Plasmid Carrying \textit{bla}_{CTX-M-15}, \textit{bla}_{PER-1}, and \textit{bla}_{TEM-1} Genes in \textit{Citrobacter spp.} From Regional Hospital in Mexico

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**ABSTRACT**

**INTRODUCTION**: 
\textit{Citrobacter spp.} is an opportunistic bacteria that have been recognized as significant pathogens in patients with underlying diseases or immunocompromised status. The aim of this study was to identify extended-spectrum \(\beta\)-lactamases in clinical isolates of 
\textit{Citrobacter spp.}

**METHODS**: This cross-sectional study was conducted at Hospital Central “Dr. Ignacio Morones Prieto” in San Luis Potosi, Mexico. Nineteen isolates of \textit{Citrobacter spp.} were obtained from clinical specimens between April to December 2015. Four isolates were resistant to third-generation cephalosporins. The presence of genes encoding ESBL (\textit{bla}_{CTX-M-15}, \textit{bla}_{TEM-1}, \textit{bla}_{VEB-1}, \textit{bla}_{SHV}, and \textit{bla}_{PER-1}) was analyzed by PCR. For this purpose, plasmid DNA was extracted and horizontally transferred to recipient \textit{E. coli} Top 10.

**RESULTS**: \textit{bla}_{CTX-M-15} and \textit{bla}_{VEB-1} genes were detected in \textit{Citrobacter freundii} and \textit{Citrobacter sedlakii}, whereas \textit{bla}_{PER-1} gene was identified in 1 isolate of \textit{Citrobacter freundii}. In contrast, \textit{bla}_{SHV} gene was not detected in any isolate. One strain carried \textit{bla}_{CTX-M-15}, \textit{bla}_{TEM-1}, \textit{bla}_{VEB-1}, and \textit{bla}_{PER-1} genes, most in a 275-kb plasmid.

**CONCLUSION**: This study shows the presence of different types of ESBL in clinical isolates of \textit{Citrobacter freundii} and \textit{Citrobacter sedlakii}, which confer resistance to broad-spectrum \(\beta\)-lactams. The plasmid identified in this study harboring ESBL genes could play an important role in the dissemination of antibiotic resistance.

**KEYWORDS**: \textit{Citrobacter}, ESBL, CTX-M-15, PER-1, VEB-1, TEM, plasmid.

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**Introduction**

Bacteria of the genus \textit{Citrobacter} belong to the family \textit{Enterobacteriaceae} and comprise 13 species; \textit{Citrobacter} are found in a variety of environmental sources, including soil and water, and occasionally are isolated from the gastrointestinal tract of animals and humans.\textsuperscript{1,2} Despite being considered an unusual nosocomial pathogen, neonates and immunocompromised patients are a frequent target of infections caused by these microorganisms.\textsuperscript{3} These conditions include sepsis, urinary tract infections, respiratory and intra-abdominal infections, and central nervous system infections.\textsuperscript{4} According to a large observational study, \textit{Citrobacter} species account for 0.8% of all Gram-negative infections in a hospital setting, with a mortality rate in hospitalized patients that ranged from 6.8% to 56%.\textsuperscript{3,5}

As expected, infections caused by multidrug-resistant \textit{Citrobacter} strains are associated with a higher rate of in-hospital mortality compared to those caused by susceptible strains. These multidrug-resistant strains show high levels of molecular class C (Amp-C) and extended spectrum \(\beta\)-lactamases (ESBL) as well as plasmid-mediated quinolone and carbapenem resistance.\textsuperscript{2}

ESBL confer resistance to penicillins, first to third-generation cephalosporins, and aztreonam, but not to cephemycins and carbapenems.\textsuperscript{6} The production of ESBL has been recognized as a global problem, mainly in the case of \textit{E. coli} and \textit{K.
pneumoniae. However, this condition has been also described in recent years in other species, including the genus Citrobacter.

Few studies have analyzed the presence and distribution of ESBL in clinical isolates of Citrobacter spp. Among them, an outbreak caused by 5 isolates of CTX-M-2 producing C. koseri in hematological patients was reported in 2006. Furthermore, CTX-M-1/3 β-lactamases have been reported in Korea, France and Spain, CTX-M-9/30 in Canada, and CTX-M-14 in China. In addition, CTX-M-14, TEM, SHV-4, and SHV-12 ESBL have been detected in Japan.

The aim of this study was to detect ESBL in clinical isolates of Citrobacter spp. at the Hospital Central “Dr. Ignacio Morones Prieto” (HCIMP), in the State of San Luis Potosi, located at the center-north of Mexico.

