

Drug Resistance in *Cedecea neteri*

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Cedecea, a genus in the *Enterobacteriaceae* family, includes several opportunistic pathogens reported to cause an array of sporadic acute infections, most notably of the lung and bloodstream. One species, *Cedecea neteri*, is associated with cases of bacteremia in immunocompromised hosts and has documented resistance to different antibiotics, including β -lactams and colistin. Despite the potential to inflict serious infections, knowledge about drug resistance determinants in *Cedecea* is limited.

Cedecea neteri

opportunistic pathogen

drug-resistance genes

β -lactamases

multidrug efflux pumps

genomic islands

1. Introduction

The genus *Cedecea* comprises Gram-negative, facultatively anaerobic bacilli that are non-sporulating and fermentative [1]. Like other genera in the *Enterobacteriaceae* family, *Cedecea* species are widely distributed in aquatic and soil environments, as well as associated with plants, insects, the human gut microbiome, and non-human animals (reviewed in [2][3]). Three validly recognized species (*Cedecea daviseae*, *Cedecea lapagei*, and *Cedecea neteri*) have documented clinical relevance in humans and collectively, have been reported to cause such diverse acute infections as pneumonia [4][5][6][7][8][9], bacteremia [8][9][10][11][12][13][14][15][16][17][18][19], cutaneous and oral ulcers [13][14][20][21], and dialysis-related peritonitis [22]. Infections attributed to *Cedecea* occur predominantly in severely immunocompromised hosts, underscoring the opportunistic nature of its pathogenicity.

While *Cedecea* infections have been reported sporadically in the literature, clinical cases of this emerging opportunistic human pathogen continue to occur worldwide. Clinical strains of *Cedecea* species exhibit natural resistance to various antimicrobial agents, including ampicillin, ampicillin-sulbactam, cefazolin, cephalothin, cefoxitin, and colistin [3]. The multidrug-resistant phenotype of one *C. lapagei* isolate was attributed, in part, to the acquisition of the *bla*_{NDM-1} gene, which encodes the New Delhi metallo- β -lactamase-1 (NDM-1) [18]. This clinical isolate was resistant to carbapenems, monobactams, and extended-spectrum cephalosporins. Recently, additional *bla*_{NDM-1}-harboring *Cedecea* isolates have been reported [23][24]. The dissemination of NDM-1 is of serious public health concern as this metallo- β -lactamase severely limits the chemotherapeutic options available for treating bacterial infections. Apart from the detection of β -lactamase expression in certain *Cedecea* strains [18][25], knowledge on the genetic basis of drug resistance phenotypes in this genus is limited. The pathogenic potential of *Cedecea* species is likely under-recognized due to its low reported frequency of association with human infections.

and the fact that these organisms are not linked to specific disease states but, instead, cause a wide spectrum of acute infections in compromised hosts.

Opportunistic *C. neteri* infections typically present as bacteremia [10][12], although recently *C. neteri* was identified as the etiological agent of a urinary tract infection in a pregnant female with polyhydramnios [26]. One of the rare fatal patient outcomes associated with clinical isolates of *Cedecea* spp. involved a *C. neteri* infection in the bloodstream of an individual with systemic lupus erythematosus (SLE) [12]. Given the potentially serious nature of these opportunistic infections, research is needed on identifying the genes implicated in drug resistance phenotypes that impact treatment of *Cedecea*. In this study, we focused our attention on *C. neteri* because whole-genome sequence (WGS) information is available for multiple strains of this species. WGS data for three environmental strains of *C. neteri* and different bioinformatics tools were utilized to provide insight into the predicted drug resistance determinants of this species. Only a draft genome at the unassembled contig level is available for the type strain *C. neteri* ATCC 33855 [10], isolated from a human foot, so we focused our queries on the completed genome sequence of *C. neteri* SSMD04 [27] and compared results to the genomes of *C. neteri* M006 [28] and ND14a. Our findings highlight the value of genome-based explorations in contributing to our understanding of antimicrobial resistance in little studied environmental microorganisms with the capability of behaving as clinically relevant opportunistic pathogens.

2. Predicted Multidrug Efflux Pumps in *C. neteri*

A ubiquitous microbial mechanism of resistance is drug extrusion via integral membrane transporters, which reduces exposure of the bacterial target to active concentrations of the drug. Five different transporter families confer clinical resistance to various antibiotic classes [29]: ATP-binding cassette (ABC), multidrug and toxic compound extrusion (MATE), major facilitator superfamily (MFS), resistance-nodulation-division (RND), and small multidrug resistance (SMR). Database searches revealed the presence of at least 34, 32, and 33 annotated efflux pump or transporter genes in *C. neteri* strains SSMD04, M006, and ND14a, respectively. Classifications of these predicted efflux pump/transporter genes were distributed across the five different families (ABC, MATE, MFS, RND, and SMR). Efflux pumps of the RND family represent some of the most clinically significant transporter proteins in Gram-negative bacteria because of their broad substrate specificity and association with multidrug resistance (MDR) [30]. Genomes for all three *C. neteri* strains encoded several RND MDR transporters generally annotated as efflux pumps.

