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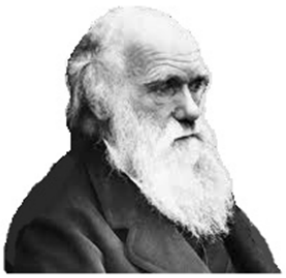

World News of Natural Sciences

An International Scientific Journal

WNOFNS 31 (2020) 110-119 EISSN 2543-5426

Evaluation Cephalosporins Resistance in Pathogenic Bacteria Isolated Clinically

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ABSTRACT

Third-generation cephalosporins are a class of b-lactam antibiotics that are often used for the treatment of human infections caused by Gram-negative and gram-positive bacteria. This study aimed to detect the pattern of bacterial antibiotic sensitivity to the third generation of cephalosporins that assist doctors with appropriate empirical therapy. Various bacteria isolated clinically from urine, high vaginal swab (cervical swab), ear, and wound samples during the period from November 2019 to March 2020 at Al-Shomali general hospital, Babil, Iraq and a private laboratory in Babil city. A total of 154 patients were involved in this study, samples were processed at the hospital laboratory during this period, a diagnosis and antibiotic sensitivity test have been done by the routine bacteriological diagnosis as well as VITEK 2 system. Three common third-generation cephalosporins; cefotaxime, Cefotazidime, and ceftriaxone are evaluated. Out of these 154 samples, 46 (30%) have bacterial growth. specimens with bacterial growth were taken from urine, cervical swab, ear discharge, and wound infection were 24, 8, 8, and 6 respectively. All 46 isolated bacteria were 100% resistant to cefotaxime and Cefotazidime, while they were 36 (78%) resistant to ceftriaxone. The prevalence of bacterial isolation in different specimens showed a high predominance of *enterococcus spp* 16 (35%) from the total samples. The current study showed an increasing burden of bacterial resistance to third-generation cephalosporins especially to cefotaxime and Cefotazidime, may due to misuse and inappropriate high administration of these drugs, early detection of development third-generation resistance in patients by restricted clinical monitoring through judicious use of antibiotics. The high rate of resistance observed in small age groups less than 15 years old.

***Keywords*:** Cephalosporins, antibiotic resistance, ceftriaxone, third-generation cephalosporins, cefotaxime, antimicrobial agents

(Received 29 April 2020; Accepted 20 May 2020; Date of Publication 21 May 2020)

1. INTRODUCTION

The third-generation cephalosporins are regarding broad-spectrum antibiotics that possess activity against both gram-negative and gram-positive bacteria. However, these drugs are more effective against gram-negative organisms and bacteria that are resistant to the first and second-generation cephalosporins [1].

Over the past decade, resistance predominance in hospital-acquired infections has risen dramatically; Infections caused by resistant organisms are thought to result in prolonged hospitalization, and higher morbidity and mortality.

Third-generation cephalosporins were started with cefotaxime 30 years ago, resistance in bacterial species emerged a few years later due to selective pressure exerted by these new cephalosporins [2]. At present, Antibiotic resistance considered a global health emergency and extended-spectrum beta-lactamase-producing bacteria that can resist third-generation cephalosporins are on the rise and increasing with time [1].

Cephalosporins are bactericidal; acts by disrupting the synthesis of the cell wall layers, as well as they have the same mode of action as other β-lactam antibiotics like penicillin but are less susceptible to β-lactamases.

During the past fifteen years, dissemination and developing of β-lactam resistance in nosocomial gram-negative bacteria and *Pseudomonas aeruginosa* became a serious problem globally, especially the increasing resistance to third and fourth generation cephalosporins [2]. As with most beta-lactam antibiotics, third-generation cephalosporins are generally well tolerated and characteristically have a low toxicity profile. However, some toxicity profiles may be particularly severe. For instance, reports exist of coagulopathies leading to bleeding with the use of third-generation cephalosporins. [1] Adverse effect od third-generation cephalosporins regarding few compared with other fetal adverse effects of some antibiotics [3, 4].

