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Original Article

Assessment of bacteriological and immunological markers in urinary tract infection and the effect of antibiotics on the isolated bacteria

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Abstract

Urinary tract infections (UTIs) are recognized as the second most common medical condition, following respiratory infections. Despite the availability of numerous efficacious antibiotics for the management of UTIs, the rising incidence of bacterial resistance presents significant challenges in the treatment of these infections. Bacteria are endowed with the ability to reproduce and develop resistance mechanisms against antibiotics. The current investigation aimed to evaluate the susceptibility of bacterial isolates from urinary tract infections (UTIs) to a variety of antibiotics, including ciprofloxacin, trimethoprim, amikacin, gentamicin, tetracycline, chloramphenicol, nalidixic acid, nitrofurantoin, meropenem, and novobiocin. Additionally, the study sought to quantify the levels of the inflammatory immune marker interleukin-6 (IL-6) in UTI patients. It also explored the correlation between IL-6 levels in UTI patients and healthy controls, as well as the relationship between IL-6 levels and blood parameters in both infected and healthy individuals. The present study involved the collection of 155 samples from patients diagnosed with urinary tract infections of both genders and varying age groups, ranging from 15 to 75 years, at Salah al-Din General Hospital. The findings revealed that 102 urine samples tested positive for bacterial growth, resulting in a prevalence rate of 68%. In contrast, 53 urine samples were negative for bacterial growth, reflecting a prevalence rate of 32%. The diagnostic outcomes for all isolates, following the application of laboratory diagnostic methodologies, revealed a diverse array of bacterial species, including *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus saprophyticus, Staphylococcus aureus, and Staphylococcus epidermidis*. The immunological analysis revealed a statistically significant increase ($p < 0.05$) in IL-6 concentrations in the positive control group compared to the levels observed in the infected cohort. Our study concluded that significant antibiotic resistance in UTI pathogens, emphasizing the need for tailored treatments.

Keywords: Urinary, Infection, Multidrug-resistant bacteria, Antibiotics, interleukin-6

1. Introduction

Urinary tract infections (UTIs) represent one of the most prevalent bacterial infections globally, exhibiting a notable increase in disease burden. They constitute a substantial public health concern, resulting from a consortium of pathogens that encompasses bacteria, Chlamydia, Trichomonas, and fungi [1]. The incidence of UTIs is widespread in both low- and high-income nations, with approximately 250 million individuals afflicted annually [2]. The prevalence of UTIs is significantly higher in females compared to males, primarily due to the anatomical proximity of the anus to the urethra, which facilitates the ingress of bacteria into the urinary tract, leading to subsequent infection. This heightened vulnerability is markedly evident in females, attributable to the anatomical structure of the female urinary system, which is characterized by a shorter urethra and a closer proximity to potential infectious agents. Additional factors, such as the menstrual cycle, further exacerbate this susceptibility among females [3]. Antibiotic resistance constitutes one of the contributing factors to the widespread incidence of UTIs in Iraq, with 23% of all bacterial infections exhibiting resistance to antibiotic treatment [4]. The etiological contributors to this condition predominantly involve bacterial and fungal agents, while parasitic and viral infections remain comparatively rare [5]. Inflammation of the urinary tract alters both the physical and chemical characteristics of urine. The physical attributes of urine encompass a variety of qualities, including color, volume, and pH reaction, with the latter indicating that urine is typically acidic and devoid of odor.

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The qualitative density of normal urine ranges from (1.015 to 1.025) and may include sediment consisting of salts [6]. The chemical characteristics of urine pertain to the concentration of dissolved substances; an increase in the concentration of specific chemical elements may precipitate their deposition, thereby leading to urinary tract inflammation [7]. The immune defenses of the body are instrumental in safeguarding human health against diseases, as evidenced by the manifestation of inflammatory responses. A principal marker of this response is the secretion of cytokines, which are synthesized in reaction to antigens. Cytokines play a crucial role in modulating the immune response by regulating the activities and functions of immune-responsive cells [8]. Interleukin-6 (IL-6) is a significant cytokine whose levels surge during inflammatory episodes and emerge early in such processes; it is responsible for eliciting fever and augmenting the synthesis of acute-phase proteins. The assessment of urinary tract injuries necessitates the quantification of cytokine levels, including IL-6, in the serum of patients experiencing urinary tract inflammation. Such measurements serve as essential indicators of both the magnitude and severity of urinary tract infections [9]. Consequently, this study sought to identify bacterial uropathogens along with their antibiotic sensitivity profiles among UTI patients at Salah al-Din General Hospital, as well as to investigate the levels of the inflammatory immune marker interleukin-6 (IL-6).

