Isolation of Citrobacters in Various Infections and Their Antimicrobial Sensitivity Rates

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Summary

The samples for culture from the patients admitted to Konya Research and Education Hospital between January 2009 and July 2010 were investigated. The obtained *Citrobacter* strains were studied for antimicrobial sensitivity rates and their distribution ratesto the clinics. The samples obtained were inoculated onto related culture media. Aseptic body samples were incubated at 37ºC into bottles of BACTEC 9120 blood culture system. For the identification and antimicrobial sensitivities of yielding bacteria, panels of Phoenix-100 automized identification device were used. Mean age rate of patients in whom *Citrobacter* strains were determined was 41.29±4.345. Of all samples with *Citrobacter* strains, 48% were isolated from urine, 29% from surgical wounds, 11% from sputum, 2% from peritoneal fluid, and 2% from vaginal samples. Of total 52 *Citrobacter* strains, the species level distribution was 46% *C. freundii,* 21% *C. youngae,* 15% *C. koseri,* 10% *C. braakii,* 6% *C. farmeri* and 2% *C. wermanii.* The distribution of samples with *Citrobacter* strains to the clinics were 29% adult intensive care unit (ICU), 21% pediatric, 11% general surgery, 10% in neonatal ICU, 10% plastic surgery, 7% urology, 6% burn unit, and 6% nephrology department. The most sensitive antimicrobial agents to *Citobacter* strains were amikacin (100%), meropenem (100%), imipenem (96%) and piperacillin/tazobactam (96%).

Keywords: Citrobacter, Antimicrobial agent, Sensitivity

Citrobacterlerin Çeşitli İnfeksiyonlardan İzolasyonu ve Antimikrobiyal Duyarlılık Oranları

Özet

Konya Eğitim ve Araştırma Hastanesi'nde Ocak 2009 ile Temmuz 2010 tarihleri arasında yatmakta olan hastalardan istenen kültürler üzerinde çalışılmıştır. Çalışmada saptanan *Citrobacter* türlerinin örnek ve kliniklere göre dağılımları ile antimikrobiyal duyarlılık durumları araştırılmıştır. Alınan örnekler ilgili besiyerlerine ekimleri yapıldı. Steril vücut örnekleri ise Bactec 9120 kan kültür sistemine ait şişelere alınarak 37ºC ısıda inkübe edildi. Üreyen bakterilerin identifikasyon ve antimikrobiyal duyarlılıkları için Phoenix-100 otomatize identifikasyon cihazına ait paneller kullanıldı. *Citrobacter* saptanan hastaların yaş ortalamaları 41.29±4.345 idi. İzole edilen Citrobacterlerin %48'i idrar, %29'u cerrahi yara, %11'i balgam, %8'i kan, %2'si periton mayi ve %2'si ise vajen örneklerinden izole edilmişlerdir. Toplam 52 *Citrobacter* suşunun %46'sı *C. freundii,* %21'i *C. youngae,* %15'i *C. koseri,* %10'u *C. braakii,* %6'sı *C. farmeri* ve %2'si ise *C. wermanii* idi. *Citrobacter* saptanan örneklerin %29'u erişkin yoğun bakım, %21'i pediatri, %11'i genel cerrahi, %10'u yenidoğan yoğun bakım, %10'u plastik cerrahi, %7'si üroloji, %6'sı yanık ünitesi ve %6'sı ise nefroloji'de yatan hastalardan izole edilmişlerdir. Citrobacterlerin en sık duyarlı oldukları antimikrobiyal ajanlar sırasıyla amikacin (%100), meropenem (%100), imipenem (%96) ve piperacillin/tazobactam (%96) oldukları saptanmıştır.

