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A pattern of antimicrobial susceptibility and the correlation of cotrimoxazole and fluoroquinolones in *Escherichia coli* resistant uropathogens in Ibn-Sena hospital in Benghazi-Libya.

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Highlights

- **Escherichia coli strains are the most prevalent bacteria in urinary tract infections.**
- **Dissemination of Escherichia coli resistant strains is one of the main causes of treatment failure.**
- **Cross-resistance to newer antibiotics may be developed by the random utilization of antimicrobial therapy.**
- **Extension of resistance to fluoroquinolones from other antibiotics is evident recently.**
- **A proper selection of antibiotic therapy based on antibiotic susceptibility tests is necessary to attenuate the cross-resistance to the newer generations of antibiotics.**

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ABSTRACT

Uncontrollable use of antibiotics to treat uropathogens is one of the major causes of increasing antimicrobial-resistant *Escherichia coli* (*E. coli*) strains. Therefore the choice of antibiotic therapy is needed to be based on their antibiotic susceptibility tests. We investigated the prevalence and antibiotic susceptibility of *E. coli* in uncomplicated urinary tract infection (UTI) in 1011 samples during 8 months period in Ibn-Sena clinic in Benghazi. The *E. coli* was the most isolated uropathogen (64%). The most resistant antibiotic to this uropathogen was amoxicillin (51.6%), followed by cotrimoxazole (47.7%) and the percentage of ciprofloxacin was 26.6%. When the utilization of ciprofloxacin increased lately as an alternative to cotrimoxazole, its resistance increased and we found that this increase was positively correlated with cotrimoxazole. In conclusion, monitoring and investigating antibiotic-sensitivity patterns may help the physician to prepare reliable strategies for better management and control of *E. coli* infections.

1. Introduction

Uncomplicated urinary tract infections (UTI) are highly prevalent in large portions of the population worldwide. It is the second common infection after respiratory infections (Gupta *et al*., 2001). The *Escherichia coli (E. coli*) is one of the most common bacterial pathogens isolated from both communities acquired and nosocomial patients with UTI (Hryniewic *et al*., 2001, Dasgupta *et al*., 2005). It accounts for more than 80% of non-serious UTIs (Kang *et al*., 2018).

In 2011, the trimethoprim-sulfamethoxazole (cotrimoxazole) is recommended by the Infectious Diseases Society of America (IDSA) as one of the best choice drugs that may be administered if the rate of resistance of bacteria attributed to acute uncomplicated UTIs is not higher than 20% (Gupta *et al*., 2011). While the resistance to the cotrimoxazole and other first-line choices such as ampicillin nitrofuranton is becoming increasingly evasive, fluoroquinolones are commonly recommended as alternatives because it is narrow-spectrum antibiotics that showed a higher range of susceptibility in the *E. coli* strains (Gupta *et al*., 2011).

Unfortunately, the rate of development of multi-drug resistance in many gram-negative bacteria, especially the *E. coli* becomes hugely evident and this is liable for developing resistance to many unrelated antibiotic classes (George and Levy, 1983). Interestingly, in recent years the resistance to fluoroquinolones such as ciprofloxacin and levofloxacin is disseminated widely (Karlowsky *et al*., 2006, Hooton, 2003).

Bacteria produce the extended-spectrum beta-lactamase (ESBL) enzymes extended to cause a resistance to the newer beta-lactam antibiotics as well as to many non-beta lactam antimicrobial agents such as the aminoglycosides and cotrimoxazole (Paterson *et al*., 2000). A cross-resistance between ciprofloxacin and other non-fluoroquinolones has increased in recent years (Ozyurt *et al*., 2008).

The ability of the *E. coli* to cause UTI and the trouble in the management of these infections can lead to proliferation of virulent *E. coli* and increase morbidity. Therefore, the health workers must update their knowledge of the current drug resistance. Antibiotic resistance may be changed according to geographic areas because it is directly related to the misuse of antibiotics. This is particularly in a community like Libya where all kinds of antibiotics are available with or without prescription. The objective of this work was to determine the antimicrobial susceptibility of *E. coli* strains isolated from urine samples of patients with UTI collected from Ibn-sena clinic, one of the biggest clinics in Benghazi city. In addition, to find the correlation of resistance between the most commonly two an-

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tibiotics used in the treatment of UTI, the cotrimoxazole and ciprofloxacin. This not only guides general practitioners to prescribe appropriate antibiotics but also for evidence-based recommendations in empirical antibiotic treatment of UTI.

