enterobacteriaceae* family. *L. adecarboxylata* was first described by H. Leclerc in 1962, and previously known as “Enteric group 410” or “*Escherichia adecarboxylata*”, since *Leclercia* spp. shares several structural and microbiological properties with the genus *Escherichia*. Due to those similarities, *L. adecarboxylata* infections might be more common than what believed so far, since past clinical cases might have been erroneously defined as *Escherichia* spp. infections. *L. adecarboxylata* is a member of the normal gut flora in animals, has been isolated from water, food, and other environmental sources, can be found in a variety of specimens and is involved in a wide range of clinical syndromes commonly related to immunocompromised hosts. Although most of *Leclercia* spp isolates show high susceptibility to antibiotics, some multi-resistant strains have been reported in literature. Here, we narratively review the most original and relevant articles available in literature to provide a state of art to the current knowledge of this emerging pathogen.

**Keywords:** *Leclercia adecarboxylata*; Emerging pathogen; Infection; Treatment; Resistance; Multi-drug resistant

## Introduction

*Leclercia adecarboxylata* is a gram-negative bacillus firstly described by H. Leclerc in 1962, and previously known as “Enteric group 410” or “*Escherichia adecarboxylata*” [1], since *Leclercia* spp. shares a lot of structural and microbiological characteristics with the genus *Escherichia*. Due to those similarities, *L. adecarboxylata* infections might be more common than what believed so far since past clinical cases might have been erroneously defined as *Escherichia* spp. infections. Moreover, most bacterial assays often could not distinguish these morphologically and metabolically similar bacteria [2,3]. In present days, the availability of more sensitive testing methods (e.g.: DNA hybridization, computer identification studies) like Matrix Assisted Laser Desorption/Ionization Time of Flight (“MALDI-TOF”) mass spectrometry allowed a more precise species identification, eventually leading to the present categorization [4]. Given this increasing number of accurate identifications, *L. adecarboxylata* has been recently recognized as an emerging bacterium [4].

Hence, we decided to review the most original and relevant articles available in the literature to provide a state of art to the current knowledge of this emerging pathogen.

## Literature Review

References for this review were identified from PubMed, Embase, and Cochrane with the following research term combination: “*Leclercia adecarboxylata*” OR “*Leclercia*” OR “*Leclercia* infection”. Only papers in English were included. The final reference list was generated based on timeline, originality, and relevance to the scope of this Review.

## Etiology and microbiology

*Leclercia adecarboxylata* is a gram-negative, motile, facultative-anaerobic, oxidase-negative, mesophilic bacillus belonging to the *Enterobacteriaceae* family [4]. It shares many structural and microbiological properties with the genus *Escherichia* [1,4], but, thanks to more sensitive testing methods such as DNA hybridization and computer identification studies, a reclassification of this bacteria was achieved [4]. However, *L. adecarboxylata* and *Escherichia* also harbor some differences: in particular, unlike *Escherichia* strains, *Leclercia* might occasionally test positive for urease hydrolysis and differ for malonate utilization and production of yellow pigment; they also grow in the presence of potassium cyanide and, unlike *Escherichia*, resulting negative to lysine and ornithine decarboxylase tests [5].

Given its low virulence, *L. adecarboxylata* rarely causes monomicrobial infection, mostly in immunocompromised patients, while it is thought that this pathogen generally requires other coinfecting microorganisms to establish infection in immunocompetent subjects [2]. In the setting of polymicrobial infections, the most co-pathogens found are Enterococci, *Acinetobacter*, *Pseudomonas aeruginosa*, *Klebsiella*, *Fusarium* and *Staphylococcus epidermidis* [3,6]. Some cases of monomicrobial infection were also described in immunocompetent patients even without significant underlying comorbidities: particularly, only in one case the patient reported a clinical history of chronic diseases [7], while in the other cases no medical history was observed [8-10].

*Leclercia adecarboxylata* shows generally high susceptibility to antibiotics, however, some Multidrug-Resistant (MDR) strains have been widely described even in local outbreaks [2,6,11-13]. Particularly, specimens harbouring blaTEM-1 and blaCTX-M group 1 and int11 genes (dfrA12-orfF-aadA2) as genetic determinants for resistance might become difficult-to-treat pathogens [11].

