

# Multi-drug Resistant *Citrobacter freundii* Isolates in a Burn Hospital in Northeast of Iran: A Single-Center Cross-sectional Study



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## ABSTRACT

**Background:** Multi-drug resistant (MDR) *Citrobacter freundii* (*C. freundii*) as a causative agent of nosocomial infections is a health threat, especially in hospitals. This study was conducted to determine the prevalence of MDR *C. freundii*, considering isolation sites and a variety of utilized antibiotics.

**Materials and Methods:** In this cross-sectional study, the clinical samples of *C. freundii* strains were collected and screened using traditional bacteriological tests in Zareh Hospital, Sari City, Iran, during 2016-2017. We used disk diffusion methods to assess the susceptibility patterns of isolates according to the Clinical Laboratory Standard Institute (CLSI) guidelines.

**Results:** Out of 3248 clinical samples, *C. freundii* strains were detected in 109 samples (32.1% females and 67.9% males). Susceptibility tests indicated that 89 isolates (81.65%) were MDR strains. Frequencies of MDR *C. freundii* strains were higher in the Behavioral Intensive Care Unit (BICU) (37.61%) and restoration ward (29.35%) compared with other hospital wards.

**Conclusion:** Considering the MDR *C. freundii* strains detected from burn hospital wards, it is necessary to implement prevention criteria for their eradication from burn hospitals. The results indicate the urgent need to design more practical methods for controlling infection in hospital wards.

## Introduction

In recent years, nosocomial infections in burn hospitals have become one of the most common causes of mortality and morbidity. Gram-negative bacteria are the leading causes of mentioned infections [1-3]. The genus *Citro-*

*bacter* belongs to a group of facultative anaerobic Gram-negative bacilli (from the Enterobacteriaceae family) frequently found in water, soil, and food [4]. Members of *Citrobacter* are also found infrequently as normal inhabitants of the intestinal tract of humans. Also, they are among the most prevalent bacteria isolated from nosocomial infections and known to play a role in the de-

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velopment of bacteremia, meningitis, diarrhea, and brain abscess. However, their role as a cause of urinary tract infections in children has not been studied well. These organisms may also be responsible for severe infections, especially in immune-compromised hosts [5].

The genus of *Citrobacter* comprised 11 different species, among which *C. freundii* is the most prevalent found in infections. *C. freundii* is associated with opportunistic nosocomial infections such as Urinary Tract Infections (UTIs), wound infections, gastrointestinal diseases, septicemia, and meningitis, especially in immune-compromised patients [6-8]. Although rare in newborns, *Citrobacter* infection usually leads to meningitis and intracranial abscesses that in 75% of patients with meningitis associates with a high rate of mortality and morbidity [5, 9, 10]. The mortality rate for meningitis caused by *Citrobacter* spp. has been reported at about 30% [11]. *Citrobacter* infections can be fatal, with 33%-48% overall death rates, and 30% in neonates [12].

In recent years, the emergence of Multi-Drug Resistant (MDR) *Citrobacter* to a wide range of antibiotic classes, including aminoglycosides, fluoroquinolones, and cotrimoxazole, has become a significant concern [13]. Multidrug-resistant mechanisms of *Citrobacter* strains have severely hampered our control efforts. Akya, in a study, showed that, out of 70 *Citrobacter* isolates, the highest rate of resistance belonged (84.8%) to cefazolin, and cotrimoxazole (36.4%), and the lowest to gentamicin (9.1%) [9]. Cleaning and observing disinfection procedures are the main approaches to prevent nosocomial infections; otherwise, the rate of antibiotic-resistant bacteria would be continuously increased, making the treatment process problematic, resulting in a longer duration of hospitalization, increased treatment costs, and higher rates of mortality [14, 15]. Therefore, the determination of resistance patterns among *Citrobacter* spp. would be of great medical value [9]. Given the overuse of antibiotics in Iran and a constant increase in antibiotic resistance, it is necessary to evaluate resistant strains via antibiotic susceptibility tests to prevent the emergence of new resistant strains [16].

