Research Article

Estimation of Interleukin 6, IL- 23 and GM-CSF concentration levels in adult and adolescent patients with urinary tract infections in Sulaymaniyah city, Iraq

Chateen I. Ali Pambuk[1]*, Fatma Mustafa Mohammed[2]*

*College of Dentistry / University of Tikrit, Iraq[1,2]
Corresponding author: Ass. Prof. Dr. Chateen I. Ali Pambuk (College of Dentistry / University of Tikrit) PhD Medical Microbiology & Immunology email: dr.chatin2@yahoo.com and/or dr.chateen@tu.edu.iq
ORCID ID: https://orcid.org/0000-0002-9893-8085

Abstract

Background

Urinary tract infections (UTIs) are classified as one of the most common infectious diseases worldwide and represent a significant public health problem. Recurrent infection is one of the major challenges associated with this disease in adults and adolescents.

Aim

This study aims to estimate the concentration levels of interleukin 6, IL-1β and 23 (IL-23) and granulocyte-macrophage colony-stimulating factor (GM-CSF) in the urine of adult and adolescent patients with acute and recurrent urinary tract infections in the city of Sulaymaniyah Iraq.

Materials and Method

This study was conducted in Sulaymaniyah on patients with acute and recurrent urinary tract infections (UTIs) who visited private clinics and were diagnosed by a specialist physician between January 2023 and July 2023. A total of 68 samples were collected, comprising 26 males and 42 females, with patient ages ranging from 22 to 76 years for adults and 15 to 21 years for adolescents. Fifteen samples were also taken as a control group. Information was accurately recorded for each sample on a questionnaire, selected based on established criteria. Interleukin-6, IL-1β and IL-23 and GM-CSF levels were measured in the urine of patients with acute and recurrent UTIs using enzyme-linked immunosorbent assay (ELISA).

Results

In the current study, the number of females with urinary tract infections was 61.3% including adult and adolescent females, while the number of males was 38.7%. The results of the current study showed that the number of samples from patients with acute urinarytract infections was higher than from those with recurrent infections, while the rate of recurrent UTI in adolescent females were higher. A significant elevated levels of IL-6 and IL-1β was found in acute UTI, while a low levels of IL-6 recorded in recurrent adults and adolescents compared to acute UTI inversely to IL-1β which scored values of 268.19± 32 ng/ml for recurrent UTI patients and 284.27 ± 40 ng/ml for those with adolescent UTI. Regarding the concentration of IL--23 in the urine of patients with acute urinary tract infections, the results showed a significant difference ($P \leq 0.05$) between the patient group and the control group, with concentration levels of (42.66 ± 10.13) and (16.03 ± 5.51) pg/ml, respectively. Similarly, in recurrent cases, there were significant differences at a probability level of ($P \leq 0.05$), with concentration levels of (35.07±8.60) and (16.0±5.51) pg/ml, respectively. As for GM-CSF, the results showed an increase, but it was not statistically significant between patients and the control group in patients with acute urinary tract infections. .Regarding GM-CSF in recurrent cases, the results showed a significant increase ($p < 0.05$) recording 39.16 ± 8.23 pg/ml.

Conclusions

The study results showed that urinary tract infections (UTIs) are more common in females, and that acute cases are more prevalent than recurrent ones. Significantly elevated levels of interleukin – 6, IL-1β and IL-23 were observed in both acute cases , while was low in recurrent regarding IL-6 and high IL-1β valeus . Furthermore, significantly elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) were observed in recurrent cases, suggesting that these two factors may contribute to the inflammatory response associated with UTIs and potentially to recurrent infection.

Keywords: Interleukin 6, IL-23, GM-CSF, adults and adolescent patients, UTIS.

