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Antimicrobial Susceptibility Patterns of *Escherichia coli* Isolates from Hospitalized Patients with Different Infections in Isfahan, Iran: Impact on Empiric Antibiotic Therapy in Associated Infections

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Abstract

Background: *Escherichia coli* is an important cause of urinary tract, bloodstream, and surgical site infections.
Objectives: We investigated the organism's antibiotic susceptibility in hospitalized patients under different clinical conditions.
Methods: This prospective study was conducted in three referral hospitals located in Isfahan, Iran. Different clinical samples were tested using standard routine microbiological methods to identify E. coli strains and determine their antibiotic susceptibility patterns by the disk diffusion method according to CLSI recommendations. After conducting a clinical investigation, contaminated samples were excluded, and the hospital or community source and infection site were identified. Data on antibiotic susceptibility testing were extracted using WHONET software. Data analysis was then conducted using SPSS Statistics version 18.0.
Results: Of 1248 *E. coli* isolates, 71.9% were from urine, 15.1% from blood, and 7.8% from skin and soft tissue samples. High susceptibility was observed to Imipenem (98%), Meropenem (98.0%), and Amikacin (94.6%); intermediate sensitivity to Gentamicin (68.6%) and Cefepime (51.9%); and low susceptibility to Ceftazidime (46.8%), Ceftriaxone (41.3%), Ciprofloxacin (39.5%), Cefotaxime (39.3%), and Trimethoprim-sulfamethoxazole (32.4%).
Conclusions: Antibiotics, including Imipenem, Meropenem, or Amikacin, would be beneficial in the empiric therapy of severe infections where *E. coli* is the main cause.

Keywords: *E. coli*,Microbial Sensitivity Tests, Drug Resistance, Microbial, Iran

1. Background

Escherichia coli is a normal inhabitant of the gastrointestinal tract of humans and animals and is commonly recovered from vegetation, soil, and water (1). It is one of the most frequent etiologies of nosocomial and community-acquired infections worldwide (1). The bacterium is the most frequent cause of urinary tract infections and a major etiology of bacteremia, sepsis, surgical site infections, and gastroenteritis in both outpatients and inpatients. It is also a common cause of meningitis in newborns and immunocompromised individuals (1). Emerging resistance of the organism to different types of antibiotics is a global concern, complicating therapy for infected patients (1, 2). One of the most important mechanisms in the resistance of the bacterium to antibiotics is the production of extended-spectrum beta-lactamase (ESBL), which makes the bacterium resistant to all Penicillins and extended-spectrum Cephalosporins (1, 2).

The development of antibacterial resistance in pathogens is a dynamic phenomenon that varies over time and across different geographical locations (1, 2).

Consequently, repeated and regular assessment of the sensitivity profile of common pathogens in different communities is a main requirement (1, 2). Few well-designed studies have been performed on the antibiotic susceptibility of *E. coli* in Iranian populations. Most earlier studies in this regard only reported the antibacterial susceptibility of uropathogenic *E. coli*. Additionally, a significant number of these investigations did not have a strategy to reject contaminated samples. Furthermore, resistance patterns had not been reported in different situations, such as outpatients versus inpatients and community-acquired versus healthcare-associated isolates (3-7).

2. Objectives

This investigation aimed to determine the susceptibility pattern of *E. coli* strains isolated from patients admitted to three large medical centers in Isfahan, Iran. This research is clinically noteworthy as it helps clinicians prescribe empiric antibiotics for patients with suspected *E. coli* infections in the area.

3. Methods

3.1. Study Design

This research aimed to report the antimicrobial susceptibility pattern of E. coli in patients with documented bacterial infections who were admitted to three large medical centers in Isfahan City, Iran, according to age category, site of infection, and community/hospital source of infection. The medical centers participating in the survey were Dr. Shariati, Al-Zahra, and Dr. Gharazi hospitals. The laboratories of these hospitals have Quality Credit for microbiological reports from the Iranian Ministry of Health. Determination of contamination, hospital/community source of infection, and the site of infection was done by trained infection control nurses and physicians in the enlisted hospitals (8).

