JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Frequency and susceptibility pattern of uropathogenic *Enterobacteriaceae* isolated from patients in Algiers, Algeria

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Abstract

Introduction: The frequency of *Enterobacteriaceae* involved in urinary tract infections (UTI) has increased significantly since the early 1990s, particularly in at-risk facilities such as resuscitation, surgery, urology and nephrology. The objective of this study was to evaluate the antimicrobial susceptibility of *Enterobacteriaceae* causing urinary tract infections (UTIs)at the University Hospital Centre of Benimessous in Algiers.

Methodology: The study was designed as a retrospective study (between January 1st 2010 and December 31st 2012) and a prospective study (between January 1standApril 30th 2013) on 13,611 urine samples. Antimicrobial resistance phenotyping was conducted on the bacterial isolates using disk-diffusion method.

Results: On 13,611 urine samples analysed, 1,790 (13.15%) fulfilled the criteria for urinary tract infection. *Enterobacteriaceae* were identified in 1,561 analysed samples (87%). *Escherichia coli* was the dominant uropathogen (66,15%) in both hospitalized and non-hospitalized patients. The other main detected *Enterobacteriaceae* members were *Klebsiella pneumoniae* (11,96%) and *Proteus mirabilis* (5,42%). Analysis of results showed also that women were more prone to UTI than men with sex ratio of 3.76(W/M).

The susceptibilities of isolated *Enterobacteriaceae* to antibiotics revealed that they had acquired resistance to several classes, particularly toward β-lactams. Resistance frequencies were relatively high to ampicillin and sulfomethoxasole, while being very low to aminoglycosides and furans. Results obtained revealed also that 7% of isolates where resistant to third generation cephalosporins by production of extended spectrum β-lactamases (ESBL).

Conclusions: The continuous monitoring of antibiotic resistance of uropathogenic *Escherichia coli* is crucial to guide the clinician to choose the best empiric treatment.

Key words: *Enterobacteriaceae*; UTI; antimicrobial resistance; ESBL, Algiers.

J Infect Dev Ctries 2018; 12(4):244-249. doi:10.3855/jidc.10017

(Received 05 December 2017 – Accepted 17 March 2017)

Introduction

Members of *Enterobacteriaceae* including overt and opportunistic pathogens are responsible for a wide range of infections. They are the major cause of nosocomial infections, being responsible for 50% of septicemias, 60% to 70% for enteric infections, and up to 70% for urinary infections [1].

The urinary tract is the site mostly affected by nosocomial infections, and urine samples constitute the largest single category of specimens examined in majority of medical microbiology laboratories. They represent about 30% to 50% of nosocomial infections [2]. The frequency of *Enterobacteriaceae* involved in urinary tract infections has increased significantly since the early 1990s, particularly in at-risk health facilities such as resuscitation, surgery and services especially where third-generation cephalosporins are frequently used as it is the case of urology and nephrology service [3].

Another increasing concern on public health is the multi-drug-resistance (MDR) among *Enterobacteriaceae.* Infections with MDR strains are responsible for higher morbidity and mortality than sensitive strains. In the last decade, MDR isolates have considerably reduced the range of antibiotics that might be used for *Enterobacteriaceae* treatment, and treatment failure has also increased significantly. In many reports, they found that resistance to antibiotics is chromosomal in 20 % and on mobile elements such as plasmids accounts for 80% of reported cases [4].

Moreover, the presence of extended spectrum β-lactamases (ESBL) genes is one of the main causes for *Enterobacteriaceae* resistance. Their presence was found to be linked to resistance to other classes of antibiotics, namely fluoroquinolones, aminoglycosides, trimethoprim + sulfamethoxazole, and β-lactam/β-lactamase inhibitor combinations [5-7].

The aim of the present study is to evaluate the etiology and susceptibility of *Enterobacteriaceae* isolated from patients having community-acquired and nosocomial infections in the university hospital centre of Benimessous in Algiers between 2010 to 2013.

Methodology

This study was carried out at the University Hospital Centre of Benimessous in Algiers. A retrospective study was conducted between January 1st2010 and December 31st2012, and a prospective study was conducted between January 1stand April 30th 2013. In total, a group of 13,611 individuals showing symptoms of UTI (pain during urination, functional disorders of urination, unexplained fever, and abnormal appearance of urine) were studied; of this group, 2,314 were hospitalized patients.