Introduction

In most countries worldwide, urinary tract infections (UTIs) are the second most common health problem after respiratory infections (1). UTIs occur in both men and women, and the likelihood of developing them increases in patients with weakened immune systems or disorders and abnormalities of the urinary system, such as congenital malformations, urinary tract stones, and permanent urinary catheters (2). The body's immune system is regulated by many factors. Dysregulation of the immune system can lead to certain medical conditions (3). UTIs are acute or chronic diseases affecting the urinary system and caused by microorganisms such as bacteria and fungi that multiply abnormally (3). The body's immune system is regulated by many factors. Dysregulation of the immune system can lead to several pathological conditions4

Individuals of all ages, including women, men, children, adolescents, and the elderly, are affected. Some suffer from acute or recurrent infections leading to serious complications. The symptoms of infection vary depending on the location and severity of the infection. In some cases, the infection can be serious if left untreated. Urinary tract infections (UTIs) have a negative impact on patients' lives(5) . Recurrent UTIs are defined as infections occurring at least three times within a 12-month period. Recurrent UTIs typically occur after more than a week, with repeated exposure to the infection, which can lead to serious complications(6)

Cytokines, hormone-like peptides, play a pivotal role in the inflammatory response. They are primarily produced by immune cells activated by an inflammatory agent (7)Several cytokines have been shown to contribute significantly to UTIs such as IL-6 (8)Interleukin-23 (IL-23) and IL-6 has received particular attention. IL-23 has gained significant attention over the past decade due to its role in inflammatory diseases and cancers (9). IL-23 is a pro-inflammatory cytokine secreted by immune cells in response to damage and infection. It regulates protection against extracellular bacteria and fungi and plays a role in several autoimmune disorders, such as psoriasis and rheumatoid arthritis (10).

Granulocyte-macrophage colony-stimulating factor (GM-CSF) was initially defined as a hematopoietic growth factor due to its ability to stimulate the differentiation of granulocytes and macrophages by promoting the proliferation and differentiation of bone marrow progenitor cells. GM-CSF is secreted as a monomeric glycoprotein and has become evident as a survival and activation factor for mature myeloid cells, such as monocytes, macrophages, and neutrophils. Recently, its source has been identified in alveolar macrophages(11). It has therapeutic effects by regulating acute inflammation. And chronic.(12)

Materials and Methods

This study was conducted in the city of Sulaymaniyah on patients with acute and recurrent urinary tract infections who visited private clinics and were diagnosed by a specialist physician between January (2023) and July (2023). 68 samples were collected, including 26 males and 42 females. The ages of the patients under study ranged from 22 to 76 years for adults and 15 to 21 years for adolescents . 15 healthy individuals were selected as a control group with no systemic diseases or clinical symptoms of any disease for comparison with the patients. Their information was recorded accurately on a questionnaire sheet for each sample under study. The samples were selected based on selection and investigation criteria. The levels of IL-6 , IL-23 and GM-CSF were measured in the urine of patients with acute and recurrent urinary tract infections.

Isolation and Identification of UTI cultures

Isolation of UTI bacterial cultures were performed by utilizing standard ordinary culture media under strict sterilization conditions. While the Identification of implicated bacteria were done by using API 20 E system an Analytical profile index (API) test strips. provided by (Biomerieux SA ,Lyon, France).appendix III

Collecting urine samples

Five-mL urine samples were collected from patients in sterile screw-cap containers. Patients were instructed to collect the sample using the clean-catch midstream urine method to minimize contamination with the normal urethral flora. The samples were then transported to the laboratory for testing. After culture media inoculation of each specimen for isolation and identification of causative bacteria , they were placed in sterile tubes and centrifuged using a cooling centrifuge. The supernatant was separated, and one mL was collected and placed in sterile Eppendorf tubes for freezing until immunological assays could be performed. Appropriate transport and storage conditions were maintained to ensure sample integrity and preserve the stability of the biological components before analysis. The sediment was used for microscopic examination, which is an important indicator of urinary tract infections.

Immunological Tests

1. Interleukin-6 in Urine

The test was performed according to the instructions of the SUNLOG company of China manufacturer, using the Human Interleukin-6 (IL-6) ELISA kit. The kit included a set of solutions and reagents.