Anahtar sözcükler: Citrobacter, Antimikrobiyal ajan, Duyarlılık

INTRODUCTION

A member of *Enterobacteriaceae* family, *Citrobacter* strains are facultative anaerobic, motile Gram-negative bacillus producing in simmons citrate culture media and hydrolyzing urea. The classification Citrobacters can still be obscure and complicated. Eleven various strains exist in this group and are localized in intestinal system. These were

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sometimes accepted to be in *Escherichia* or *Salmonella*. Bacteria having used to be called *Bethesta- Ballerup* group have been categorized and evaluated in the group of *Citrobacter freundii* in recent times. Previously called *Levinea malonatica* and *Levinea amalonatica* in a different bacteria group termed Levinea, bacteria were also classifield into *Citrobacter* strains in terms of their characteristics and called *Citrobacter koseri* and *Citrobacter amalonaticus*, respectively. Existing in Citrobacter group, biovars are difficult to be classified and have led to confusions. The most encountered in this group are *Citrobacter freundii* [1-3]. Primary infection development due to *Citrobacter* is so rare in immunocompetent patients. They are mostly the cause of nosocomial infections in newborns and immuno-compromised patients. *Citrobacter koseri*, for instance, has been noticed to be a microorganism giving rise to menengitis and cerebral abcess in newborns [4]. *Citrobacter freundii* was also first identified in 1932 and has been increasingly developing a high resistance against anti-microbial agent [5]. As well as bringing about *Salmonella*-like intestinal and other infections caused by coliform bacteria, *Citrobacter* strains are present in feces existing in humans and animals. *Citrobacter* strains have been also determined as an etiologic agents in bacteremia, menengitis, mastitis and brain abcess [6-10]. They lead to diarrehea and severe sepsis, especially in immunocompromised patients. Their pathologic mechanisms still remain unknown. Despite of their unfrequency, *Citrobacter* strains are also linked to infections with nosocomial origins of urinary or respiratory systems. *Citrobacter* strains are in need of complicated administration of antibiotcs due to the development of multible antibiotic resistance. Therefore, the implementation of antimicrobial sensitivity tests is of a crucial role in the treatment of *Citrobacter* infections [11,12].

MATERIAL and METHODS

In order to investigate the resistance rates of *Citrobacter* strains to antimicrobial agents and of the effects on infections in our hospital, total 24293 materials referred to the Microbiology Laboratory between January 2009 and July 2010 were evaluated. The samples obtained were inoculated onto culture medium of 5% defibrinated sheep blood Colombia agar (DIFCO-USA), and onto culture media of Mac Conkey agar (DIFCO-USA), Eosine Methilen Blue agar (DIFCO-USA) and SS agar (DIFCO-USA). Aseptic body samples, such as blood, CSF and bone marrow, however, were incubated 10 days most at 37°C, being put into BACTEC 9120 (Becton Dickinson-USA) blood culture bottles. After determining mainly morphologic criteria of producing bacteria via Gram-dying, panels of automized identification device Phoenix 100 (Becton Dickinson-USA) was used in order to determine the certain identification and anti-microbial sensitivity rates.

Statistical Analysis: In the assessment of pooled data, chi square test was performed through SPSS 15.0 package software. Values with P<0.05 were accepted to be statistically significant.

RESULTS

Among the patients with Citrobacter, 24 (46%) were men, and 28 (54%) were women; 4 of them were at the first year of age. Mean age rate of other patients, between 1 and 82 years of age, was 41.29±4.345. Of all samples with *Citrobacter*, 15 (29%) were obtained from adult ICU, 11 (21%) from pediatric department, 6 (11%) from general surgery department, 5 (10%) from newborn ICU, 5 (10%) from plastic surgery department, 4 (7%) from urology department, 3 (6%) from burn unit department and 3 (6%) from nephrology department. All of the subjects were in-patients.

Of total 52 *Citrobacter* strains, 24 (46%) were *C. freundii*, 11 (21%) *C. youngae*, 8 (15%) *C. koseri*, 5 (10%) *C. braakii*, 3 (6%) *C. farmeri,* and 1 (2%) *C. wermanii*.

