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Estimating the Level of Interleukin-22 in Sera of Patients with Uropathogenic *Escherichia coli* Infection in Mosul City

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ABSTRACT

Background: Urinary tract infections (UTIs) were infectious diseases of the urinary system, that were caused by the different causative agents, including fungi, parasites, viruses, and bacteria. The current study was designed to isolate different bacteria from UTI and choose *E. coli* isolates to study levels of interleukin-22 in patients infected with it. Furthermore, studying the prevalence of type 1 fimbriae (*fim*H) virulence gene from isolated *E. coli* of above patients. **Methods:** In the present study, a total of (140) midstream urine and serum samples were collected from patients (110 females and 30 males) with the age ranged between 10 to 65 years, who had signs and symptoms and primarily diagnosed with UTI by physician in Al-Salam Teaching Hospital – Mosul/Iraq during the period between January and March 2021, while thirty-four healthy individuals were studied as controls for the ELISA test. Identification of bacterial isolates was done by microscopical examination, biochemical tests, and (API 20E). Furthermore, disc diffusion method was used in antibiotic sensitivity test, and DNA from *E. coli* isolates was extracted for gene detection. In addition, serum interleukin-22 level was determined via ELISA technique. **Results:** The mean ± SD age in UTI patients were (32.95 ± 12.80) years, while in the healthy controls group were (35.55 ± 13.51) years. Additionally, *E. coli* were the most common isolated bacteria from the patient group with a frequency and percentage of 50 (35.7%). Furthermore, when compared to the control group, serum IL- 22 level was significantly higher in the patient's group due to *E. coli* infection (P<0.001). Moreover, the prevalence of the *fim*H gene in *E. coli* isolates was 47 (94.0%) were positive for that gene. **Conclusion**: The present study revealed that *E. coli* was the most bacterial infection in patients with urinary tract infection, while the highest *E. coli* sensitivity was to Meropenem, Nitrofurantoin (F15) and Chloramphenicol also the higher serum IL- 22 level in patients with UTIs due to *E. coli* compared to controls group. Therefore, IL-22 could be used as a biomarker for UTI. Additionally, the prevalence of the *fim*H gene in *E. coli* isolates was present in most isolates.

Keywords: - UTI, IL-22, *fim*H, and virulence gene.

INTRODUCTION

Urinary tract infection (UTI) is the infection of the urothelium, take place at any part of the urinary tract which includes kidneys, ureters, bladder, and urethra, and were considered the second most common bacterial infections after respiratory tract infections (Kumar *et al.*, 2015). Interestingly the presence of microbes in the bladder indicates an infectious process because the bladder is a sterile organ (Singh, 2020). However, several classifications are available for UTIs, one of them is based on the part of the urinary tract that is infected which consists of the bladder (cystitis), urethral (urethritis), and kidneys infection (pyelonephritis). Furthermore, the second classification of UTI (Both cystitis and pyelonephritis) is based on the degree of complication of the infection which are uncomplicated or complicated infections (Flores-Mireles *et al.*, 2015). However, pain and frequent urination are the most common symptoms associated with cystitis whereas pyelonephritis is commonly characterized by high fever and flank pain (Demilie *et al.*, 2012).

Additionally, there are many factors that contribute to UTI, including sexual activity, age, diabetes, anomalies of the urinary tract, immuno-compromised patients, and previous treatment for UTI (bacterial resistance) (Zaidi *et al.*, 2020). Nevertheless, the most common causative agent of UTIs is *Escherichia coli* which accountable for 80% of the cases (Demirci *et al.*, 2019). Furthermore, other infectious agents of UTIs include *Klebsiella* species, *Staphylococcus* species, *Proteus* species, in addition to *Candida* species (Patel *et al.*, 2019).