This information would be helpful in establishing empiric therapy guidelines to prevent the emergence of further resistance and to contribute data to larger and more extensive surveillance programs.

2. MATERIAL AND METHODS

The study protocol has been approved according to the Ethical Committee in the Babil Health Directorate on October 20, 2019. Besides, verbal approval was taken from the patients before obtaining the sample. Health safety was taken during sampling. Also, this work was done according to the Ethics Committee of the Iraqi Ministry of Health and was performed and agreed with all national regulations.

A total number of 154 patients with various bacteria isolated clinically from urine, high vaginal swab, ear, and wound samples during the period from November 2019 to March 2020 at Al-Shomalli general hospital, Babil, Iraq and a private laboratory in Babil city.

UTI patients were suffering from clear symptoms of UTI as a complaint of frequent urge to urinate and painful, non-repetitive midstream urine samples were included in the study.

Other samples as ear and wound were associated with pus and discharges, high vaginal swab samples taken by the specialist doctor from the cervical area. All these specimens send to our main laboratory by clinicians. Samples for direct examination and basic bacterial-cultured methods have been done. Direct inoculation on agar media was performed immediately.

The bacterial diagnosis was identified by VITEK 2 (Biomerieux). Further identification was done as per routine laboratory protocols. Also, a questionnaire survey has been taken from patients. Antimicrobial susceptibility investigation was done as to Kirby–Bauer's disc diffusion method, [7] three most common cephalosporins were tested, Ceftriaxone (30 mg), Ceftazidime (30 mg), Cefotaxime (30 mg).

3. RESULTS

Out of 154 samples clinically collected 114 (74%), 20 (13%), 12 (8%), and 8 (5%) from urine, cervical swab, wound infection, and ear respectively (Figure 1).