2. Interleukin-1β in Urine

The test was performed according to the instructions of the SUNLOG company of China manufacturer, using the Human Interleukin-1beta (IL-1β) ELISA kit. The kit included a set of solutions and reagents.

3. Interleukin-23 in Urine

The test was performed according to the instructions of the manufacturer, SUNLOG, using the Human Interleukin-23 (IL-23) ELISA kit. The kit included a set of solutions and reagents.

4. GM-CSF in Urine

The GM-CSF ELISA test was performed according to the instructions of the manufacturer, SUNLOG, using the Stimulating Factor (GM-CSF) ELISA kit. The kit included a set of solutions and reagents.

Statistical Analysis

The data were statistically analyzed using Prism software. The results were presented as the mean ± standard deviation. The p-value was used to indicate statistical significance ($p<0.05$) and high significance ($p<0.01$).

Results and Discussion

1-Numbers and Percentages of Samples by Gender

The study results, as shown in Table 1, indicate that urinary tract infections (UTIs) were more common in females than males, with 62.2% of cases in females compared to 37.8% in males. This finding aligns with several previous studies. This higher incidence is attributed to anatomical and physiological differences between the sexes. The shorter urethra and its proximity to the anus in females are key factors that facilitate bacterial migration to the bladder and increase the risk of UTIs(13).

Table 1. Distribution of the Study Samples by Gender (Number and Percentage)

gender	NO	%
Male	26	%38.2
Female	42	%61.8
Total	68	%100

Estrogen deficiency also contributes to increased UTI incidence in females. Other contributing factors include childbirth, pregnancy, methods of delivery, contraceptive devices, and frequent intrauterine examinations (14). The prostate gland contains a bactericidal substance and zinc, which play a crucial role in killing microorganisms (15).

2-Numbers and percentages according to clinical condition(Acute and Recurrent Cases).

Table 2 shows the clinical cases from which samples were collected for urinary tract infections. These cases were diagnosed by a urologist based on the patients' clinical symptoms, laboratory tests, and cultures. The diagnosis was either acute or recurrent. The results of the current study, , indicate that the number of samples from acute urinary tract infections was 37, with 37.8% being males and 62.2% females. Adolescent females were 8 (n. 8) with UTI even just 2 females had acute UTI with No males with UTI scored under the adolescent age groups between 15-21. These results are consistent with a study showing that 40-60% of women experience a single urinary tract infection [16] . Furthermore, 60% of women will develop an acute infection. Females are more susceptible to acute infections, which often resolve spontaneously within a few days and are easily treated with antibiotics. However, sometimes the infection may recur within weeks or months(16,17). Factors contributing to recurrence include pregnancy, childbirth, sexual activity, hormonal changes, menstruation, menopause, immune status, genetic predisposition, unhealthy lifestyle, poor personal hygiene, and a weak innate or adaptive immune response.

Table 2. Distribution of Samples by Clinical Condition (Acute and Recurrent Cases).

Study group / Gender	Acute		Recurrent	
	NO	%	NO	%
Male	14	37.8	12	38.7
female	23	62.2	19	61.3
Adolescent Female	2	12.5	6	75
Total	68	100%		

Regarding patients with recurrent UTIs, the percentage of males was 38.7%, while the percentage of females was 61.3% in which 6 out of 8 of adolescent women (75%) had recurrent UTI. Half of the women with recurrent UTIs experience a recurrence within one year18