2. Materials and Methods

2.1.Total samples, Urine Collection

Samples were collected from Salahaddin General Hospital-Tikrit from December 2021 to April 2022. The patients' ages ranged from 15 to 75 years. All samples were collected from individuals who had not taken antibiotics, and blood samples were collected by 5 milliliters of blood were withdrawn per patient and placed inside plastic tubes. The tubes were then left for (10-15 minutes) at room temperature, The samples were then placed in a centrifuge for (15 minutes) at 3000 rpm to separate the serum from the blood. The serum was then kept at a temperature of (-20 degrees Celsius) for blood serum after its fragmentation in several tubes to carry out the chemical tests to be studied, Bacterial isolation and identification were carried out on agar plates according to the method described by [10]. The special form included general and specific medical information, such as sample number, date of collection, age, sex, and various physical characteristics (appearance, reaction, odor, specific gravity, epithelial cells, bacteria, casts, crystals, red blood cells, pus cells, and others). Additionally, it recorded antibiotic test results, transplant outcomes, antibiotic or treatment usage, history of previous UTIs, and housing conditions.

2.2. Diagnosis with the VITEK 2 Compact System

This method was used to identify several bacterial isolates from different species, The results for these bacterial isolates are shown in Annex No., (1), The VITEK 2 diagnostic kit was used to enhance the diagnosis of isolates to the species level, This system requires that a bacterial isolate was obtained from the inoculated samples, The isolate is then placed in an inoculum tube, and the suspension is automatically transferred to a card containing approximately 64 biochemical tests, The card is incubated under controlled temperature conditions and the metabolic activity of the bacteria causes color changes in the card, These changes are measured every 15 minutes by a densitometer, The information is then analyzed, automatically stored and printed. The method is explained in more detail by the manufacturer of the Biomerieux device as follows [11]. Antibiotic susceptibility testing was done by using the Kirby-Bauer disc diffusion method and according to [12]. Determination of serum IL-6 concentration was performed using a kit provided by BioMérieux, following the manufacturer's instructions.

2.3. Antibiotic susceptibility testing

The sensitivity of all bacterial isolates in this study was evaluated using the Kirby-Bauer disc diffusion method [12]. Following laboratory and clinical research guidelines (CLSI, 2015). The process began by transferring colonies grown on nutrient agar after 24 hours into a tube containing 3 ml of sterile saline solution. The turbidity of the bacterial suspension was adjusted to match the standard McFarland 0.5 solution, which corresponds to 1.5×10^8 cells/ml, a sterile cotton swab was then used to collect the bacterial suspension and spread it evenly along the inner wall of the tube to remove any excess. The swab was subsequently applied to Mueller-Hinton agar plates, ensuring even coverage by spreading the suspension in multiple directions. The plates were left to dry for 15 minutes. Antibiotic discs were placed onto the agar at equal distances, using sterile forceps to press them gently into the surface. The plates were incubated at 37°C for 24 hours. After incubation, the diameter of the inhibition zones around each antibiotic disc was measured. The results were compared to the reference values provided by the Clinical and Laboratory Standards Institute (CLSI, 2020) to determine the effectiveness of the antibiotics.

2.4. Determination of serum interleukin 6 concentration

The level of (IL-6) was measured using Enzyme Linked Immune Sorbent Assay (ELISA) technology. Blood samples were collected, and serum was separated and stored at -80°C. Samples were carefully added to the precoated ELISA plate, which was covered with monoclonal antibodies for IL-6. After an incubation period, the plate was washed to remove any unbound proteins. A detection antibody conjugated to an enzyme was then added, followed by another washing step to remove any unbound conjugated antibodies. A substrate solution (A + B) was added, allowing the enzyme to react with the substrate, resulting in a color change whose intensity is directly proportional to the concentration of IL-6, the test was performed according to the manufacturer's instructions. All samples, materials, and reagents were kept at room temperature for 30 minutes before use. The validation included generating a standard curve for quantification, ensuring reproducibility through multiple sample replicates, and confirming specificity by testing against other cytokines. Standard concentrations were prepared through a series of dilutions in five sterile tubes to obtain IL-6 concentrations of 5, 10, 20, 40, 60, and 90 pg/ml, one hindered fifty microliters of each diluted standard solution were transferred into the first five wells of the ELISA plate, the blank well was left empty, as instructed by the manufacturer, and 10 microliters of serum samples, along with 40 microliters of sample dilution solution, were added to the remaining wells and

gently mixed. The plate was covered with an adhesive and incubated for 30 minutes at 37°C. The wash solution was diluted 30 times with distilled water. The plate cover was carefully removed, and the wells were washed with the washing solution, repeating the process 5 times. The plate was then turned onto blotting paper to remove any residual solution, fifty microliters of HRP-conjugated enzyme solution were added to each well, except for the blank control. The adhesive cover was returned, and the plate was incubated again under the same conditions. After incubation, the wells were washed as previously described, Fifty microliters of coloring solution A, followed by 50 microliters of solution B, were added to each well, avoiding direct light. The plate was incubated for 15 minutes at 37°C. Finally, 50 microliters of stop solution were added to all wells to terminate the reaction, the optical density (O.D.) of the samples was read using an ELISA reader at a wavelength of 450 nanometers and the standard curves for the studied proteins.

2.5. Statistical analysis

The Statistical Analysis System (SAS) software (2018) was employed to identify the influence of various factors on the study parameters. The least significant difference (LSD) test, a component of analysis of variance (ANOVA), was utilized to make significant comparisons between means in this study, Additionally, using Excel Worksheet 2010, suitable graphs of various kinetic models were constructed and the corresponding release constants were determined from their slopes.