2. Material and methods

2.1. Study design

A retrospective descriptive study at Ibn-Sena clinic in Benghazi-Libya was conducted after approval from the local authority. A total of 1011 samples of patients with urinary tract infections were collected in the period from the 1st of August 2019 to the 30th of April 2020. The samples were of different ages and sex and were collected by early morning samples according to the midstream method and in a sterile container, and sent to the laboratory .

2.2. Bacterial isolates and Antibiotic susceptibility testing

Urine samples were put on cysteine lactose electrolytes deficient (CLED) agar incubated at 37°C for 24 hours. A growth of >105 colony-forming units per mL of any type of organism was considered as significant bacteriuria (Murray *et al.*, 1999). Identification of the *E. coli* was done by observing colonial morphology on CLED medium (Murray *et al.*, 1999). The antibiotic susceptibility of this pathogen was investigated by the Clinical and Laboratory Standards Institute's disc diffusion method (Institute of C. A. L. S, 2006). The following antibiotics were tested: amoxicillin, co-amoxiclav (Augmentin), cotrimoxazole, ciprofloxacin, nitrofurantoin, cefotaxime, ceftriaxone, levofloxacin, gentamicin, and imipenem.

2.3. The relationship of cotrimoxazole and ciprofloxacin resistance

The *E. coli* isolates were grouped as either cotrimoxazole susceptible or resistant. Each group was further subdivided into ciprofloxacin susceptible and resistant organisms. The number of susceptible and resistant organisms in each group was recorded. The statistical significance of cross-resistance between the cotrimoxazole and ciprofloxacin was calculated by Fisher's exact test and Odd ratio was calculated.

3. Result

From a total of one thousand and eleven samples, only 199 samples had shown bacterial growth, while 664 samples had no bacterial growth. The rest of the samples (148) had shown a non-specific growth, Fig, 1. The prevalence of UTI in the eight months was 19.7%. 71.4% of bacterial growth was in the female patients, while 25.6 % of cases were male patients, Fig. 2. The *E. coli* was the most prevalent isolated uropathogen with (64%), followed by *Klebbsilla pneumonia* (*K pneumonia*) and *Pseudomonas aeruginosa (P. aeruginosa) (11.6% each). Proteus mirabillis* (*P. mirabillis*), *Staphylococcus aurous (S aurous), and* Enterococcus faecalis (*E. faecalis*) had prevalence values of (4.5, 2.5, and 2 % respectively). *Streptococcus pneumonia* (*S. pneumoniae*) and *Actinomyces isrealii* (*A. isrealii*) had a lower prevalence with a value of (1.5 % each) and *Neisseria gonorrhea* (*N. gonorrhea*) had the lowest rate (0.5%) Fig. 3.

In this study, isolated *E. coli* showed resistance to a wide range of used antimicrobial agents including the recently produced and expensive ones as imipenem, the beta-lactam antimicrobial agent. The most resistant antibiotic to *E. coli* was amoxicillin (51.6%), followed by cotrimoxazole (47.7%), then nitrofurantoin (45.3%). The prevalence of the strain resistance to augmentin was (35.2%). The *E. coli* also showed ciprofloxacin and levofloxacin resistance at a rate of 26.6 & 18 % respectively. The resistance toward gentamicin was lower at 10.9%. 6.3 & 7% of *E. coli* strains were resistant to cefotaxime and ceftriaxone respectively. The resistance to imipenem had the lowest rate of bacterial resistance by 3.9% Fig. 4.

As shown in the present work, 47.5% of cotrimoxazole-resistant *E. coli* were resistant to ciprofloxacin too and 89.4 % of cotrimoxazole susceptible *E. coli* showed susceptibility to ciprofloxacin antibiotic Fig. 5. The Fisher's exact test at α level of 0.05 revealed that there was a direct relationship between the bacterial resistance of both antibiotic and the Odd ratio was 7.6.

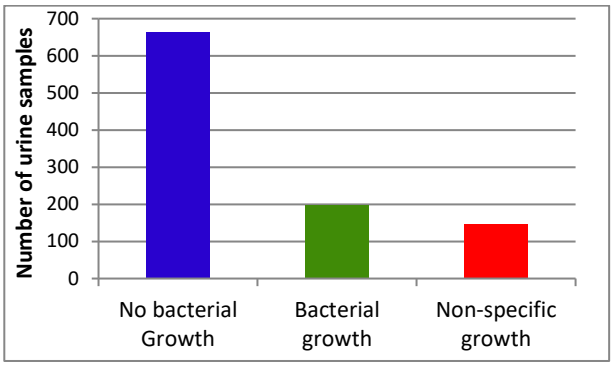

Fig. 1. Results of urine culture tested for bacterial growth in Ibn-sena clinic.