3.2. Bacterial Isolation and Antibiotic Susceptibility Testing

For the detection of microbial agents, samples were collected using aseptic techniques from urine, bloodstream, cerebrospinal fluid, deep collections, draining surgical sites, or bronchoalveolar lavage (BAL) (8). Identification of isolates as *E. coli* was done by routine conventional tests such as gram staining and biochemical tests (catalase and oxidase tests), reactions on triple sugar iron (TSI) agar, Methyl Red (MR) and Voges-Proskauer (VP) tests, indole production, urease test, citrate utilization, lysine iron agar (LIA) test, and motility.

The sensitivity pattern of *E. coli* was obtained by the disk diffusion method according to the Clinical Laboratory Standard Institute (CLSI) recommendations (9). Commercially prepared dehydrated antibiotic discs from MAST, Merseyside, UK, were used. Laboratories assessed the sensitivity of isolates to the following antibiotics: Gentamicin 10 μg or amikacin 30 μg, cefotaxime 30 μg, ceftriaxone 30 μg, ceftazidime 30 μg, cefepime 30 μg, ciprofloxacin 5 μg, trimethoprim-sulfamethoxazole 1.25/23.75 μg, and imipenem 10 μg or meropenem 10 μg.

Isolates that exhibited resistance to cefotaxime or ceftazidime underwent screening for ESBL production via the combination disc method as recommended by CLSI. A positive test for ESBL production was indicated by a ≥ 5 mm increase in the inhibition zone diameter for both antimicrobial agents when tested in combination with clavulanate versus the inhibition zone diameter of the agents when tested alone.

3.3. Identification of Contaminated Isolates

Assuming that *E. coli* has been isolated from a patient with clinical or paraclinical findings of infection at the isolation site, such as fever or focal signs of infection, it is considered a true pathogen. Otherwise, isolates are considered contaminated (8).

3.4. Differentiation of Community from Nosocomial Isolates

If *E. coli* was isolated from a clinical specimen after 48 hours of admission with new signs of infection, it was considered a nosocomial organism; all other isolates were defined as community-acquired (8).

3.5. Statistical Analysis

Antimicrobial sensitivity, ESBL production, and the hospital/community source of the isolates, in addition to the diagnosis and age group of the infected patients, were prepared using WHONET v 5.6 software. Analysis

was done with SPSS Version 18.0. Comparisons of antibiotic susceptibility in different infections, age groups, ESBL production, and the hospital/community source of the isolates were made using chi-square and Fisher exact tests. A P-value of less than 0.05 was considered significant.

4. Results

A total of 1679 *E. coli* isolates were found, with 25.7% (431) classified as contamination. Of 1248 patients with documented *E. coli* infections, 45.8% were males, 11.8% were less than 20 years old, and 85.4% were community-acquired. Most E. coli isolates were cultivated from inpatients with urinary tract infections (UTIs) (71.9%), followed by bloodstream infections (15.1%), skin and soft tissue infections (7.8%), and other infections (5%).

Antimicrobial sensitivity of *E. coli* isolates revealed that the bacterium was more susceptible to Meropenem (98.0%), Imipenem (98.0%), and Amikacin (94.6%), followed by Gentamicin (68.6%), Cefepime (51.9%), Ceftazidime (46.8%), Ceftriaxone (41.3%), Ciprofloxacin (39.5%), Cefotaxime (39.3%), and Trimethoprim-sulfamethoxazole (32.4%). In contrast to Imipenem, which was more effective in patients older than 20 years, the sensitivity of the isolates to Ciprofloxacin was lower in that age group. In addition, *E. coli* isolates were more susceptible to Ceftazidime in community-acquired infections than in nosocomial infections (Table 1).

ESBL producers comprised 388 (31.1%) of the isolates. The frequency of ESBL production was more prevalent in nosocomial isolates (42.3%) compared to community-acquired ones (29.1%), and in bloodstream (52.9%) or skin and soft tissue infections (57.1%) compared to other infections. The rate of ESBL production was less common in UTI isolates (25.6%) than in other infections. Susceptibility of *E. coli* ESBL producers was significantly lower to all examined antibiotics, including Ceftazidime, Cefotaxime, Gentamicin, Amikacin, Trimethoprim-sulfamethoxazole, and Ciprofloxacin, than non-ESBL producing *E. coli* isolates (Table 2).