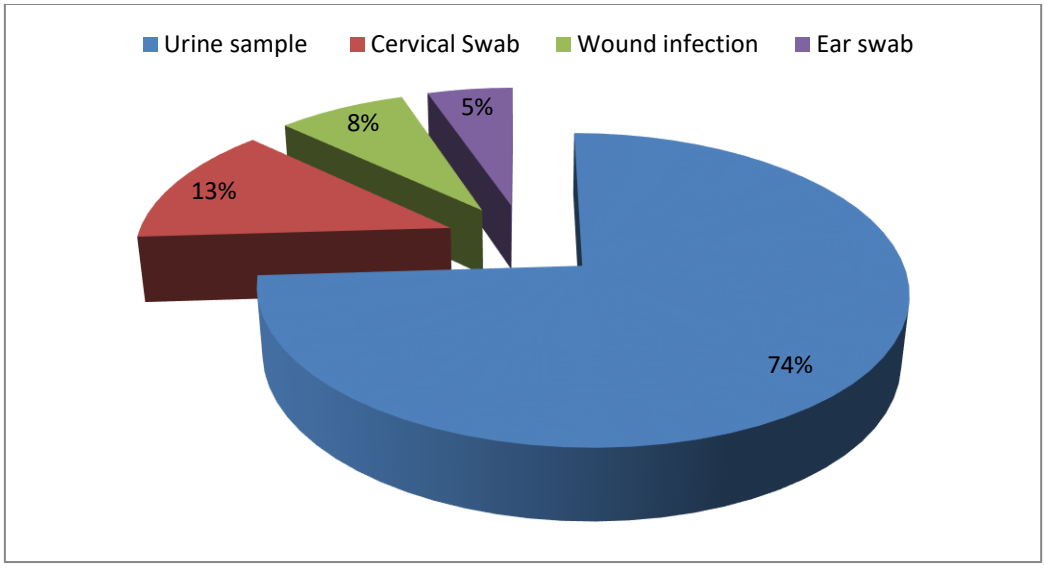

Figure 1. Distribution of samples included in this study

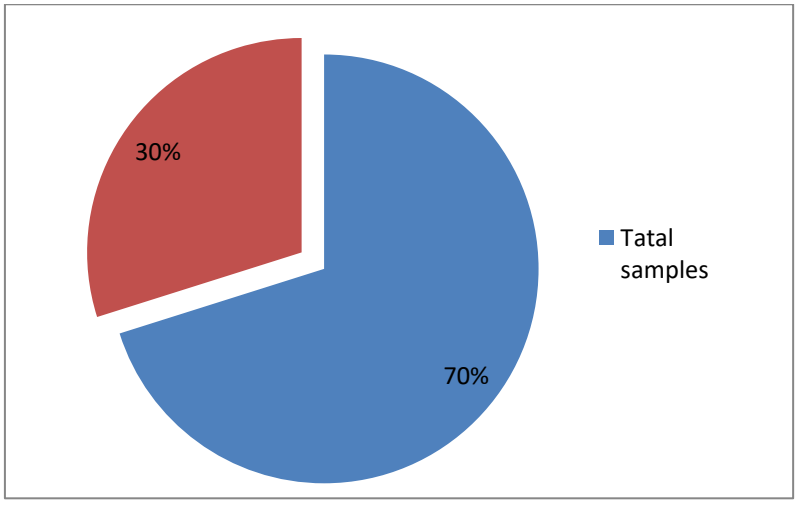

Figure 2. Growth rate of all clinical isolated bacteria

From 154 specimens, just 46 (30%) samples were had bacterial growth on artificial media as 24, 8, 8, and 6 clear growth in urine, cervical, ear, and wound respectively (Figure 2 and Figure 3).

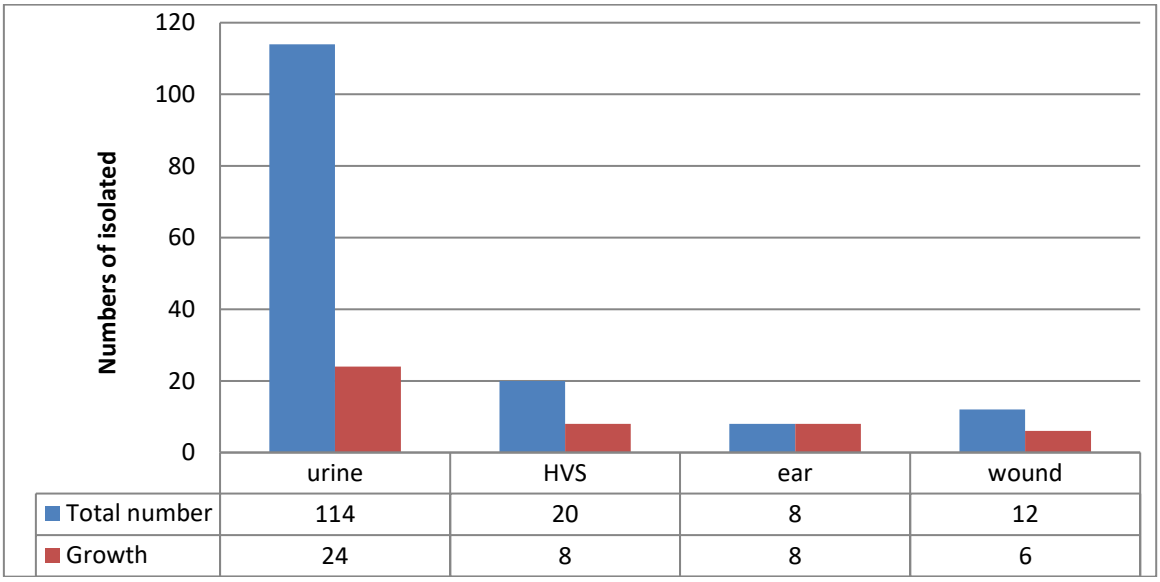

Figure 3. Numbers of growth samples

Bacterial isolates in urine were 12 *Enterococcus spp* and 6 *E. coli*, while *Staph aureus*, *Staph saprophyticus*, and *Klebsiella oxytoca* were 2 for each one. 91% (N = 22) of patients with UTI were females, while males were represented just 9% (N = 2) (Figure 4).