In the patients with pediatric age group, citrobacters have frequently been isolated as the agent of urinary tract infections. Of citrobacters isolated, 25 (48%) were isolated from urine, 15 (29%) from surgical wounds, 6 (11%) from sputum, 4 (8%) from blood, 1 (2%) from peritoneal fluid and 1 (2%) from vaginal samples. Distribution rates of *Citrobacter* strains according to samples and clinics were presented in *Table 1* and *2*.

Antimicrobial agents to citrobacters were amikacine

Table 1. *Distribution rates of Citrobacter strains based on the samples (n)*
Tablo 1. *Citrobacter türlerinin örneklere göre dağılım oranları*

Citrobacter Species	Urine	Surgical Wounds	Sputum	Blood	Peritoneal Fluid	Vaginal Samples	Total	%
C. freundii	14	5	2	3	-	-	24	46
C. youngae	2	6	2	-	1	-	11	21
C. koseri	4	2	2	-	-	-	8	15
C. farmeri	2					1	3	6
C. braakii	2	2		1			5	10
C. werkmanii	1	-	-	-	-	-	1	2
TOTAL	25	15	6	4	1	1	52	100

(100%), meropenem (100%), imipenem (96%) and piperacillin/tazobactam (96%). Sensitivity rates of isolates to antimicrobial agents were also presented in *Table 3*.

It was determined that *C. freundii*, the most frequently determined strain in our hospital, was found to be sensitive (100%) to amikacin, cefazolin, imipenem, levofloxacin, meropenem and piperacillin/tazobactam; *C. youngae* to be sensitive (100%) to amikacin and meropenem; and *C. koseri* to be sensitive (100%) to amikacin, imipenem, meropenem and piperacillin/tazobactam.

Statistical Findings

Mean age rate was defined to be 41.29±4.345. Upon evaluating gender differences and distribution rates of *Citrobacter* strains, two different hypothesis were set up. In H_0 hypothesis: no relation is present between type of

Citrobacter strains and gender. In H_1 hypothesis: between type of *Citrobacter* strains and gender, a relation ship exists. In this comparison, significance was $P<0.05$, and the association was accepted to be significant.

When distribution rates of the samples of *Citrobacter* strains, two different hypothesis were set forth. In H_0 hypothesis: there is no association between type of the *Citrobacter* and distribution of samples. In H_1 hypothesis, however: an association exists between type of the *Citrobacter* and distribution of samples. In the comparison, significance rate was $P<0.05$, and the association was found to be significant.

When evaluating distribution rates of *Citrobacter* strains according to clinics, two different hypothesis were also established. In H_0 hypothesis: between distribution rates to the clinics and *Citrobacter* strains, there is no association.

Table 2. Distribution rates of Citrobacter strains based on the clinics (n)
Tablo 2. Citrobacter türlerinin kliniklere göre dağılım oranları

Citrobacter Species	Adult ICU	Pediatrics	General Surgery	Newborn ICU	Plastic Surgery	Urology	Burn Unit	Nephrology	Total
C. freundii	8	5	3	2	1	3	2	-	24
C. youngae	3	1	3	2	1	-	1	-	11
C. koseri	2	2	-	-	2	-	-	2	8
C. braakii	2	1	-	-	1	1	-	-	5
C. farmeri	-	1	-	1	-	-	-	1	3
C. werkmanii	-	1	-	-	-	-	-	-	1
TOTAL	15	11	6	5	5	4	3	3	52

Table 3. Sensitivity and resistance rates of Citrobacter strains to antimicrobial agents
Tablo 3. Citrobacter türlerinin antimikrobiyal ajanlara duyarlılık ve direnç oranları

