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The Prevalence of Antibiotic Resistance of Enterobacteriaceae Strains Isolated in Community- and Hospital-Acquired Infections in Teaching Hospitals of Hamadan, West of Iran

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ABSTRACT

Background: The prevalence of antimicrobial resistance among Enterobacteriaceae is increasing worldwide. Identification of pathogens and their resistance to antimicrobials is mandatory for successful empiric antibiotic treatment. The aim of this study was to investigate the prevalence of antimicrobial resistance of Enterobacteriaceae isolated from hospital-acquired and community-acquired infections.

Methods: In a descriptive-comparative study, during 2010, all clinical isolates of Enterobacteriaceae and their antibiograms from laboratories of Sina and Bessat Hospitals, Hamadan, west of Iran were included. Hospital-acquired infections were identified by records from infection-control units. A questionnaire containing information about demographic characteristics, source of specimen, kind of Enterobacteriaceae and their antimicrobial resistance was filled for each patient. Data were analysed using SPSS.

Results: A total of 574 samples were collected, out of which the most prevalent pathogens were Escherichia coli and Klebsiella pneumoniae. Almost all isolates of Enterobacteriaceae were resistant to ampicillin (98.8%), and the least resistance was to piperacillin (3.7%). In addition, most isolates were resistant to cefazolin, cefixime, and co-trimoxazole. Among third generation cephalosporins, the highest resistance to ceftriaxone and the least resistance to ceftizoxime were observed. 19.3% of isolates were resistant to imipenem. In terms of fluroquinolones, nosocomial infections and community acquired infections were resisitant to ciprofloxacin 33% and 4.1% respectively. The rate of resistance in nosocomial infections was higher than that of community-acquired infections.

Conclusion: The prevalence of multidrug resistant Enterobacteriaceae is increasing both in community-acquired and hospital-acquired infections. Because of propable increasing resistance to fluoroquinolones and newer betalactams, reassessment of resistance of Enterobacteriaceae must continue in future years.

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Introduction

Enterobacteriaceae is a large and heterogeneous family of gram-negative, facultative anaerobic, enteric bacilli whose normal place is in gastrointestinal tract of human and animals. Drug resistance in enteric bacilli is largely attributed to the vast transfer of resistance plasmids among different genera of Enterobacteriaceae. Today, in many regions of the world; about half of *Shigella* species are resistant to numerous drugs. The *Salmonella* carried by animals also is resistant especially against drugs (particularly tetracycline) used in animal foods. Use of drugs in animal foods leads to faster growth of animals, however, this is associated with an increase in drug-resistant intestinal organisms in fecal flora of farm workers [1].

Plasmids carrying drug resistance genes are observed in many gram-negative bacteria of normal flora. Extensive use of antimicrobial drugs, especially in hospitalized patients, has resulted in inhibition of drug-sensitive organisms in intestinal flora and sustained presence and growth of drug-resistant bacteria including *Enterobacter, Klebsiella, Proteus, Pseudomonas, Serratia*, and fungi. Such organisms make various problems especially for patients with immunodeficiency and granulocytopenia. Closed environment of hospitals makes transfer of these resistant organisms easier through aerosols and direct contact from personnel [2].

Contamination and infection in medical environments are among the important public health problems of the present century [2]. Over recent years, on one hand, application of new treatment methods has saved lives, and on the other hand, it has had many fatal consequences by making the ground for nosocomial resistant infections [2,3]. In addition to increased mortality, nosocomial infections lead to an increase in hospitalization period, tasks of medical staff, taking medications, and consequently, considerable increase in treatment costs [4].

According to previous studies performed in Iranian hospitals, Enterobacteriaceae isolated from nosocomial infections were mostly resistant to ampicillin and cotrimoxazole and more than 70% of the isolates were resistant to one of the third-generation cephalosporins [5,6].

Given the increased prevalence of antibiotic resistance and also inappropriate and uncontrolled use of antibiotics by hospitalized and other patients, it is necessary to determine and compare the prevalence of antibiotic resistance in nosocomial and community-acquired infections in order to take required actions toward control of antibiotic resistance.

The present study was conducted to determine the frequency of antibioticresistance ofEnterobacteriaceaeisolated fromnosocomial andcommunity-acquired infections in Hamadan, west of Iran.

Methods

In this descriptive-comparative study conducted in April 2010- April 2011 (a full year), all clinical samples with positive culture for Enterobacteriaceae along with their antibiogram results were requested from laboratories of Sina and Besat hospitals in Hamadan.