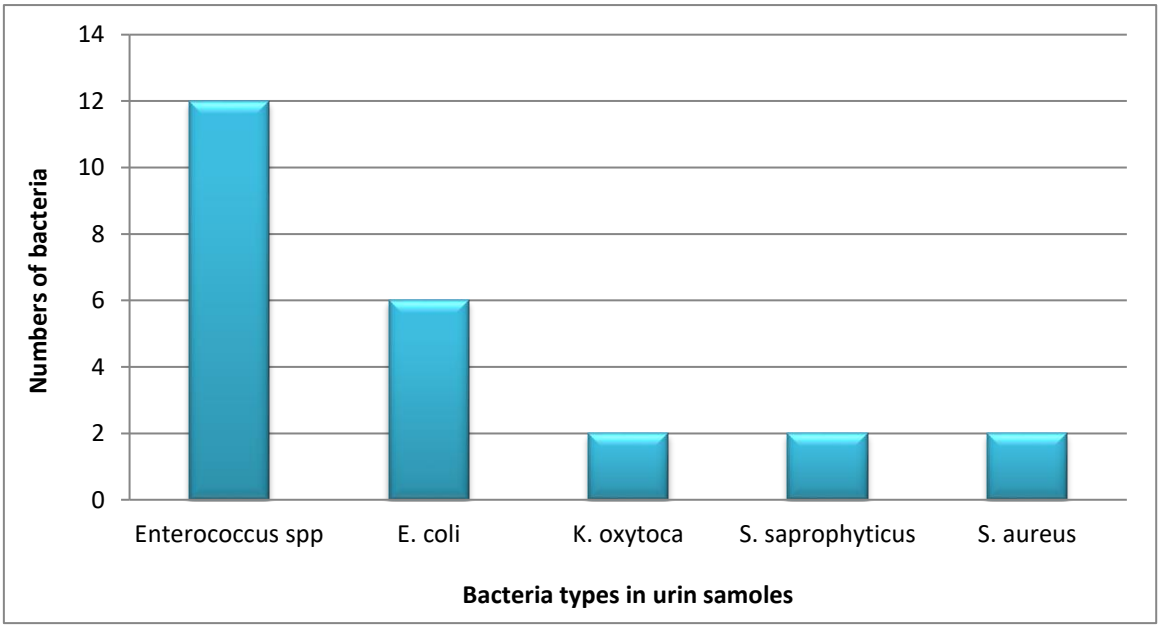

Figure 4. Numbers of isolated bacteria in urine samples.

Bacterial types in ear discharge, two *Proteus mirabilis*, 4 *Staph aureus*, one *P. aeruginosa*, and one mix growth of *Staph aureus* plus *P. aeruginosa*. In cervical, 4 *Enterococcus* spp, 2 *E. coli*, and 2 *staph aureus*. In wound, 3 *P. aeruginosa*, 2 *Proteus* spp, and one mix growth *P. aeruginosa* plus *E. coli* (Table 1).

Table 1. Bacteria distribution among specimens.

	Ear swab	**Cervical swab**	**Wound infection**	**Urine samples**	**Total**
P. aeroginosa	1	-	3	-	4
S. aereus	4	2	-	2	8
E. coli	-	2	-	6	8
Proteus spp	2	-	2	-	4
Enterococcus spp	-	4	-	12	16
K. oxytoca	-	-	-	2	2
S. saprophyticus	-	-	-	2	2
P. aeroginosa plus S. aureus	1	-	-	-	1
S. aereus plus E. coli	-	-	1	-	1
Total	8	8	6	24	46

Age of involved persons in the current study ranged from 2 to 63 years for all specimens. Distribution of specimens according to age group appeared that 16-30 years of age group is the most common infected groups for urine, cervical, and wound specimens. However, half of the patients with ear discharge were in the age group 0-15 years (Table 2).

Table 2. Age group distribution among specimens.