Biological diagnosis

Samples with important enumeration on microscope using Malassez's method were subjected for culture. Biological diagnosis of urinary tract infections has been carried out on a bacteriuria out of 10^5 CFU/mL.

Bacterial isolation and identification

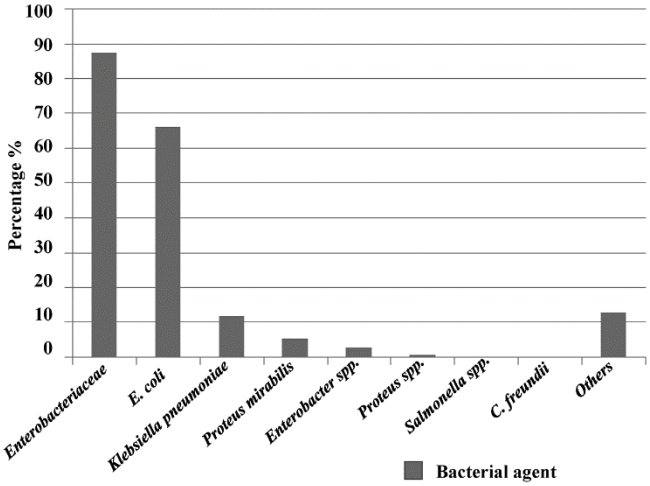
Growth was quantified and bacteria were identified according to results of the following tests: catalase, nitrate reductase, oxidase, triple sugar iron, use of citrate, indole, Voges-Proskauer, methyl red, arginine dihydrolase, lysine decarboxylase, ornithine decarboxylase, urease and mobility [8,9].

Antibiotic resistance testing

The antimicrobial susceptibilities of isolates to several antibiotics were determined by disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [16].Antibiotic disks used for susceptibility testing were ampicillin (10 µg), amoxicillin-clavulanic acid (20/10 µg), cefazolin (30 µg), cefoxitin (30 µg), cefotaxime (30 µg), imipenem (10 µg), amikacin (30 µg), gentamicin (10 µg), nalidixic acid (30 µg), ciprofloxacin (5µg), colistin (10 µg), chloramphenicol (30 µg), furans (300 µg), trimethoprim + sulfamethoxazole (1.25/23.75 µg) and fosfomycin (200 µg). Detection of ESBL production was carried out by double disc synergy technique using third generation cephalosporins and clavulanic acid [10].

E. coli ATCC 25922was used as reference strain for quality control purposes.

Figure 1. Percentage of uropathogenic *Enterobacteriaceae* isolated from patients from Benimessous hospital in Algiers (during January2010 to April 2013). *Enterobacteriaceae* are the dominant family of Gram-negative bacteria responsible of UTIs in Benimessous Hospital. *E. coli* was the predominant identified genus followed by *K. pneumoniae* and *P. Mirabilis.*



Results

Distribution of urinary tract infections caused by Enterobacteriaceae in Algiers

Different *Enterobacteriaceae* were isolated in both hospitalized and non-hospitalized patients, with a range of 19.28% and 80.72% respectively.

Table 1. Characteristics of patients infected with urinary tract infections caused by *Enterobacteriaceae* at Benimessous hospital in Algiers.

Years/period		2010(J-D)		2011(J-D)		2012(J-D)		2013(J-A)		Total	
Number/percentage		N	%	N	%	N	%	N	%	N	%
Gender	Female	395	78.22	359	79.25	378	78.75	98	79.67	1230	**78.8**
	Male	110	21.78	94	20.75	102	21.25	25	20.33	331	**21.2**
	Sex-ratio									**3.76**	
Origin	Hospitalized	89	17.62	75	16.56	105	21.88	32	26.02	301	**19.28**
	Non-hospitalized	416	82.38	378	83.44	375	78.12	91	73.98	1260	**80.72**

J-D: from January to December, J-A: from January to April, N: Number, %: Percentage.

Table 2. Distribution of uropathogenic germs isolated from January2010 toApril2013 at Benimessous hospital in Algiers.