By performing in-depth homology searches against the KEGG database, we found homologs of the RND MDR efflux systems AcrAB-TolC, AcrD, OqxAB, and MdtABCD in the SSMD04 genome (Figure 3). BLAST searches indicated that one predicted RND efflux system resembled both OqxAB and AcrAB. Cnt17100 (ORF JT31_17100) has 95% identity to OqxB in *Enterobacter cloacae* and 84% identity to AcrB in *Xanthomonas citri* at the amino acid level. Both OqxB and AcrB are RND transporters that share a consistent transmembrane helical structure [31]. Immediately upstream of JT31_17100 is a gene with 88% amino acid identity to AcrA in *E. cloacae* and 85% identity to OqxA in *Klebsiella variicola*. OqxA and AcrA function as membrane fusion proteins (MFPs) in the RND MDR efflux system. Upstream of the oqxAB/acrAB gene cluster is a gene (JT31_17110) encoding an AraC family

transcriptional regulator that is transcribed divergently. The deduced gene product shares 84% amino acid identity to the transcriptional activator MarA in *Enterobacter ludwigii* and 78% identity to RarA in *Klebsiella pneumoniae*. A second putative regulatory gene (JT31_17095), encoding a Rrf2-type regulator, is located immediately downstream of the *oqxAB/acrAB* gene cluster and may be involved in repressing transcription of the putative RND MDR efflux system based on its homology to OqxR. Substrates of the AcrAB efflux pump include cationic dyes (acriflavine), detergents, and antibiotics such as penicillins, cephalosporins, fluoroquinolones, macrolides, chloramphenicol, and tetracycline [32]. OqxAB confers resistance to multiple antimicrobial agents (quinoxalines, quinolones, tigecycline, nitrofurantoin, and chloramphenicol), as well as detergents and disinfectants [31]. The function of the *E. coli* AcrB transporter is dependent on TolC, a multifunctional outer membrane channel [33][34], and a homologous gene with 75% amino acid sequence identity to TolC in *Salmonella enterica* was identified upstream of the *C. neteri* *acrB/oqxB* gene (JT31_17100), suggesting a similar tripartite system in this species (Figure 1). Additionally, the small adaptor protein, AcrZ, which interacts with the AcrAB efflux pump, was identified some distance downstream of the *acrB* gene in a similar genetic organization as the *E. coli* cluster [35]. The AcrZ protein was shown to aid in the binding and export of chloramphenicol and tetracycline by the AcrAB efflux pump, thus enhancing the drug resistance phenotype of *E. coli* [36].

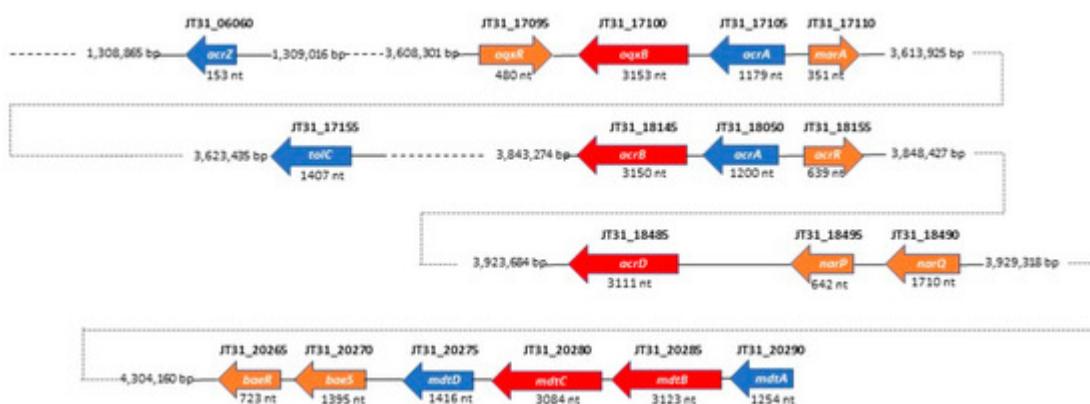


Figure 1. Schematic representation showing the position and size of predicted RND family efflux pump systems and associated genes in the *C. neteri* SSMD04 genome. RND efflux pumps are displayed in red, structural components in blue, and regulatory genes in orange.