	0-15	**16-30**	**31-45**	**>45**	**Total**
Urine	6	14	-	4	24
Cervical	-	6	2	-	8
Ear	4	2	2	-	8
Wound	-	4	2	-	6
Total	10	26	6	4	46

Table 3 explains the distribution of isolated bacteria according to age groups of involved individuals in this search that showed *Enterococcus* spp most prevalent in the age group 16-30 years, while *P. aeruginosa* and *S. aureus* are most predominant in 0-15 years (Table 3).

Table 3. Age groups with bacteria distribution.

	0-15	16-30	31-45	> 45	Total
P. aeroginosa	2		2	-	4
S. aereus	4	4	-	-	8
E. coli	-	4	2	2	8
Proteus spp	-	4	-	-	4
Enterococcus spp	3	10	1	2	16
K. oxytoca	-	2	-	-	2
S. saprophyticus	-	2	-	-	2
P. aeroginosa plus S. aureus	1	-	-	-	1
S. aereus plus E. coli	-	-	1	-	1
Total	10	24	6	4	46

Cephalosporin resistance was very high among all isolates that reached 100% (N = 46) resistance to cefotaxime and ceftazidime, while resistance to ceftriaxone was 78% (N = 36) from total clinical isolated bacteria (Figure 5).

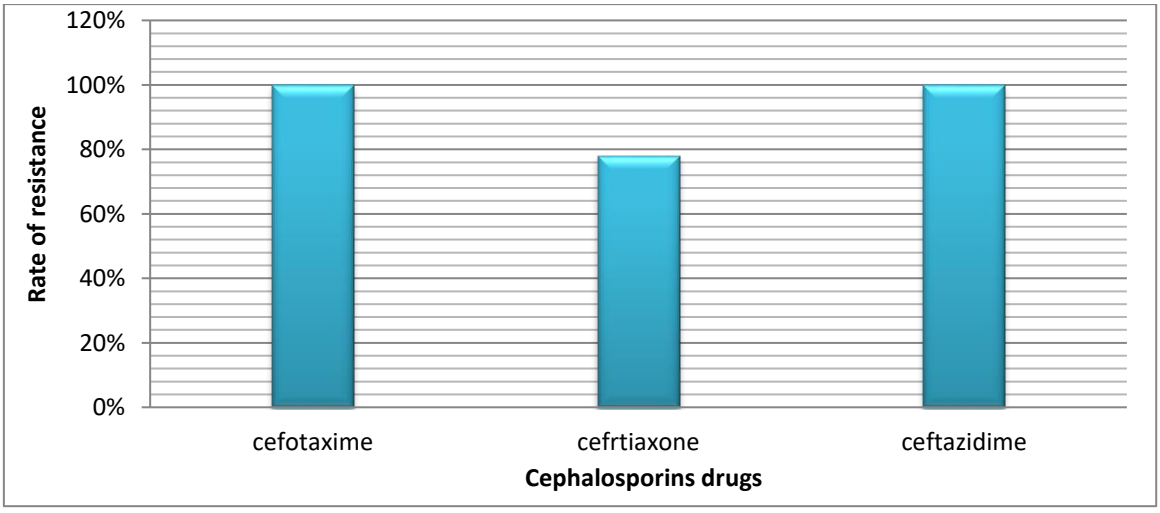

Figure 5. Rate of cephalosporins resistance profile in all samples

Figure 6, revealed the prevalence of bacterial isolation in different specimens that showed a high prevalence of *Enterococcus* spp in 16 (35%) samples, followed by both *E. coli* & *S aureus* in 8 (17.5%) specimen for each one (Figure 7).