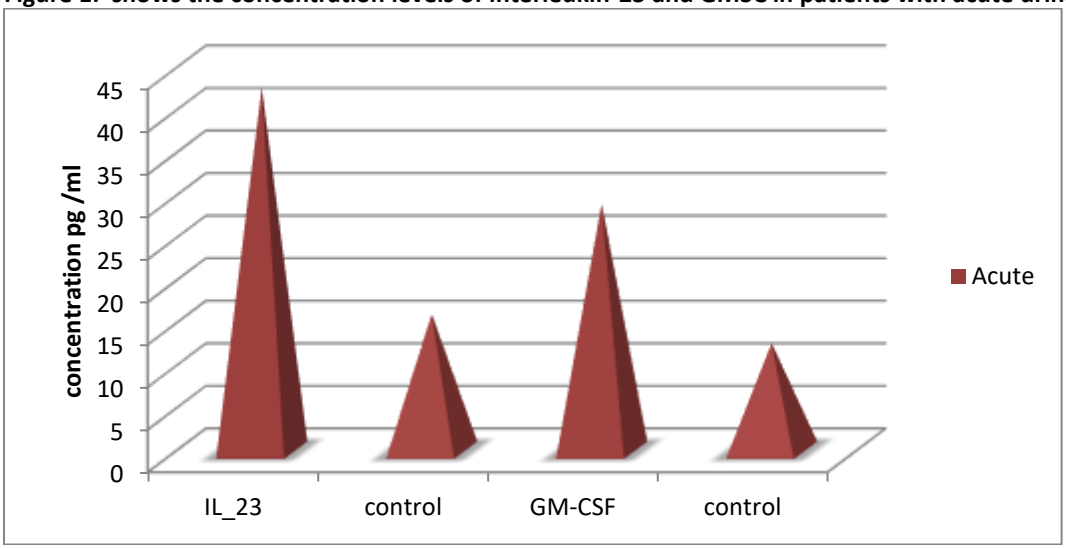
A history of infection is a significant risk factor for recurrent infections. Behavioral patterns such as douching, failure to control recurrent infections, and weakened immunity are all indicators that may contribute to the development of UTIs and the deterioration of the patient's condition. Therefore, it is crucial to take medications precisely and without interruption, following the doctor's instructions. Taking supplements may reduce the strains that threaten to make cases chronic and recurrent, and preventative measures can be taken to treat UTIs.

3-Interleukin-23 and GMCSF Concentration Levels in Patients with Acute UTI

Regarding the levels of the variables under study, measured in the urine of patients with acute urinary tract infections, the results for interleukin-23 showed a significant difference ($P \leq 0.05$) between the patient group and the control group. Its concentration levels were (42.66±10.13) and (16.03±5.51) pg/ml, respectively. As shown in Figure1, most studies measure the levels of these variables in serum, not urine. There were very few studies, especially in the clinical cases selected for this study (recurrent acute infections). Therefore, it was difficult to make similar comparisons due to the lack of comparable studies.

Studies have indicated that IL-23 is essential in many inflammatory conditions by activating proinflammatory mediators. IL-23 also plays a role in host defenses against infection. In a study conducted on patients who underwent urinary catheterization, the concentration of IL-23 in urine was elevated (19). This increase in urinary IL-23 levels may be due to the type and virulence of the bacterial isolates, age, sex, the individual's health status, and the state of their immune system—all factors that may influence this.

Figure 1: shows the concentration levels of interleukin-23 and GMSC in patients with acute urinary tract infections



Studies have revealed that elevated levels of IL-23 may play a role in persistent inflammation of the male urinary tract, particularly in those suffering from chronic prostatitis (20). Another study indicated elevated IL-23 levels in male patients with chronic prostatitis compared to healthy individuals (21). Excessive IL-23 production has been linked to several chronic inflammatory diseases, and it is also overexpressed in cancer patients. Therefore, the possibility of inhibiting the activity of inflammatory molecules in cases of chronic inflammation represents a strategy to halt tumor growth (22).

As for GM-CSF, the results showed an elevation, but it was not statistically significant between patients and the control group. Its concentration in patients with acute urinary tract infections was (28.99±6.17), while in the control group it was (12.60±3.25). This contradicts other studies where GM-CSF levels rise and increase, and activate phagocytic cell functions in acute inflammation (23).