Several virulence factors of UPEC participate in its virulence, including fimbriae (P fimbriae and type 1), flagella, toxins (e.g., hemolysin), and iron-uptake systems (enterobactin, aerobactin, salmochelin) which play role in evading the immune system and increase their infectivity (Malekzadegan *et al.*, 2018). Type 1 fimbriae are one of the most essential virulence factors for UPEC, which play role in surface colonization of the uroepithelium, escaping host protection mechanisms, and promoting inflammatory response, and causing disease (Lüthje *et al.*, 2013). It encoded by *fim*H gene and associated with powerful UTIs (Tajbakhsh *et al.*, 2016). Urothelial cells produce cytokines as a result of infection such as IL−22 in response to UPEC. Interleukin-22 is a member of the interleukin-10 cytokine family, which involves IL-10, IL-19, IL-20, IL-24, and IL-26 (Ouyang and O'garra, 2019).

Interestingly, many cells produce IL-22 such as neutrophils, mucosal-associated invariant T cells, macrophages, T helper 22 cells, natural killer T cells, group 3 innate lymphoid cells (mucosal surfaces colonizer), αβ T cells and γδ T cells (Dudakov *et al.*, 2015).

In the mucosa, the main trigger for IL-22 secretion is the interaction of antigen-presenting cells (APCs) with invading causative agents. As a result, IL-23 is released from APCs, which enhances the epithelial cells and lamina propria lymphocytes to secrete cytokines such as IL-22 and IL-17(Khader and Gopal, 2010). In addition, IL-23 regulates the appearance of IL-22 from numerous T cell populations including CD4 and Th17 cells (Buonocore *et al.*, 2010). However, the secretion of IL-22 may be beneficial or harmful (a two-edged sword) depending on the site and context of its expression. The beneficial effect includes releasing and upregulation of lipocalin-2 as an antimicrobial proteins, cellular repairing and regeneration (Ingersoll and Starkey, 2020). On the other side, the harmful effect involves deleterious consequences of pro-inflammatory responses and homeostasis disturbances due to the modification of microbiota in the UTIs (Zindl *et al.*, 2013).

This study is designed to estimate the level of IL-22 in patients with UTI caused by UPEC in comparison to the control group using the ELISA technique. Furthermore, studying the prevalence of type 1 fimbriae (*fimH*) gene in strains of *E. coli* isolates by Polymerase Chain Reaction (PCR) technique.

MATERIALS AND METHODOLOGY

In the current study, a total of (140) urine and serum samples with the age ranged between (10 to 65) years, were collected from patients who were diagnosed with UTI in Al-Salam Teaching Hospital – Mosul during the period between January till March 2021, while 34 healthy individuals were studied as controls for ELISA test, whose age ranged between 12 to 70 years. Inclusion criteria were based on presence of signs and symptoms of UTI and clinical examination by the physicians at the clinic, in addition to positive results for bacteria and pus cells (≥ 8-10/HPF) in general urine examination (GUE). On the other side and for exclusion criteria, patients were excluded if they had no signs and symptoms of UTI and negative results for bacteria and pus cells in GUE. Furthermore, patients who have chronic diseases and those who declined to participate in the study are also excluded from sample collection. Moreover, the control subjects had no signs and symptoms of UTI or any other infection, in addition to negative urine culture. Samples were collected on-site.

Blood agar, MacConkey's agar, and chocolate agar were used to culture urine samples. Colonies grown on these media were diagnosed according to their shape, size, color, and type of lysis. Further identification of bacterial isolates was done by microscopical examination through Gram stain and biochemical tests. In addition, *E. coli* strains were confirmed by analytical profile index 20 (API 20E). Additionally, a disc diffusion method was used in antibiotic sensitivity test, and eleven antibiotics were employed according whether Gram positive or negative isolates (nine antibiotics for each isolate).