According to the possible source of infection, samples from one or more sites including blood, urine, sputum, wound srcretion, tracheal secretion, cerebrospinal fluid, joint fluid, or stool were obtained. Enterobacteriacea strains were identified by standard microbiological methods, but specific species using standard biochemical methods[7]. Antimicrobial susceptibility testing was performed by Kirby-Bauer disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute [8]. The following antibiotic disks were used: ampicillin (10 µg), cefazolin (30 µg), cefotamime (30 µg), ceftriaxone (30 µg), ceftizoxime (30 µg), ceftazidime (30 µg), cefixime (5 µg), gentamicin (10 µg), amikacin (30 µg), imipenem (30 µg), piperacillin (100 µg), cotrimoxazole (25 µg), nalidixic acid (30 µg), ciprofloxacin(5 µg) , and nitrofurantoin (30 µg) (Padtan Teb Co., Iran). Strains showing resistance to at least three antibiotics were considered as multidrug resistant (MDR).

The collected information contained origin of sample, admission ward, species of the pathogenic Enterobacteriaceae, and antibiogram results of the samples. Cases with nosocomial infection were requested from hospitals' infection control unit in order to determine the type of infections (nosocomial or community-acquired infections). The obtained data were recorded in the questionnaire. Nosocomial infections refer to clinically significant infections which occur due to the hospitalization process of patients. The infections which were manifested clinically after 48 hours of hospitalization were considered as hospital-acquired (nosocomial) infections [9]. Patients who went to clinics, emergency rooms, and physician offices and had positive culture for Enterobacteriaceae were included in the study as the community-acquired infections.

The data were analyzed using SPSS software. The qualitative variables were described using percentage frequency distribution and the groups were compared using Chi-square test. Percentages were used for description of antibiotic resistance with respect to Enterobacteriaceae strains. Chi square test was done for comparing the prevalence of antibiotic resistance among hospital and community acquired infections. *P* values less than 0.05 were considered significant.

Results

Totally, 574 samples were collected from 505 patients, of which, 303 samples (52.8%) and 271 samples (47.2%) were in nosocomial infection and community-acquired infection groups, respectively.

Based on their origin, the collected samples contained urine (69.3%), tracheal secretions (19.3%), blood (6.6%), wound infection (2.8%), sputum (0.9%), stool (0.3%), cerebrospinal fluid (0.3%), and joint fluid (0.3%).

Most of the samples were collected from emergency rooms and ICUs (144 samples (25.1%) from emergency rooms and 143 samples (24.9%) from ICUs, in that order) and the fewest samples were from Dermatology Ward (1 sample).

Among the 574 strains of Enterobacteriaceae, *E. coli* was the most prevalent species (70.6%). In the order of prevalence, other species of Enterobacteriaceae included 84 cases of *Klebsiella*spp. (14.6%), 45 cases of *Proteus* spp. (7.8%), 17 cases of *Enterobacter* spp. (3%), 12 cases of *Serratia* spp. (2.1%), two cases of *Shigella* spp. (0.3%), two cases of *Morganella* spp. (0.3%), and one case of *Salmonella* spp. (0.2%).

Sensitivity of the grown Enterobacteriaceae was assessed for 15 antibiotics which were effective against Gram-negative bacteria including ampicillin, amikacin, ceftriaxone, cefazolin, ceftizoxime, ceftazidime, cefixim, cefotaxime, ciprofloxacin, nitrofurantoin, gentamicin, imipenem, nalidixic acid, cotrimoxazole, and piperacillin. Frequency of antibiotic resistance in all samples is shown in Figure 1. The highest resistance and the lowest resistance were observed in ampicillin (99.8%) and piperacillin (3.7%), respectively.

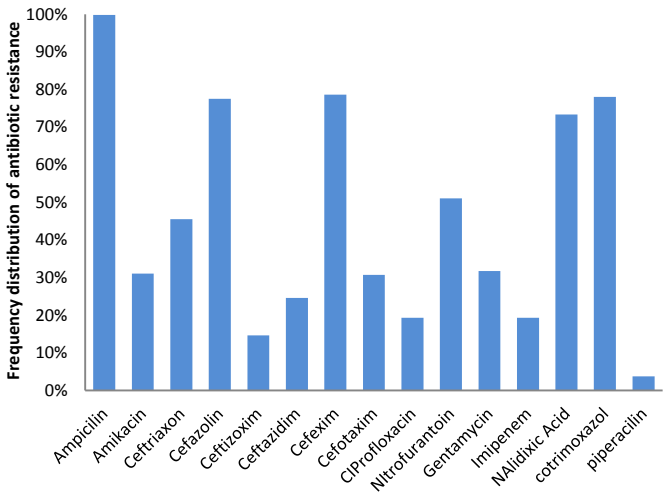

Figure 1: Frequency distribution of antibiotic resistance in *enterobacteriaceae* isolated in teaching hospital of Hamadan