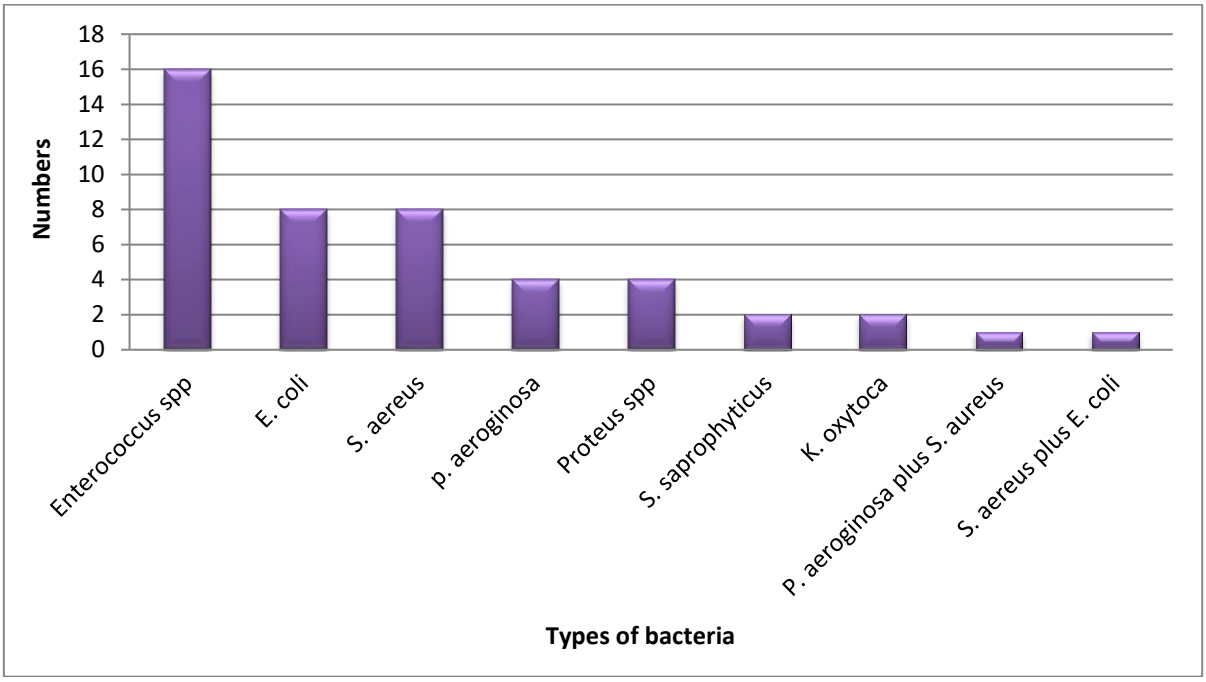

Figure 6. Numbers of bacterial isolation in all specimens

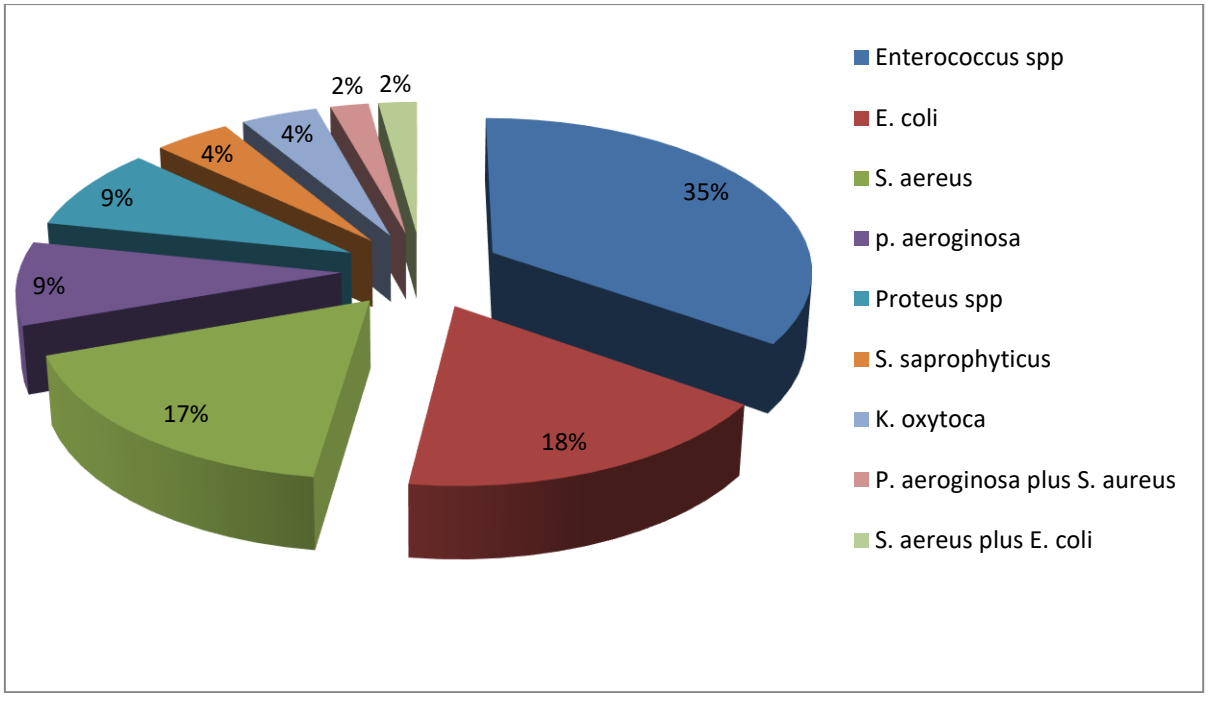

Figure 7. Percentage of isolated bacteria in all specimens

Figure 8, showed the distribution of ceftriaxone resistance among different age groups, 100% resistance in the age group 0-15 years, followed by age group 16-30 years with resistance rate as 83%. While resistance in the age group 31-45 years was 66%. Cefotaxime and ceftazidime were resistance in 100% for all isolated with different ages.

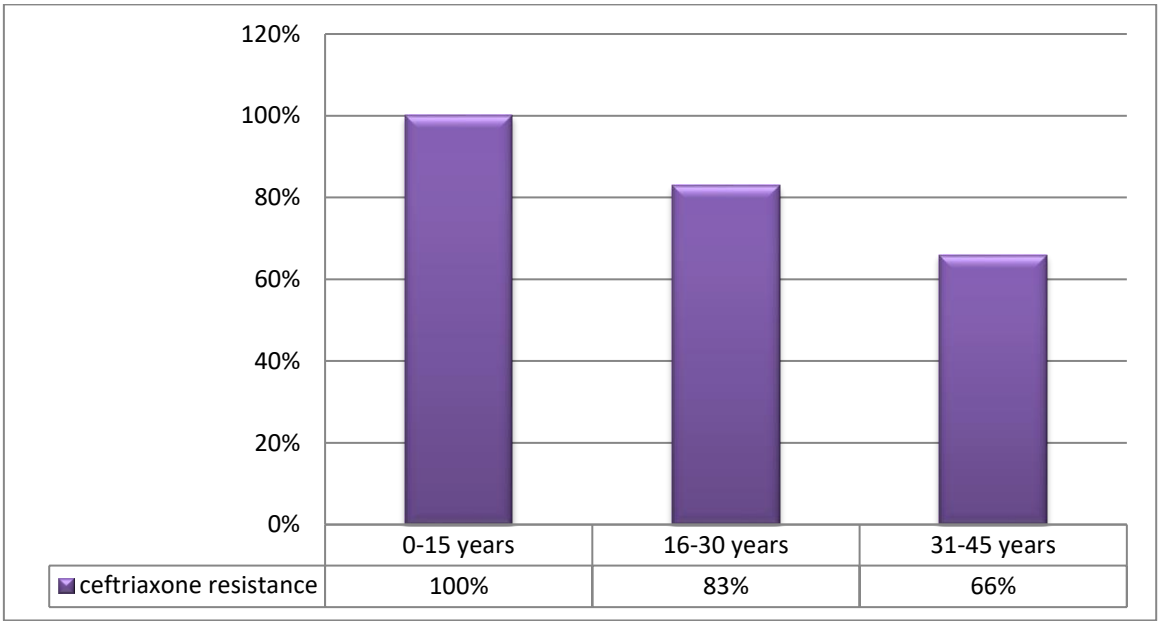

Figure 8. Ceftriaxone resistance according to age group

4. DISCUSSION

Antibiotic-resistant bacteria are becoming a crucial problem of all populations, and are being implicated in increasing morbidity among the patients. Infections with resistant species regarding cause to prolonged stays in hospitals; compromised immune persons along exposures to multiple antibiotics are main factors that increase the risks for infections and multidrug resistance. The emergence of antibiotic resistance in various bacteria from different specimens is associated with significant adverse outcomes.