The sensitivity of the isolates to examined antibiotics was similar in different infections, except for Gentamicin and Trimethoprim-sulfamethoxazole, which were more effective in UTI isolates, Meropenem, which was less effective in bloodstream infection isolates, and Cefepime and Ciprofloxacin, which were less effective in skin and soft tissue infection isolates compared to other infections (Table 3).

5. Discussion

Our findings revealed that most *E. coli* isolates from hospitalized patients in our region had high susceptibility to Imipenem, Meropenem, and Amikacin; moderate sensitivity to Gentamicin and Cefepime; and low susceptibility to Ceftazidime, Ceftriaxone, Ciprofloxacin, Cefotaxime, and Trimethoprim-sulfamethoxazole. In total, 31.1% of the isolates in our study were ESBL producers.

The present study showed that more than 90% of the *E. coli* isolates were susceptible to Imipenem, Meropenem, and Amikacin. Susceptibility to these antibiotics was high across all age groups, associated infections, and sources of infection acquisition (hospital versus community). As a result, these drugs can be effectively used in the empiric treatment of severe infections across different ages, various infections, and different acquisition sources. Other studies have reported similarly high susceptibility of *E. coli* to Carbapenems and Amikacin, indicating that these antibiotics can be used in severe infections caused by these bacteria in many parts of the world (10-12).

In our study, resistance to third- and fourth-generation cephalosporins, including Cefotaxime, Ceftriaxone, Ceftazidime, and Cefepime, was high (60.7%, 58.7%, 53.2%, and 48.1%, respectively). These drugs, which were the antibiotics of choice for many years in urinary tract, bloodstream, and wound infections, can now only be advised for non-severe cases or during the de-escalation phase of antibacterial therapy in such infections. High resistance to extended-spectrum cephalosporins was observed in all ages, all infections, and all acquisition sites (community or hospital). The resistance rate to Ceftazidime in hospital-acquired infections (73.1%) was statistically higher than in community-acquired infections (51.4%). However, in practice, a high level of resistance in both groups precludes recommending its use in the empiric treatment of severe infections that *E. coli* may cause. This high resistance level to third- and fourth-generation cephalosporins necessitates reconsideration in the blind treatment of urinary tract, bloodstream, surgical

Table 1. Sensitivity Profile of *E. coli* in Accordance to Age Group and Source of the Infection in Patients Admitted in three Hospitals in Isfahan, Iran [a]

Antibiotic	Age Group				Source of the Infection				Total
	<20 yrs n/N [b]	>20 yrs n/N [b]	P- Value	Odds Ratio (95CI)	Community n/N [b]	Hospital n/N [b]	P- Value	Odds Ratio (95	
ESBL +	47/147	341/1101	0.805	1.048	311/1066	77/182	<0.001	0.562	388/1248
	(31.9)	(30.9)		(0.724-1.516)	(29.1)	(42.3)		(0.407-0.775)	(31.1)
Imipenem	99/104	694/705	0.043	3.181	727/742	66/67	1.000	0.734	793/809
	(95.2)	(98.4)		(1.084-9.363)	(98.0)	(98.5)		(0.095-5.647)	(98.0)
Meropenem	102/105	734/749	0.476	0.695	683/698	148/150	0.751	.615	831/848
	(97.1)	(98.0)		(0.198-2.442)	(97.9)	(98.7)		(0.139-2.720)	(98.0)
Ceftazidime	64/127	474/1023	0.387	0.850	460/974	65/176	0.004	1.612	538/1150
	(50.4)	(46.3)		(0.588-1.229)	(48.6)	(36.9)		(1.158-2.245)	(46.8)
Ceftriaxone	41/87	183/462	0.191	1.359	209/498	16/47	0.291	1.401	225/545
	(47.1)	(39.6)		(0.857-2.153)	(42.0)	(34.0)		(0.747-2.628)	(41.3)
Cefotaxime	37/88	180/464	0.567	0.874	201/512	16/40	0.926	0.969	217/552
	(42.0)	(38.8)		(0.550-1.388)	(39.3)	(40.0)		(0.503-1.870)	(39.3)
Cefepime	67/118	495/971	0.234	1.263	486/914	76/169	0.500	1.390	562/1083
	(56.8)	(51.0)		(0.859-1.857)	(53.2)	(45.0)		(0.999-1.932)	(51.9)
Gentamicin	80/106	357/531	0.095	0.667	399/589	38/48	0.101	0.553	437/637
	(75.5)	(67.2)		(0.413-1.076)	(67.7)	(79.2)		(0.270-1.133)	(68.6)
Amikacin	684/120	924/977	0.848	0.919	872/921	166/176	0.846	1.072	1038/1097
	(95.0)	(94.6)		(0.387-2.184)	(94.7)	(94.3)		(.632-2.159)	(94.6)
Trimethoprim- sulfamethoxazole	45/124	246/775	0.315	0.816	250/776	41/123	0.806	0.951	291/899
	(36.3)	(31.7)		(0.549-1.213)	(32.2)	(33.3)		(0.635-1.424)	(32.4)
Ciprofloxacin	77/113	378/1040	0.000	0.267	399/983	56/170	0.060	1.391	455/1153
	(68.1)	(36.3)		(0.176-0.404)	(40.6)	(32.9)		(0.986-1.962)	(39.5)