Wizard® Genomic DNA Purification Kit- (Promega – USA) was used for extraction DNA of *E. coli* strains, according to manufacturer's guidelines. Furthermore, BioDrop was used for measuring the concentration and purity of the DNA. Additionally, a specific primer has been used for *fim*H detection (Macrogen - South Korea) which includes forward primer 5' GAGAAGAGGTTTGATTTAACTTATTG 3' and reverse primer 5' AGAGCCGCTGTAGAACTGAGG 3' (Raeispour and Ranjbar, 2018). In Addition, serum interleukin-22 level was determined by using a commercially available sandwich enzyme-linked immunosorbent assay (Elabscience Human Interleukin-22 ELISA Kit) according to the producer's guidelines.

RESULTS AND DISCUSSIONS

The mean ± standard deviation of ages in UTI patients were (32.95 ± 12.80) years, while in the healthy controls group were (35.55 ± 13.51) years.

Furthermore, the distribution of infection was 110 (78.6%) in female patients, while 30 (21.4%) in male patients. However, shorter and wider urethra in women makes them prone to higher rates of UTIs compared to men (Henderson *et al*., 2009).

The results of the study revealed that patient's age categorized into six groups and the results cross-tabulated in the (Table 1) show that most patients were adults with ages between 21 - 30 and 31 - 40 years with a frequency and percentage of 45 (33.3%) and 31 (23.0%) respectively. These results were in agreement with Almukhtar *et al.,* (2018) who found that 58.4% of participants belonged to the 21-30-year followed by 26% who belonged to the 31−40 year age group (Almukhtar, 2018).

Table 1: Distribution of UTI Patients According to the Age group

Age Group	Gender		Total	%
	Male	Female		
11 - 20	3	22	25	18.5
21 - 30	7	38	45	33.3
31 - 40	5	26	31	23.0
41 - 50	9	11	20	14.8
51 - 60	4	7	11	8.2
61 - 75	2	1	3	2.2
Total	**30**	**105**	**135**	**100**

However, several reasons make these groups at higher rates with UTI, including physiological changes in the urinary tract, rate of sexual activity is higher compared to other age groups, and the pregnancy participates in increasing the sensitivity rate of infection among women (Al-Badr and Al-Shaikh, 2013).

The reason behind these differences in the observed percentages may be due to differences in size, number, site of collection, season, and medication especially exposure to antibiotics.

The distribution of microbial agents of UTIs in the study as shown in (Table 2) were as follows*: E. coli* = 50 (37.0%), *S. epidermidis* = 23 (17%), *K. pneumoniae* = 13 (9.6%), *S. aureus* = 11 (8.1%), *P. mirabilis* = 10 (7.4%), *C. albicans* = 10 (7.4%), *P. aeruginosa* = 9 (6.7%), *K. oxytoca* = 6 (4.4%), and *P. vulgaris* = 3 (2.2%), while 3 (2.1%) of the specimens were considered mixed growth and 2 (1.4%) of the samples regarded contaminated.

Table 2: Prevalence of microbial isolates in the study

Causative agents	No. of Samples	Percentage
E. coli	50	37.0
S. epidermidis	23	17.0
K. pneumoniae	13	9.6
S. aureus	11	8.1
P. mirabilis	10	7.4
C. albicans	10	7.4
P. aeruginosa	9	6.7
K. oxytoca	6	4.4
P. vulgaris	3	2.2
Sub Total	135	100
Mixed Growth	3	-
Contaminated Growth	2	-
Total	140	-

However, variation in the percentages of causative agents among studies could be due to the level of education, water accessibility, methodology, and sample size (Al-Gosha'ah *et al.*, 2014). As

it is a part of the intestinal normal flora, the majority of UTIs were caused by *E. coli* compared to other agents in different studies (Singer, 2015).