Bacterial agent	Number	Percentage
Positive for CBEU test	1790	100
E. coli	1184	66,15
K. pneumoniae	214	11,96
P. mirabilis	97	5,42
Enterobacter spp.	48	2,68
Proteus spp.	10	0,56
Salmonella spp.	5	0,28
C. freundii	3	0,17
Enterobacteriaceae	1561	87,21
Others	229	12,79

Table 3. Resistance to antibiotics of the main *Enterobacteriaceae* responsible of urinary tract infections at Benimessous hospital in Algiers.

Antimicrobial agent	Percentage (%) of resistance according to the Bacterial agent			Percentage (%) of resistance according to the origin of patients for total isolates (N)	
	***E. coli* (N = 1184)**	***K. pneumoniae* (N = 213)**	***P. mirabilis* (N = 97)**	**Hospitalized**	**Community**
Ampicillin	67,31	100 (*)	60,82	69,95	66.77
Amoxicillin + Clavulanic acid	28,89	34,27	21,65	31.53	28.34
Cefazolin	18	30,05	25,77	24.14	16.51
Cefoxitin	1,52	5,16	1,03	3.45	1.12
Cefotaxime	5,66	23	0	9.36	4.89
Imipenem	0	0	0	0	0
Amikacin	0,76	5,63	0	1.97	0.51
Gentamicin	6,39	20,66	6,19	9.85	4.99
Nalidixic acid	27,79	34,27	54,64	32.51	26.81
Ciprofloxacin	17,72	23,94	12,37	22.17	16.31
Colistin	0	0	100 (*)	0	0
Chloramphenicol	10,39	15,02	24,74	12.32	9.99
Furans	8,7	44,6	100 (*)	9.85	8.46
Trimethoprim + Sulfamethoxazole	40,02	37,09	29,9	45.81	37.92
Fosfomycin	0,5	2,04	1,39	0.99	0.2
Total				**100 % (N = 203)**	**100 % (N = 981)**

(*): Naturally resistant, N: total number, n: number.

Table 4. Evolution of ESBL production of the main uropathogenic *Enterobacteriaceae* isolated from humans at Benimessous hospital in Algiers.

Bacterial agent	2010(J-D)		2011(J-D)		2012(J-D)		2013(J-A)		Total	
	N	%	N	%	N	%	N	%	N	%
E. coli	17/381	4,46	14/337	4,15	19/367	5,18	5/99	5,05	55/1184	4,65
K. pneumoniae	14/76	18,42	14/65	21,54	13/59	22,03	5/14	35,71	46/214	21,5
P. mirabilis	0/31	0	0/34	0	0/27	0	0/5	0	0/97	0
Enterobacteriaceae	36/505	7,13	31/453	6,84	37/480	7,71	10/123	8,13	114/1561	7

(J): January, (A): April, (D): December, (N): Number, %: Percentage.

On the other hand, infection among the female population was higher than infection detected in the male population with a range of 79% and 21% respectively, corresponding to a sex ratio (W/M) 3.76 (Table 1).

Diversity of Enterobacteriaceae isolated in patients infected with urinary tract infections

Of the total of 1,790 positive CBEU (Cyto-Bacteriological Examination of Urines), 1,581 were identified as *Enterobacteriaceae* with frequency of 87,21. *Escherichia coli* is by far the most frequently isolated genus that causes UTIs in most patients (76%), followed by *Klebsiella pneumoniae* (14%) and *Proteus mirabilis* (6%) (Figure 1, Table 2).

Resistance to antimicrobial agents

Results obtained show that most isolates had acquired resistance to at least one of tested antibiotics (Table 3). Resistance of *E. coli* to ampicillin and Trimethoprim/sulfamethoxazole has reached very high levels, 68% and 40% respectively, while resistance to amoxicillin-clavulanic acid, nalidixic acid and ciprofloxacin was lower with a range of 17% to 29%. Likewise, *E. coli* isolates had showed more or less resistance to gentamicin, cefotaxime, and cefoxitin (<7%), whereas they were susceptible to imipenem, colistin, fosfomycine and amikacin. For what concerned *Klebsiella pneumoniae,* isolate resistance was relatively high to amoxicillin-clavulanic acid, cefazolin, nalidixic acid, furans and trimethoprim/sulfamethoxazole with rates ranging from 30% to45%. Of these isolates, 23% were ESBL producers (Table 4). On the other hand, frequencies of resistance in *Proteus mirabilis* were similar to those of *E. coli*. However, all isolates were sensitive to cefotaxime and amikacin.