3. Results

3.1. Bacterial Transplant Results Samples in UTI Patients

The results of bacterial isolation from 155 urine samples collected from both female and male patients aged 15 to 75 years with urinary tract inflammation were obtained using blood agar, MacConkey agar, and Mannitol salt agar. All samples had a cell count exceeding 10^5 cells/ml. Of these, 102 samples (65.8%) showed bacterial growth, while 53 samples (34.2%) did not exhibit any bacterial growth, as indicated in Table 1. It is important to note that the absence of bacterial growth, despite the presence of purulent cells, may be attributed to several factors. These include the possibility of fungal, viral, or parasitic pathogens, antibiotic usage by the patient, or the presence of anaerobic bacteria, which were not the focus of our current study.

3.2 Diagnosis of Isolated Bacteria

Bacterial isolates from urinary tract infections (UTIs) were initially identified based on the visual characteristics of the colonies grown on agar plates and microscopic examination following Gram staining. Identification was further confirmed using the BIOMÉRIEUX VITEK® 2 system. Several physical and chemical tests were performed on the bacteria isolated from individuals with UTIs to confirm the diagnosis, including the motility test. This test determines whether the bacteria are motile (capable of movement) or non-motile. It can be carried out using methods such as the hanging drop technique or semi-solid agar. The motile bacteria observed under the microscope exhibited movement and spread throughout the agar medium, while non-motile bacteria remained confined to the initial site of inoculation. Biochemical tests were conducted to evaluate the metabolic activities of the bacteria by examining their ability to metabolize specific substrates. These tests, including the oxidase test, catalase test, coagulation test, and various fermentation tests, provided crucial information about the enzymatic properties of the bacteria and aided in their identification. In the catalase test, bacteria that produce the enzyme catalase break down hydrogen peroxide into water and oxygen gas. When hydrogen peroxide was added to a bacterial sample, the presence of catalase was indicated by the formation of bubbles or fizzing. The indole test was performed to detect the presence of tryptophanase, an enzyme that breaks down the amino acid tryptophan into indole, pyruvic acid and ammonia. A positive result was indicated by the formation of a red ring at the top of the culture after adding Kovach's reagent, the urea hydrolysis test assessed the ability of bacteria to hydrolyze urea into ammonia and carbon dioxide, facilitated by urease enzyme. The resulting ammonia increased the pH, causing a pH indicator in the medium to shift from yellow to pink. Sugar fermentation tests were used to determine whether the bacteria could ferment specific sugars like glucose, lactose, or sucrose. Fermentation produced acids, which lowered the pH and changed the color of the medium due to the pH indicator. The coagulation test was specifically employed to identify *S. aureus*, which produces the enzyme coagulase. Coagulase causes plasma or blood to clot, with the presence of coagulation activity indicated by visible clot formation or agglutination, microscopic examination was another essential diagnostic tool. Bacterial morphology and cell arrangement were observed under the microscope to determine their shape (*cocci*, *bacilli*, spirals, or *vibrios*) and arrangement (*diplococci*, *streptococci*, or *staphylococci*). Most of these bacteria did not show hemolysis on blood agar, 32 colonies of *Klebsiella* Sp were isolated. Pink colonies appeared large-sized mucous on the center of MaCcconky agar and were characterized by being violet mucous in the middle of EMB, and were required to test Catalyst, Eurez, Fukas Proscauer and test vest consumption (Fig. 1).

The 14 isolated *Pseudomonas* bacteria appeared as pale

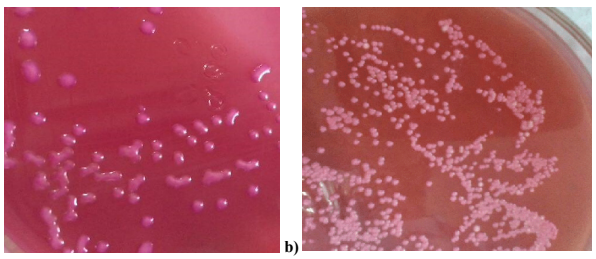

Fig. 1. Aspect of a: *Klebsiella* Sp and b: *E.coli* on MacConkey Agar.

Table 1. Results of bacterial transplantation.

Total number of samples	Positive Growth		Negative Growth	
	number	Percentage (%)	Number	Percentage (%)
155	102	65.8	53	34.2

Fig. 2. *Proteus* on MacConkey Agar.

colonies, non-fermenting for lactose, at the center of the MacConkey agar and presented as zigzag dry colonies in the middle of the blood agar. Upon microscopic examination, the specimen exhibited negative Gram staining and tested positive for alkalinity, oxidase activity, and gelatin consumption. Initially, it showed a weak positive result for the urease test after 24 hours, with the strength of the result increasing after 4 to 5 days. Its green transparent colonies produced pigments on the solid nutrient medium.