## Epidemiology

*L. adecarboxylata* is a ubiquitous microorganism, which may be found in both aquatic environments and soil, as well as in the commensal gut flora of certain animals [1]. Asymptomatic carriage or colonization in healthy individuals is also described, rising concerns in regards to the spreading of the infection to immunocompromised people [14].

Prolonged antibiotic therapies, invasive interventions to the gastrointestinal tract, concomitant use of immunomodulators and the simultaneous presence of vascular graft or hemodialysis catheter could represent a risk factor for developing *L. adecarboxylata* infections.

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Indeed, several articles associate *L. adecarboxylata* with haematological malignancies, solid cancer in general, or immunomodulator therapy. Moreover, several other underlying conditions might favor *L. adecarboxylata* infections: for instance, wounds may be represented an access into the tissue, thus easing the pathogenicity as well as catheters in catheter-related bacteraemia or peritonitis could be developed in patients undergoing dialysis or chemotherapy [2]. A recent *L. adecarboxylata* outbreak was reported in 25 patients receiving total parenteral nutrition (TPN): this pathogen was isolated after an extensive epidemiological investigation in one sealed, unopened bottle of TPN belonging to the same batch administered to all patients [12].

### Clinical manifestations and diagnosis

*L. adecarboxylata* is implicated in several clinical syndromes, such as endocarditis [4,15,16], bacteraemia [2,7], wound infection and cellulitis [10,17,18], pharyngeal and peritonsillar abscesses [9], urinary tract infections [19], pneumonia [20] and peritonitis [21,22]. Cases of keratitis with corneal abscess from *L. adecarboxylata* infection have also been reported in patients with a history of exposure to the aquatic environment [17]. Most of the cases described regards immunocompromised adults, however, wound infections and peritonitis were reported even in immunocompetent children [18,21]. Two cases of pediatric septic arthritis of the knee caused by *L. adecarboxylata*, following an injury with residual foreign bodies, were reported in otherwise healthy Australian children without any significant pre-existing condition [23].

Other common clinical presentations are catheter-associated urinary tract infections in males, with translocation through the genitourinary tract, ventilator-associated pneumonia, peritonitis and vascular graft infections. Bacteremia can also occur after translocation across the intestinal mucosal barrier, in the setting of megacolon, prolonged antibiotic therapies or mucosal alterations due to invasive interventions to the gastrointestinal tract [2,14,24]. As reported before, most infections have been linked to immunosuppression, but also to the simultaneous presence of central vascular catheter [7] as it appears from several reports, catheters could be considered as important reservoirs for *L. adecarboxylata* bloodstream infection regardless of the patients' immune status [6,11,25]. In light of this, Dotis, et al., recently conducted a systematic review of the case reports in international literature, identifying 13 cases of peritonitis in patients with peritoneal dialysis. All the patients included had a favourable outcome and showed a good response to the antibiotic therapy [26].

Currently, considering the wide distribution and use of MALDI-TOF, the diagnosis of a *L. adecarboxylata* infection does not require any significant clinical or microbiological efforts. This pathogen might be isolated also from several biological specimens, such as blood culture, wound pus, faeces, urine, gallbladder, peri-ciliary and ciliary abscesses, synovial fluid, peritoneal fluid from peritoneal dialysis, sputum, cerebrospinal fluid, catheters, skin wounds, peritoneal fluid and abscesses (e.g.: peritonsillar and periovarian) [7].

### Treatment

The isolates more commonly mentioned in literature usually show a high susceptibility to antibiotics [2,3] and might be controlled with a variety of antibiotics, such as beta-lactams, witnessing therapeutic to therapeutic failures or needing second line treatments. [11]. A more comprehensive evaluation regarding natural antimicrobial susceptibility patterns was reported by Stock et al from 94 *L. adecarboxylata* strains, collected from several human specimens: the bacteria were naturally resistant to numerous antibiotic molecules, such