In antibiotic sensitivity test, the highest *E. coli* sensitivity was to Meropenem (MEM, 10mg/disc) 50 (100%) followed by Nitrofurantoin (F, 300mg/disc) and Chloramphenicol (C, 30mg/disc) 44 (88%) respectively, while Gentamicin (CN, 10mg/disc) 37 (74%), Nalidixic acid (NA, 30mg/disc) 17 (34%), Tetracycline (TE, 30mg/disc) 3 (6%), Cephalexin (CL, 30mg/disc) 2 (4%), and Cefotaxime (CTX, 30mg/disc) 1 (2%), as shown in Fig. (1). Interestingly, regular and misuse of the antibiotic agent are the most common cause of antibiotic resistance (Katongole *et al.*, 2019).

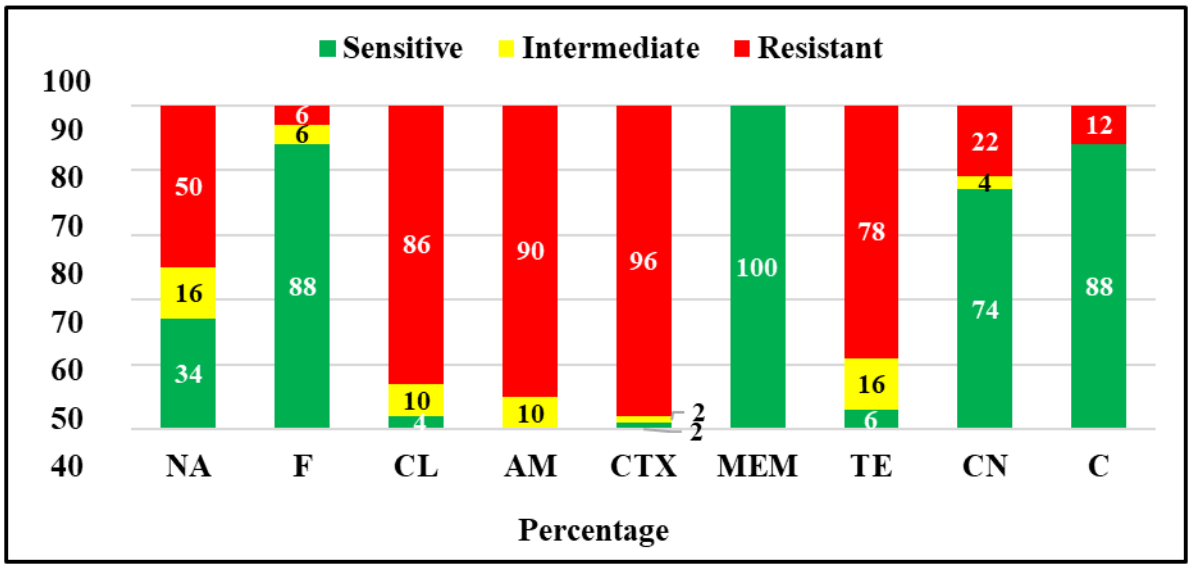

Fig. 1: Percentage of susceptibility of strains of *E. coli* against antibiotics under study.

NA: Nalidixic acid (30 mg/disc), F: Nitrofurantoin (300 mg/disc), CL: Cephalexin (30mg/disc), AM: Ampicillin (10mg/disc), CTX: Cefotaxime (30mg/disc), MEM: Meropenem (10mg/disc), TE: Tetracycline (30mg/disc), CN: Gentamicin (10mg/disc), C: Chloramphenicol (30mg/disc).

On the molecular side, the *fim*H gene was detected in 47 (94%) of the strains, as shown in Fig. (2).