The 12 isolates of *Proteus* were characterized by their ability to ferment lactose sugar, resulting in pink colonies when cultured on the center of MacConkey agar. Conversely, when grown on blood agar, they did not produce anticipated growth. Furthermore, they exhibited an inability to grow on the center of mannitol salt agar but displayed an advantage of ivory coloration when cultured on blood agar. These isolates tested negative for the Gram dye but yielded positive results for the urease test within two hours, as well as the gelatin and methyl red tests. However, they tested negative for the indole and Voges-Proskauer tests, as illustrated in (Fig. 2).

The results of the *Staphylococci* microscopic examination have shown to be monococci, binary, or conjugal. It has also been characterized as a positive test for catalase and *Staph* colonies have emerged, *S. aureus* appears as grey or golden-yellow beta-type colonies on the media of the blood agar and as a mannitol fermenter in the center of the mannitol agar, changing the middle color from red to yellow, while the rest of the isolated *Staphylococcus* species did not ferment mannitol and gave a positive result for the coagulase test while being negative for the staphylic.

3.3. Diagnosis of isolated, antibiotic-resistant bacteria using VIETK 2

According to US Food and Drug Administration bacteriological analysis and guidelines, biochemical identification of isolated bacteria is time-consuming. Therefore, we used the VITEK 2 device (BioMerieux) to identify and examine bacteria because of its very accurate results. This device excels in determining bacterial resistance to antibiotics. and is almost inexpensive in terms of materials used to diagnose bacteria. After the cultivation process on the selective medium, samples of the isolated bacteria were taken to the VITEK 2 device for accurate diagnosis and confirmation of their authenticity, a sample of all isolated species was examined using VITEK 2 technology and the results appeared. Results of various biochemical and physical tests were performed to determine positive or negative tests (Supplementary Fig. 1-7).

3.4. Number and percentage of isolated bacterial species

During the current study, 155 bacteria were isolated, including 119 Gram-negative isolates and 36 Gram-positive bacteria. Table 2 shows the predominance of *E. coli* bacteria in first place among other bacterial species causing urinary tract infections. Following *E. coli* bacteria ranked second isolated in 20.6% of cases. *Pseudomonas* Sp was isolated in 9.0% of cases.

Proteus Sp was isolated in 7.7% of cases, *S. aureus, S. epidermidis*, and *S. saprophyticus* were isolated in our study at rates of 12.2%, 5.1%, and 5.8% respectively.

3.5. Bacterial Susceptibility to Antibiotic.

An investigation into the allergenic responses of seven bacterial isolates was performed utilizing antibiotic 10, which is predominantly employed in the therapeutic management of urinary tract inflammatory conditions, by distributing the tablets centrally on Müller-Hinton agar to evaluate the allergic reactions of the isolated bacterial strains. The bacterial isolates were categorized into sensitive, moderately sensitive, or resistant classifications in accordance with the Clinical and Laboratory Standards Institute (CLSI, 2020) (Table 3).

3.6. Results of microscopy of urology patients.

As shown in Table 4 the results of the microscopic examination of the incidence of infected people showed that all had an increase in red blood cells, which was more than 4 cells per large microscopic field due to the presence of inflammation. As for sludge cells, their proportion was

Table 2. Number of isolated bacterial species from UTIs.

Isolated bacteria	Number of isolations	Percentage (%)
Escherichia coli	61	39.4
Klebsiella Sp	32	20.6
Pseudomonas Sp	14	9.0
Staphylococcus aureus	19	12.3
Staphylococcus epidermidis	8	5.2
Staphylococcus saprophyticus	9	5.8
Proteus Sp	12	7.7
Total	**155**	**100**

very low, as depicted in (Supplementary Fig. 8-16).

3.7. Evaluation of the serum level of interleukin 6 (IL-6) in patients with urinary tract infection.

One of the objectives of the current study is to measure the serum level of interleukin-6 in patients with urinary tract infection, to confirm that it is an important diagnostic marker for indicating urinary tract infection, In general, the study included 102 patients and 53 healthy people (as a control group), as shown in Table 5, It was found that there was a significant difference, as it was noted that the level of IL-1β in infected people was higher compared to healthy people.

We found that the differences in IL-6 levels among the bacterial strains were statistically significant at a p-value of less than 0.05. This suggests that the variations in IL-6 levels are unlikely to have occurred by chance alone.

3.8. Evaluation of level the of IL-6 in the serum of infection patients according to the results of Gram stain for bacterial isolates

The results of the current study showed that there were differences in the serum level of IL-6 in patients with urinary tract infections depending on the positive and negative results of the Gram stain, as a higher concentration of IL-6 was recorded in the Gram-ve bacteria (pg/ml 0.1028 ± 0.0241), compared to Gram+ve bacteria (0.0972±0.0274 pg/ml), but not a statistically significant difference as shown in (Fig. 3). mentioned in their study that the concentration of IL-6 (10.462±2.991 pg/ml) in patients with negative bacteria is higher than its concentration in patients with positive bacteria (10.703±9.720 pg/ml).

3.9. The relationship between bacterial species and IL-6 level.

The results of our current study showed that the highest level of IL-6 was in infections resulting from *E. coli* bacteria (12.26±5.85 pg/ml) and its lowest level was in infections resulting from *S. epidermidis* and *Staphylococcus saprophyticus*, where its average level reached (9.43±1.26 pg/ml) and (9.66 ± 1.13 pg/ml) compared to other bacterial species, but the differences were not significant. There were no significant differences in the level of IL-6 between infection resulting from gram-negative bacteria and infection resulting from gram-positive bacteria, as shown in (Table 6).