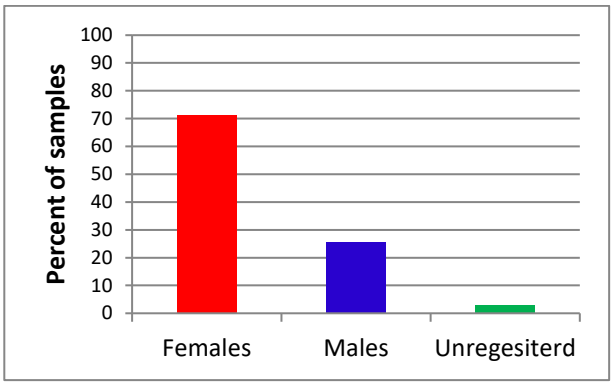

Fig. 2. Gender differences of patients with bacterial growth

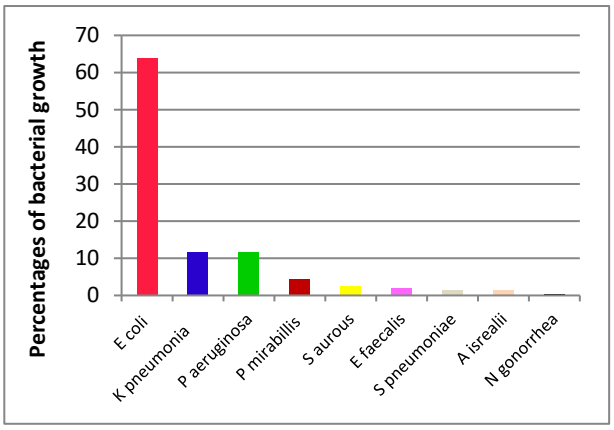

Fig. 3. Prevalence of uropathogens in the collected growth samples.

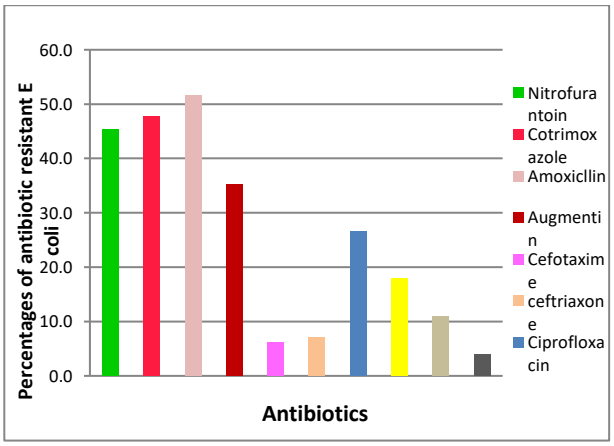

Fig. 4. Prevalence of antibiotics resistance in *E coli* strains

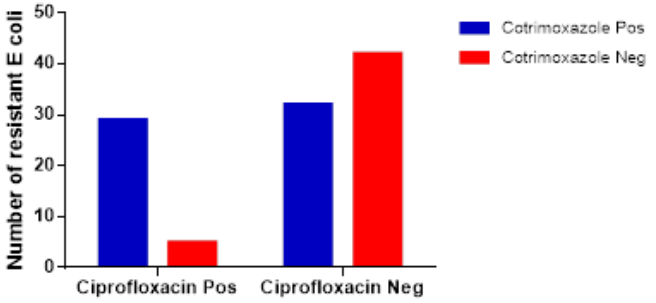

Fig. 5. Cross resistance of cotrimoxazole and ciproflaxacin in *E coli* strains.

4. Discussion

The progressive increase of antimicrobial resistance has serious consequences such as rapid deterioration of UTI. Therefore, providing information on regional antimicrobial resistance can improve the clinician decision for prescribing the appropriate antibiotic to the specific bacteria and good disease management. In addition, It is an evidence-based recommendation in empirical antibiotic treatment of UTI. Compared to the finding of the present study, there is a variation of the pattern of antimicrobial resistance rate in *E. coli* at different durations in Libya.