Accordingly, regarding the undeniable role of *C. freundii* in the development of nosocomial infections in burn hospitals and its high resistance to several antibiotics, the present study was conducted to evaluate the prevalence of *C. freundii* and its antibiotic susceptibility pattern.

## Materials and Methods

### Sample Collection and Isolation

In this cross-sectional study (2016- 2017), a total of 3248 clinical samples, including wound, urine, sputum, blood, feces, and trachea, were isolated during one year from Zareh Burn Hospital, Sari City, Iran. The samples were grown on selective media, including blood agar, MacConkey agar, and thioglycollate broth based on bacteriology standards. Furthermore, blood samples were grown on TSB (Tryptic Soy Broth), and following 24-48 hours of incubation at 37°C, Gram-staining procedure was done to differentiate Gram-negative bacilli.

### Identification of Bacterial Isolates

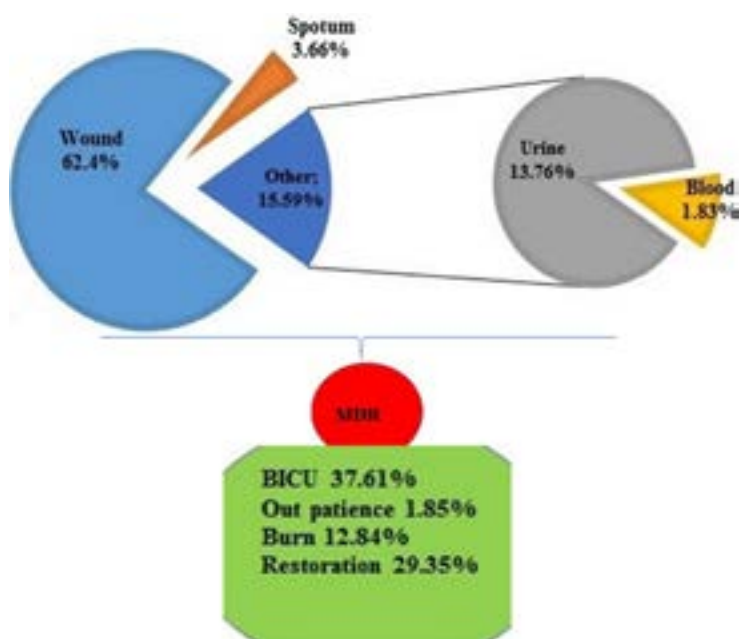
Bacterial identification of the isolates was performed according to conventional protocols mentioned in the Manual of Clinical Microbiology book [17]. In brief, biochemical tests, including oxidase, catalase, and motility detection in SIM medium, citrate, indole, methyl red, Voges-Proskauer, malonate utilization, H<sub>2</sub>S production lysine decarboxylase, and arginine dehydrogenase were done, and 109 samples were detected as having *C. freundii*. All of the utilized media were prepared as commercial media from HiMedia inc, India.

### Antibiotic Susceptibility Tests

Isolates confirmed as *C. freundii* by biochemical tests underwent disk diffusion susceptibility test based on the CLSI protocol [18]. In short, following preparation of 0.5 McFarland standards of each isolate, inoculation of the Mueller-Hinton agar plate with the test organism was carried out by streaking the swab in back and forth motions. Antimicrobial impregnated disks (BD BBLTM Sensi-Disc™), including amikacin (30 µg), ceftazidime (30 µg), cephalexin (30 µg), ciprofloxacin (5 µg), imipenem (10µg), meropenem (10 µg), gentamicin (10 µg), tobramycin (10 µg), co-trimoxazole (25 µg), and nitrofurantoin (10 µg) were put on the surface of the agar, and the plates were incubated for 24 hours at 37°C. Following incubation, inhibition zone sizes to the nearest millimeter were measured using a ruler. Using published CLSI guidelines, susceptibility, or resistance of the organism to each tested drug was determined.