3.10. Diagnostic value to IL-6

The receiver operating characteristic curve was used to determine the diagnostic value of IL-6 In distinguishing between patients and controls, For IL-6, area under the curve was 0.743, 95% confidence interval = 0.845-0.641, $p < 0.001$, The sensitivity and specificity of the test at the cut-off value of IL6 = 9.34 ng/ml were 66% and 65%, respectively.

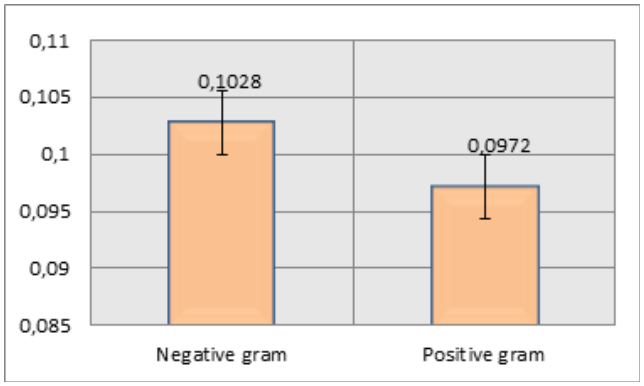

Fig. 3. Evaluation of IL-6 level in Gram-positive and Gram-negative bacteria.

Table 4. Results of microscopic examination of the diabetes of people with UTI.

Profiling qualities		Cas Number	Percentage (%)
Appearance	Turbid	102	100
Interaction	Acidic	87	85.2
	Alkaline	15	14.7
Color	Yellow	79	77.4
	Brown	14	13.7
	Red or pink	9	8.8
Presence of sugar		18	17.6
WBC	+ + or more	71	69.6
Pus cells	+ or ++ +	32	31.4
Painted	<10	10	9.8
Red Blood Pellets	+ or ++ +	53	51.9
Bacteria	++	78	67.4
Specific gravity	Q.N.S.	102	100
Total samples examined		**102**	

Table 5. The level of IL-6 in affected patients.

Samples	number	IL-6 (Pg/ml)	p-value
The patients	102	0.0957 ± 0.0245	0.0002**
People with a urinary tract infection but a non-bacterial cause	53	0.0825 ± 0.0064	

** Significant difference ($p<0.05$).

Table 6. Evaluation of IL-6 level in the bacterial isolates under study.

Types of bacteria	IL-6 (pg/ml)
E. coli	5.85±12.26
S. aureus	1.89±11.20
K. pneumonia	1.46±11.62
S. epidermidis	1.26±9.43
P. aeruginosa	2.83±12.40
S. saprophyticus	1.13±9.66

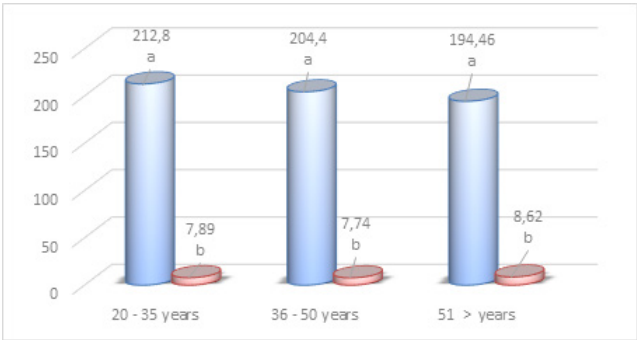

Fig. 4. IL- 6 level according to age groups of patients (Blue) and healthy people (Red).

3.11. Measurement of interleukin 6 level based on human age

As presented in (Fig. 4). there are no significant differences in interleukin 6 level between patients in spite of their ages, The same results were obtained with healthy cases.

4. Discussion

The results of bacterial isolation showed that bacteria were successfully isolated from 102 out of 155 samples, resulting in a rate of 65.8%. From these cases, 155 bacteria isolates were diagnosed, including 119 Gram-negative isolates and 36 Gram-positive bacteria, with the predominance of *E. coli* bacteria in first place among other bacterial species causing urinary tract infections, accounting for 39.4%. The high isolation rate of this bacterium may result from its adaptation to the urinary tract environment and its tolerance to inadequate environmental conditions. Moreover, it possesses many strong virulence factors that enable it to cause injury. These include adherence factors that facilitate attachment, the first step of injury, as well as the production of capsule portfolio and toxins analyzed for host tissue. The high isolation rate of this bacterium in urinary tract infections may be attributed to the transmission of bacteria from the digestive system to the outlet hole for which the natural environment nearby is considered the exit point Rizvi and Khan (2022) [13,14]. This result was consistent with the findings of other reports [15, 16]. However, the isolation rate varied according to Rizvi and Khan (2022) [17] who reported a lower isolation rate in the city of Tikrit.

