A Study of Some Clinical &Bacteriological Aspects of Patients with Chronic Pyelonephritis in Hilla Teaching Hospital.

A thesis

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وَإِن مِّن شَيءٍ إِلاَّ عِندنا خزآئنه وما ننزّله إِلاَّ بِقدَرٍ مّعلومٍ

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Dedication:

To my kids, Ahmed &Sally.

To my husband, Hussam.

To my father and mother.

To all members of my family.

Aknowledgement

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Rafal

Summary

The subjects of this study were ١٠٢ patients having chronic pyelonephritis visited Hilla Teaching Hospital-department of Urology whose ages ranged between ٧-٨٨ years old; (٦١.٨٪) of them were females and (٣٨.٢٪) were males. The more affected age group in females was between ٤٠-٦٠ years old (٣١.٥٪) and in males was between ٥٠-٧٠ years old (٢٠.٥٪) but in older age group (>٧٠ years), males were more affected than females and only ٥.٩٪ of patients below ١٩ years.

Clinically, only two patients were presented asymptomatically and the remainders were presented with classical symptoms of UTI including loin pain (٩٨.٢٪) with or without urinary symptoms (frequency (٨٣.٣٪), dysuria (٧٩.٤٪), nocturia (٧٥.٥٪), polyuria (٦٧.٦٪), nausea or vomiting (٣١.٤٪), loss of appetite (٢٧.٥٪) and loss of weight (١٧.٤٪)). Some of the patients were presented with complications like hypertension in ١٣.٧٪ and chronic renal failure in ٩.٨٪. The patients with history of urinary tract infection were ٨٦.٣٪, only ٦٢.٧٪ of them were associated with stone and ٤.٨٪ underwent surgical repair for VUR.

As regard the results of Ultrasound findings, ٦٥.٧٪ of the patients were unilateral and ٣٤.٣٪ were bilateral. In addition, GUE results showed that most of the patients were presented with pyuria (٩٤.١%) with or without RBC (٦٩.٩٪), ٣٧.٢٪ of them were with albuminuria and only ١٩.٥% had renal casts in their urine. ٢٩.٦٪ of patients had alkaline urine.

As far as urine culture results, only ٨١ patients had positive urine culture, ٢٩.٦٪ *E.coli*, ٢٥.٩٪ *Staphylococcus epidermidis*, ١٢.٣٪ *Klebsiella pneumoniae*, ٧.٤٪ *Corynebacterium spp.*, ٧.٤٪ *Proteus mirabilis*, ٣.٧٪ *Pseudomonas aeruginosa*, ٣.٧٪ *Enterobacter spp.*, ٣.٧٪ *Acinetobacter spp.*, ٢.٥٪ *Enterococcus spp.*, ٢.٥٪ *Staphylococcus saprophyticus* and only one isolate (١.٢٪) was *Staphylococcus aureus*.

The effects of some antibiotics, which are commonly used in treatment of pyelonephritis on these bacterial isolates, showed that ٨٦.٤٪ resisted tetracycline, ٨٢.٧٪ resisted amoxicillin, ٨١.٥٪ resisted trimethoprim-sulfamethoxazole, ٧٤.١٪ resisted vancomycin, ٥٦.٧٪ resisted doxycycline, ٤٦.٩% resisted gentamicin, ٤٣.٢٪ resisted cefixime, ٤١.٩٪ resisted nitrofurantoin but the most sensitive antibiotics were ciprofloxacillin and cefotaxime whose resistant rate was ٣٩.٥% for both.

The invading microorganisms must have an important virulence factors to invade the urinary tract and cause infection. The majority of isolates produced siderophores found in ٧٥.٣% of them followed by capsules seen in ٦٧.٩% and then the colonization factor antigens in ٦٠.٧٪ as the CFA/I was found in ٣٣.٣% and CFA/III in ٥٣.١%. The extracellular protease production was found in ١٣.٦% of them and the hemolysin production was found in ١٤.٨% of them. In addition the production of urease and the ability to be motile were represented an important factors for chronic pyelonephritis as ٥٨٪ of isolates were found with positive urease production and ٤٤.٤٪ were motile.

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List of Abbreviations

Abbr.	Meaning
BPH	Benign Prostatic Hyperplasia
CFA	Colonization Factor Antigen
CT scan	Computerized Tomographic scan
EMB	Eosin-Methylene Blue
GUE	General Urine Examination
IVU	Intravenous Urography
KIA	Kliglar Iron Agar
LF	Lactose fermentation
MR	Methyl Red test
MR/K	Mannose-resistant fimbriae like *Klebsiella*
MR/P	Mannose-resistant fimbriae like *Proteus*
MRSA	Methicillin-resistant *Staphylococcus aureus*
PAP	Pyelonephritis associated pili
RBC	Red Blood Cell
RNA	Ribose Nucleic acid
TMP-SMX	Trimethoprim-Sulfamethoxazole
TSI	Triple Iron Sugar
UTI	Urinary Tract Infection
VCUG	Voiding Cystourethrogram
VP	Voges–Proskaur test
WBC	White Blood Cell

١.١. INTRODUCTION:

Chronic pyelonephritis is a renal injury induced by recurrent or persistent renal infection. It occurs exclusively in patients with major anatomic anomalies, including urinary tract obstruction, struvite calculi, renal dysplasia or most commonly, vesicoureteral reflux (VUR) in young children. The diagnosis established on radiological evidence characterized by renal scarring and destructive changes in the calyceal system mostly associated with pyuria. The patients suffered from constant dull flank pain with polyuria and nocturia. There are two types of chronic pyelonephritis, which are either reflux chronic pyelonephritis or obstructive chronic pyelonephritis (Simon, ٢٠٠٢).

The bacteria are the commonest pathogenic cause of chronic pyelonephritis; however, *Mycoplasma* and *Chlamydia* have a role in the etiology of the disease (Thomsen, ١٩٨٣). Furthermore, *E.coli* is the most common bacterial agents cause chronic pyelonephritis. Other gram-negative rods including *Klebsiella spp.*, *Proteus spp.*, and *Enterobacter spp.*, which are also isolated from patients with renal infection. *Pseudomonas spp.* and *Serratia spp.* may occur in hospital-acquired urinary tract infection as opportunistic pathogens. In addition, coagulase-negative *Staphylococcus* might represent an important agent to cause pyelonephritis. Moreover, *Enterococcus spp.* may be isolated from patients with renal disease but *Hemophilus* and *Neisseria spp.* are uncommon pathogens which cause upper urinary tract infection usually in childhood. *Staphylococcus aureus* renal infection occurred in patients

with bacteremic *Staphylococcal* infection. Recently, *Corynebacterium group D*٢ and *Acinetobacter spp.* have been identified in nosocomial urinary tract infection (Schrier and Gottschall, ١٩٩٦).

Long-term antibiotic therapy has been recommended to decrease the severity of infection and to obtain normal renal function as soon as possible. However, if the infection persists, the renal function had decreases leading to renal failure that is the main destructive complication of chronic pyelonephritis (Falkiner *et.al.*, ١٩٨٣). The risk of pyelonephritis has increased in people with obstruction of the ureters, diabetes, in people with a weakened immune system which reduces the body's ability to combat infection (Beers *et.al.*, ٢٠٠٤).

The aims of this study are to assess clinically and bacteriologically the patients with chronic pyelonephritis, to study the in vitro antimicrobial sensitivity pattern of bacteria isolated from urine of those patients and to detect the pathogenic factors (*virulence factors*: capsule, hemolysin, extracellular protease, colonization factor antigen and siderophores) related to these bacterial isolates and their relations with the disease.

١.٢. LITERATURE REVIEWS

١.٢.١. *Anatomy and Histology of The kidneys*

١.٢.١.١. *Anatomy:* The kidney is seen to be made up of an outer cortex, a central medulla, internal calices and pelvis. The cortex is homogeneous in appearance. The medulla consists of numerous pyramids formed by the converging collecting tubules, which drain into the minor calices at tip of papillae. These calices unite to form ٢ or ٣ major calices, which join to form renal pelvis. The pelvis may be entirely intrarenal or partly intrarenal and partly extrarenal. Inferomedially, it tapers to form the ureter (Williams *et.al.*, ١٩٨٩).

١.٢.١.٢. *Histology:* The functional unit of the kidney is a nephrone, which is composed of a tubule that has both secretory and execratory functions. Secretory portion is within the renal cortex and consists of renal corpuscle and secretory part of renal tubule. Execratory portion lies in medulla and consists of collecting tubule and distal end of ascending limb of convoluted tubule. The walls of calices and pelvis are composed of transitional cell epithelium which lies on a loose connective tissue and then smooth muscular layer including helical and longitudinal fibers (Sampaio and Aragao, ١٩٩٠)

١.٢.٢. *Kidney Infection (pyelonephritis)*

It is an inflammation of the kidney and renal pelvis that is commonly due to causative agents (Richet and Mayaud, ١٩٧٨). It is divided into two types:

١.٢.٣. *Acute Pyelonephritis*

It is the bacterial infection of kidney causing inflammation of its parenchyma. It is characterized by abrupt onset of high fever and loin pain but the condition can be treated (mostly hospitalized treatment) and the kidney can be reversed to normal size and function after the cure (Olsson *et.al.*, ١٩٨٠).