## Results

In the present cross-sectional study, 109 isolated samples from outpatients of Zareh Burn Hospital were detected as *C. freundii* positive by biochemical tests. A total of 35 iso-



**Figure 1.** Frequency of MDR *C. freundii* isolates based on the clinical specimen and hospital wards



lates (32.1%) belonged to females, and 74 isolates (67.9%) belonged to males. Isolates were collected from the patients with a mean age of 49.7982 years. The eldest patient was 84 years old, while the youngest was only two years. Out of 109 obtained isolates, 79 (72.5%) were from the wound, 21 (19.3%) from urine, and 6 (5.5%) from sputum and 3 (2.7%) from the blood.

According to the results, in BICU, 41 isolates (37.61%) were identified as MDR strains. A total of 32(29.35%) were from the hospitals’ restoration department; moreover, 40 (36.69%) of BICU *C. freundii* isolates were detected among patients aged 21-70 years. Evaluation of the prevalence of antibiotic resistance showed that cephalexin (87.15%), co-trimoxazole (87.15%), and ciprofloxacin (79.81%) possess the most strength. (Detailed data are list-

**Table 1.** Antimicrobial susceptibility pattern of (*C. freundii*) isolates

Antibiotics	Susceptibility Patterns		
	No.(%)		
	Sensitive	Resistant	Intermediate
Ciprofloxacin	22 (20.2)	86 (79.81)	1(0.9)
Cephalexin	14 (12.8)	95 (87.15)	0
Ceftazidime	25 (22.93)	81 (74.31)	3(2.8)
Nitrofurantoin	24 (22.01)	83 (76.14)	2(1.83)
Amikacin	52 (47.7)	53 (48.6)	4(3.7)
Gentamicin	22 (20.2)	87 (79.8)	0
Tobramycin	33 (30.3)	75 (68.8)	1(0.9)
Co-trimoxazole	12 (11)	95 (87.15)	2 (1.83)
Imipenem	32 (29.35)	77 (70.64)	0
Meropenem	33 (30.3)	76 (69.7)	0



**Table 2.** Frequencies of isolated *C. freundii* according to the age, hospital wards, and specimens

Age Range	Hospital Wards					Clinical Specimens			
	No. (%)								
	BICU,	Out patience	Burn	Restoration	Psychology	Wound	Urine	Sputum	Blood
0-10	1 (2.1)	1 (20)	-	-	-	2 (2.5)	-	-	-
11-20	3 (6.2)	-	1 (6.7)	-	-	3 (3.8)	-	-	1 (33.33)
21-30	9 (18.8)	-	1 (6.7)	4 (10)	-	9 (11.4)	2 (9.5)	2 (33.3)	1 (33.33)
31-40	9 (18.8)	-	4 (26.7)	1 (2.6)	-	10 (12.7)	4 (19.15)	-	-
41-50	5 (10.4)	2 (40)	2 (13.35)	9 (23)	-	13 (16.4)	5 (23.85)	-	-
51-60	10 (20.8)	1 (20)	5 (33.3)	4 (10.3)	1 (100)	12 (15.2)	7 (33.3)	1 (16.7)	1 (33.33)
61-70	7 (14.6)	-	2 (13.3)	16 (41)	-	21 (26.6)	2 (9.5)	2 (33.3)	-
71-80	3 (6.2)	-	-	3 (7.7)	-	6 (7.6)	-	-	-
81-90	1 (2.1)	1 (20)	-	3 (7.7)	-	3 (3.8)	1 (4.8)	1 (16.7)	-
	48 (100)	5 (100)	15 (100)	39 (100)	1 (100)	79 (100)	21 (100)	6 (100)	3 (100)

**Table 3.** Percentage of MDR isolates based on the number of tested antibiotics

Clinical Specimens	Percentage of MDR Isolates to the Number of Antibiotics							
	No. (%)							
	R to 10	R to 9	R to 8	R to 7	R to 6	R to 5	R to 4	R to 3
Wound	15 (16.85)	8 (8.98)	1 (1.12)	14 (15.73)	12 (13.48)	14 (15.73)	2 (2.24)	2 (2.24)
Urine	7 (7.86)	4 (4.49)	2 (2.24)	0	1 (1.12)	0	0	1 (1.12)
Sputum	22 (2.24)	22 (2.24)	0	0	0	0	0	0
Blood	1 (1.12)	0	1 (1.12)	0	0	0	0	0
Trachea	0	0	0	0	0	0	0	0
Stool	0	0	0	0	0	0	0	0



R: Resistant; 2-10: The number of resistant patterns to tested antibiotics. The percentage has been calculated based on the 109 *C. freundii* isolates.