Materials and Methods

Bacterial isolates

This study was conducted after approval (July 23, 2015) by the Research Committee [COFEPRIS 14 CI 24 028 083] and the Research Ethics Committee of the Hospital Central “Dr. Ignacio Morones Prieto” [CONBIOETICA-24-CEI-001-20160427]. The registration number was 48-15. A written informed consent was obtained from all participants or legal guardians/parents for those under the age of 16 years.

The HCIMP has 250 beds and 32 beds in the intensive care unit and provides medical services to mid-and low-income populations from all over the State of San Luis Potosi.

Between July and December 2015, the Microbiology Laboratory of HCIMP identified 19 consecutive and non-repeated isolates of Citrobacter spp. The clinical isolates were identified using Vitek 2C (bioMérieux, Marcy l’Etoile, France) and were transferred to the Section of Medical Genomics from the Research Center of Health Sciences and Biomedicine, UASLP for molecular characterization.

ESBL phenotypic confirmatory test

The phenotypic confirmatory test of ESBL was performed by using the combined disk method on Mueller Hinton Agar, according to the Clinical and Laboratory Standards Institute (CLSI) recommendations. Briefly, antibiotics were serially diluted 2-fold in the broth microdilution method, according to CLSI recommendations. The ESBL phenotypic confirmatory test was performed by incubating on LB/ampicillin (100 µg/mL) agar plates at 37°C for 24 h. ESBL genes in these bacteria were detected as described above.

Molecular identification of β-lactamases

DNA amplification of β-lactamase genes was carried out with specific primers (Table S1). In brief, 3 colonies of an overnight culture were suspended in 100 µL of DNase free water and incubated at 94°C for 5 min and at –70°C for additional 5 min. Then, tubes were centrifuged at 13000 rpm for 5 min and the supernatant was used as DNA template. The PCR reaction mixture contained 1X buffer, 2.0 mM of each dNTP, 5.0 µM of oligonucleotides for blaTEM, blaCTX-M, blashaV, blaper-1, and blaPER-1 genes, 1.0 U of Taq DNA polymerase, bacterial genomic DNA, and 1.5–3.0 mM MgCl2. PCR conditions were performed at 94°C for 5 min for initial denaturation, followed by 30–40 cycles of 30 s at 94°C, 1 min at 50–60°C, and 1 min at 72°C, followed by a final extension of 5 min at 72°C, using a Multigene thermo-cycler (Labnet International Inc, New Jersey, United States). The amplified products were analyzed by electrophoresis on 2% agarose gels. PCR products were purified using a Wizard DNA Clean-Up system (Promega), according to the manufacturer’s instructions and were sequenced by using the dideoxynucleotide method, in a 3130 Genetic Analyzer device (Applied Biosystems, Foster City, California). BLAST analysis was performed in the NCBI database [http://www.ncbi.nlm.nih.gov/].
50 μL of Mueller-Hinton broth, mixed with 50 μL of bacteria at a density of 10⁶ colony-forming units/mL and incubated for 18 h at 37°C. Quality control was performed using the reference E. coli Top 10 and results were expressed as the minimum inhibitory concentration (MIC).

**Results**

**Bacterial isolates**

The Microbiology Laboratory identified 14 isolates of C. freundii, 2 isolates of C. koseri, 2 isolates of C. braakii, and 1 isolate of C. sedlakii in the different samples studied (Table 1).

**ESBL phenotypic confirmatory test**

Three isolates resistant to third-generation cephalosporins showed an ESBL phenotype: C. freundii R-086, R-135, and C. sedlakii R-099. Moreover, the C. freundii R-134 isolate, which was also resistant to third-generation cephalosporins, did not exhibit a resistance phenotype indicative of the presence of ESBL (Table 2).

**Molecular identification of β-lactamases**

As shown in Figure 1, bla<sub>TEM</sub> and bla<sub>CTX-M</sub> genes were identified in C. freundii R-086 and R-135. In 2 additional isolates (C. freundii R-135 and C. sedlakii R-099), bla<sub>VEB-1</sub> genes were detected Figure 1c, whereas the bla<sub>PER-1</sub> gene was identified in C. freundii R-135 Figure 1d. In contrast, the bla<sub>SHV</sub> gene was not identified in any isolate (data not shown). Moreover, bla<sub>TEM</sub>-CTX-M, bla<sub>VEB-1</sub>, and bla<sub>PER-1</sub> genes were identified in the C. freundii R-135 isolate (Table 2). Finally, DNA sequence analysis showed that the TEM β-lactamase detected in C. freundii R-086 had 100% homology to TEM-1 (GenBank accession number: ALW82937.1), whereas the predicted amino acid sequence of the CTX-M β-lactamase showed 99% homology to CTX-M-15 (GenBank accession number: AKO22374.1).