١.٢.٤. *Chronic Pyelonephritis*

The term chronic pyelonephritis means a persistent renal infection leading to chronic renal lesion and it is associated with bacterial infection (Heptinstall, ١٩٨٣). It represents ٢٥٪ of all renal diseases (Sakran *et.al.*, ٢٠٠٣).

١.٢.٤.١ *Pathology of Chronic Pyelonephritis*

There is irregular scarring of kidney with irregularity of surface and marked atrophy of cortex in relation to dilated calyces associated with current acute bacterial infection of renal parenchyma (Thomsen and Ladefoged, ٢٠٠٢).

Interstitial fibrosis, plasma cell infiltration, periglomerular fibrosis, dilated lymphatics and sometimes endarteritis are presented in biopsies of chronic pyelonephritic patients with proteinuria and renal failure (Kincaid-Smith, ١٩٧٥).

١.٢.٤.٢. *Predisposing Factors of Chronic Pyelonephritis*

- ***Kidney Stones:*** In some cases, kidney stones can cause urinary tract obstruction that leads to infection, particularly pyelonephritis If the destruction persists for a long time, it leads to chronic pyelonephritis (Ng *et.al.*, ٢٠٠٢).
- ***Diabetes:*** Diabetes has significantly higher risk for asymptomatic bacteriuria. The risk for symptomatic complicated UTIs may also be higher in people with diabetes and chronic pyelonephritis is the common feature of diabetic urinary tract infection (Harding *et.al.*, ٢٠٠٢).
- ***Immunosuppressed Individuals:*** Those individuals are with higher risk for most common types of opportunistic infections including the recurrent UTI and the pyelonephritis (Hedges, ١٩٩٢).
- ***Prostate Conditions in Men****:* Benign prostatic hyperplasia (BPH) can produce obstruction in the urinary tract and increase the risk for infection; if the condition persists for a long time, it may cause kidney infection (Eykyn *et.al.*, ١٩٨٢).
- ***Genetic Factors:*** The blood group P١ individuals are more susceptible to the chronic pyelonephritis than others (Kinane *et.al.*, ١٩٨٢).

- ***Chronic Spinal Cord Injury (Neurogenic bladder) and Catheters:*** The use of the catheter for long time or all the life gives higher risk for pyelonephritis and sometimes with no symptoms that the chronic spinal injury may cause a hyperreflexic bladder, and the most common outflow problem in this group was type ٣ detrusor-sphincter dyssynergia which lead to silent upper tract damage (Gerridzen *et.al.*, ١٩٩٢).
- ***Analgesic Nephropathy:*** The use of analgesia and more specifically NSAIDs affects the function of kidneys and some time it leads to serious condition like obstructive type of chronic pyelonephritis (Fairley and Kincaid-Smith, ١٩٧٨).

١.٢.٤.٣. *Age Incidence*

The disease affects all ages but commonly the middle age group is more susptable. In upper urinary tract infection, the male is affected mostly between ٦٠-٨٠ years and the female is between ٢٠-٦٠ years (Bryan and Reynolds, ١٩٨٤).The vesicouretric reflux represents ٥٪ of all causes of chronic pyelonephritis and it is with greatest frequency in children and is less frequently documented in adults (Rossleigh, ٢٠٠٢).

١.٢.٤.٤. *Sex Incidence*

The disease is more common in female than in male. The prevalence of recurrent upper UTI has increased from twofold to sixfold in female than in male (Kosakai *et.al.*, ١٩٩٠). Although, two third and three quarters of reflux nephropathic patients are females (Winberg *et.al.*,

١٩٨٢). Generally, the females are more susceptible to UTI than males because the urethra is shorter and nearer to anus more in females; in addition to the vaginal pathogens (Mims *et.al.*, ٢٠٠٤).

١.٢.٤.٥. *Types of Chronic Pyelonephritis*

Chronic pyelonephritis may be divided into two groups:

- Reflux chronic pyelonephritis (reflux nephropathy).
- Obstructive chronic pyelonephritis (Gowda *et.al.*, ٢٠٠٤).

١.٢.٤.٥.١. *Vesico-Ureteric Reflux (VUR)*

Vesico-ureteric reflux (VUR) can be described as an abnormal backflow of urine from the bladder into the ureter and the kidney. It is one of the most common abnormalities of the renal tract, predisposing to infection and leads to necessitating thorough investigation of childhood urinary tract infection (Dillon and Goonasekera, ١٩٩٨).

VUR is increased in twins and in several members of family that means it is an inherited defect. It is recorded greater in children and infants than in adults that up to ٣٠-٥٠٪ of children with UTI will have VUR detected at first presentation and one third of this group will have unilateral reflux nephropathy. It is more likely to be in female than in male (١٤٪ of female and ٣٪ of male infants) (Kohler *et.al.*, ١٩٩٧). Furthermore, Wolfish *et.al.* (١٩٩٣) pointed out that ٨٠٪ of VUR is transient and resolves spontaneously while Tepmongkol *et.al.* (٢٠٠٢)

observed that ٥٩.٢٪ of children with VUR have developed chronic pyelonephritis.

١.٢.٤.٥.٢. *Obstructive Chronic Pyelonephritis*

Obstruction of the urinary tract results in either increasing in back-pressure on the kidneys or increasing in frequency of urinary tract infections. Both of these factors are caused recurrent episodes of renal inflammation, scarring and parenchymal atrophy. Obstructive chronic pyelonephritis may be bilateral or unilateral, but in most cases, it is unilateral (Stamey, ١٩٧٢).

The most common cause of obstructive type is the renal stone that is represents ٧٧٪ of causes of chronic pyelonephritis (Ng *et.al.*, ٢٠٠٢). Their composition and size vary widely depending upon metabolic alterations and presence of infection. The staghorn calculi are the commonest cause of obstructive chronic pyelonephritis and they lead to superimpose of infection that is due to either mucosal trauma and/or obstruction (Nemoy and Stamey, ١٩٨١).

Other less common cause of obstructive chronic pyelonephritis is a renal papillary necrosis that represents ٧٪ of all causes of chronic pyelonephritis (Ng *et.al.*, ٢٠٠٢). This occurred mostly due to analgesic nephropathy or diabetes. It is associated commonly with sterile pyuria (Fairley and Kincaid-Smith, ١٩٧٨).

١.٢.٤.٦. *Clinical Features*

Asymptomatic: It is important to note that there may be no history of previous urinary symptoms with radiological signs of chronic pyelonephritis in absence of acute infection (Schaeffer, ١٩٨٧). Gaymans *et.al.* (١٩٨٦) showed that ٣٪ of female with upper urinary tract infection have asymptomatic in age between ١٦-٦٥ years.

Symptomatic: Most patients with non-obstructive chronic pyelonephritis do not have specific symptomatology of the disease and present with the sequels of hypertension or end-stage renal disease. Significant urologic symptoms usually occur in patients with obstruction (Massey, ٢٠٠٤). The clinical features in those with chronic renal damage differ slightly in children than in adults but the commonest clinical features are (Jacobson, ١٩٩١):

- Constant dull flank pain and some time back pain.
- Intermittent fever.
- Urinary symptoms (frequency, polyuria, nocturia, dysuria and urgency).
- Nausea with or without vomiting, loss of appetite and weight.

١.٢.٤.٧. *Diagnosis*

- **Urinalysis:**

A- Pyuria: is a common feature in chronic pyelonephritis and it is more important than bacteriuria but the patients may be presented with sterile

urine. Pus cells are present in urine of normal subjects if there are no more than ٢-٣ leukocytes in high power field (Spencer, ٢٠٠٤).

B- RBCs: There should be only an occasional red blood cell in the urine (٢-٣/high power field) and more than these might commonly associate with sever infection or stones (Hamburger *et.al.*, ١٩٧٨).

C- Crystals: may give an idea about the type of stone present there. There are cystine, oxalate, phosphate, struvite, urate and uric acid crystals (Bradley *et.al.*, ١٩٨٤).

D- Casts: are protein coagulum that formed in the renal tubules and trap any tubular luminal contents within the matrix. Thamm-Horsfall mucoprotein is basic matrix of all renal casts. These types are hyaline, cellular (RBC cast and WBC cast), granular and waxy cast. They appeared in urine only due to renal insufficiency (Wagner *et.al.*, ١٩٨٦). WBC casts may be presented in the patients with chronic pyelonephritis (Massey, ٢٠٠٤).

E- Proteinuria: is presented in the patients with chronic pyelonephritis as part of complication of disease. Proteinuria means greater than ٢ gm of protein excreted per ٢٤ hours. Its component is albumin and it means abnormal protein excreted in urine due to renal insufficiency (Robinson, ١٩٨٥).