**Table 4.** Frequencies of MDR isolates considering age, samples, and hospital wards

Ages Interval	Hospital Wards					Clinical Specimens			
	No. (%)								
	BICU	Out Patience	Burn	Restoration	Psychology	Wound	Urine	Sputum	Blood
0-10	-	1 (50)	-	-	-	1 (1.5)	-	-	-
11-20	2 (4.9)	-	1 (7.1)	-	-	2 (3)	-	-	1 (50)
21-30	8 (19.5)	-	1 (7.1)	3 (9.7)	-	8 (11.9)	2 (13.3)	2 (50)	-
31-40	7 (17.1)	-	3 (21.5)	1 (3.2)	-	9 (13.4)	2 (13.3)	-	-
41-50	5 (12.2)	-	2 (14.3)	7 (22.5)	-	11 (16.4)	3 (20)	-	-
51-60	10 (24.4)	-	5 (35.7)	2 (6.5)	-	10 (14.9)	5 (33.4)	1 (25)	1 (50)
61-70	6 (14.6)	-	2 (14.3%)	15(46.9)	-	20 (29.4)	2 (13.3)	1 (25%)	-
71-80	3 (7.3)	-	-	2 (6.5)	-	5 (7.5)	-	-	-
81-90	-	1 (50)	-	2 (6.5)	-	2 (3)	1 (6.7)	-	-
Total	41 (100)	2 (100)	14 (100)	32 (100)	-	68 (100)	15 (100)	4 (100)	2 (100)



ed in Tables 1 and 2). Among all 109 samples isolated as *C. freundii*, 89 isolates (81.65%) were reported as MDR. Table 2 presents the frequencies of *C. freundii* isolates.

As illustrated in Table 3, 4 and Figure 1, 68 (62.38%) wound samples were MDR. Also, from wound and urine samples, 2 (2.53%) and 3 (14.28%) were susceptible to all tested antibiotics, respectively. The highest rates of antibiotic resistance in wound, urine, blood, and sputum were related to cephalexin, ciprofloxacin, tobramycin, and co-trimoxazole, in the descending order. Tables 3 and 4 presents detailed information.

## Discussion

The prevalence of nosocomial infections caused by *C. freundii*, as an opportunistic pathogen in immune-compromised patients, has considerably increased over the past decade [9, 19]. Given the overuse of antibiotics in Iran, and constant rise in antibiotic resistance, evaluation of resistant strains by antibiotic susceptibility test seems to be critical to prevent the emergence of new resistant strains. In the present study, *C. freundii* isolates showed 47.7% susceptibility to amikacin, while in a study conducted in India, sensitivity to the mentioned antibiotic was reported as 53.4%. Also, Jasemi, in a similar study, reported the susceptibility rate as 71.5% [6, 20]. Antibiotic resistance patterns not only differ in each country but also in each region due to genetic alteration and improper prescription of antibiotics [21].

In the current survey, *C. freundii* isolates demonstrated 70.64% susceptibility to imipenem, while, Akya reported a susceptibility rate of 100% for this bacterium to imipenem. Rate of resistance to carbapenems, as the last effective antibiotics against *Citrobacter*, has increased and become a primary concern worldwide, probably due to adopting improper infection control strategies in hospitals. Similar to the study conducted by Basavaraj in India, herein, most of *C. freundii* strains were isolated from the highest to the lowest from the wound, urine, body fluids, and blood samples [6, 9].