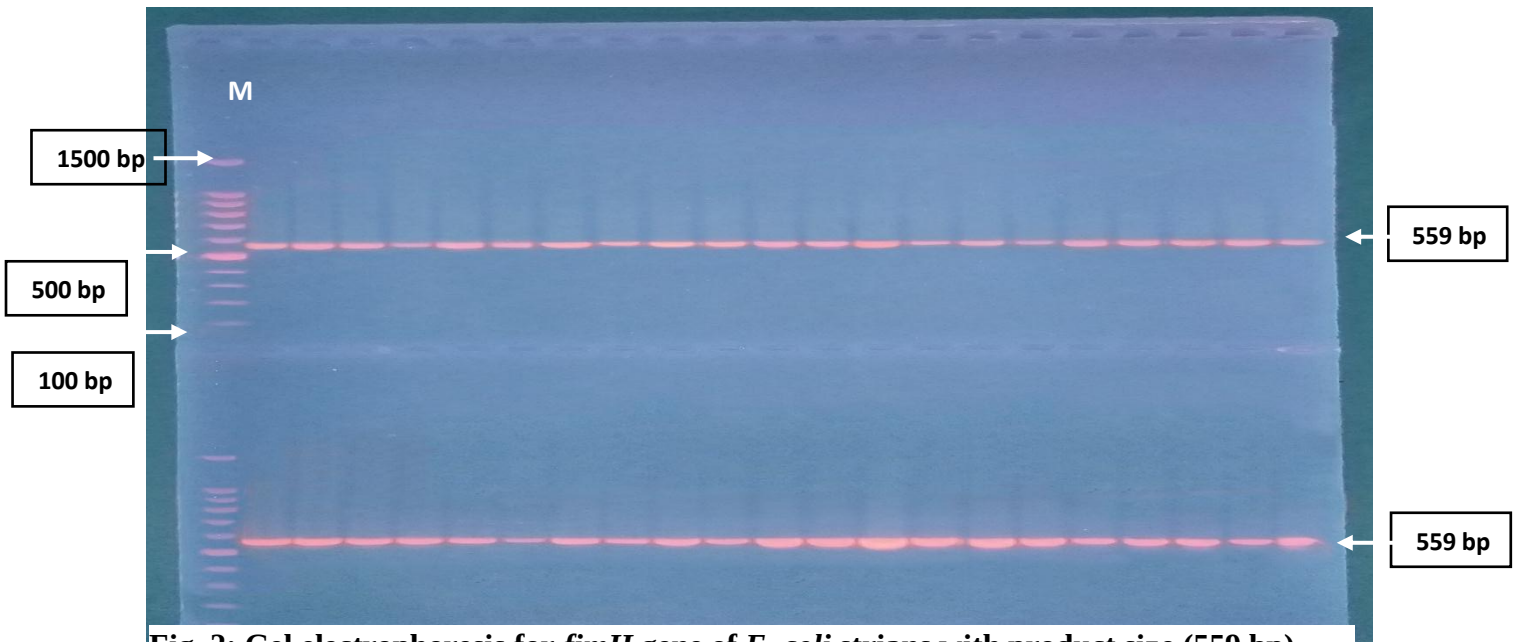

Fig. 2: Gel electrophoresis for *fimH* gene of *E. coli* strians with product size (559 bp). Agarose 1.5%, at 150v for 1.5 hrs. M: DNA ladder (100 bp).

The most important function of the *fim*H gene during UPEC infection was participating in attachment to uroepithelial cells and plays role in biofilm formation (Kallau *et al.*, 2018). The distribution of virulence genes was more prevalent in UPEC isolates than in commensal ones (Rezatofighi *et al.*, 2021). The results were in close concordance with the results reported by Daga *et al.*, (2019), who found that (95.8%) of *E. coli* isolates carry the *fim*H gene in patients with UTI (Daga *et al.*, 2019). By contrast, a higher frequency of the *fim*H gene has been described by Ali *et al.*, (2019) who mentioned that (100%) of UPEC isolates harbor the *fim*H gene (Ali *et al.*, 2019).

On the immunological side, the mean levels of serum IL-22 in the patient's group were (200.88 ±63.25 pg /ml), which were significantly elevated (P<0.01) in comparison to the controls group (54.76±72.06 pg /ml), as shown in Fig. (3). However, these results were in agreement with result of Sakamoto *et al.*, (2017) who declared that IL-22 participates in host protection toward enteric pathogens including *E. coli* and *Citrobacter rodentium*.