F- Reaction: is measured by dipstick that normal pH is between ٥.٥-٦.٥. In UTI, it is important to reflect the bacterial agents or the type of the stone that if pH is greater than ٧.٥ (alkaline urine) which may mean

Proteus is a causative agent or struvite stone is presented (Woolhandler *et.al.*, ١٩٨٩).

- **Urine culture**: to detect the causative microorganism, the culture may be negative.
- **Blood sample**: to assess the renal function including blood urea and serum creatinine (Baum *et.al.*, ١٩٨٥).
- **Renal ultrasonography images** may show size, scarring of kidney, and the calculi if present (Farmer *et.al.*, ٢٠٠٢).
- **Intravenous Urography (IVU):** It helps to establish the diagnosis of pyelonephritis because they reveal caliceal dilatation and blunting with cortical scars. Ureteral dilatation and reduced renal size also may be evident. There may be also cortical thinning over pelvo-calyceal lesions (Teplick, ١٩٨٨).
- **Computerized Tomographic scan (CT scan):** It is the procedure of choice to help diagnose chronic pyelonephritis (Gerzof and Gale, ١٩٨٢).

- **Voiding cystourethrogram (VCUG):** The findings may document the reflux of urine to the renal pelvis and ureteral dilatation in children with gross reflux (Ilyas *et.al.*, ٢٠٠٢).
- **Radioisotopic scanning with technetium dimercaptosuccinic acid:** It is more sensitive than intravenous urography for helping detect renal scars. This is the preferred test for many pediatric nephrologists and radiologists because it is sensitive and easy to

perform and can detect VUR and renal scarring (Carroll *et.al.*, ١٩٨١).

- **Cystoscopy:** It is showed the evidence of reflux at the ureteral orifices or site of kidney stone (Ilyas *et.al.*, ٢٠٠٢).

١.٢.٤.٨. *Management*:

The management of recurrent urinary tract infection required more prolonged treatment. Therefore, the management of chronic pyelonephritis can be treated according to the cause and stage of disease into the following:

A- Medical Care

- Long-term antibiotics therapy had been used. Single antibiotic was recommended while frequent alteration in antibiotic therapy may lead to development of resistance (Falkiner *et.al.*, ١٩٨٣). Previously amoxicillin, first-generation cephalosporins and trimethoprim–sulfamethoxazole (TMP–SMX) were first-choice agents for treating of chronic pyelonephritis. However, because of the development of resistance, amoxicillin and first-generation cephalosporins are no longer empirically recommended for these patients. In addition, there is increasing concern about the long use of TMP–SMX resistance rates; therefore, other antibiotic are recommended for treating these cases like third generation cephalosporins and fluoroquinolones or according to the culture and sensitivity (Robert, ١٩٩٩).

- Analgesia to relief the pain.

***B*- Surgical Care**

- Surgery for severe reflux involves reimplantation of the ureters with the creation of an adequate submucosal tunnel and detrusor support (Noe, ١٩٩٢)
- Surgery for removing the kidney stones if they cannot release by supportive treatment (Gleckman *et.al.*, ١٩٨٢).
- Nephrectomy is indicated in unilateral chronic pyelonephritis when the diseased kidney contributes less than ٢٠٪ of total renal function with or without large infected stone or in renin-mediated hypertension (Gleckman *et.al.*, ١٩٨٢).

١.٢.٤.٨.١ *Antibiotics for Patients with Chronic Pyelonephritis:*

١) Amoxicillin

It is semisynthetic antibiotic from penicillin group that interferes with synthesis of cell wall mucopeptides during active multiplication of bacteria, resulting in bactericidal activity against gram-positive and gram-negative bacteria. In past, it has been used frequently for treatment of UTI. Now, most bacteria presented in UTI have high resistance to amoxicillin as shown by Sakran *et.al.* (٢٠٠٣) who observed that only ٥٢% of bacterial UTI responded to amoxicillin. In addition, Leblebicioglu and Esen (٢٠٠٣) and Aggarwal *et.al.* (٢٠٠٣) showed that more than ٧٣٪ of *E.coli* and ٨٨.٥٪ of *K.pneumonia* isolated from patients with UTI were resistant to amoxicillin. *Enterobacter,*

Acinetobacter and *Corynebacterium spp.* have a high resistance to amoxicillin (Zhou *et.al.*, ٢٠٠٢; Savov *et.al.*, ٢٠٠٢; Suarez *et.al.*, ٢٠٠٢).

٢) Cephalosporins

All first three generations of cephalosporins have oral preparations that have used for treatment of recurrent UTI (Wilhelm and Edson, ١٩٨٧).

a- ***First generation cephalosporins****:* They arrest bacterial growth by inhibiting bacterial cell wall synthesis. The bactericidal activity is against gram-positive bacteria and the administration is either oral (cefadroxil, cephalexin and cephradine) or parenteral (cephalothin, cephazolin and cephradine). Now, the usage of first generation cephalosporins is limited because of high resistance to it (Martinez *et.al.*, ١٩٩٥).

b- ***Second generation cephalosporins:*** They have bactericidal activity that inhibits bacterial cell wall synthesis. It has greater activity against anaerobic bacteria and the administration is either oral (cefaclor and cefuroxime axetile) or parenteral (cefamandole, cefmetazole, cefotetan, cefoxitin and cefuroxime). Second generation cephalosporins has limited use that Dumpis *et.al.* (٢٠٠٣) showed that only ٢٦٪ of patients with hospital-acquired UTI responded to second-generation cephalosporins.

c- ***Third generation cephalosporin*****s:** They have bactericidal action that inhibits cell wall synthesis. They are highly stable in the presence of ß–lactamase enzyme and they are effective in wide range of hospital-acquired and nosocomial bacterial infections. The administration is either oral (cefixime, cefpodoxime and ceftibuten) or parenteral

(cefotaxime, ceftriaxone, ceftazidime and ceftizoxime). These drugs are excreted in bile, therefore they may use for patients with renal insufficiency (Katzung, ٢٠٠٢).

The third generation cephalosporin has been affected in bacterial UTI that more than ٨٠٪ and ٧١٪ of bacteria isolated from patients with UTI were sensitive to cefotaxime and ceftriaxone respectively (Gordon and Jones, ٢٠٠٣ and Ghiro *et.al.*, ٢٠٠٢). In addition, ٧٨٪ of *Acinetobacter* isolated from patients with UTI were also sensitive to cefotaxime (Irgbu *et.al.*, ٢٠٠٣) but Zhou *et.al*. (٢٠٠٣) showed that *Enterobacter* had high resistance to cefotaxime.

٣) Trimethoprim-sulfamethoxazole (TMP-SMX)

A combination of trimethoprim and sulfamethoxazole inhibits bacterial growth by inhibiting synthesis of dihydrofolic acid. It is represented the essential co-factor of purine, pyrimidine and amino acid synthesis. Its antibacterial activity includes most common urinary tract pathogens except *Pseudomonas aeruginosa*. The combination is contributed to the efficacy in treatment of upper UTI via synergistic bactericidal effect and may diminish the emergence of resistance (Burman, ١٩٨٦).

Nowadays, the resistance to TMP-SMX is slightly increased that ٤٥٪ of bacterial UTI were resistant to it including ١١٪ of *E.coli* and ٤٢٪ of *S.epidermidis* isolated from patients with UTI (Ghiro *et.al.*, ٢٠٠٢ and Jureen *et.al.*, ٢٠٠٣).

٤) Nitrofurantoin

It is synthetic nitrofuran that interferes with bacterial carbohydrate metabolism by inhibiting acetylcoenzyme A. It is bacteriostatic at low concentrations, bactericidal at higher concentrations, and effective against most uropathogens but not *Pseudomonas* and *Proteus* species. It is presented for brief periods at high concentrations in the urine and leads to repeated elimination of bacteria from urine (Stamey *et.al.*, ١٩٨٧). The risk of adverse reaction increases with age and long-term therapy; therefore, should be monitored (Holmberg *et.al.*, ١٩٨٠).

Nitrofurantoin has low resistant rate than other old antibiotics that only ٤٪ of bacteria isolated from patients with recurrent UTI were resistant to it (Leblebicioglu and Esen, ٢٠٠٣).

٥) Fluoroquinolones

They are bactericidal drugs that act as inhibitors of bacterial DNA gyrase enzyme (which responsible for supercoiling of bacterial DNA). They affected against gram-positive and gram-negative bacteria. Recently, the oral administration of fluoroquinolones like nalidixic acid, ciprofloxacillin, levofloxacillin, ofloxacillin, norfloxacillin and others used for empirical treatment of UTI. They increased considerably for managing of complicated UTI particularly chronic pyelonephritis due to the ability to treat difficult pathogens with high antibiotic resistance like *Pseudomonas*. They can be administered parenterally, and then they can easily switch to oral administration and have limited use in patients with renal insufficiency (Dalkin and Schaeffer, ١٩٨٨).