Antimicrobials	C. freundii		C. youngae		C. koseri		C. farmeri		C. braakii		C. werkmanii	
	S	R	S	R	S	R	S	R	S	R	S	R
Amikacin	24	0	11	0	8	0	3	0	5	0	1	0
Amox/Clav *	1	23	2	9	6	2	2	1	0	5	1	0
Ampicillin	1	23	0	11	1	7	1	2	0	5	0	1
Cefazolin	24	0	1	10	2	6	1	2	0	5	0	1
Cefepime	21	3	8	3	3	5	2	1	5	0	1	0
Cefotaxime	16	8	6	5	5	3	2	1	5	0	1	0
Cefoxitin	7	17	0	11	4	4	0	3	0	5	0	1
Ciprofloxacin	23	1	6	5	7	1	2	1	5	0	1	0
Gentamicin	23	1	8	3	1	7	2	1	5	0	1	0
Imipenem	24	0	9	2	8	0	3	0	5	0	1	0
Levofloxacin	24	0	7	4	7	1	2	1	5	0	1	0
Meropenem	24	0	11	0	8	0	3	0	5	0	1	0
Piperacillin	20	4	5	6	7	1	1	2	5	0	1	0
Piper/Tazo **	24	0	9	2	8	0	3	0	5	0	1	0
Trim/Sulfa ***	23	1	4	7	6	2	2	1	4	1	1	0

** Amoxicillin/Clavulanate, ** Piperacillin/Tazobactam, *** Trimethoprim/Sulfamethoxazol, **S:** Sensitive, **R:** Resistant*

In H₁: there is an association between two assets. In this comparison, significance rate was P<0.05, and the association was accepted as significant.

In the assessment performed, a significant association was found to be in the distribution rates of producing *Citrobacter* strains according to sex, samples and clinics (P<0.05).

DISCUSSION

The education and application of personal hygene are important in that *Citrobacter* strains are excreted as fecal wastes. Epidemics occuring in hospitals are closely related to the fact that hospital staff carry the bacterium in their hands and gastrointestinal systems. *Citrobacter* strains are mostly isolated from the infections of urinary and respiratory systems as nosocomial infection causes [13,14]. The most significant risk factor is gastrointestinal system for microorganisms in order to form colonization. In studies performed, the rate of gastrointestinal colonization in nosocomial epidemics was determined to be 27%. Bacteremia and sepsis of *C. freundii* originate from primary foci in urinary system and gallbladder, mainly from gastrointestinal system [13]. Three of *C. freundii* and one of *C. braakii* strains determined in our study were isolated from the blood samples of patients over 60. Most of *Citrobacter* strains were isolated from urine, surgical wounds and sputum samples. The treatment of urinary system infections caused by *Citrobacter* strains is of a vital importance. These infections, if untreated, may lead to high mortality sepsis. Adult ICUs, pediatric and general surgery departments were witnessed to be the settings where citrobacters were determined most. In the statistical analysis of the data pooled in our study, a significant association was found in the distribution rates of *Citrobacter* strains according to sex, samples and clinics (P<0.05). Since the number of *Citrobacter* strains determined in our study were 52, a significant correlation was determined in statistical assessment. However, it was concluded that as the number of strains grows, varieties could also be defined in statistical values.

Studies related to citrobacter infections and their antimicrobial sensitivity are limited in Turkey. The sensitivity rates determined in the present study were 100% to meropenem and amicacin, and 96% to imipenem and piperacillin/tazobactam. In line with the results in our study, Gulhan et al.[15] reported sensitivity rates of 99% and 93% to meropenem and amicacine, respectively. In the study performed by Durmaz et al.[16] in 1997, 100%, 63%, 40% and 29% of sensitivity rates were reported to be to imipenem, cefoxitin, piperacillin and ampicillin, respectively. In the present study, sensitivity rates to imipenem, sefoxitin, piperacillin and ampicillin were determined to be 96%, 21%, 75%, and 6%, respectively.

In Konya, Arslan et al.[17] reported the sensitivity rate of *Citrobacter* strains from blood cultures to imipenem to be 97.7%. In Ankara, Aksaray et al.[18] reported antimicrobial sensitivity rates of imipenem, piperacillin/tazobactam, cefepime, gentamicin, amikacin and ciprofloxacin to *C. freundii* to be 75%, 25%, 25%, 50%, 75% and 50%, respectively.