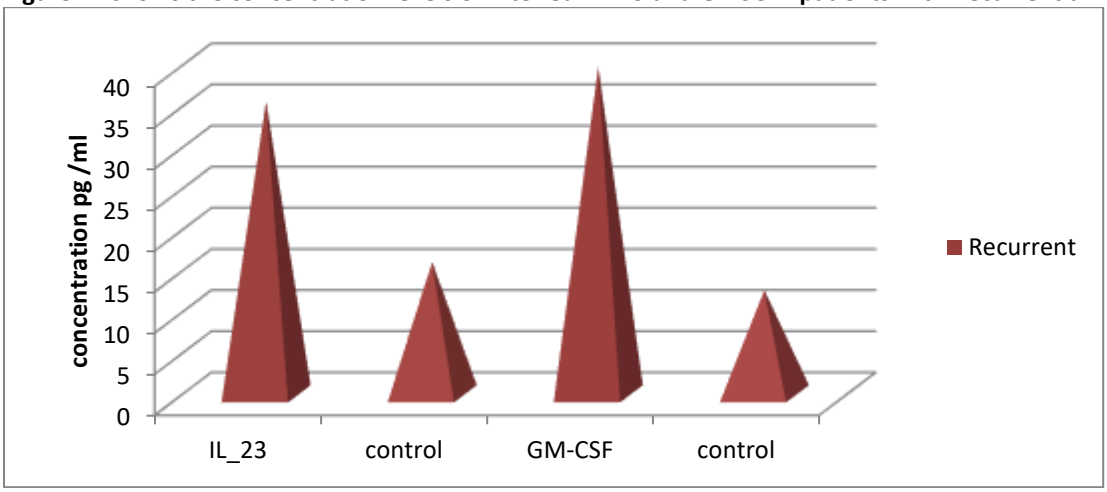
4-Interleukin-23 and GMCSF Concentration Levels in Patients with Recurrent UTI

Regarding the levels of interleukin-23 (IL-23) in the urine of patients with recurrent urinary tract infections (UTIs), the results showed a significant difference (P ≤ 0.05) between the patient group and the control group, with concentrations of(35.07± 8.60) and(16.03± 5.51) (pg/ml) respectively.

For patients with recurrent UTIs, and specifically regarding IL-23, the results in this study showed that IL-23 levels in recurrent cases were lower than in acute cases. The researchers found that a deficiency in IL-23 increases susceptibility to bacterial colonization. This decrease in IL-23 concentration may play a role in the recurrence of infection, or perhaps the patient's condition and the frequency of the infection affected the IL-23 concentration. Recurrent UTIs are often serious and can lead to infection progression. Therefore, searching for specific markers for the early detection of UTIs is an important aspect of prevention and early treatment. IL-23 plays a role in exacerbating disease severity.

Repeated exposure to bacteria leads to a state of inhibition or functional exhaustion of dendritic cells and macrophages, the main source of IL-23, thus reducing their ability to produce it with repeated infections. (24) In cases of recurrent bladder infections, the immune response tends to be Th2-mediated, responsible for repairing the damaged epithelium, at the expense of the inflammatory response dependent on the IL-23/Th17 axis, and consequently, IL-23 production decreases. (25) Frequent use of antibiotics alters the composition of the urinary microbiome and affects the signaling of toxin-recognizing receptors (TLRs) that stimulate IL-23 production, leading to a decrease in its levels. (26)

Figure 2 : shows the concentration levels of interleukin-23 and GMSC in patients with Recurrent urinary tract infections.



Regarding GM-CSF in recurrent cases, the results demonstrated a significant increase (P < 0.05) in patients compared with the control group, with a concentration level of 39.16 ± 8.23 pg/ml, whereas the concentration in the control group was 12.60 ± 3.25 pg/ml.

Another study reported an increase in urinary GM-CSF levels (27), which is consistent with the findings of the present study. GM-CSF is known to be overexpressed in several chronic inflammatory diseases (28). Furthermore, GM-CSF concentrations were higher in recurrent cases than in acute cases. In the context of chronic tissue inflammation, GM-CSF produced by tissue-infiltrating lymphocytes exerts detrimental effects through promoting excessive inflammation and tissue damage (29).