Discussion

Enterobacteriaceae are still pathogens responsible for the majority of UTIs, and the uropathogenic *E. coli* (UPEC) is the leading uropathogen. These findings are in agreement with results found in Constantine hospital (eastern Algeria) [11] and in Tunisian Universal Health Coverage Partnership UHC [12]. The development of UTIs depends essentially on anatomical factors, the integrity of host defence mechanisms, and the virulence of the infecting organisms. The perineum is highly colonized by *Enterobacteriaceae* of digestive origin in particular uropathogenic *E. coli*. This pathogen is able to adhere to urogenital epithelium via specific adhesins; this adhesion prevents its removal by bladder emptying. While *Klebsiella* and *Proteus* are able to produce urease to alkaline the urine, this ability allows these pathogens to proliferate. Furthermore, mobility by peritrichous flagella is a factor that facilitates their ascent to the bladder [13].

Results of this study showed that UTIs are more frequent in women than men. This is mainly explained by anatomical reasons: the short urethra allows pathogenic bacteria to reach the bladder easily. In contrast, the male is much less susceptible to urinary tract infections due to the length of urethra and the presence of bactericidal substances in prostatic fluid [14]. These findings come in agreement with those found in Tunisia at the UHC Rabtain Tunis, with sex ratio of 3.15 [5], but lower frequency than those found in different laboratories in the city of El-Jadidain Morocco with sex-ratio of 5.67 [8].

Findings from this study and those obtained by Ben Hadj and his colleagues in Tunis [15] show that the frequency of UTIs was very high in non-hospitalized patients in comparison with UTIs acquired at hospitals. This may be due essentially to the fact that diagnosis of UTIs outside hospitals is based in most cases on symptoms, and treatment is prescribed unsightly without antibiogram [12].

Enterobacteriaceae are naturally susceptible to most antibiotics that are no longer the case for a large number of strains. This general situation is the result of selection pressure due to the extensive use of antibiotics and the great ability of this acquired resistance to spread, because most resistance genes are located on mobile elements (plasmids, transposons) [15]. *E. coli* was the predominant uropathogen, while its antimicrobial resistance was significantly lower than that presented by *K. pneumoniae*. This uropathogen was relatively high resistant to some important antibiotics usually used to treat UTIs such as ampicillin, trimethoprim/sulfamethoxazole, amoxicillin-clavulanic acid (AMC), cefazolin, nalidixic acid, and ciprofloxacin. Resistance rates have reached very high levels (Table 3). Similar results were obtained in a public hospital in Constantine, Algeria [11]. Resistance is alarming for all antibiotics used to treat UTI and there is no clear first choice, which limits their use in probabilistic treatment. This finding should prompt to decrease the overuse of antibiotics and to establish an adequate prescription based on an antibiogram. To avoid treatment failure and selection pressure of MDR clones, clinicians must reconsider prescription of these molecules.

K. pneumoniae was the second frequently isolated uropathogen, but it was the most resistant to nearly all

antibiotics. It showed a significant resistance rate to cefotaxime, gentamicin, and ciprofloxacin. Instead, *Proteus mirabilis* was less resistant to most tested antibiotics than *E. coli* and *Klebsiella pneumoniae,* especially to aminoglycosides and third generation cephalosporins.

The present study showed also that *Escherichia coli* still moderately susceptible to some antibiotics such as cefotaxime (CTX), gentamicin (GEN), chloramphenicol, and furans, in view of resistance rates that do not exceed 10%. Similar findings were found for *Proteus mirabilis*, with the exception to furan, to which this bacterium is naturally resistant. However, *Klebsiella pneumoniae* was more resistant with resistance rates above the threshold of 20% for the majority of tested antimicrobials. In addition, *K. Pneumoniae* isolates were the strongest ESBL producers, and this phenotype is often associated with other resistance markers such as resistance to gentamicin. During the period of the present study, we increasingly noticed an evolution of ESBL production by *K. pneumoniae* (Table 4). Whereas, *E. coli* was less resistant to 3GCs in comparison to *Klebsiella pneumoniae*; only 5.66% were resistant to CTX by ESBL production with non-significant evolution during the last three years. While the genus *Proteus* was completely sensitive to this antibiotic.