Types of antibiotic resistance of Enterobacteriaceae are shown in Table 1 for community-acquired and nosocomial infections separately. In both groups of infections, ampicillin and piperacillin showed the highest and the lowest resistance, as well. Of those types of antibiotic resistance, only the antibiotic resistance to ampicillin of nosocomial infection group was not significantly different from that of community-acquired infection group, however, other cases of antibiotic resistance of one group were significantly different from those of other group(P<0.001).

As Table 2 indicates, in nosocomial infections, resistance against all antibiotics for isolated samples from ICU Ward were significantly higher than isolated from Emergency Ward (P<0.001) except for ampicillin.

Tables 3 and 4 show antibiotic resistance according to infectious organism in nosocomial and community-acquired infections. Accordingly, more than 20% of nosocomial and community-acquired *E. coli* species were resistant to 14 and 8 types of antibiotics respectively. Twenty-five percent of the nosocomial *Proteous* species were resistant to 12 types of antibiotics and 20% of the community-acquired ones were resistant to 10 types of antibiotics. Eight percent of the community-acquired *Klebsiella* and more than 29% of the nosocomial species were resistant to 8 types and 13 types of antibiotics respectively.

Table 1: The prevalence of antibiotic resistance by source of infections (hospital and community acquired infections)

	Hospital acquired		Community acquired		
Antibiotic	**N**	**%**	**N**	**%**	***P* value**
Ampicillin	302	99.7	271	100.0	0.344
Amikacin	127	41.9	51	18.8	< 0.001
Ceftriaxone	178	58.7	83	30.6	< 0.001
Cefazolin	271	89.4	174	64.2	< 0.001
Ceftizoxime	71	23.4	13	4.8	< 0.001
Ceftazidime	116	38.3	25	9.2	< 0.001
Cefixime	280	92.4	171	63.1	< 0.001
Cefotaxime	111	36.6	65	24.0	< 0.001
Ciprofloxacin	100	33.0	11	4.1	< 0.001
Nitrofurantoin	211	69.6	82	30.3	< 0.001
Gentamycin	117	38.6	65	24.0	< 0.001
Imipenem	99	32.7	12	4.4	< 0.001
Nalidixic acid	267	88.1	154	56.8	0.008
Co-trimoxozole	249	82.2	199	73.4	< 0.001
Piperacillin	21	6.9	0	0.0	< 0.001

Table 2: The prevalence of antibiotic resistance in nosocomial infections by the ward of admission (ICU & Emergency Wards)

	Ward of admission		
Antibiotic	**ICU (%)**	**Emergency (%)**	***P* value**
Ampicillin	100.0	100.0	1.000
Amikacin	53.1	15.3	<0.001
Ceftriaxone	75.5	26.4	<0.001
Cefazolin	95.8	58.3	<0.001
Ceftizoxime	28.0	5.6	<0.001
Ceftazidime	57.3	6.2	<0.001
Cefixime	97.2	58.3	<0.001
Cefotaxime	58.7	23.6	<0.001
Ciprofloxacin	42.7	2.8	<0.001
Nitrofurantoin	88.1	27.1	<0.001
Gentamycin	50.3	22.9	<0.001
Imipenem	46.2	3.5	<0.001
Nalidixic acid	98.6	52.8	<0.001
Co-trimoxozole	93.0	68.1	<0.001
Piperacillin	7.0	0.0	<0.001

Table 3: The prevalence of antibiotic resistance by Entrobacteriace strains in nosocomial infections