In the current study, bacterial isolates in urine were 12 *Enterococcus* spp and 6 *E. coli*, while *Staph aureus*, *Staph saprophyticus*, and *Klebsiella oxytoca* were 2 for each one. *Enterococcus* spp was the most prevalent bacterial pathogen in UTI, this finding may disagree with other studies that found *E. coli* was the most common prevalent pathogen isolated from UTI, [5] that mentioned *E. coli* prevalence was (42,2 %), also disagree with [6].

This study showed 91% (N = 22) of patients with UTI were females, while males were represented just 9% (N = 2). This finding agrees with many studies [7, 8].

Because cephalosporins can cure and penetrate various tissues, so this study evaluated third-generation cephalosporins sensitively of clinical bacteria isolated from different parts of the body. Third-generation cephalosporins can cross the genitourinary tract infections bone and joint infections, blood-brain barrier, and skin and soft tissue Infections [1]. Ceftriaxone revealed 78% resistance and it is less than other antibiotics used in this study, maybe due to Ceftriaxone has high protein binding capacity and has the longest-half life of antibiotics in this generation

and is administrable as a once-daily dose. Pharmacokinetically, some third-generation compounds are poorly absorbed in the gastrointestinal tract and are administered only intramuscularly or intravenously like ceftriaxone, ceftazidime, and cefotaxime. [1]

Some studies also showed increased resistance to cephalosporins, analysis of 31 strains of *P. aeruginosa* showed high resistance ceftazidime, Mutation-dependent overproduction of intrinsic -lactamase is considered the main cause of resistance [9]. Another study revealed in 2019 that resistance to ceftriaxone 86%, cefotaxime 80%, and ceftazidime 93 to the *Klebsiella pneumonia* [10].

In this work, *K. oxytoca* was resistant to cephalosporin as Ceftriaxone, Cefotazidime, and Cefotaxime and this agrees with [11]. Almost all isolates of *Klebsiella* species were initially considered to be susceptible to cephalosporin; studies over the last two decades have shown variable susceptibility to this antibiotic class, this resistance is mediated by plasmid-mediated extended-spectrum beta-lactamases (ESBLs) [12-14]

This high rate of cephalosporins resistance that reaches to 100% resistance may due to prolonged inappropriate administration of these drugs described by doctors, and also few personal education presented by an incomplete full course of antibiotics to eradicate the pathogen to improve infection cure rates and avoid the development of any resistance or treatment failures [1].

5. CONCLUSIONS

Worryingly, the incidence of human infections caused by third-generation cephalosporin-resistant is increasing worldwide, this considered serious public health challenges to patients and to clinicians that emerged in recent years, so we need to direct more attention to antimicrobial resistance monitoring and surveillance, this must be fundamental for creating and developing effective antimicrobial resistance control strategies and for accurate antibiotic prescriptions in clinical settings. Regular monitoring of the judicious use of antibiotics assists in conserving the effectiveness of sensitive antibiotics and prevent the emergence of further resistance, as well as resistance to multiple antibiotics limits the therapeutic options for infections. In this search, all 46 clinical isolated bacteria were 100% (N = 46) resistant to cefotaxime and Cefotazidime, while they were 78% (N = 36) resistant to ceftriaxone. *Enterococcus* spp was the most prevalent bacterial pathogen in UTI. Resistance to third-generation cephalosporins in small age groups less than 15 years old considered more than other groups. Prevalence of bacterial isolation in different specimens showed the high predominance of *Enterococcus* spp in 16 (35%) samples, followed by both *E. coli* & *S aureus* in 8 (17.5%) specimen for each one.

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