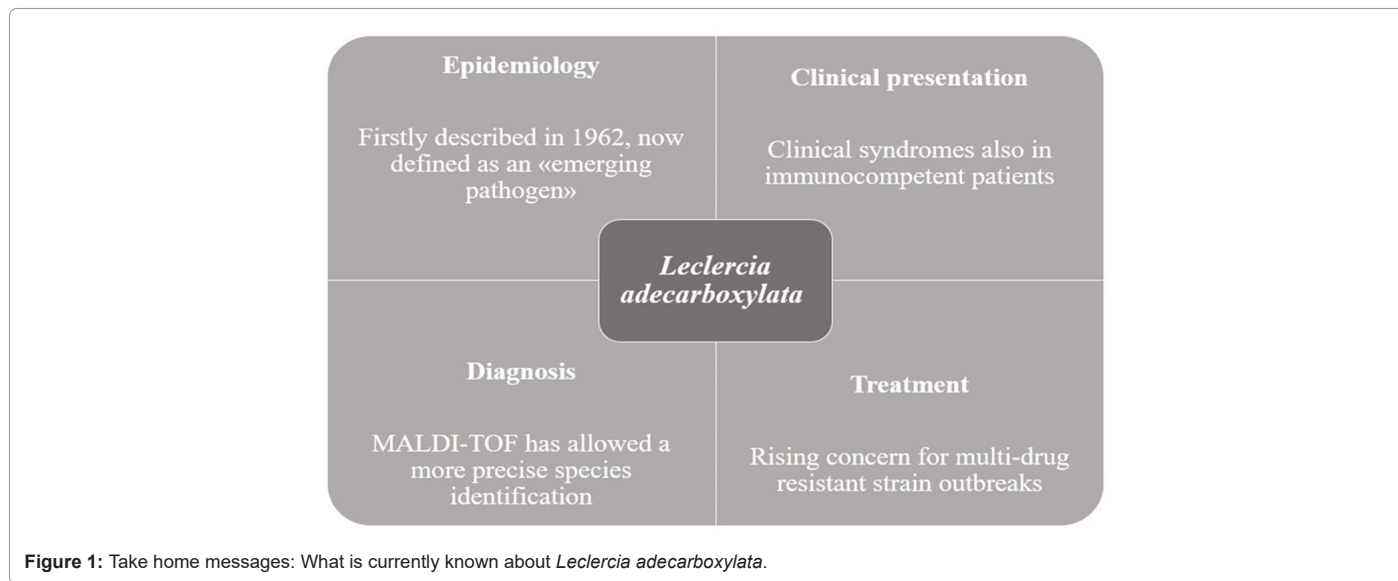
as oxacillin, clarithromycin, erythromycin, roxithromycin, ketolides, rifampin, glycopeptides, streptogramins, fusidic acid, lincosamides, penicillin G, and fosfomycin but susceptible to most beta-lactams, quinolones, aminoglycosides, tetracyclines, nitrofurantoin folate pathway inhibitors, azithromycin and chloramphenicol.

However, some multi-resistant strains have been reported in the literature. Recently a case of Catheter-Related Bloodstream Infection (CRBSI) was described in a patient affected by gastric and duodenal diffuse large B-cell lymphoma with TPN through a tunneled central venous catheter. A multi-drug resistant *L. adecarboxylata* was isolated from either peripheral and CVC blood culture, with an antibiogram showing full resistance to amoxicillin/clavulanate, fosfomycin, and trimethoprim-sulfamethoxazole [13]. In addition, Extended-Spectrum Beta-Lactamase (ESBL), New Delhi Metallo-Beta-Lactamase 1 (NDM)-producing and carbapenem-resistant *L. adecarboxylata* are also described. Three cases of ESBL producer isolates were in fact reported: the first case was described from a patient with acute myeloid leukaemia [27], the second in a 47-year-old female with breast cancer [11] and the third one in a 50-year-old female with end-stage renal disease [6]. In relation to NDM-producing *L. adecarboxylata*, two cases were reported: the first regarding a patient hospitalized for a foot trauma-related injury [28] while the second concerned an outbreak of 25 patients in intravenous TPN [12]. Regarding carbapenem-resistant *L. adecarboxylata* strain, one case was reported from a healthy newborn in China, with a resistance pattern to both meropenem and ertapenem [29]. However, as only case reports and case series report resistant *L. adecarboxylata* strains, it is impossible to infer whether risk factors are implicated in this concerning process.