Bacterial resistance to fluoroquinolones initially appeared to be uncommon, but it is reported at increasing rate due to indiscriminate use of these agents (Acar and Francoul, ١٩٩٠; Wright *et.al.*, ١٩٩٣)

٦) Aminoglycosides

It is bacteriostatic action such as streptomycin, gentamicin, amikacin, netilmicin and tobramycin. Gentamicin is effective but it is associated with a risk of nephrotoxicity and ototoxicity, making tobramycin possible alternatives. Because gentamicin is stored in renal tissues, it can prevent acute retrograde pyelonephritis. Since different aminoglycosides accumulate and persist to various degrees in the kidney parenchyma, they have protective activity of aminoglycosides against renal scarring (chronic pyelonephritis). These results suggest that renal accumulation and persistence of aminoglycosides may be used to advantage in the prophylaxis or in the treatment of kidney infections (Robert, ١٩٩٩). Gentamycin is cost-effective parenteral therapy because only once-daily dosing needed and has a good sensitivity against gram-negative uropathogens (٩٠%) and it can be in combination with TMP-SMX against gram-positive uropathogens (٧٠٪) (Ghiro *et.al.*, ٢٠٠٢).

٧) Tetracycline and Doxycycline

Tetracycline is a broad-spectrum bacteriostic antibiotic prepared from the cultures of certain *Streptomyces* species. It is active against wide rang of gram-positive and gram-negative bacteria with *Mycoplasma* and *Chlamydia*. It is used as alternative antibiotic when Pencillin is contraindicated (Yu *et.al.*, ١٩٩٩).

Doxycycline is a semisynthetic tetracycline with lower side effect, sensitive for treatment of the complicated UTI with *Staphylococcus* or *Pseudomonas spp*. (Saberi, ٢٠٠٢).

٨) Vancomycin

It is glycopeptides with very large molecules therefore it has difficulty penetrating into gram-negative cells and it is poorly absorbed orally therefore it is given intravenously for therapy of systemic infections (Abernethy *et.al.*, ٢٠٠٢).

The bactericidal action of it results primarily from inhibition of cell wall biosynthesis. In addition, vancomycin alters bacterial cell membrane permeability and RNA synthesis and there is no cross resistance between vancomycin and other antibiotics. It is active against *Staphylococcus*, *Streptococcus, Clostridium difficile* and *Diphthriods* and when the patients have allergy to pencillin, vancomycin used as alternative against gram-positive bacteria. It has nephrotoxic, ototoxic, and some time haemopoietic toxicity (Moellering *et.al.*, ١٩٩١)

Staphylococcus spp., Enterococcus spp. and *Corynebacterium* spp. isolated from patients with complicated UTI may have sensitivity to vancomycin (Guirguitzova *et.al.*, ٢٠٠٢; Ryan and Murray, ١٩٩٤).

١.٢.٤.٩. *Complications*

(A) Proteinuria: The patients with radiological evidence of VUR and chronic pyelonephritis without associated glomerulonephritis might have proteinuria (more than ٢ gm/٢٤ hours) with or without reducing in renal function (Dayan and Smith, ١٩٨٦).

(B) Hypertension: Hypertension contributes to the accelerated loss of renal function in persons with this disease. Reflux nephropathy is the most common cause of hypertension in children, occurring in ١٠-٢٠٪ of children with VUR and renal scars. Chronic pyelonephritis may develop after repeated episodes of acute pyelonephritis and this may lead to impaired renal function and hypertension (Huland *et.al.*, ١٩٨٢). Gower (١٩٨٦) showed that ٤٠٪ of women with chronic pyelonephritis have hypertension at first presentation (٢٨٪ unilateral and ١٢٪ bilateral).

(C) Renal failure: The principal complication of bilateral chronic pyelonephritis is end stage renal failure that ٣٠٪ of all childhood renal failure and ٢٠٪ of adult renal failure caused by chronic pyelonephritis (Huland and Busch, ١٩٨٢). Uremia, acidosis, hypocalcaemia and hyperphosphataemia are represented the early complications of renal failure in patients with chronic pyelonephritis. These symptoms presented insidiously and associated with stage of renal failure. In UK, ١.٩٪ of patients with chronic pyelonephritis had end-to-end stage renal failure (Nuutiuen *et.al.*, ١٩٩٩).

١.٢.٥. Bacteriological Agents

١.٢.٥.١. *Enterobacterieceae*

They are gram-negative bacilli; normally habituate in the intestinal tract of human being. Some of them act as a part of a normal flora and incidentally causes the diseases while others are pathogenic for humans. They possessed a complex antigenic structure and produced a variety of enzymes and toxins with other virulence factors (Mims *et.al.*, ٢٠٠٤).

Table (٢.١) Biochemical tests of *Enterobacterieceae* modified from (Brooks *et.al.*, ٢٠٠١).

Test	*E.coli*	*K.pneumonia*	*Proteus*	*Enterobacter*	*Serratia*
EMB	metallic	Centrally dark	pale	Centrally dark	Centrally dark
LF	+	+	–	+	+
Catalase	+	+	+	+	+
Oxidase	–	–	–	–	–
Indol	+	–	±	–	–
MR	+	–	±	–	–
VP	–	+	–	+	+
Urease	–	+	+	–	–
Citrate	–	+	±	+	+
Motility	±	–	+	+	+
TSI	A/Alk± G	A ± G	Alk±G	A ± G	Alk ± G
H٢S	–	–	+	–	–

A acid.
Alk alkaline.
G gas.

١.٢.٥.١.١. ***E.coli***

It is a member of *Enterobacteriaceae* and it is the most common cause of urinary tract infections arising outside of a hospital setting. These strains have PAP pili as well as CFA's (CFA/I, CFA/II, CFA/III). The pili are responsible for adherence in the urinary tract epithelium that the adhesin has important role in pathogenesis of chronic pyelonephritis and associated with severity of disease (Matsumoto *et.al.*, ١٩٩٠). The capsule of *E.coli* represented the antigenic structure (K antigen) and it is highly associated with the pathogenesity of pyelonephritis, so that K antigen of *E.coli* help in the attachment of bacteria to the epithelial cells prior to the urinary tract invasion. Nephropathogenic *E.coli* may produce

hemolysin as a part of the virulence factors in complicated UTI and this is not well clear on blood agar (Eisenstein and Azaleznik, ٢٠٠٠). Some strains are urease-producing *E.coli* and they are commonly presented in complicated UTI (Collins and Falkow, ١٩٩٠). The antibiotic resistance of *E.coli* isolated from UTI is highly increased due to the abuse of antibiotics from the patients in addition to the toxins and enzymes like endotoxin and β-lactamase that play an important role in the virulence of bacteria.

The recent studies showed that ٤٧٪ of patients with UTI have *E.coli* in their cultures (Gordon and Jones, ٢٠٠٣). The incidence of urinary tract infection with *E.coli* is decreased due to the increase of the nosocomial infection of urinary tract (Schrier and Gottschalk, ١٩٩٦).

١.٢.٥.١.٢. ***Klebsiella pneumoniae***

Klebsiella is a member of the family *Enterobacteriaceae*. Colonies are large and highly mucoid. It is most common cause of hospital-acquired urinary tract infections or burn wound infections. The autoimmune disease (ankylosing spondylitis) is thought to be a possible sequel of *Klebsiella* infection (Abbott, ١٩٩٩) but the virulence of *Klebsiella* is not well understood, but its antiphagocytic capsule plays a role in the infections by preventing phagocytosis. It is thought that aerobactin, an iron-binding protein, and the production of ß-lactamase enzyme contribute to pathogenicity and antibiotic resistance of bacteria. Some strains of *Klebsiella* produced hemagglutinins (may be a mannose-sensitive phenotype) and they may be associated with the pathogenicity

of the bacteria in UTI (Podschun and Sahly, ١٩٩١). Agapova *et.al.* (١٩٩٩) showed that ٣٥٪ of *Klebsiella* isolated from UTI produced gelatinase enzyme that play an important role in the inflammatory process of UTI.

١.٢.٥.١.٣. ***Proteus mirabilis***

Proteus is a member of the family *Enterobacteriaceae*. *Proteus spp.* cannot ferment the lactose, can produce disease only when leave the intestinal tract, and they produce the urease enzyme. This enzyme urease, which catalyzes the splitting of urea into ammonia and carbon dioxide, causes the pH of urine to rise with allowing unchecked growth of the bacteria. The higher pH is also toxic to renal cells and potentiates the formation of urinary stones. These stones can cause *Proteus* infections to be chronic, as organisms can remain viable within the stones during therapy (Farmer, ٢٠٠٠). The adhesin for urinary epithelium and the organism's rapid motility are also involved in the pathogenesis of the urinary tract infections. In addition, the endotoxin may play a role in the antibiotic resistance and the virulence of bacteria (Gilchrist, ١٩٩٥).