The significance of *Klebsiella* Sp, bacteria in urinary tract inflammation stems from its presence as a natural component of the intestine, increasing the likelihood of urinary tract contamination. Additionally, its capsule wallet protects it from adverse conditions and aids in resistance against the body's immune defenses such as phagocytosis. Moreover, its cilia help it adhere, further increasing its chance of causing injury [18].

Pseudomonas Sp was isolated in 9.0% of cases. This finding was consistent with the results of some previous reports [19, 20], but differed from those of Bader et al (2020) [21]. Due to its higher isolation rate. The presence of this bacterium in the urinary tract is attributed to its possession of adhesive mechanisms such as pili and etiology, as well as its ability to form biofilm.

Proteus Sp was isolated in 7.7% of cases. Our results were consistent with some previous reports [22, 23]. But differed from some others [24, 25]. Their pathogenicity lies in their motility, activation of the swarming phenomenon, as well as their ability to degrade red blood cells and biomembrane composition, which confers resistance. *S. aureus, S. epidermidis*, and *S. saprophyticus* were isolated in our study at rates of 12.2%, 5.1%, and 5.8% respectively. Our results were consistent with those of [26 - 29]. However, they differed from the findings of the Jalil et al (2022) [30], as well as those of Rao et al (2022) [31]. Possibly due to differences in health habits as well as variations in study methods and techniques. Studies have demonstrated that *S. epidermidis* possesses many virulence factors, such as having a capsule and a sticky layer, which contribute to its resistance to body defenses, antibiotics and sanitizers [32]. It is noteworthy that 20% of the isolates from this bacterium possessed a capsule and demonstrated the ability to produce a sticky layer. Their presence in urinary infections may be attributed to their natural colonization on the skin.

Urinary tract infections with these different types of bacteria often occur due to their natural presence in the intestine or on the skin, which can transmit to the urinary system. Their virulence also contributes to urinary tract inflammation. Bacterial motility increases morbidity by enabling them to ascend to the upper urinary tract and obstruct urine flow, which may lead to urinary tract inflammation [33].

Recognizing some limitations is crucial for understanding the scope and possible biases inherent in our research. The degree to which the sample is representative may affect the generalizability of our findings. Insufficient control of confounding variables such as age or comorbidities could alter the perceived associations. A restricted sample size and lack of diversity may undermine the rigor and applicability of our results. Potential biases in data collection could have impacted our conclusions. The omission of relevant variables may have obscured potential correlations within our analysis.

Antibiotic sensitivity test was performed for 102 bacterial isolates using 10 antibiotics most commonly used to treat UTIs, including Meropenem (MEM), Ciprofloxacin (CIP), Trimethoprim (TM), Amikacin (AK), Rifampicin (RA), Gentamicin (GN), Nitrofurantoin (Ni), Chloramphenicol (C), Nalidixic acid (NA), and Tetracycline (TE) and

the results were interpreted according to CLSI, 2020. The specific antibiotics tested in the study were selected based on their common use in treating urinary tract infections (UTIs) and previous resistance patterns observed in the patient population. Meropenem, Ciprofloxacin, and Trimethoprim are frequently prescribed and represent a range of classes with varying mechanisms of action. The rationale also included the need to assess the effectiveness of these antibiotics against prevalent pathogens like *E. coli* and *Klebsiella* Sp, which have shown significant resistance in past studies. By focusing on antibiotics that are commonly utilized and have documented resistance issues, the study aimed to provide relevant insights for optimizing treatment strategies in the local context.

E. coli showed alarming resistance rates, particularly 100% resistance to Rifampicin (RA) and high levels of resistance to Amikacin (AK), Nitrofurantoin (Ni), and Tetracycline (TE), at 88.5%. Additionally, resistance to other antibiotics such as Gentamicin (GN) and Ciprofloxacin (CIP) was notable, with rates of 85.7% and 65.7%, respectively. In contrast, all *E. coli* isolates were 100% sensitive to Meropenem (MEM), indicating its effectiveness as a treatment option. These results align with findings from some studies [34, 35], which reported sensitivities of up to 99.9% for MEM.

Our results were consistent with those of Rychel et al [36] who found that E. coli isolates exhibited resistance to R and A in 93.5% of cases. However, the results of our study disagreed with Mohammed et al (2022) [37], who reported resistance rates for RA and CIP of 57.7% and 56.25%, respectively. Similarly, our findings agreed with TM resistance (51.42%) reported by Al-Najar et al (2021) [38]. But, they disagreed with those of Maldonado-Barragan et al (2023) [39]. Regarding GN, with a resistance rate of 30%, and agreed with those of Elmanama et al (2021) [40]. For TE resistance, with rates of 75% each. Our results also disagreed with Soni et al (2024) [34].