[a] Values are expressed as (%).

[b] n/N (%); number of sensitive isolates/ total number of examined isolates (percent).

site, or other infections. Other research in Bangladesh (13), Iraq (11), and Iran (6) has observed similarly high levels of resistance to third- and fourth-generation cephalosporins.

The resistance of isolated *E. coli* strains in this study to Ciprofloxacin and Trimethoprim-sulfamethoxazole was high (60.5% and 67.6%, respectively). Therefore, these drugs are unsuitable for the empiric treatment of severe infections caused by this bacterium. In previous studies, resistance to these drugs has differed in different regions. The resistance rate to Fluoroquinolones has been reported as 5.5% in North America (14), 27% in Bangladesh (14), 45.5% in Iraq (11), 62.5% in Ethiopia (15), and 82.5% in India (16). On the other hand, resistance to Trimethoprim-sulfamethoxazole was 62.5%, 17.3%, 45.6%, 52.2%, and 82.5% in similar investigations in Ethiopia (15), North America (17), Bangladesh (14), Iraq (11), and India (16), respectively. This difference in the resistance of *E. coli* can be associated with different sampling sites or geographic variations in the organism's resistance.

In the present study, more than 31% of *E. coli* strains produced ESBL. These strains were significantly more prevalent in hospital-acquired (42.3%) than community-acquired infections (29.2%) and in bloodstream (52.9%) or skin and soft tissue infections (57.1%) compared to other infections. The rate of ESBL production was less common in UTI isolates (25.6%) compared to other studied infections. The susceptibility of these strains to all examined antibacterials, including Imipenem, Ceftazidime, Cefotaxime, Amikacin, Gentamicin, Ciprofloxacin, and Trimethoprim-sulfamethoxazole, was significantly lower than strains that did not produce this enzyme. In other studies from Iran, a similar prevalence of *E. coli* strains that produce this enzyme was observed (4-6).

In conclusion, our study showed the high susceptibility of *E. coli* strains in hospitalized patients to Imipenem, Meropenem, and Amikacin, and a high level of resistance to Ceftazidime, Cefotaxime, Ceftriaxone, Ciprofloxacin, and Trimethoprim-sulfamethoxazole. Clinical guidelines for treating infections where *E. coli* is

Table 2. Sensitivity of *E. coli* Isolates in Accordance to Diagnosis of Infected Patients in Three Hospitals in Isfahan, Iran