١.٢.٥.١.٤. ***Enterobacter spp.***

They are one of member of *Enterobacteriaceae* and they are one of the causes of opportunistic urinary tract infections in human being. They have a small capsule but their ability of adherence to urinary epithelium, their motility and the siderophore production contributed to the pathogenesity in UTI. In addition, the production of enzymes and

endotoxins has an important role in virulence and antibiotic resistance of bacteria (Gilchrist, ١٩٩٥). *Enterobacter* can produce antibacterial substance that has antagonistic activity against a wide range of bacteria except *Acinetobacter* and *Pseudomonas* (Ya-ping *et.al.*, ٢٠٠٣).

١.٢.٥.١.٥. ***Serratia spp.***

They are lactose-fermented gram-negative short rods *Enterob-acteriaceae* with one to two flagella. They represented as opportunistic pathogens with wide ranges of infectivity in nosocomial infections like respiratory or urinary tracts infections. The virulence of bacteria commonly associated with the production of urease enzyme, haemolysin enzyme, siderophore and extracellular protease like gelatinase enzyme with presence of fimbriae help in adhesion of bacteria (either mannose-sensitive or mannose-resistant fimbriae) (Marumo *et.al.*, ١٩٩٠). Swarmming motility characterized to the bacteria on solid or viscous media due to presence of flagella. The production of ß-lactamase enzyme has given to bacteria high resistance to several antibiotics like that in *Pseudomonas* bacteria (Kouda *et.al.*, ١٩٩٠).

١.٢.٥.٢. ***Staphylococcal spp.***

They are gram-positive spherical bacteria usually arranged in grap like irregular clusters. They are a normal flora of human skin and mucous membranes and their spread is either endogenously or from infected skin. They have many species but the main three species are *S.aureus, S.epidermidis* and *S.saprophyticus*. The pathogenicity of *Staphylococci* is contributed to hemolysis of the blood, coagulation of

the plasma and production of extracellular enzymes and toxins (Mims *et.al.*, ٢٠٠٤).

Table (٢.٢): Biochemical tests of *Staphylococcal spp* modified from (Brooks *et.al.*, ٢٠٠١).

Test	*S.aureus*	*S.epidermidis*	*S.saprophyticus*
Catalase	+	+	+
Oxidase	–	–	–
Coagulase	+	–	–
Mannitol ferm.	+	–	–
Resist to Novobiocin	†	–	+
Urease	–	±	±
Hemolysin	+	–	±

† Novobiocin used only to distinguish between *S.epidermidis* and *S.saprophyticus*.

١.٢.٥.٢.١. ***S.aureus***

It is coagulase positive *Staphylococci*, presented significantly in greater percentage of people in the hospital setting that the carrier state serves as reservoir for infection of hospitalized patients (Todar, ٢٠٠١). *S.aureus* has a polysaccharide capsule to protect it from phagocytosis and the cell wall composed of peptidoglycan and teichoic acid moieties that protect it from lyses by osmotic condition and aid the bacteria to attach to mucosal surfaces. The virulence of the bacteria occurred by secretion of toxins and enzymes which act on host cell membrane and mediated the cell destruction. It is penicillin-resistance bacteria due to produce of ß-lactamase enzyme that is chromosomally resistance.

Clinically significant methicillin-resistant *S.aureus* (MRSA) caused nosocomial infections and hospital–acquired UTI and it is the commonest cause of bacteremia in human being (Takahaski *et.al.*, ١٩٩٩). The kidney infection caused by bacteremia is ٣٠٪, only ٣٪ caused by *S.aureus* (Horcajada *et.al.*, ١٩٩٩).

١.٢.٥.٢.٢. ***S.epidermidis***

It is a coagulase negative *Staphylococci* and a common member of the normal flora of skin and mucous membranes. Its large numbers and ubiquitous distribution make it one of the most commonly isolated organisms in the clinical laboratory. The first appearance of *S.epidermidis* in clinical material could dismiss as contamination; it is now one of the most important agents of hospital-acquired infections. Immunosuppressed patients are particularly at risk, as are individuals with indwelling catheters or prosthetic devices (Baron *et.al.*, ١٩٩٦). The hydrophobic nature of the organism's cell surface facilitates its adherence to synthetic devices. Following initial colonization, a copious amount of extracellular polysaccharide or slime is synthesized that forming a protective biofilm around the colony. Because many isolates are multiple antibiotic resistant, these infections are very serious and can even be fatal. In complicated UTI, *S.epidermidis* is represented more than ٢٠٪ as a nosocomial infection (Guirguitzova *et.al.*, ٢٠٠٢).

١.٢.٥.٢.٣. ***S.saprophyticus***

It is coagulase negative *Staphylococci*, commonly isolated from uncomplicated urinary tract infection in nonhospitalized patients,

notably sexually active woman. *S.saprophyticus* may also be involved in recurrent infection and in stone formation that the incidence of *S.saprophyticus* in urinary tract infection varies according the institutions and the geographical areas (Todar, ٢٠٠١). It is resistant to several antibiotics such novobiocin and nalidixic acid. Although the species do not produce number of extracellular products but it may produce hemolysin and the antiphagocytic capsule that the production of the slime may correlate with pathogenicity and bacterial adherence (Baron *et.al.*, ١٩٩٦).

١.٢.٥.٣. *Pseudomonas and Acinetobacter*

Table (٢.٣): Diagnostic and biochemical tests of *P.aeruginosa* and *Acinetobacter* modified from (Brooks *et.al.*, ٢٠٠١).

Test	*P.aeruginosa*	*Acinetobacter*
LF	–	–
Catalase	+	+
Oxidase	+	–
Indol	–	–
MR	+	–
VP	–	+
Urease	±	–
Citrate	+	–
Motility	+	–
TSI	Alk ± G	Alk ± G
H٢S	–	–

Alk alkaline.
G gas.

١.٢.٥.٣.١. ***Pseudomonas aeruginosa***

It is non-fermentative aerobic gram-negative bacilli. It has one of the broadest ranges of infectivity among all pathogenic microorganisms as opportunistic pathogens. It is a significant cause of burn wound infection and nosocomial infection in human body like respiratory tract infection in patients with cystic fibrosis, eye infection and genitourinary tract infection in immuno-compramized patients (Bodey, ١٩٨٣).

The pathogenicity of the bacteria contributed to the virulence factors of it. The capsule or slime layer is associated in adherence and effectively protected the bacteria from phagocytosis. The productions of extracellular protease, cytotoxins and hemolysin have an important role in virulence; in addition, the siderophore production under low iron condition helps the growth of pathogen (Woods and Iglewski, ١٩٨٣).

١.٢.٥.٣.٢. ***Acinetobacter spp.***

Non-lactose fermented gram-negative cocci bacteria are related to the *Neisseria* group. They are an important cause of nosocomial infection in human being like burn infection, respiratory tract infection and urinary tract infection and they affected severally ill patients (Koelman *et.al.*, ١٩٩٧). The long established catheterization is commonly associated with *Acinetobacter* infection that ٢٢٪ of bacteria isolated from patients with UTI are *Acinetobacter spp.* (Ayan *et.al.*, ٢٠٠٣; Joshi *et.al.*, ٢٠٠٣). The pathogenicity of bacteria is related to presence of small capsule and production of ß-lactamase enzyme similar to that of MRSA bacteria with high antibiotic resistance (Iskandar *et.al.*, ٢٠٠٣). In addition, they have no adhesive agents like that of *E.coli* and

some species produced lipase, histamine, siderophore, and other produced haemolysin (Hostacka, ٢٠٠٣).

Table (٢.٣): The diagnostic and biochemical tests of *Corynebacterium and Enterococcus spp* modified from (Brooks *et.al.*, ٢٠٠١).

Test	*Corynebacterium*	*Enterococcus*
On MacConcky	–	+
Catalase	+	–
Oxidase	+	–
Esculin	–	+
Urease	+	–
Motility	–	–

١.٢.٥.٤. *Corynebacterium spp.*

Nineteen species with the genus of *Corynebacterium* recovered from human clinical material. The commonest species that cause UTI in human being is *C.urealyticum* that was isolated from ٠.٣٢٪ patients with recurrent UTI, ١٦٪ of them had complicated UTI mostly with prolonged hospitalization and urological manipulation (Suarez *et.al.*, ٢٠٠٢). *C.urealyticum* (formerly *Corynebacterium group D* ٢) has implicated as a cause of alkaline-encrusted cystitis and urinary tract struvite calculi. Despite preselecting urine specimens with neutral and alkaline pH and using prolonged incubation on blood and chocolate agars, isolation of this organism was rarely observed in a population of hospitalized patients (Ryan and Murray, ١٩٩٤). The routine cultures are not recommended for this organism unless the urine is alkaline and struvite

crystals, leukocytes, and erythrocytes are present in urine examination (Craig *et.al.*, ١٩٩٤).