Klebsiella Sp. isolates exhibited 100% sensitivity to Ciprofloxacin and 95.4% to Meropenem but showed complete resistance to Rifampicin. *Proteus* Sp. also demonstrated 100% sensitivity to Meropenem while exhibiting resistance to several other antibiotics: RA, NI, NA, AK, TM, TE, GN, and C, with resistance rates of 100%, 81.18%, 45.4%, 36.3%, 36.3%, 40.9%, 22.7%, and 4.5% respectively. These resistance patterns highlight the increasing challenges in treating infections caused by these pathogens, emphasizing the need for continuous monitoring and the development of targeted treatment strategies. Understanding these trends is crucial for guiding antibiotic use and improving patient outcomes in clinical settings. Our results are similar to those of Allami et al (2021) [41], who found that Klebsiella species exhibited 100% sensitivity to MEM. Additionally, our findings agreed with Jalil et al (2022) [30]. Regarding RA resistance and showed an approach to the result of TM sensitivity (66.6%). However, our findings disagreed with AK and agreed with the results of Ni resistance reported by Polse et al (2020) [18].

Proteus Sp, isolates exhibited 100% total sensitivity to MEM, these results disagreed with Salman et al (2022) [42], who found that resistance rates of 10%. These isolates were resistant to other antibiotics, including CIP, TM, NA, GN, TE, C, RA, AK, and NI, with resistance rates of 19%, 71.4%, 38.09%, 52.38%, 90.4%, 61.2%, and 9.5% respectively. Hussein EI et al [15] reported a 100% resistance rate to RA, which aligns with our findings and noted a 32% resistance rate to NA, consistent with the results of Saleem et al (2020) [43]. They also found a GN resistance rate of 58.7%. Our results agreed with Allami M, et al (2021) [41]; however, they disagreed with another finding from Salman et al (2022) [41], which reported resistance rates of 20%, 10%, and 100% for C, GN, and NA antibiotics, respectively.

S. epidermidis exhibited sensitivity to half of the antibiotics used in the study, showing total sensitivity to MEM, CIP, C, AK, and Ni antibiotics, and total resistance to TM, NA, GN, TE, and RA antibiotics. These findings were consistent with Rao et al (2022) [31]. For MEM sensitivity, CIP and AK sensitivity. Our results also agreed with Bobadilla et al. (1989)[10] for GN resistance and showed an approach to the results obtained by Bhargava et al (2022) [14].

S. aureus bacteria showed resistance to NA, GN, and TE, while their resistance to other antibiotics varied, with 20% resistance to CIP, C and RA, and for AK, 40% resistance to Ni, MEM and 60%. The resistance to TM that was recorded in our results agreed with the findings of Ahmed et al (2022) [44]. Regarding NA and GN, it was found to be 100% resistant to these antibiotics and also to those of Bhargava et al (2022) [14]. Who recorded that bacteria sensitivity at a rate of 60%. Additionally, our results were consistent with Salman et al (2022) [42] concerning resistance to C 25%. Regarding RA, AK exhibited 25% resistance, and our results agreed with Rao et al (2022) [31] for CIP sensitivity (80%). However, AK showed 100% sensitivity in our study, contrary to the findings of Park and Koo (2022) [45] reporting that *S. aureus* was sensitive to A.K. at the rate of 100%. *S. saprophyticus* isolates showed sensitivity to TM (100%) and resistance to NA (100%), while it is resistant at the rate of 50% to MEM, CIP, GN, C, RA, TE, AK and Ni. These results were consistent with Bobadilla et al. (1989)[10] for absolute sensitivity to TM and agreed with 50% resistance to C, TE, GN, RA, AK. *Pseudomonas* Sp, exhibited multiple resistance, being totally resistant to TM, NA, GN, C, AK, RA, and Ni, while being fully sensitive to MEM and CIP, and 50% of them was resistant to TE, These results agreed with other reports[42,45] showing that *Pseudomonas* Sp was sensitive to MEM and resistant to NA and C in rate of (100%). In comparison with the results of Hussein et al (2020) [23] who recorded that *Pseudomonas* Sp was resistant to GN and TE (87.5% and 75% respectively) and sensitive to AK at the rate of 100% sensitive in our study (Supplementary Fig. 17) (A-E) in Appendix.

For the determination of IL6 level, depending on the results of the culture, the samples taken were divided into 3 groups. The first group included 79 samples, representing those with a positive culture result. The second one included 23 samples with negative results, while the third one represented the control group with 53 samples, as shown by the obtained results. From our study, there was a significant increase in the level of IL-6 in the first group, which consisted of culture-positive samples (0.09959 ± 0.02599 Pg/ml), while the other two groups recorded a lower level, as the second group with negative samples recorded (0.08094 ± 0.00700 Pg/ml) as a level IL-6 As for Figurethe control group, which is the third group, the level of IL-6 was recorded (0.08250 ± 0.00638 Pg/ml). This study showed that the serum level of IL-6 was higher in