The mentioned isolates showed resistance to ciprofloxacin (79.81%) and ceftazidime (74.31%); however, in a study carried out in Kermanshah, Iran, resistance rate to mentioned antibiotics has been reported as 76.2% and 66.6%, respectively. Consistent with the study by Jasemi, in the present research, amikacin and imipenem were the most effective antibiotics against *C. freundii* infections.

Furthermore, the highest rate of resistance was reported for co-trimoxazole, ciprofloxacin, and ceftazidime [20].

Resistance to tobramycin (68.2%), ceftazidime (76.4%), amikacin (46.6%), and gentamicin (75.5%) were also reported, which was in line with results of a study carried out in 2014 (6). Over the past years, due to the overuse of antibiotics, the emergence of MDR *C. freundii* strains has occurred, making it a globally primary concern [13]. Resistance rates to cephalosporin were evaluated in this survey, and resistance to ceftazidime (74.31%) and cefalexin (87.15%) was also shown, while in previous studies, resistance to ceftazidime (76.4%) and ceftriaxone (40%) has been demonstrated [22]. Resistance to ceftazidime (86.3%) has also been reported in a similar experiment by Jafari.

Moreover, resistance to fluoroquinolone, such as ciprofloxacin (79.81%), has also been reported. Results of our survey showed that 2 out of 3 *C. freundii* isolates obtained from blood were MDR, which was consistent with the results of the study by Mahmoodi conducted in Hamadan, Iran [23]. In a study performed in Ethiopia,  $\frac{3}{4}$  of blood samples were reported positive for *C. freundii* [24]. Metri and his colleagues by conducting a retrospective study in 2013 to that patient with confirmed urine tract infection observed that *Citrobacter* isolates were found to be the third most common organism causing UTI in hospitalized patients. UTIs caused by *Citrobacter* species have been described in 5% to 12% of bacterial urine isolates in adults [6].

MDR Enterobacteriaceae isolates are responsible for creating a variety of infections in humans and animals. Considering the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC), to create a standardized international terminology with which to describe acquired resistance profiles in PDR in Enterobacteriaceae are as follows: MDR: non-susceptible to  $\geq 1$  agent in  $\geq 3$  antimicrobial categories, and XDR (extensively-drug resistant): non-susceptible to  $\geq 1$  agent in all but  $\leq 2$  categories [25].

At the current research, 21 isolated *C. freundii* were determined in the urine sample, and the prevalence of the mentioned bacterium from urine specimens was higher than other clinical specimens (except for wound specimens). In research conducted by Belachew in 2018, in Ethiopia, 11% of isolated bacteria from river water samples were identified as *C. freundii* strains. Moreover, 60% of isolates were MDR *C. freundii* as well [26]. In 2011, Poirel was reported an isolated *C. freundii* from an 18 years old cauterized patients that were highly resistant to  $\beta$ -lactams such as carbapenems, aminoglycosides, sulfonamides, tetracycline, and fluoroquinolones [26]. In this study, by conducting an antibiogram as a standard test for the evaluation of pheno-

typic resistance to antibiotics out of 109 isolated *C. freundii*, 88 isolated were screened as MDR isolates according to the CDC and ECDC guidelines.

## Conclusion

In the current study, the prevalence of MDR *C. freundii* was 81.65%, highlighting the need for precise identification, eradication, and evaluation of antibiotic susceptibility pattern of this microorganism. The results call for the urgent design of more practical methods for infection control in hospital wards.

## Ethical Considerations

### Compliance with ethical guidelines

This study was approved by Mazandaran University of Medical Sciences ethics committee. All performed on the enlarged ethical statement IR.MAZUMS.REC1397.061 meeting number in Mazandaran University of Medical Sciences. In this study, all ethics including Ethics and Consent to participate from their parents have been collected in the research.

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### Authors contribution's

Experimental tests: Zahra Norouzi Bazgir; Preparation of Manuscript and interpretation of results: Bahman Mirzaei; Writing the manuscript draft: Mohammad Reza Haghshenas; Experimental researches: Hamid Reza Goli; Final editing of manuscript: Ebrahim Shafaie

### Conflict of interest

The authors declared no conflict of interest.

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