Antibiotic	***E. coli***	***Proteus***	***Klebsiella***	***Salmonella***	***Enterobacter***	***Citrobacter***	***Seratia***	***Morganella***
Ampicillin	99.5	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Amikacin	38.5	77.8	37.0	0.0	43.8	0.0	45.5	0.0
Ceftriaxone	55.7	59.3	74.1	0.0	56.2	0.0	54.5	0.0
Cefazolin	86.5	96.2	92.6	100.0	100.0	100.0	100.5	100.0
Ceftizoxime	23.4	25.9	18.5	0.0	50.0	0.0	9.1	0.0
Ceftazidime	32.8	70.4	44.4	0.0	31.2	0.0	36.4	100.0
Cefixime	89.6	100.0	94.4	100.0	100.0	100.0	100.0	100.0
Cefotaxime	33.9	55.6	35.2	0.0	37.5	0.0	54.5	0.0
Ciprofloxacin	35.9	7.4	29.6	0.0	56.2	0.0	36.4	0.0
Nitrofurantoin	58.9	100.0	75.9	100.0	100.0	100.0	100.0	100.0
Gentamycin	35.9	55.6	55.6	0.0	12.5	0.0	9.1	0.0
Imipenem	32.3	11.1	35.2	0.0	56.2	0.0	54.5	0.0
Nalidixic acid	85.9	100.0	83.3	100.0	100.0	100.0	100.0	100.0
Cotrimoxazole	81.8	100.0	77.8	0.0	81.2	0.0	81.8	100.0
Piperacillin	5.2	0.0	0.0	0.0	31.2	100.0	36.4	100.0

Table 4: The prevalence of antibiotic resistance by Entrobacteriace strains in community acquired infections

Antibiotic	*E. coli*	*Proteus*	*Klebsiella*	*Shigella*	*Enterobacter*	*Citrobacter*	*Seratia*	*Morganella*
Ampicillin	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Amikacin	19.7	22.2	16.7	0.0	0.0	0.0	0.0	0.0
Ceftriaxone	30.5	16.7	40.0	50.0	100.0	20.0	0.0	0.0
Cefazolin	63.8	72.2	63.3	50.0	100.0	40.0	100.0	100.0
Ceftizoxime	3.8	5.6	10.0	0.0	0.0	20.0	0.0	0.0
Ceftazidime	8.5	22.2	10.0	0.0	0.0	0.0	0.0	0.0
Cefixime	64.3	61.1	63.3	5.0	100.0	40.0	0.0	0.0
Cefotaxime	24.9	22.2	16.7	0.0	0.0	60.0	0.0	0.0
Ciprofloxacin	4.2	0.0	6.7	0.0	0.0	0.0	0.0	0.0
Nitrofurantoin	23.9	72.2	46.7	50.0	100	20.0	100	0.0
Gentamycin	24.9	22.2	26.7	0.0	0.0	0.0	0.0	0.0
Imipenem	4.2	0.0	6.7	0.0	100.0	0.0	0.0	0.0
Nalidixic acid	58.7	50.0	43.3	100.0	100.0	60.0	100.0	0.0
Cotrimoxazole	76.1	66.7	53.3	100.0	100.0	100.0	100.0	0.0
Piperacillin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

In terms of nosocomial *Enterobacter* species there was more than 30% resistance to 11 types of antibiotics and community–acquired species were resistant to 8 types of antibiotics.

Discussion

In this study, the most prevalent bacteria in Enterobacteriaceae family in nosocomial and community-acquired infections were *E. coli* and *Klebsiella* spp. The Enterobacteriaceae family with *E. coli* on the top has been known as the most prevalent agent of urinary tract infection (UTI), bacteremia, and sepsis and it is also among the prevalent agents of intra-abdominal and genital region infections. The Enterobacteriaceae species play a major role in most community-acquired infections with origins from urogenital system, lungs, gastrointestinal tract, bed sores, surgical wounds, and venous catheters [10,11]. In this study, almost all isolated species of Enterobacteriacea (98.8%) were resistant to ampicillin and they were least resistant (3.7%) to piperacillin. Moreover, most species were resistant to cefazolin, cefixime, and cotrimoxazole. The resistance against nitrofurantoin was rather high. Among the third-generation cephalosporins, the highest resistance was observed against ceftriaxone and the least resistance was observed against ceftizoxime. The resistance against aminoglycosides, ciprofloxacinand imipenem was high. In most of the cases, the resistance of Enterobacteriaceae in nosocomial infection was greater than that in community-acquired infections. In this manner, our findings about the higher resistance rates of Enterobacteriacea isolates from ICUs compared to those from emergency rooms is explained by the fact that almost all isolates from ICUs have nosocomial origin. Conversely, most bacteria isolates from emergency room patients are community-acquired.