The present study observed that GM-CSF levels were lower in patients with acute urinary tract infections compared with recurrent cases. This may be explained by the fact that recurrent infections result in persistent stimulation of the immune system due to repeated exposure to bacterial antigens, which activates macrophages, dendritic cells, and T lymphocytes to produce higher amounts of GM-CSF. This process helps sustain the inflammatory response and enhances the survival and function of immune cells (30). In contrast, acute infections are characterized by an early and transient immune response that primarily depends on the release of pro-inflammatory cytokines and neutrophil recruitment. Therefore, GM-CSF production is lower than in recurrent infections, which are associated with persistent inflammation and immunological alterations in the bladder and urinary tract tissues (31,32). In addition, enhanced macrophage activity during recurrent episodes contributes to the continued production of pro-inflammatory cytokines, including GM-CSF, leading to higher levels compared with acute cases (33).

5- Interleukin-6 and IL-1β Concentration Levels in Patients with Acute and Recurrent UTI

In this study, the IL-6 levels in urine were checked for the all groups under study. The first group represented the patients with an acute UTI , which scored a highly significant increase in IL-6 levels (562.91± 166 ng/ml) compared to control as shown in Fig

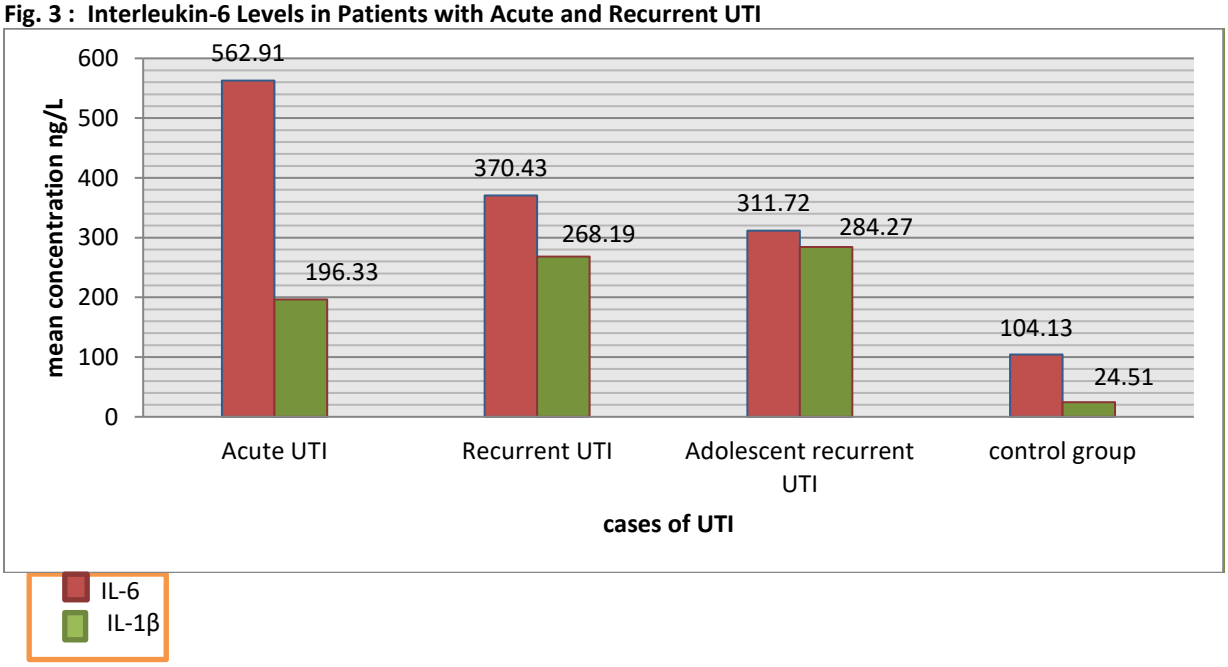
(3) . While the in recurrent UTI , in both adolescents and adults, the levels was also significantly increased compared to control , but in contrary significantly decreased when compared to acute UTI values scoring a values of 370.43± 102 ng/ml and 311.72 ± 85 ng/ml in acute and adolescent UTI patients. The results showed a statistically significant difference, with an F-value of 11.633 at degrees of freedom 3, which was significant at both the 0.05 and 0.01 levels.