Regarding treatment options, there are no shared guidelines nor any recommendation for *L. adecarboxylata* infections. Most isolates described are sensitive towards most of all tested antibiotics [2]. However, as described by Spiegelhauer et al., several strains of *L. adecarboxylata* displayed resistance to ampicillin (9/30 isolates resistant) and inherent resistance to fosfomycin, unlike other *Enterobacteriaceae* (8/10 isolates resistant) [30], so these antibiotics should not be used as the first line for treatment. Stock et al. described the natural susceptibility patterns of *L. adecarboxylata*, showing that most of the isolated strains were sensible to beta-lactams suggesting that *Leclercia* could be treated with this antibiotic class [11]. Lastly, in regards to infection where a graft is present (e.g. Tenckhoff or vascular catheter), a strict recommendation to remove the catheter is uncertain; although some evidence suggests that removal was necessary to achieve therapeutic success [31], the ability of *L. adecarboxylata* to produce biofilm remains unknown, even if the role of *L. adecarboxylata* in catheter-related bloodstream infections is increasing (Figure 1) [2].

### Discussion

Infections caused by *L. adecarboxylata* have likely been underestimated for decades due to the difficulty in identifying the microorganism, leading to underreporting in the medical literature [29,32-40]. An electronic search was employed to find the published articles which reported *L. adecarboxylata* infections throughout the United States National Library of Medicine, PubMed (last accessed October 2023). All prospective studies, retrospective studies, case series, or case reports published in peer-reviewed medical journals, regarding the search topic were included. We excluded articles published in non-English languages, pre-print or ahead of print analysis, pre-clinical studies (including *in vitro* or animal model studies), short communications, letters to the editor, and commentaries. Our findings are summarized in Table 1.



First author	Year	Type of study	Number of patients	Age	Immunestatus	Type of infection	Resistance spectrum
Spiegelhauer MR [2]	2019	Case report	1	Adult	Immunocompromised	Pneumonia	Monoresistance [TMP/SMX]
Forrester JD [32]	2012	Case report	1	Adult	Immunocompetent	CRBSI	No resistance detected
Hurley EH [18]	2013	Case report	1	Pediatric	Immunocompetent	BSI	NA
Temesgen Z [33]	1997	Case series	5	Adult	Immunocompetent (4), immunocompromised (1)	ABSSSI (3), BSI (1), Pneumonia (1)	No resistance detected (3), NA (2)
Savage PM [34]	2023	Case report	1	Adult	Immunocompetent	ABSSSI	NA
Shaikhain T [7]	2021	Case report	1	Adult	Immunocompetent	BSI	No resistance detected
De Mauri A [25]	2013	Case report	1	Adult	Immunocompromised	CRBSI	No resistance detected
Keyes J [35]	2020	Case series	2	Pediatric	Immunocompetent (1), Immunocompromised (1)	ABSSSI (1), UTI (1)	No resistance detected (1) Monoresistance [ampicillin] (1)
Myers KA [36]	2011	Case report	1	Pediatric	Immunocompetent	BSI	No resistance detected
Harper H [37]	2022	Case report	1	Adult	Immunocompromised	CRBSI	NA
Bronte Anaut M [38]	2022	Case report	1	Pediatric	Immunocompetent	BSI	No resistance detected
Aarab A [39]	2021	Case report	1	Pediatric	Immunocompetent	BSI	ESBL-producer
Matsuura H [40]	2018	Case report	1	Adult	Immunocompetent	BSI	No resistance detected
Tan R [41]	2022	Case report	1	Adult	Immunocompetent	IE	No resistance detected
Sethi K [42]	2013	Case report	1	Pediatric	Immunocompetent	BSI	No resistance detected
Mayfield CK [43]	2019	Case report	1	Adult	Immunocompetent	ABSSSI	No resistance detected
Grantham WJ [44]	2015	Case report	1	Pediatric	Immunocompetent	ABSSSI	No resistance detected
Malik K [4]	2021	Case report	1	Adult	Immunocompetent	IE	No resistance detected