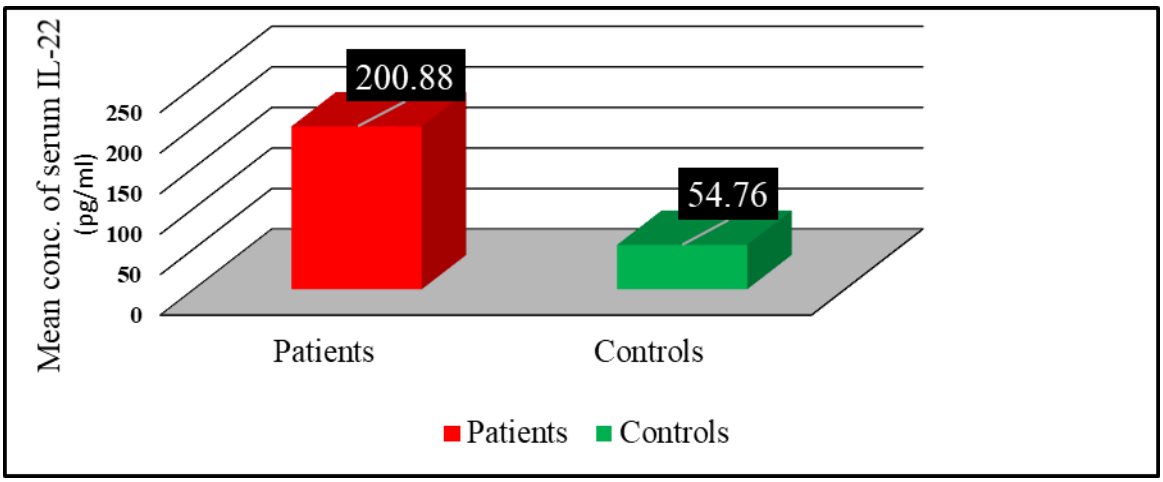

Fig. 3: Mean concentration of IL-22 (pg/ml) in the patients' sera with *E. coli* in comparison to the control group.

Furthermore, IL-22 prevents the dissemination and replication of pathogenic bacteria by enhancing RegIIIβ and RegIIIγ production from the epithelium (De Luca *et al.*, 2010). While De Luca *et al.*, *(*2010) also showed the contribution of IL-22 in the immune response during UTI by *E. coli*.

On the gender level, there was no significant difference in the mean concentration of IL-22 in sera of males (198.24 ± 66.83 pg/ml) when compared with its concentration in sera of females (201.30 ± 63.47 pg/ml) (P> 0.05), as presented in Fig. (4). The reason behind this result could be related to the fact that the production of cytokine was affected by the infection itself and not by gender.

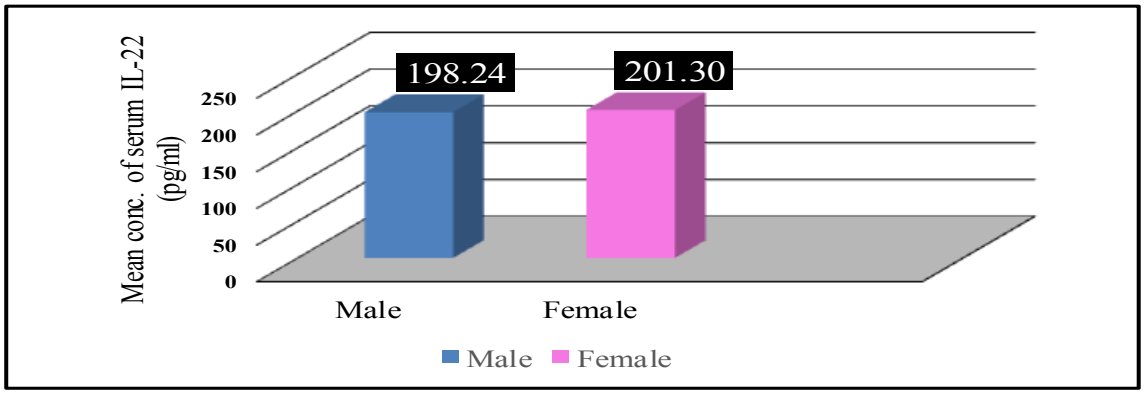

Fig. 4: Mean concentration of IL-22 (pg/ml) in the patients' sera with *E. coli* according to gender.