Diagnosis	UTI			Sepsis/Bacteremia			Skin and Soft Tissue Infection		
Antibiotic	n/N [a]	P- Value	Odds Ratio (95CI)	n/N [a]	P- Value	Odds Ratio (95CI)	n/N [a]	P- Value	Odds Ratio (95CI)
ESBL +	230/898	<0.001	0.327	100/189	<0.001	2.850	56/98	<0.001	3.122
	(25.6)		(0.250-0.428)	(52.9)		(2.077-3.912)	(57.1)		(2.051-4.753)
Imipenem	640/653	1.000	0.965	108/111	0.472	0.683	21/21	1.000	0.974
	(98.0)		(0.272-3.429)	(97.3)		(0.192-2.437)	(100)		(0.962-0.985)
Meropenem	561/571	0.450	1.454	135/140	0.035	0.272	86/88	0.694	0.866
	(98.2)		(0.548-3.863)	(96.4)		(0.085-0.868)	(97.7)		(0.195-3.850)
Ceftazidime	383/810	0.599	1.071	93/180	0.153	1.261	30/98	0.001	0.472
	(47.3)		(0.830-1.380)	(51.7)		(0.917-1.734)	(30.6)		(0.302-0.738)
Ceftriaxone	178/434	0.800	0.947	37/79	0.278	1.303	4/18	0.142	0.396
	(41.0)		(0.621-1.444)	(46.8)		(0.807-2.103)	(22.2)		(0.128-1.218)
Cefotaxime	175/445	0.989	1.003	31/79	0.989	0.997	5/13	1.000	0.964
	(39.3)		(0.651-1.545)	(39.2)		(0.612-1.623)	(38.5)		(0.311-2.986)
Cefepime	404/760	0.201	1.185	90/175	0.893	0.978	37/95	0.008	0.563
	(53.2)		(0.913-1.538)	(51.4)		(0.708-1.352)	(38.9)		(0.366-0.866)
Gentamicin	338/508	0.026	0.602	70/92	0.094	1.543	13/16	0.414	2.013
	(66.5)		(0.385-0.943)	(76.1)		(0.925-2.574)	(81.2)		(0.567-7.146)
Amikacin	732/773	0.866	1.050	159/172	0.168	0.640	93/97	0.813	1.353
	(94.7)		(0.594-1.857)	(92.4)		(0.338-1.212)	(95.9)		(0.480-3.817)
Trimethoprim- sulfamethoxazole	204/673	0.023	0.695	51/135	0.145	1.326	19/53	0.577	1.179
	(30.3)		(0.507-0.952)	(37.8)		(0.907-1.938)	(35.8)		(0.661-2.105)
Ciprofloxacin	322/821	0.792	0.966	80/180	0.137	1.276	23/94	0.002	0.470
	(39.2)		(0.744-1.253)	(44.4)		(0.925-1.759)	(24.5)		(0.289-0.764)

[a] n/N (%); number of sensitive isolates/ total number of examined isolates (percent).
[b] Values are expressed as (%).

Table 3. Sensitivity Profile of *E. coli* in Accordance to Production of ESBL in Infected Patients Admitted in Three Hospitals in Isfahan, Iran [a]

Antibiotic	ESBL			
	Producers n/N [b]	Non - producers n/N [b]	P-Value	Odds Ratio (95CI)
Imipenem	195/203	598/606	0.020	0.326
	(96.1)	(98.7)		(0.121 - 0.880)
Ceftazidime	14/386	524/764	< 0.001	0.017
	(3.6)	(68.6)		(0.010 - 0.030)
Cefotaxime	0/195	217/357	< 0.001	2.393
	(0.0)	(60.8)		(2.109 - 2.715)
Gentamicin	98/204	339/433	< 0.001	0.256
	(48.0)	(78.3)		(0.179 - 0.366)
Amikacin	346/374	692/723	0.026	0.554
	(92.5)	(95.7)		(0.327 - 0.938)
Trimethoprim - sulfamethoxazole	56/326	235/573	< 0.001	0.298
	(17.2)	(41.0)		(0.214 - 0.416)
Ciprofloxacin	63/376	392/777	< 0.001	0.198
	(16.8)	(50.5)		(0.146 - 0.268)

[a] Values are expressed as (%).
[b] n/N (%); number of sensitive isolates/ total number of examined isolates (percent).

a major cause should be revised to include Imipenem, Meropenem, or Amikacin in the empiric therapy of severe infections.

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Footnotes

Authors' Contribution: SNM and SR contributed in concept and design of the study and data acquisition; SR and ShP contributed in data collection; SNM, SR, and ShP contributed in data analysis and statistical analysis; SNM and ShP prepared the manuscript. All authors have substantial work in drafting of the work and final review and approve of the manuscript.

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