patients suffering from urinary tract infections, especially the group with positive urine culture results, compared to the healthy group. These results agreed with Park and Koo (2022) [46] reporting a level of IL-6 (10.948 ± 2.982 pg/ml) in urinary tract infection patients higher than that of healthy controls (0.945 pg/ml ± 0.794). It agrees with our study in that the level of IL-6 in patients is higher than in healthy controls, but it is different from our results in terms of IL-6 level values. The reason for this disagreement may be the difference in the quality of the kit used and its manufacturer, as well as the difference in the quality of the device used in the ELISA technique. It should be noted that the results of our study were within the limits of the IL-6 Standard curve prepared by the kit manufacturer. When the types of bacteria that cause urinary tract infections enter the host's body, the host, for its part, expresses resistance through its immune mechanisms as a response to the entry of a foreign body and this in turn leads to the occurrence of an inflammatory response, in which cellular elements are stimulated and the production of some important proteins, including IL- 6, It is one of the pro-inflammatory cytokines and is considered one of the basic elements in the innate immune response. This interleukin performs its immune role by rapidly recruiting neutrophils to inflammatory sites and stimulating other cytokines. In addition, it has an important role in the appearance of pathological symptoms, especially fever, which was the reason why IL-6 was first discovered. Despite this, IL-6 is produced in the form of inactive primitive proteins. It needs stimuli to be activated and released from cells to carry out its immune functions. Studies are still ongoing to discover these stimuli, but among the proven ones to this day is the involvement of NLRP3 and Caspase-1 in the activation process [47].

When studying the ship between IL6 level and bacterial species showed that highest level of IL-6 was in infections resulting from *E. coli* bacteria (12.26±5.85 pg/ml) and its lowest level was in infections resulting from *S. epidermidis* and *Staphylococcus saprophyticus*, where its average level reached (9.43±1.26 pg/ml) and (9.66 ± 1.13 pg/ml) compared to other bacterial species, but the differences were not significant. The study by Ali (2022) [48] showed that the highest level of interleukin IL-6 was in the cases infected with *E. coli* bacteria, as its level reached (7.768±83.928) pg/ml, while the average level of this cellular activity was in the sera of people suffering from urinary tract infections resulting from *Klebsiella pneumoniae* bacteria (58.930±2.011) pg/ml in the study of Folliero et al (2020) [13] showed that the level of interleukin IL-6 increases in the case of infection with *E. coli* at a rate of (118.64 ng/L) more than the rest of the other bacterial species isolated in his work. The results of these studies are consistent with those of our current study. Interleukin IL-6 plays an important role in urinary tract infections [49]. The relationship between IL-6 and all electrolytes (potassium, sodium, calcium) was negative (r = - 0.023), (r = - 0.106), and (r = - 0.221), respectively. The results also indicated a positive relationship between IL-6 and the levels of urea and creatinine (r = 0.114) and (r = 0.063) respectively. The increase in IL-6 levels is attributed to the immune and inflammatory responses involving IL-6 and kidney receptors. This cytokine plays a significant role in conditions such as immunoglobulin nephropathy, lupus nephritis, and cell-mediated diabetic nephropathy, particularly within the kidneys [50]. Additionally, low electrolyte levels can result from impaired urea and creatinine function, which are crucial for regulating sodium and potassium ions. This impairment may also be linked to disorders affecting the thyroid and kidney glands. This in turn indicates that there is a positive relationship between IL-6, urea, and creatinine, and the reason for high urea and creatinine is the presence of other complications, including high blood sugar and blood pressure [51]. The results also indicated that when the value of urea is high, the value of sodium is low. This could be due to cellular inflammation in the kidney tissue that affects kidney functions and the possibility of stones forming in the kidneys which prevent urine from exiting. This leads to a rise in the level of urea in the blood due to irregular blood pressure. The reason for the low sodium value is due to disorders in the thyroid and adrenal glands, or the use of diuretics [50]. The results of the study also indicated that there is a positive relationship between blood sugar and all electrolytes (potassium, sodium, calcium), respectively. Electrolytes, including calcium, are considered one of the vital salts that the body consumes to maintain the balance of blood pressure and control the contraction and relaxation of skeletal muscles [49]. It is also important in building and growing muscles, and due to the significantly high percentage of calcium, potassium and sodium and not excreting them outside on a regular basis leads to their deposition in the kidneys which leads to high blood pressure [52].

5. Conclusion

The predominant therapeutic approach for bacterial-induced urinary tract inflammation involves the administration of antibiotics. The primary apprehension associated with antibiotic utilization is its role in fostering the emergence of antibiotic-resistant bacterial strains. To facilitate optimal experimental interventions for urinary tract infections and to bolster antibiotic stewardship initiatives within healthcare institutions, it is imperative to systematically engage in research across all strata of healthcare to ascertain the prevalence, etiologies, and trends of antibiotic hypersensitivities. Advancements in scientific methodologies enable us to investigate this interaction at both the molecular and cellular dimensions, thereby elucidating the underlying mechanisms of this prevalent ailment. Furthermore, as our comprehension deepens and the issue of bacterial resistance escalates, there exists the potential to devise targeted therapeutic strategies that mitigate infections without dependence on conventional antibiotics. The extensive array of pathogens possessing diverse virulence determinants, coupled with the elevated incidence of recurrent urinary tract infections, signifies that antibiotics do not exhibit universal efficacy in the management of all urinary tract infections. Consequently, substantial resources should be allocated toward forthcoming clinical trials, which will be instrumental in translating these novel antimicrobial strategies into innovative treatments aimed at alleviating the discomfort associated with urinary tract infections. A comprehensive understanding of the intricate immune response to urinary tract infections holds significant promise in enhancing our capability to treat and prevent these prevalent and challenging infections, ultimately elevating patient well-being and lessening the strain on global healthcare systems.

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