CONCLUSIONS

E. coli was the most bacterial infection in patients with UTI. The highest *E. coli* sensitivity was to Meropenem, Nitrofurantoin (F15) and Chloramphenicol. IL-22 could be used as a biomarker for UTI due to *E. coli*, as its level was significantly higher in the patient group compared to the control group. Additionally, the *fim*H gene may also play role in the pathogenesis of UPEC, as its prevalence in *E. coli* isolates was 47 (94.0%).

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تقدير مستوى انترلوكين-22 فى مصل المرضى المصابين بالاشيريشيا القولونية الممرضة للمسالك البولية في مدينة الموصل

الملخص

التهاب المسالك البولية (UTI)

هو نوع من الأمراض المعدية التي تسببها الفطريات والطفيليات والفيروسات والبكتيريا. هدفت هذه الدراسة إلى تقدير مستويات انترلوكين- 22 ودراسة انتشار جين الضراوة (*fimH*) في المرضى الذين يعانون من التهاب المسالك البولية الناجمة عن الايشيريشة القولونية. **طرائق العمل:** تم جمع 140 عينة إدرار ومصل من المرضى (110 إناث و30 ذكر) تتراوح أعمارهم بين 10 إلى 65 عامًا والذين ظهرت عليهم علامات وأعراض المرض وتم تشخيص إصابتهم بالتهاب المسالك البولية من قبل الاطباء في مستشفى السلام التعليمي – الموصل / العراق خلال الفترة بين يناير ومارس 2021، و34 عينة تم اختيارهم كعينات سيطرة (اصحاء). وتم تشخيص البكتريا المعزولة عن طريق الفحص المجهري، الفحوصات الكيمياوية واختبار API 20E . وأيضا تم استخدام طريقة Disk Diffusion في اختبارحساسية المضادات وتقنية ELISA في تقدير مستوى IL – 22 في عينات المصول. النتائج: متوسط العمر± الانحراف المعياري في المرضى كانت (32.95 ± 12.80) في حين في مجموعة الاصحاء كانت (35.55 ± 13.51). وبالإضافة إلى ذلك، فإن الايشيريشة القولونية كانت الأكثر شيوعا وعزلاً في مجموعة المرضى 50 (35.7 في المائة). وعلاوة على ذلك، فإن مستوى الـ IL - 22 في المرضى الذين يعانون من عدوى ايشيريشة قولونية كان أعلى بكثير من تلك الموجودة في مجموعة الاصحاء ($P<0.001$). وبالإضافة إلى ذلك، فإن معدل انتشار جين الضراوة *fimH* في عزلات الايشيريشة القولونية كانت 47 (94 %). الخلاصة: أظهرت هذه الدراسة الى ان الايشيريشة القولونية هو الأكثر تسبباً لالتهابات المجاري البولية، في حين أنها كانت اكثر تحسساً للـ Meropenem، Nitrofurantoin ، Chloramphenicol. وأيضا كانت مستوى IL – 22 في مجموعة المرضى نتيجة الايشيريشة القولونية اعلى بكثير من مجموعة الاصحاء، ولهذا يمكن استخدام الـ IL – 22 كمؤشر حيوي لالتهابات المجاري البولية.

الكلمات الدالة: التهابات المجاري البولية، انترلوكين- 22، جين *fimH* ، جين ضراوة.