**Plasmid isolation and bacterial transformation**

A 275-kb plasmid DNA was isolated from C. freundii R-086 (R-086p) and R-135 (R-135p) strains (data not shown). On the other hand, In the Top 10-R-135 E. coli transformant we were able to amplify the bla<sub>CTX-M-15</sub>, PER-1, and TEM-1 genes Figure 2. In contrast, the bla<sub>VEB-1</sub> gene was not amplified in R-135p or Top-10-R-135.

**Antimicrobial susceptibility testing**

The MIC of antimicrobial agents for C. freundii R-135, E. coli Top 10-R-135, and E. coli Top 10 are shown in Table 3.

**Discussion**

In recent years, infections caused by Citrobacter spp. have become important because they cause nosocomial outbreaks, mainly affecting neonates and immunocompromised patients.12 Although C. koseri has been most frequently identified in sporadic cases and hospital outbreaks,6 in our study, the predominant species was C. freundii.

Since its first description in the 1990s, ESBL of the CTX-M family have shown an increased frequency in Enterobacteriaceae, followed by SHV and TEM as well as, to a lesser extent, by the OXA, Tla, GES, VEB, and PER types. However, the frequency of these types is variable in different geographical regions.6 In our study, we detected that the C. freundii R-086 and R-135
strains synthesized CTX-M-15, an ESBL worldwide distributed and characterized by its efficient ceftazidime hydrolyzing activity.\textsuperscript{13,14} The first report of CTX-M-15 in Mexico was in 2011, in \textit{E. coli} isolate,\textsuperscript{11} when 2 different groups reported strains of \textit{E. coli}, \textit{Enterobacter cloacae}, and \textit{K. pneumoniae} as carriers of CTX-M-15 ESBL.\textsuperscript{9,15} Two years later, 58 isolates of \textit{E. coli} and 16 isolates of \textit{K. pneumoniae} producers of CTX-M-15 ESBL were detected in a tertiary care hospital in the city of Guadalajara, State of Jalisco, México.\textsuperscript{11} The present study is the first report of \textit{Citrobacter spp.} able to synthesize CTX-M-15 ESBL in Mexico. In the same strain the TEM-1 β-lactamase was identified, which efficiently hydrolyze penicillins and low spectrum cephalosporins and that is not considered an ESBL.

The presence of VEB-1 ESBL in the genus \textit{Citrobacter} had not been described so far and in the case of PER ESBL, there is only a previous report of \textit{C. koseri} PER-2 producer.\textsuperscript{16} This

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**Figure 1.** Agarose gel electrophoresis for the PCR products of ESBL: (a) the \textit{bla}\textsubscript{TEM} gene. Line M: 100 bp ladder, line 1: positive control, line 2: negative control, lines 3 and 6: R-086 and R-135 strains (\textit{bla}\textsubscript{TEM} positive), lines 4 and 5 \textit{bla}\textsubscript{TEM} negative strains, (b) the \textit{bla}\textsubscript{CTX-M} gene. Line M: 100 bp ladder, line 1: negative control, line 2: positive control, lines 3 and 6: R-086 and R-135 strains (\textit{bla}\textsubscript{CTX-M} positive), lines 4 and 5: R-099 and R-134 strains (\textit{bla}\textsubscript{CTX-M} negative), (c) the \textit{bla}\textsubscript{VEB-1} gene. Line M: 100 bp ladder, line 1: negative control, line 2: positive control, lines 3 and 6: R-086 and R-134 strains (\textit{bla}\textsubscript{VEB-1} negative), lines 4 and 5: R-099 and R-135 strains (\textit{bla}\textsubscript{VEB-1} positive), and (d) the \textit{bla}\textsubscript{PER-1} gene. Line M: 100 bp ladder, line 1: negative control, line 2: positive control, line 5: R-135 strain (\textit{bla}\textsubscript{PER-1} positive), lines 3, 4, and 6: \textit{bla}\textsubscript{PER-1} negative strains.