On the other hand, cefoxitin (FOX) and amikacin (AMK) are agents that could be effectively used as empiric therapy to treat *Enterobacteriaceae* due to their highly effective activity: their resistance rates were lower than 6% for *Klebsiella pneumoniae* and lower than 2% for *Escherichia coli* and *Proteus mirabilis.*

Results of this study also revealed that the most active antibiotics on the main uropathogenic *Enterobacteriaceae* were imipenem, fosfomycin and colistin, with the exception of the genus *Proteus* which is naturally resistant to colistin. However, these molecules are prescribed only when antimicrobial therapy with other antibiotics such as CIP, SXT, and CTX become ineffective.

In order to administer an appropriate empirical therapy, it is crucial to know the most effective antibiotics to the main bacteria usually involved in the urinary tract infection. In this study, imipinem, colistin and fosfomycin were the only antibiotics that remained highly active against most uropathogenic *Enterobacteriaceae*, with the exception of natural resistance of *P. mirabilis* to colistin. Amikacin and cefoxit in were also relatively highly active on most uropathogens.

As frequently detected in other studies [16-18], findings of this study show that resistance to antibiotics was more significantly associated with hospital acquired UTI (HA-UTI) than community acquired UTI (CA-UTI) among all frequently isolated uropathogens. This may be explained by overuse of antibiotics in hospitals, which contributes in the selection and dissemination of MDR clones.

Enterobacteriaceae resist to β-lactams mainly by the production of β-lactamases. At the UHC of Benimessous in these past years, *Klebsiella pneumoniae* was the highest ESBL producer genus with a significant evolution. ESBLs are frequently encoded by plasmids that also carry other antibiotic-resistance genes. To understand reasons of this evolution at the regional level, an advanced epidemiological and genotypic study should be conducted. All these details might improve knowledge about the resistance profile of circulating uropathogenic *Enterobacteriaceae* and thus identify the emerging phenomena within the UHC of Benimessous and more generally in Maghreb. This would provide a wider choice of drugs for antibiotherapy against MDR strains.

The most commonly used antibiotics in the hospital practice for the treatment of UTIs in Algeria and several other developing countries around the world are cephalosporins and fluoroquinolones. The mortality rate of patients infected with ESBL producing *Enterobacteriaceae* and treated with antibiotics to which the organism exhibits high level of resistance has ranged from 42%-100% [19,20]. To decrease risks of mortality due to treatment failure, the selection of efficient antibiotics should be based on local resistance patterns. Some antibiotics should not be used as a first-line option for empiric treatment especially for serious UTIs. Antibiotics concerned by this finding in Algeria are quinolones and fluoroquinolones in the first place, followed by second and third generation cephalosporins, and aminoglycosides especially gentamycin.

Conclusion

In conclusion, urinary tract infections in Algeria are primarily caused by *Enterobacteriaceae*, and *E. coli* is the predominant genus. Resistance rates not only are different over various centres but also vary over the time, which suggest a narrow spectrum of empiric therapy for *Enterobacteriaceae* and indicate that different approaches in empiric therapy across age groups and gender could be implemented. Resistance to antimicrobials is increasing worldwide; for this reason, Algeria needs to initiate active surveillance and define

proper empiric therapy based on the data obtained. To avoid the potentially devastating outcomes, appropriate diagnostic procedures, antibiotic and surgical treatment, and appropriate follow-up are required. The incidence of complicated UTI will grow in the future due to general number of immunocompromised and immunosuppressed patients. It is of key importance to timely recognize complicated UTI, and treat it judiciously and aggressively to reduce disease duration and antibiotic resistance risk.

Another factor that may play a central role in increasing of UTI is hygiene. In Algeria, hygiene conditions are inappropriate. Under such conditions, multi-resistant *Enterobacteriaceae* are the major cause of mortality in this country especially in infants. Cooperation between clinicians, microbiologists and hygienists is strongly recommended to control the dissemination of multidrug resistant *Enterobacteriaceae* and also to improve patient care and to reduce medical costs, morbidity and mortality.

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Conflict of interests: No conflict of interests is declared.