Kaushik M [45]	2020	Case report	1	Adult	Immunocompetent	ABSSSI	Monoresistance [ampicillin]
Li J [46]	2021	Case report	1	Adult	Immunocompetent	UTI	No resistance detected
Anuradha M [8]	2014	Case reports	2	Adult	Immunocompetent	ABSSSI (1) Vaginosis (1)	No resistance detected (1), Monoresistance [fosfomycin] (1)
Jean SS [47]	2013	Case report	1	Adult	Immunocompetent	BSI	No resistance detected
Kashani A [24]	2014	Case report	1	Adult	Immunocompetent	BSI	No resistance detected
Arasu R [48]	2022	Case series	2	Pediatric	Immunocompetent	Septic arthritis (1)	No resistance detected (1), Monoresistance [cefazolin] (1)
Lonneman MK [49]	2020	Case report	1	Adult	Immunocompetent	ABSSSI	No resistance detected
Adapa S [50]	2019	Case report	1	Adult	Immunocompromised	Abdominal infection	No resistance detected
Hess B [10]	2008	Case report	1	Adult	Immunocompetent	ABSSSI	No resistance detected
Garza-González E [12]	2021	Case series	25	Adult	NA	BSI	NDM-1-producer
Broderick A [17]	2019	Case report	1	Adult	Immunocompetent	ABSSSI	No resistance detected
Merza N [51]	2019	Case report	1	Adult	Immunocompetent	BSI	No resistance detected
Hassan I [52]	2020	Case report	1	Pediatric	Immunocompetent	SBP	No resistance detected
Gómez-Arroyo B [53]	2020	Case report	1	Adult	Immunocompetent	PJI	NA
Householder NA [54]	2022	Case report	1	Adult	Immunocompetent	Arthritis	No resistance detected
Alosaimi RS [6]	2020	Case report	1	Adult	Immunocompromised	CRBSI	ESBL-producer
Voulalas G [55]	2016	Case report	1	Adult	Immunocompetent	Mycotic aneurysm	No resistance detected
Nelson MU [56]	2013	Case report	1	Pediatric	Immunocompetent	BSI	No resistance detected
Sanchez Porto A [57]	2014	Case report	1	Adult	Immunocompromised	BSI	No resistance detected
Colangelo C [13]	2023	Case report	1	Adult	Immunocompromised	CRBSI	Multi-drug resistance [amoxicillin, fosfomycin, TMP/SMX]
Atas DB [58]	2017	Case report	1	Adult	Immunocompromised	Abdominal infection	NA
Marina VP [59]	2011	Case report	1	Adult	Immunocompromised	CRBSI	No resistance detected
Shah A [60]	2011	Case report	1	Pediatric	Immunocompromised	ABSSSI	No resistance detected
Eiland EH [61]	2013	Case report	1	Adult	Immunocompetent	Pneumonia	Multi-drug resistance [ampicillin, gentamycin, TMP/SMX]
Michael Z [62]	2013	Case report	1	Adult	Immunocompetent	ABSSSI	Penicillinase-producer

Papacharalampous G [63]	2015	Case report	1	Adult	Immunocompetent	Mycotic aneurysm	No resistance detected
Jover-Sáenz A [64]	2008	Case report	1	Adult	Immunocompetent	Abdominal infection	No resistance detected
Keren Y [65]	2014	Case report	1	Adult	Immunocompetent	ABSSSI	No resistance detected
Haji S [66]	2014	Case report	1	Adult	Immunocompetent	BSI	No resistance detected
Allawh R [67]	2015	Case report	1	Adult	Immunocompetent	ABSSSI	No resistance detected
Fattal O [68]	2000	Case report	1	Pediatric	Immunocompromised	Abdominal infection	No resistance detected
de Baere T [69]	2001	Case series	2	Adult	Immunocompetent	Abdominal infection (1), BSI (1)	No resistance detected (1), Monoressitance [ampicillin] (1)
Tam V [70]	2012	Case report	1	Adult	Immunocompetent	ABSSSI	No resistance detected
Riazzo C [28]	2017	Case report	1	Adult	Immunocompetent	ABSSSI	NDM-1 producer
Bali R [9]	2013	Case report	1	Adult	Immunocompetent	ABSSSI	No resistance detected
Prakash MR [71]	2015	Case series	3	Adult	Immunocompetent (2), immunocompromised (1)	Pneumonia	No resistance detected (2), Monoressitance [ampicillin] (1)
Lee B [72]	2009	Case report	1	Adult	Immunocompetent	IE	No resistance detected
Chao CT [73]	2014	Case report	1	Adult	Immunocompromised	Peritonitis	No resistance detected
Longhurst CA [74]	2001	Case report	1	Pediatric	Immunocompromised	BSI	No resistance detected
García-Fulgueiras V [75]	2014	Case report	1	Adult	Immunocompetent	Osteomyelitis	Penicillinase-producer
Dalamaga M [76]	2008	Case report	1	Adult	Immunocompetent	BSI	Multi-drug resitant [ampicillin, tobramycin, TMP/SMX]
Shin GW [11]	2012	Case report	1	Adult	Immunocompromised	CRBSI	Multi-drug resitant [penicillins and cephalosporines, tobramycin, TMP/SMX]
Kim HM [77]	2008	Case report	1	Adult	Immunocompromised	Abdominal infection	Monoressitance [ampicillin]
Fernández-Ruiz M [78]	2009	Case series	2	Adult	Immunocompromised	CRBSI	No resistance detected
Mazzariol A [79]	2003	Case report	1	Adult	Immunocompromised	BSI	ESBL-producer
Sawamura H [80]	2005	Case report	1	Adult	Immunocompetent	Pyelonephritis	No resistance detected