١.٢.٥.٥. ***Enterococcus spp.***

Enterococcus spp. is gram-positive bacteria that they are modern classification *group D Streptococci* and they can use as indicators of water faecal contamination (Baron *et.al.*, ١٩٩٦). *Enterococci* have become recognised as serious nosocomial pathogens causing bacteraemia, endocarditis, urinary tract infections and other infections. This is in part explained by the resistance of some of these bacteria to most antibiotics that are currently in use. Resistance is acquired by gene transfer systems. Virulence of *Enterococci* is not well understood but adhesins, haemolysin, hyaluronidase, aggregation substance and gelatinase are putative virulence factors (Franz *et.al.*, ١٩٩٩).

١.٢.٥.٦. ***Mycoplasma spp.***

They are important pathogens that infected the human genitourinary tract. They are the smallest organisms which are able to survive extracellularly and highly pleomorphic because they lack a rigid cell wall therefore they are completely resistance to ß-lactam groups but they can inhibit by tetracycline and erythromycin groups (Waites and Taylor-Robinson, ١٩٩٩).

The species that infect the genitourinary tract of human are *M.hominis*, *M.genitalium* and *Ureaplasma urealyticum*. The first two species may cause urethritis or postpartum fever and lead to recurrent UTI or may be asymptomatically present. *U.urealyticum* is caused a non-gonococcal urethritis in males but in females, it may lead to

chorioaminionitis and causes low birth weight baby. *M.hominis* also causes arthritis, wound infection, neonatal meningitis and bacteremia (Taylor-Robinson, ٢٠٠٠).

١.٢.٥.٧. ***Chlamydia spp.***

They are obligate intracellular bacteria. The species that causes genitourinary tract infections is *Chlamydia trachomatis* that leads to sexually transmitted disease including non-gonococcal urethritis, cervisitis, proctitis and epididymitis which may lead to chronic pyelonephritis with pyuria and no usual bacteria. In addition, ٦٠٪ of patients with non-gonococcal urethritis are caused by *C.trachomatis* mostly in males (Fraiz and Jones, ١٩٨٨).

١.٢.٦. *Virulence Factors*

For a UTI to occur, the pathogens must be able to attach to the urinary epithelium, avoid removal by the host and then cause inflammation. Since, they posses a variety of virulence factors which are involved in the sequence of events leading to infection (Johnson *et.al.*, ١٩٩٨).

١.٢.٦.١. *Capsule of the Bacteria*

Some strains of bacteria may have a capsule around the bacterial wall which is a polysaccharide material and it is represented an important virulence factor in some bacterial species such as *Streptococcus* and *Klebsiella*. It is contributed to adhesion and prevented from

phagocytosis. Most of these antiphagocytic surface structures show much antigenic heterogeneity that the antibodies against one type of the antiphagocytic factor protect the host from disease caused by bacteria of that type but not from those with other types of the same factor (Robbins *et.al.*, ١٩٨٠).

Although, the slime layer is enclosed around the bacterial wall and it consisted of polysaccharide and proteins, it has toxic effect on the phagocytic cells and T lymphocytes that leading to deficiency in the immunity of the host. The slime layer is commonly presented in most *Enterobacteriaceae* (Obana and Nishino, ١٩٨٨).

١.٢.٦.٢. *Haemolysin Production*

It is a metabolic virulence factors that allows the colonising bacteria to survive. The synthesis of cytotoxic hemolysins is common between both gram-positive and gram-negative bacteria. The production of α-haemolysin or ß-hemolysin has lysed the host cells by creating transmembranous pores (Nassif and Sansonett, ١٩٨٧). Beta-haemolysins inhibit phagocytosis and chemotaxis of neutrophils. This hemolytic phenomenon was shown to be cell associated and could be demonstrated only by actively growing and multiplying cells in the presence of erythrocytes. The hemolytic factor seems to be strongly cell associated and not stable, since no hemolytic activity was observed in cell-free supernatants and filtrates of bacterial cultures (Falkow, ١٩٨٨).

١.٢.٦.٣. *Extracellular Protease Production*

Many species of bacteria produce some enzymes that are not intrinsically toxic but play important roles in the infectious process like collagenase enzymes, which promote the spread of infection in tissue or elastase (or called gelatinase) enzymes that cleaves the collagen, IgG, IgA and complement leading to lyses the fibronectin and promote bacterial attachment on the surface. In addition, alkaline protease (or metalloproteases) is another extracellular protease enzyme that interferes with fibrin formation leading to lyses the fibrin (Fredricks and Relman, ١٩٩٦).

These extracellular protease enzymes are allowed the pathogens to inactivate the primary antibody found on mucosal surfaces, eliminate the protection of the host by the antibody and acting on various steps related to nutrition acquisition. They are regulatory enzymes than as enzymes participating in processes of inactivation and catabolism (Juarez and Stinson, ١٩٩٩).

١.٢.٦.٤. *Colonization Factor Antigens*

Fimbriae and adherence ability

Bacterial adhesion to epithelial surfaces is thought to be one of the most important virulence factors, playing a significant role in the initiation of UTI. The bacterial adhesion capacity is most frequently associated with the presence of fimbriae on bacterial cells. It has been shown that fimbriae are responsible for the attachment of bacteria to

uroepithelial cells. By electron microscopy, it was possible to see bacteria with fimbriae bound to renal pelvic mucosa. In contrast to this effect, fimbriae diminished the ability of bacterial rods to infect the renal parenchyma by the hematogenous route. Studies in vitro have shown that fimbriae enhance the binding of bacterial cells to uroepithelial cells but the pathogen becomes more susceptible to phagocytosis (Silverblatt and Ofek, ١٩٨٨). Previous ultrastructural studies of bacterial strains have shown two types of fimbriae (١) thick (approximately٧ nm in filament diameter) and (٢) thin (٤ nm in diameter). The first type, also known as type IV fimbriae, found to be mannose resistant and was named *Proteus*-like fimbriae (MR/ P). The second type is the type III fimbriae, which are mannose- resistant and was named *Klebsiella*-like fimbriae (MR/K). These types of fimbriae are associated with their ability to hemagglutinate untreated (MR/P) or tannic acid-treated (MR/K) erythrocytes from several animal species. The MR/K phenomenon was associated only with the hemagglutination pattern of bacteria and loosely correlated with the expression of fimbriae; therefore, it was called MR/K hemagglutinins rather than MR/K fimbriae (Clegg and Gerlach**,** ١٩٨٧).

Pyelonephritis-associated pili (pap-fimbriae) are related to type ١ fimbriae or MS- fimbriae. Uroepithelial cells from the patients with chronic pyelonephritis and renal insufficiency had a higher binding capacity of P-fimbriated *Escherichia coli* than uroepithelial cells from patients with a normal glomerular filtration rate (Matsumoto *et.al.*, ١٩٩٠).

١.٢.٦.٥. *Siderophores Production*

Iron is critical to growth and metabolism of nearly all living organisms, prokaryotic and eukaryotic. Limiting the concentration of free extracellular iron is a strategy of host defense against pathogenic microorganisms that practiced by many animal species. Many bacterial pathogens secrete highly efficient low-molecular-weight iron chelating agents, termed siderophores (Bradley *et.al.*, ٢٠٠٠).

These agents compete for and bind available iron. The siderophore-iron complexes are recognized by the bacteria, which then internalize the iron. It is a high-affinity iron assimilation system. This system has the ability of induction of multivalent cationic metals and it is unaffected when the cells are depleted of ATP or when receptor-mediated endocytosis is inhibited with dihydrocytochalasin. The ability to produce siderophores has linked to the pathogenic potential of many bacterial species including *Pseudomonas aeruginosa*, *Escherichia coli*, *Vibrio cholerae* and others. At least some bacteria are also able to use exogenous siderophores that are present in the environment, with the presence of an iron chelate inducing synthesis of the cognate receptor. In the best characterized system, that of ferric-citrate uptake in *Escherichia coli*, binding of ferric citrate to outer membrane receptor protein initiates a signal-transduction pathway (Weinberg and Weinberg, ١٩٩٥).

٢. ١. *PATIENTS AND MATERIALS*

٢. ١. ١. *Patients*

From September ٢٠٠٣ to June ٢٠٠٤, one handered and two (١٠٢) chronic pyelonephritic patients visited Hilla Teaching Hospital-Department of Urology. Their ages range between ٧-٨٨ years with a mean (٤٩±١.٦), ٦٣ females and ٣٩ males. All patients underwent the following laboratory investigations that included (General Urine Examination (GUE), Urine culture, B.urea, S.creatinine and R.B.sugar) and radiological investigation that included (abdominal Ultrasonography, Intravenous Urography (IVU) and Computerized Tomographic scan (CT scan). Urine samples were obtained from them either from midstream, bladder catheter, ureteric catheter of cystoscopy or direct from renal pelvis. None of them was on antibiotics; six (٦) patients were diabetic.