In our analysis, a BLAST search suggested that *C. neteri* JT31_18485 is a homolog of *E. coli* AcrD, an aminoglycoside efflux pump from the RND family [37]. The JT31_18485 gene product showed 87% identity in amino acid sequence to AcrD from *E. coli* and *Shigella sonnei*. In addition, homologous genes encoding the MdtABCD efflux pump system were identified on the *C. neteri* SSMD04 chromosome (Figure 3). The *C. neteri* *mdtABCD* locus encodes a putative membrane fusion protein (*mdtA*), two RND-type transporters (*mdtB* and *mdtC*), and an MFS-type transporter (*mdtD*). The predicted MdtB and MdtC transmembrane exporter subunits in *C. neteri* exhibited high amino acid sequence identity (89% and 90%, respectively) to their counterparts in *E. cloacae* and *E. coli*. MdtABCD has previously been shown to comprise a multidrug efflux system that confers resistance to novobiocin and deoxycholate [38][39]. The genes *baeS* and *baeR*, which encode a two-component signal transduction system, were identified immediately downstream of the *C. neteri* *mdtABCD* locus in a similar genetic

organization as described for *E. coli*. The BaeSR two-component system positively regulates drug resistance in *E. coli* via the MdtABCD multidrug efflux system [39][40], suggesting that the predicted *mdtABCD* locus in *C. neteri* may be under the transcriptional control of the BaeR response regulator. These putative RND efflux pump systems likely contribute to the intrinsic antimicrobial drug resistance reported for clinical isolates of *C. neteri*. However, the functional role of these homologs of RND efflux pumps and the identity of the specific drug substrates of each pump remain to be established.

A KEGG database search also revealed two pairs of linked genes annotated as *emrA*-like and *emrB*-like MDR transporters of the MFS family on the chromosomes of all three *C. neteri* strains. In *C. neteri* SSMD04, these *emrA*/*emrB*-like gene pairs are JT31_07770/JT31_07775 and JT31_16920/JT31_16915. Multiple sequence alignment showed that the JT31_16920/JT31_16915 pair had the highest sequence identity with the known EmrAB counterpart in *Klebsiella pneumoniae*, *Salmonella enterica*, and *E. coli*. The *emrAB* locus in *E. coli* encodes a MDR pump involved in the extrusion of chemically unrelated antimicrobial agents, including the antibiotics nalidixic acid and thiolactomycin [41]. The putative SSMD04 *emrB*, which encodes a MFS-type efflux pump, shared 93% amino acid sequence identity with *K. pneumoniae* EmrB, 92% identity with *E. coli* EmrB, and 90% identity with *S. enterica* EmrB. The putative *emrA*, which encodes a membrane fusion protein, shared high amino acid sequence identity (82%-86%) with EmrA in *K. pneumoniae*, *E. coli*, and *S. enterica*. In addition, a gene (JT31_16925) annotated as *mprA* is located adjacent to *emrA*. Previous research demonstrated that *mprA* (renamed *emrR*) is part of the *emrAB* operon and functions to repress transcription of *emrAB* [42]. A recent study showed that the EmrAB pump system contributes to colistin resistance in the nosocomial pathogen *Acinetobacter baumannii* [43]. Colistin resistance has been noted as one of the defining properties characterizing *Cedecea* species and is a trait shared by established opportunistic pathogens in the genus *Serratia* [1][10], but the specific mechanism conferring this resistance in *Cedecea* is not known. The possibility that the predicted MFS-type EmrAB efflux pump system may be responsible, at least in part, for the colistin resistance phenotype in *Cedecea* should be explored further, particularly since these species are gaining increased recognition as opportunistic pathogens in the clinical setting.

3. Conclusions

Cedecea species are members of the *Enterobacteriaceae* family that have been found in a wide range of natural environments, as well as in human clinical specimens. Reported clinical isolates have been associated with a spectrum of acute infections (e.g., pneumonia, bacteremia, oral ulcers, and dialysis-related peritonitis) in primarily immunocompromised hosts, and antibiotic susceptibility testing has indicated varying degrees of drug resistance among documented isolates. As emerging opportunistic pathogens of environmental origin, *C. neteri* and the closely related species *C. davisae* and *C. lapagei* have received little research attention to date. This study exploited whole-genome sequence information for three *C. neteri* strains (SSMD04, M006, and ND14a) to gain a deeper understanding of the genetic potential for drug resistance in this species and to identify drug-resistance candidate genes for further investigation. We focused our genomic analyses on *C. neteri* SSMD04, an isolate originating from retailed sashimi, since only a draft genome was available for type strain *C. neteri* ATCC 33855. Our work reports the presence of multiple β -lactamase-encoding genes in the *C. neteri* SSMD04 chromosome,

including four putative MBLs, a CMY/ACT-type AmpC variant, and a novel β -lactamase gene not described previously. Homologous genes encoding RND- and MFS-type efflux pumps were also identified, along with associated regulatory genes known to be involved in the control of these efflux systems in other bacteria. Comparative analysis of predicted genomic islands suggested the acquisition of some drug resistance determinants and virulence factors by horizontal genetic transfer. The findings of this study advance our currently limited understanding of the molecular basis of antimicrobial resistance in *C. neteri*. Future research is needed to correlate the genetic data with resistance phenotypes impacting public health management of this opportunistic pathogen.

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