In this study, the high sensitivity of Enterobacteriaceae to ceftizoxime and less sensitivity to ceftriaxone may be due to routine and extensive use of ceftriaxone in outpatients and inpatients and also limited use of ceftizoxime. Despite the availability of ceftizoxime, it has not been much received by physicians due to its higher dose and shorter half-life as compared to ceftriaxone.

In recent years, many studies have reported the increasing resistance of Enterobacteriaceae to ampicillin, cotrimoxazole and first-generation cephalosporins. The resistance to third-generation cephalosporins has also been increasing, though less than the first-generation, in many countries. Currently, among the beta-lactam antibiotics, carbapenems are the most effective drugs [12].

Studies in early last decade showed that the Enterobacteriaceae resistance in nosocomial infections is higher than that in community-acquired infections [13-15], especially in case of *Klebsiella* bacteremia which is more prevalent and causes higher mortality in nosocomial infections and is also more resistant to cephalosporins and ciprofloxacin [14-16]. However, the resistance to the above antibiotics in community-acquired infections is increasing parallel to that in nosocomial infections [17-18].

Two studies by Tsai et al. in 2010 and Wollheim et al. In 2011, considered the appearance of *E. coli* and *Klebsiella* producing extended-spectrum beta-lactamase (ESBL) and their release among different species of Enterobacteriaceae as the cause of resistant nosocomial infections and increase in mortality [19,20].

A review by Pitout et al. and a study on the course of Enterobacteriaceae resistance in Europe by Hawser et al. reported that the Enterobacteriaceae infection producing ESBL was increasing in recent decade both in hospitals and in communities and this has led to the fact that the empirical treatment's guidelines are not effective in community-acquired infections and require further reviews [21-22]. Given that most of the resistant species of Enterobacteriaceae are sensitive to carbapenems, physicians may use carbapenems as an empirical treatment for severe community-acquired urinary tract infection in near future [23].

According to the previous reports from different hospitals in Iran, ESBL producing Enterobacteriaceae have been common in the last decade [24-27]. Indeed, resistance

to carbapenems has been uncommon. Only 58.4% of *Klebsiella pneumoniae* isolates were sensitive to imipenem [28]. In the present study, resistance to imipenem was 19.3% which showed that the resistance to carbapenems in Iran is increasing faster than in European countries and that the uncontrolled use of this antibiotic warns about further resistance in near future. In the United States, carbapenem-resistant Enterobacteriaceae have been reported more commonly over the last years. The emergence of carbapenemase has contributed to an increased prevalence of carbapenem-resistant Enterobacteriaceae [29]. Studies performed in some Asian, African, and South American countries also have shown the global increase in MDR Enterobacteriaceae [30-32].

In a study from Kuwait in 2004, those species of Enterobacteriaceae causing community-acquired UTI showed increased resistance to ciprofloxacin and gentamicin [33]. Another study from Kuwait in 2009, showed the increased resistance of those species of Enterobacteriaceae causing nosocomial and community-acquired UTI to ciprofloxacin and piperacillin. In the above study, the multidrug resistance of *E. coli* and *Klebsiella* was observed in one third of both nosocomial and community-acquired infections. The ESBL producing species in nosocomial infections were more than those in community-acquired infections and the highest sensitivity was observed against carbapenems, piperacillin/tazobactam, and nitrofurantoin [30].

In a study by Khanfar in Saudi Arabia in 2009, all isolated types of *E. coli* and *Klebsiella* were sensitive to imipenem, however, the highest resistance was observed against ciprofloxacin and aminoglycosides [31]. The studies performed on community-acquired UTI in Senegal, Mexico, Madagascar, and Nicaragua have shown increased Enterobacteriaceae resistance in community-acquired infections especially against cotrimoxazole and ciprofloxacin [32,34-36].

In general, various studies have shown that the prevalence of MDR Enterobacteriaceae in nosocomial and community-acquired infections is increasing in Iran and different parts of the world.

Conclusion

The Enterobacteriaceae resistance to quinolones and carbapenems and its multidrug resistance in nosocomial and community-acquired infections are increasing in our region. To overcome these problems, the trend of Enterobacteriaceae resistance must be continually reassessed in future years due to the probable increase in resistance to new beta-lactams and quinolones.

In order to use antibiotics properly, awareness of epidemiological information on antibiotic resistance is helpful. Moreover appropriate guidelines for empirical treatment of community-acquired infections can prevent uncontrolled use of antibiotics and reduce the increasing process of antibiotic resistance in future.

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Conflict of interest statement

There was no conflict of interest for authors in this project.

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