٢. ١. ٢. *Materials*

Many types of instruments and chemical materials, in addition to biological materials were used in this thesis to complete the research of it. These materials were taken from different sources and companies which listed in tables (٢.١) and (٢.٢). The potency of antibiotics disks was listed in table (٢.٣).

Table (٢.١): List of Instruments Used.

No	*Instruments*	*Company*
١.	Sensitive electronic balance	A&D, Japan.
٢.	Autoclave	Stermite, Japan.
٣.	Incubator	Memmert, Germany.
٤.	Water bath	Memmert, Germany.
٥.	Distillator	GFL-Germany.
٦.	Centrifuge	Hermle, Japan.
٧.	Oven	Memmert, Germany.
٨.	Refrigerator	Concord, Italy.
٩.	Benson burner	Germany.
١٠.	Millipore filter	Satorius membrane filters Gm bH, W.Germany.
١١.	Light microscope	Olympus, Japan.
١٢.	Micropipette	Oxford, USA.
١٣.	pH meter	Hoeleze&Cheluis,KG, Germany.
١٤.	Inoculating loop	Japan
١٥.	Inoculating needle	Japan
١٦.	Biconcave slid	GFL-Germany.

Table (٢.٢): List of Biological and Chemical Materials.

No	*Chemical Materials*	*Company*
١.	**Na_2HPO_4,KH_2PO_4,NaCl,NH_4Cl,$MgSO_4$,$CaCl_2$, KOH,K_2HPO_4,$FeCl_3$**	**Merk-Darmstadt.**
٢.	**Methyl red, α-naphthol, esculin, Tannic acid, Tetramethyl-P-paraphenylene diamine dihydrochloride, Kovac's Reagent.**	**B.D.H.**
٣.	**H_2O_2, Kovac's reagent, Urea solution, D-mannose, Glucose, ٢-٢dipyridyl (Mwt.١٥٦.١٩), ٩٩٪Ethanol.**	**Fluka chemika-Switzerland**
٦.	**MacConcky agar, Blood base agar, Muller-Hinton agar, Nutrient agar, Nutrient broth, Tryptic soy agar, Agar-Agar media, Peptone broth.**	**Mast Lab.-UK**
٧.	**Urea base agar, Simon citrate agar, Kliglar Iron Agar, MR-VP broth.**	**Difco-Michigan.**

Table (٢.٣): Antibiotics disk potency (OXIOD-England and TROGE-Hamburg).

Antibiotics	AMX	GM	CF	TE	TMX	VAN	CE	CXM	DOX	TF
Potency	١٠	٣٠	٣٠	٣٠	٣٠	٣٠	١٠	١٠	٣٠	٣٠

- AMX – Amoxicillin, GM – Gentamicin, CF – Ciprofloxacillin, TE – Tetracycline, TMX – Trimethoprim-Sulfamethoxazole, VAN – Vancomycin, CE – Cefotaxime, CXM – Cefixime, DOX – Doxycycline, TF-Nitrofurantoin.

٢. ٢. *METHODOLOGY*

٢. ٢. ١. *The Preparation of Reagents*

١) ***Methyl red reagent:*** ٠.١ gm of Methyl red was dissolved in ٣٠٠ ml of ٩٩٪ ethanol and then the volume was completed to ٥٠٠ ml by distill water (Macfaddin, ٢٠٠٠).

٢) ***Voges-Proskauer reagent***

Reagent A) ٥ gm of α-naphthol was dissolved in ١٠٠ ml of ٩٩٪ ethanol.

Reagent B) ٤٠ gm of KOH was dissolved in ١٠٠ ml of distill water (Collee *et.al.*, ١٩٩٦).

٣) ***Oxidase reagent:*** It was prepared by dissolving of ٠.١ gm of Tetra-P-paraphenylene diamine dihydrochloride in ١٠ ml of distill water and stored in a dark container (Baron *et.al.*, ١٩٩٦).

٤) ***Catalase reagent:*** It was prepared by dissolving ٣ gm of H_2O_2 to ١٠٠ ml of distill water and was stored it in dark container (Baron *et.al.*, ١٩٩٦).

٢. ٢. ٢ *The Preparation of Media*

١) M٩ media: ٦ gm of Na٢HPO٤, ٣ gm of KH٢PO٤, ٠.٥ gm of NaCl, ١ gm of NH٤Cl**;** all of them were dissolved in ٩٥٠ ml of distill water with ٢٪ agar and then were sterilized into autoclave and after cooling the mixture to ٥٠^{o}C, ٢ ml of ١M MgSO٤, ١٠ ml of ٢٠٪ glucose and ٠.١ ml of ١M CaCl٢ (all of them was sterilized separately by filtrations) were added to it, then the volume was completed to ١٠٠٠ ml. (Miniatis *et.al.*, ١٩٨٢)

٢) Esculin media: The esculin was ٦, ٧-dihydroxy coumarin ٦-glucoside which had inhibitory effect on xanthin oxidase enzyme (Capell *et.al.*, ١٩٩٥). Esculin media was made from nutrient agar with ٠.٤ gm ferric ammonium citrate and ٥gm esculin then the volume was completed to ١٠٠٠ ml. After that, the media were poured into tubes and sterilized them in autoclave then slants of media was formed (Macfaddin, ٢٠٠٠).

٢. ٢. ٣. *The Preparation of Solutions*

١) Doxycycline solution: ٠.٢ gm of Doxycycllin powder was dissolved in ٩٠ ml of ٧٠٪ ethanol then the volume was completed to ١٠٠ ml. (the concentration is ١٠٠ µg/ml).

٢) Cefixime solution: ١ gm of Cefixime powder was dissolved in ٩٠ ml of sterile distill water then the volume was completed to ١٠٠ ml. (the concentration is ١٠٠ µg/ml) (Miniatis *et.al.*, ١٩٨٢).

٢. ٢. ٤. *The Preparation Phosphate Buffer Saline*

٨٠ gm of NaCl, ٠.٣٤ gm of KH٢PO٤, ١.١٢ gm of K٢HPO٤; all of them were dissolved in ١٠٠٠ ml of distill water. The pH was ٧.٣ then it was sterilized in autoclave (Baron *et.al.*, ١٩٩٦).

٢. ٢. ٥. *Urine sample*

The samples of urine were obtained from patients suffering from chronic pyelonephritis who visited Hilla Teaching Hospital-Department of Urology.

١. Bladder Sample

- ***Sample from Midstream Urine:*** After cleaning the urethral area and allow the first drops of urine to pass, the samples of urine were collected in the sterilized screw-cap container.
- ***Sample from Bladder Catheter:*** At first, the urethral area was cleaned with soap and water and then the catheter was inserted into the bladder; allowing the first drops of urine to pass then collecting the remainder in the screw-cap container (Baron *et.al.*, ١٩٩٦).

٢. Kidney Samples

- ***Sample from nephrostomy:*** The sample was obtained from the catheter of nephrostomy; which was collected in the screw-cap container.
- ***Sample Direct from Renal Pelvis during Operation:*** The sample was obtained from renal pelvis by sterile disposable syringe and putting it in a screw cap container.
- ***Sample from Cystoscopy:*** The sample was obtained by ureteric catheter of cystoscopy through passage of the catheter to renal pelvis and collecting the urine from the end of the catheter in sterial screw-cap container (Walsh *et.al.*, ١٩٩٧).

٢. ٢. ٦. *Urinalysis*

A urinalysis involved a physical and chemical examination of urine (color, reaction and albumin).

The urine was spun in a centrifuge to allow sediments containing:

- Pus cells (WBC).
- RBC.
- Crystals.
- Casts (Massey, ٢٠٠٤).

٢. ٢. ٧. *Identification of Bacteria*

A single colony was taken from each primary positive culture and it was identified by depending on its morphology of it (shape, size, borders and texture) and then examined it under microscope after staining it with gram stain or other specific stain (such as Albert stain for *Corynebacterium spp.* to observe a metachromatic granules).

After staining, the biochemical tests were done to each isolates to reach to the final identification according to Bergy's Manual for Determinative Bacteriology (Holt *et.al.*, ١٩٩٤).

٢. ٢. ٨. *Biochemical Tests*

٢. ٢. ٨. ١. *Catalase Test*: A colony of the organism was transfered to a drop of ٣٪ H_2O_2 on a microscope slide. The presence of catalase was meant that the formation of gas bubbles has occurred which indicated the positive result (Collee *et.al.*, ١٩٩٦).

٢. ٢. ٨. ٢. *Oxidase Test*: A piece of filter paper was saturated in a petri dish with oxidase reagent then a colony of organism was spread onto

the filter paper. When the color around the smear turned from rose to purple, the oxidase test was positive (Collee *et.al.*, ١٩٩٦).

٢. ٢.٨.٣. *Coagulase Test:* Several colonies of bacteria were transferred with a loop to a tube containing ٠.٥ ml of plasma. The tube was covered to prevent evaporation and incubated at ٣٧^{o}C overnight. The test was read by tilting the tube and observing for clot formation in the plasma. Negative test results in the plasma remained free-flowing with no evidence of a clot (Collee *et.al.*, ١٩٩٦).