**Note:** CRBSI: Catheter-Related Bloodstream Infection; BSI: Bloodstream Infection; ABSSSI: Acute Bacterial Skin and Skin Structure Infection; IE: Infective Endocarditis; UTI: Urinary Tract Infection; TMP/SMX: Cotrimoxazole; ESBL: Extended-Spectrum Beta-Lactamase; NDM: New Delhi Metallo-Beta-Lactamase; VIM: Verona Integron-Encoded Metallo-Beta-Lactamase; NA: Not Available.

**Table 1:** Published original articles and clinical cases in English, peer-reviewed medical journals (last accessed 22nd October 2023).

A total of 160 papers were identified through our search, but, eventually, only 64 were included as describing a clinical case of *L. adecarboxylata* infection. While 99 patients were affected by a generally multi-sensible *L. adecarboxylata* infection, the number of multi-drug resistant strain is rising over time [41-62]. Among the documented cases of pediatric infection, even a colonization of a carbapenem-resistant *L. adecarboxylata* isolated from a healthy newborn has been reported in 2023 [29,63-70]. All things considered; it is hard and incorrect to define *L. adecarboxylata* as an “opportunistic pathogen” as often happen in literature [71-80], even if most of the infections occur in immunocompromised hosts.

Carbapenems are always considered when treating a multidrug-resistant Gram-negative bacterial infection, but carbapenem-resistant Enterobacteriaceae have become a major public health threat, leading to severe infections, limited treatment options, and mortality rates of 26%-44% [29]. As previously shown despite most cases of *L. adecarboxylata* infection are susceptible to common antibiotics, some drug-resistant strains have recently been detected in literature [29]. Moreover, even animal studies raise concern on the emergence of resistant strain of *L. adecarboxylata* as suggested by a recent paper regarding a genomic investigation of a multiple fluoroquinolone-resistance from a diseased synanthropic pigeon [81,82].

## Conclusion

*L. adecarboxylata* infections occur rarely in immunocompetent patients and the pathogen usually shows good sensibility patterns to most antimicrobial agents. However, severe infections from difficult-to-treat strains are increasing. Given the absence of specific guidelines on *L. adecarboxylata* management and treatment, there is a need to create a multicentric international network sharing experiences to increase knowledge about this emerging pathogen.

## Author Contributions

Conceptualization, E. F.; writing-original draft preparation, M.D.G., G.T., C.C., and E.F.; validation, M.D.G., G.T., C.C., and E.F.; investigation, M.D.G., G.T., C.C., and E.F.; data curation, M.D.G., G.T., C.C., and E.F.; writing-review & editing, M.D.G., G.T., C.C., S.C., F.C., A.C., F.C., and E.F.; visualization, M.D.G., G.T., C.C., S.C., F.C., A.C., F.C., and E.F.; supervision, A.C., F.C., and E.F. All authors have read and agreed to the published version of the manuscript.

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