It is worth mentioning that so many studies conducted all over the world confirms the elevated levels of IL-6 in urine of acute and recurrent UTI (35,36). While the recurrent level of the present study was significantly lower the acute UTI .

Regarding IL-1β in urine were also measured for all the groups being studied. In acute urinary tract infection, they showed a highly significant rise in IL-1β levels (significant at both the 0.05 and 0.01 levels), measuring 196.33±37 ng/ml, which was much higher than the control group, as illustrated in Figure (3). In cases of recurrent urinary tract infections, both in adolescents and adults, the levels were also significantly highly increased compared to the control group. However, in contrast, these levels were significantly higher when compared to those observed in acute UTI cases, with values of 268.19± 32 ng/ml for recurrent UTI patients and 284.27 ± 40 ng/ml for those with adolescent UTI. The results indicated a statistically significant difference.

The current study aligns with the findings of [37], which demonstrated a highly significant relationshin between the level of IL-1beta in the patient group, (PG/ML), there is no strong agreement on a highly significant relationship between the level of IL-1 between the acute and recurrent . ($P < 0.01$). In contrast, it was found that the levels of IL-1b were higher in patients with bacterial growth compared to those without bacterial growth [38].

Fig. 3 : Interleukin-6 Levels in Patients with Acute and Recurrent UTI



6- Distribution of Isolated Bacteria among Acute and Recurrent UTI in Adult and Adolescents.

According to how the bacteria were found in the different groups studied among Acute UTI, as shown in Figure (4) , the most common bacteria found in acute UTI was E.coli, making up 39%. Next common bacteria implicated was S.aureus at 21% , followed by K.pneumonia at 19%, The least common was Pseudomonas aeruginosa, which was found in 9% of cases. Furthermore , adult recurrent UTI was less then acute (Table 2), while the adolescent females (n :8) scored a higher recurrent (75%) with predominant E coli scored 83.33 % followed by Staph. saprophyticus 16.33 % Fig. 5 .It is worth mentioning that too many studies all over the world were found nearly the same results.

Fig. 4 : Distribution of Isolated Bacteria among Acute and Recurrent UTI in Adult and Adolescents.