**Figure 2.** Agarose gel electrophoresis for the PCR products of Top10R-135 strain: (a) the \textit{bla}\textsubscript{CTX-M-15} gene. Line M: 100 bp ladder, line 1: negative control, line 2: R-135 strain (\textit{bla}\textsubscript{CTX-M-15} positive), line 3: R-135p, line 4: Top10R-135 (transformant strain), and 5: \textit{E. coli} Top-10, (b) the \textit{bla}\textsubscript{PER-1} gene. Line M: 100 bp ladder, line 1: negative control, line 2: R-135 strain (\textit{bla}\textsubscript{PER-1} positive), line 3: R-135p, line 4: Top10R-135 (transformant strain), and 5: \textit{E. coli} Top-10, and (c) the \textit{bla}\textsubscript{TEM} gene. Line M: 100 bp ladder, line 1: negative control, line 2: R-135 strain (\textit{bla}\textsubscript{TEM} positive), line 3: R-135p, line 4: Top10R-135 (transformant strain), and 5: \textit{E. coli} Top-10.
ESBL has emerged in clinical isolates of *E. coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Klebsiella spp., and *Proteus mirabilis*. The first report on the resistance to β-lactams in *C. sedlakii* was an isolate resistant to aminopenicillins, carboxy-penicillins, low spectrum cephalosporins (but sensitive to broad-spectrum cephalosporins, and carbapenems), which was mediated by a β-lactamase called Sed-1. In our study, the *C. sedlakii* R-099 isolate was resistant to aminopenicillins, carboxy-penicillins, broad-spectrum cephalosporins including cepfepime. In this case, the PCR analysis showed the presence of VEB-1 but not of *bla* TEM, SHV, CTX-M or PER-1. At our best knowledge, this is the first report of a *C. sedlakii* strain able to produce VEB-1 ESBL.

We identified the *bla* _TEM-1_ and *bla* _CTX-M-15_ genes in *C. freundii* R-086, an isolated that also showed resistance to quinolones, aminoglycosides, and inhibitors of the folate pathway (data not shown). Moreover, in the *C. freundii* R-135 strain, *bla* _TEM-1_ , *bla* _CTX-M-15_ , *bla* _VEB-1_ , and *bla* _PER-1_ genes were identified. This phenomenon may be related to the presence of genetic mobile structures such as integrons, transposons, and plasmids that have been previously described in other species of Gram-negative bacilli. In this regard, an analysis of 40 isolates of *Citrobacter* spp. performed in 2010, the simultaneous presence of *bla* _CTX-M_ , *ampC*, SHV and _TEM_ genes was observed, and in 32.5% of these isolates class 1 integron was identified. In addition, in 48% of CTX-M-15 positive isolates the insertion sequence IS26 was detected. In the same year, a class 1 integron and ISCR1 insertion sequence were identified in a multi-resistant *C. freundii* isolate, which showed resistance to quinolones and β-lactams by presence of CTX-M-15 ESBL.

Previous reports suggest that different plasmids are responsible for the global spread of CTX-M-15 ESBL since _blaCTX-M-15_ has been identified in plasmids ranging from 40 to more than 200-Kb and belonging to IncFI and IncI1 groups. In these mobile elements, more resistance determinants have been identified, as _bla_ _TEM-1_ and _bla_ _ampC_ genes. However, there is only 1 previous report on a plasmid containing the _blaCTX-M-15_ and _blaPER-1_ genes, which was detected an *Aeromonas caviae* strain, which was isolated from a wild-growing Mediterranean mussel. Thus, this is the first report of a plasmid R-135p carrying the _blaCTX-M-15_ _TEM-1_ , and _PER-1_ genes in *C. freundii*. The genetic context of _blaCTX-M-15_ includes an IS _Ecp1_ sequence, upstream of the gene, which can be an efficient factor for the mobilization and expression of _blaCTX-M-15_ as it has been observed in previous reports.

We consider that it would be important to investigate the genetic context of β-lactamase genes in both, plasmids and chromosome as well as to determine the structure of the plasmid identified in *C. freundii* R-135.

In conclusion, our study shows the presence of different ESBL types in clinical isolates of *C. freundii* and *C. sedlakii*, which mediate the resistance to broad-spectrum β-lactams. The simultaneous presence of several antibiotic resistance genes seems to be related to genetic mobile elements that may favor their dissemination.

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**Author Contributions**

CNG acquired clinical data and samples, interpreted results, and drafted the manuscript. CNG and MBM performed the experiments. ETM and PNM co-designed and supervised the study and interpreted the results of experiments. DEN analyzed and interpreted data. RGA and LPG critically revised and edited the manuscript. All authors have read and approved the manuscript.

**Ethical Statement**

This study was conducted at Hospital Central Dr. Ignacio Morones Prieto (HCIMP) in San Luis Potosí, Mexico after approval by the Research Committee [COFEPRIS 14 CI 24 028 083] and the Research Ethics Committee of the HCIMP [CONBIOETICA–24-CEI-001-20160427]. The registration number was 48-15.
Supplemental Material

Supplemental material for this article is available online.

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