The prevalence of *E. coli* in UTI in this study was 64%. A comparable prevalence was reported in other studies (Cullen *et al.*, 2012, Søraas et al., 2013). In the current study, the antibiotic resistance of amoxicillin was (51.6%), followed by cotrimoxazole (47.7%), then nitrofurantoin (45.3%). The prevalence of the bacterial resistance to ciprofloxacin and levofloxacin resistance was at a rate of 26.6 & 18 % respectively. In previous studies, however, the rate of amoxicillin resistant *E. coli* during early 1993 was very high (97%) (Altomi *et al.*, 1997), the trend decreased to 74 and 75 % as shown in two studies were done Tripoli and Benghazi during the early of 2000 (Ghenghesh *et al.*, 2003, Tobgi *et al.*, 2001). A further reduction of amoxicillin resistance in *E. coli* in both cities in 2006-2010 was up to 59 and 57% respectively (Buzayan *et al.*, 2010, Ghenghesh *et al.*, 2009). A better improvement has been noticed in the susceptibility of amoxicillin in this study (48.4%). This may be due to the reduction of amoxicillin prescription in the treatment of UTI recently.

The cotrimoxazole-resistant *E. coli* showed the same pattern of ampicillin resistance. While the rate was higher in different studies in Libya (45-55%) during 1995 (Ghenghesh *et al.*, 2003, Tobgi *et al.*, 2001). It reduced in 2006 to (24-31%) (Buzayan *et al.*, 2010, Ghenghesh *et al.*, 2009). The isolated uropathogens in our study showed increased resistance to cotrimoxazole and this is consistent with other worldwide studies (Ahmed *et al.*, 2000, Hima-Lerible *et al.*, 2003, Ndugulile *et al.*, 2005, Sabrina *et al.*, 2010). Also, Koen B Pouwels *a*nd his research group have reported that the prevalence of cotrimoxazole resistance among *E. coli* isolated was high, even after a substantial decline in cotrimoxazole use (Koen *et al.*, 2017).

Conversely, the resistance of isolated uropathogens to ciprofloxacin and levofloxacin had increased. It ranged from 2-17 % in 2002- 2006 in different regions in Libya (Bagar *et al.*, 2007, Buzayan *et al.*, 2010, Ghenghesh *et al.*, 2009). The current study showed an increase in the prevalence of the bacterial resistance to ciprofloxacin and levofloxacin was 26.6 & 18 % respectively. A previous study was done in Benghazi during 2012 where the *E. coli* isolates showed resistance to ciprofloxacin in 40% of samples (Marei *et al.*, 2012). The decrease in susceptibility of *E. coli* to ciprofloxacin was also in line with other studies (Kahlmeter *et al.*, 2015, Seitz *et al.*, 2017, Stapleton *et al.*, 2017). In Germany the rate of resistance raised from 2.2 to 20.2%, in Spain it increased from 14.7 to 30.8%, in the UK, the rate also changed from 0.6 to 15.3% (Kahlmeter *et al.*, 2015). Since the widespread use of these fluoroquinolones as an alternative to the cotrimoxazole and other first-line therapy in the treatment of UTI causes emerge of their recent resistance.

In the present study, the co-resistance within different classes of antibiotics was significantly high for the cotrimoxazole and ciprofloxacin. ESBL-producing *E. coli* was reported at a high rate of resistance to non-beta lactam antibiotics (Ndugulile *et al.*, 2005, Alhambra *et al.*, 2004). It has been shown that 89.8% of ESBL-producers *E. coli* were non-susceptible to trimethoprim-sulfamethoxazole and 69% were resistant to ciprofloxacin (Dejenie *et al.*, 2019). These findings reported in several studies (Schwaber *et al.*, 2005, Obeng-Nkrumah *et al.*, 2013, Ouedraogo *et al.*, 2016) may indicate that ESBL-producing Enterobacteriaceae were the major cause of resistance to various antibiotics classes. The emergence of resistance in different classes of antimicrobial agents may be explained by the fact that ESBL is plasmid-mediated enzymes that are transferable between one bacterium to another and such transferable plasmids also code for resistance determinants to antimicrobial agents other than beta-lactams (Paterson, 2006).

In conclusion, the results presented in this study indicate that the empirical use of antimicrobial agents, in particular cotrimoxazole and fluoroquinolones, in the treatment of UTI should be reconsidered to develop clear guides to reduce the development of further resistance. Furthermore, periodic antimicrobial resistance surveillance systems should be recommended in different regions and durations to detect the emergence of resistance patterns. This helps in the selection of the most efficacious empirical therapy at the local level.

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