As a result of the study performed between 1999 and 2000 in USA and on 4488 bacterial strains isolated from various centers according to MYSTIC program, 96% of sensitivity rate of *Citrobacter* was announced against meropenem, imipenem, cefepim and piperacillin/tazobactam [19], and the result is consistent with the one in teh present study. Cheng et al.[20] found the sensitivity rates of imipenem, cefepime and amikacin to be 94%, 80% and 80% in China, respectively. Samonis et al.[21] reported amikacin, gentamicin, imipenem and ciprofloxacin to be the most effective agents against 27 *C. freundii* strains.

While the sensitivity rates to carbapenem were found to be 100% and 96%, respectively in our study, Lockhart et al.[3] in USA and Ishii et al.[22] in Japan reported the sensitivity rates of citrobacters to carbapenem to be quite positive in ICUs in the study performed in 100 different centers. In their study performed in 15 centers in China, Yang et al. reported that carbapenem and piperacillin-tazobactam were effective at the rate of more than 80% on citrobacters determined as nosocomial agents [23]. Morosoni at al. reported the sensitivity rates of meropenem, imipenem, amikacin and piperacillin-tazobactam to be 100%, 100%, 93.3% and 93%, respectively [24]. In Taiwan, Wang et al. investigated the sensitivity rates of 61 *C. freundii* isolates to 15 antimicrobial agents and reported that imipenem and cefepim were the most influential agents. In the same study, they also reported a considerable decrease in aminoglycosid sensitivity during the period between 1987 and 1990 [5]. A 12% of decrease was also determined in the sensitivity rate of gentamicin in the present study.

Samonis et al.[25] isolated majority of Citrobacter strains as *C. freundii*, *C. koseri* and *C. braakii* in a study performed in Greece. They isolated *Citrobacter* strains mostly from the infections of urinary tract, surgical wounds and respiratory tract. In their study, imipenem (97.4%), gentamicin (89.5%), ciprofloxacin (80.6%) and cefepime (73.7%) were reported to be the most effective agents.

Although the sensitivity to large spectrum beta-lactam antibiotics and carbapenems has been decreased in Gram-negative bacilli recently, Carbapenems are still the most effective antibiotics [26,27]. In various studies, imipenem, meropenem and ciprofloxacin were reported to be the most effective antimicrobial agents [28,29]. It was also witnessed in both our study and other studies that the most effective antimmicrobial agents in the treatment of Citrobacter infections are still imipenem, meropenem, amikacin, ciprofloxacin and piperacillin/tazobactam.

In the treatment of infections with antimicrobial agents, the use of antibiotics, especially those with large spectrum, should be avoided as possible. In patients with immunocompression, multiple trauma or treated with large surgical interventions or implanted with allien materials, antibiotic treatment regime should be well-planned in the treatment of infections. In these patients, as a result of long-term antibiotic administration, resistance of various bacteria may be able to develop to antibiotics. It is a must that in patients in whom small spectrum antimicrobial agents are sufficient, the administration of large-spectrum antibiotics should be avoided. With the monitoring of antibiotic use and determination of resistance development, the success rate of the treatment can be elevated [30].

As a consequence, such epidemiologic studies will guide clinicians to choose accurate empirical treatment options and provide mortality rates from infections to decrease. It is more significant to prevent the resistance development in microorganisms and to lend the accurate information to clinicians in terms of the use of antibiotics in appropriate period. Considering the correlation between the use of antibiotics and resistance development, the control of Citrobacter infections will be likely with the reasonable use of antibiotics. Due to the limited number of studies on *Citrobacter* strains and their antimicrobial sensitivity rates in Turkey, the present study presents important information on this field and will potentially enlighten future studies in Turkey.

ACKNOWLEDGEMENTS

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