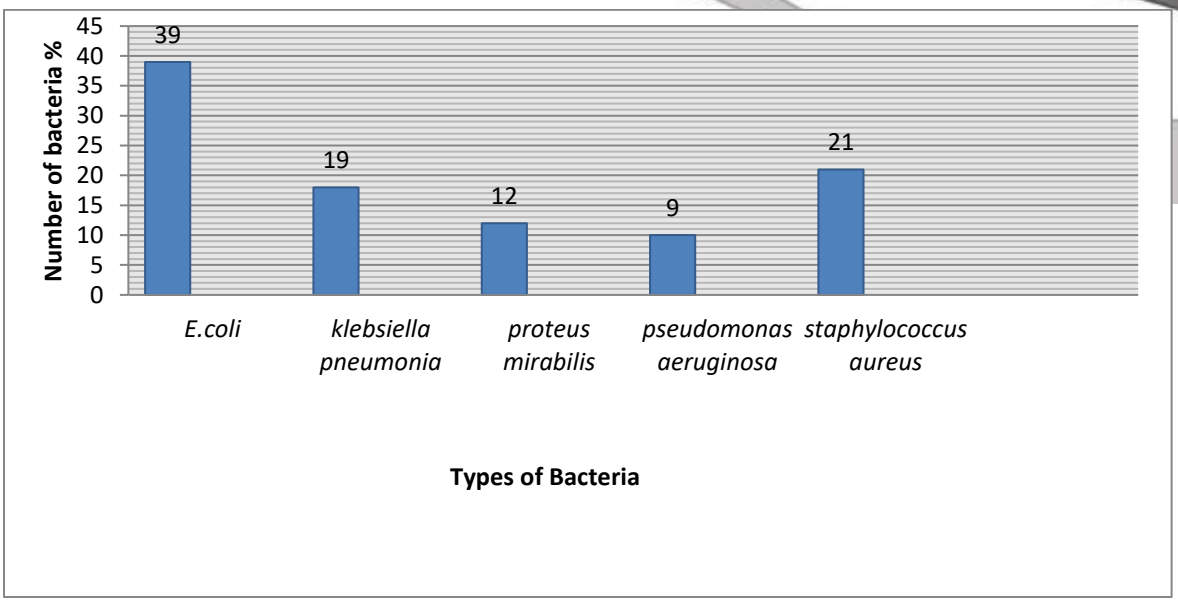
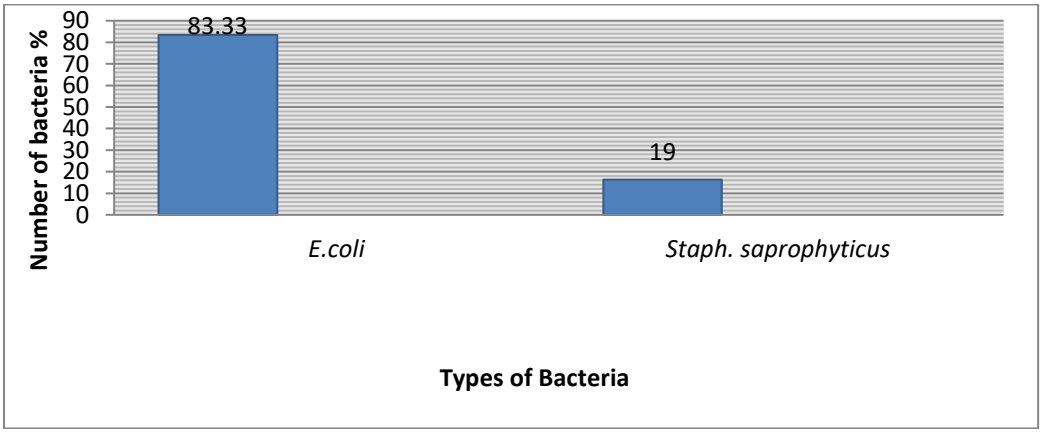


Fig. 5 : Distribution of Isolated Bacteria among Recurrent UTI in Adolescent females.



Conclusions

The study results showed that urinary tract infections (UTIs) are more common in females, and that acute cases are more prevalent than recurrent ones. Significantly elevated levels of interleukin – 6, IL-1β and IL-23 were observed in both acute cases , while was low in recurrent regarding IL-6 and high IL-1β valeus . Furthermore, significantly elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) were observed in recurrent cases, suggesting that these two factors may contribute to the inflammatory response associated with UTIs and potentially to recurrent infection.

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Authors' Contributions

All the authors listed have contributed significantly, directly, and intellectually to the work and have approved it for publication. All the authors clearly state their full or partial involvement in various aspects of the paper, including the development and planning of the study, gathering of data, analyzing and interpreting the results, and writing the manuscript. All of the authors have examined the findings and given their approval for the final version of the manuscript.

Ethics statements: The study has been approved by the research ethics board of Sulaymaniyah Health Directorate with reference number 25541. The study was also approved by the ethics board of the University of Tikrit the Research Ethics Committee in the College of Dentistry of reference No 56 and project No 56726. Written consent was obtained from the patients themselves or from their substitute decision-makers in an informal manner.

Financial & conflict interests disclosure
This work was not supported by any institution or company. The author does not have any other relevant connections or financial relationships with any organization that has a financial stake or potential conflict of interest concerning the topic of the manuscript, aside from what has already been stated. No writing assistance was used in creating this manuscript.
There were no conflicts of interest involved in the conduct of this study.

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