٢. ٢.٨.٤. *Indol Test:* A ١٪ solution of tryptone broth was prepared in the tubes then it was sterile into the autoclave. After that the broth inoculated with bacterial colonies and it was incubated for ٤٨-٧٢ hours at ٣٧°C. Testing for indole production was done by adding ٦-٨ drops of Kovac's Reagent (p-dimethylaminobenzaldehyde in amyl alcohol). The formation of red color ring at top of broth was a positive reaction. A yellow color ring was a negative result (Macfaddin, ٢٠٠٠).

٢. ٢.٨.٥. *Methyl Red Test*: The test was performed on ٥ ml of MR-VP broth cultured by the organism and then it was incubated for ٢٤ hours at ٣٧^{o}C. After that the ٦-٨ drops of Methyl Red reagent were added to culture. The change of color to orange-red was a positive reaction (Collee *et.al.*, ١٩٩٦).

٢. ٢.٨.٦. *Voges–Proskaur Test*: The test was performed on ٥ ml of MR-VP broth cultured by the organism and then it was incubated for ٢٤ hours at ٣٧^{o}C. After that ١٥ drops of ٥٪ alpha naphthol (reagent A) were added followed by ١٠ drops of ٤٠٪ KOH (reagent B) and shaken well

and allowed standing for up to ٣٠ minutes before calling a reaction negative. The positive culture was turning to red at the surface of the liquid, and the color was spread gradually throughout the tube (Baron *et.al.*, ١٩٩٦).

٢. ٢.٨.٧. *Simon Citrate Test:* After the sterilization of Simon citrate slants by autoclave, inoculated the bacterial cultures and incubated it for ٢٤-٤٨ hours at ٣٧°C. The positive result was a change of the color of media from green to blue. The unchanging of the color was a negative reaction (Benson, ١٩٩٨).

٢. ٢.٨.٨. *Urease Test:* The urea base agar was sterilized by autoclave. After cools it to ٥٠°C, the urea substrate was added to it and was poured in sterile tubes; then inoculated by bacterial cultures and it incubated them for ٢٤-٤٨ hours at ٣٧°C. The positive result was a deep pink color. Failure of deep pink color to develop was a negative reaction (Benson, ١٩٩٨).

٢. ٢.٨.٩. *Kliglar Iron Agar (KIA) Test:* The aim is to differentiate the *Enterobacteriaceae* according to carbohydrate fermentation and hydrogen sulfide production. The organism was grown on KIA slant by stab and streak and then it was inoculated at ٣٧°C for ٢٤-٤٨ hours. The changing of the color of the media from orange-red to yellow was due to carbohydrate fermentation with or without gas formation at butt of slant. In addition, the formation of Hydrogen sulfide was given a black color precipitation at butt (Macfaddin, ٢٠٠٠).

٢. ٢.٨. ١٠. ***Esculin Test:*** The organisms were grown in an Esculin slants. The dark brown color was the positive result. The unchanging of the color was a negative reaction (Capell *et.al.*, ١٩٩٥)

٢. ٢.٨. ١١. ***Mannitol Salt Agar:*** The medium was turned from pink to bright yellow when the bacteria were Mannitol fermented and the test was positive (Macfaddin, ٢٠٠٠).

٢. ٢.٨. ١٢. ***Eosin Methylene Blue (EMB) Agar.*** Lactose fermenting colonies were either dark or possess dark centers with transparent colorless peripheries, while organisms that did not ferment lactose remain uncolored. This purple color was due to the absorption of the esoin-methylene blue complex, which formed in the presence of acid. Certain members of the coliform group, especially *Escherichia coli*, exhibited a greenish metallic sheen in the reflected light (Collee *et.al.*, ١٩٩٦).

٢. ٢.٨. ١٣. ***Motility test by using semisolid media:*** ١٠ ml of semisolid media was dispensed in test tubes and leave to set the vertical position, inoculate with a straight wire, making a single stab down the center of the tube to about half the depth of the medium. The culture was incubated after ٣٧°C and examine at ٦ hours, ١ and ٢ days. Non-motile bacteria had generally confined to the stab-line and given sharply defined margins with leaving the surrounding medium clearly transparent. Motile bacteria were typically given diffuse hazy growths that spread through out the medium rendering it slightly opaque (Macfaddin, ٢٠٠٠).

٢. ٢. ٩. *The Antibiotics Sensitivity Tests*

٢. ٢. ٩. ١. *Antibiotics Diffusion Tests by Kirby-Bauer Susceptibility test*

- It was performed using a pure culture of previously identified bacterial organism. The inoculum to be used in this test was prepared by adding growth from ٥ isolated colonies grown on a blood agar plate to ٥ ml of broth. This culture was then incubated for ٢ hours to produce a bacterial suspension of moderate turbidity. A sterile swab was used to obtain an inoculum from the standardized culture. This inoculum was then streaked on a Mueller-Hinton plate.
- The antibiotic discs were placed on the surface of the medium at evenly spaced intervals with flamed forceps or a disc applicator. Incubation was usually overnight with an optimal time being ١٤ hours at ٣٧°C. Antibiotics inhibition zones were measured using a caliber. Zone size was compared to standard zones to determine the susceptibility or resistance of the organism to each antibiotic (Macfaddin, ٢٠٠٠).

٢. ٢. ٩. ٢. *The Preparation of Antibiotics Media*

Muller-Hinton agar was prepared then sterilized it into autoclave. After cooling it to ٥٠°C, the antibiotic solution was added (prepared in ٢.٢.٤), then it was poured it in sterilized peteridishs and inoculate the organisms on media by Pinking and Patching procedure for ٢٤ hours at ٣٧°C. The detection of sensitivity of antibiotics was done by presence of bacterial growth or not (Miniatis *et.al.*, ١٩٨٢).

٢. ٢. ١٠. *The Virulence Factors*

٢.٢.١٠.١. *Capsule stain*

- A heavy smear of organism was prepared and allowed to dry in the air.
- ١٪Crystal violet was applied to non-heated fixed smear and waiting for ٥-٧ min.
- The smear was washed with ٢٠٪ Copper sulfate solution as counter stain then was gently blot dry and later it was examined it under oil immersion that the capsule appeared as a light blue in contrast to a deep purple of the cell (Cruickshank *et.al.* ,١٩٧٥).

٢.٢.١٠.٢. *Production of Hemolysin:* Hemolysis production was shown on Blood agar media. The results were obtained after incubation of the non-cultured plates for ٢٤ hours at ٣٧°C to exclude any contamination of blood, then the organism was inoculated at this blood agar plates and it was incubate again for ٢٤-٤٨ hours at ٣٧°C and detected if any hemolysis presence around the colonies (either α or ß hemolysis) (De Boy *et.al.*, ١٩٨٠).

٢.٢.١٠.٣. *Extracellular Protease production:* The nutrient broth was supplemented with ١٢٪ gelatin then it was poured into tubes which were sterilized them into autoclave and after cooling it to room temperature, the organisms were inoculated by stabbing technique and incubated for ٢٤-٤٨ hours at ٣٧°C and then it was placed in a refrigerator at ٤°C for ٣٠ min. Cultures that remained liquefied meant gelatinase was produced and demonstrated gelatin hydrolysis (Benson, ١٩٩٨).

٢.٢.١٠.٤. *Siderophores production:* M٩ media was prepared and then supplemented with ٢٪ agar. After sterilization in autoclave and cooling it at ٥٠°C, ٠.٢٥ gm/L glucose was added (sterilized by filtration) and ٢٠٠µM of ٢-٢-dipyridyl. Then the organisms were inoculated into this media and incubated it for ٢٤-٤٨ hours at ٣٧°C. The results were checked to see if there was any presence of growth of organism (Nassif *et.al.*, ١٩٨٩).

٢.٢.١٠.٥. *Colonization Factor Antigens*

A) *Detection of (CFA/I):* After culturing the organism on Tryptic Soy Agar; the agglutination of RBC with bacteria was occurred in presence of D-mannose as following:

- Bacterial solution was prepared separately for each isolate by adding a plenty of bacterial growth into ١ ml of normal saline in test tube.
- ٣٪ RBC solution was prepared from the human blood (group A) after it was centrifuged at least ٣ times with adding sterilized phosphate buffer saline to it. Then added to sediment of blood sterilized phosphate buffer saline to complete the preparation of the solution (vol/vol).
- On clean slide, their was mixing a one drop of bacterial suspension to a one drop of ٠.١ M D-mannose on one side and with a one drop of ٣٪ RBC suspension on another side.

The agglutination of RBC with bacteria was detected after ١-٢ min (Giron *et.al.*; ١٩٩٥).

B) ***Detection of (CFA/III):*** After culturing the organism on Tryptic Soy Agar, the agglutination of RBC with bacteria was occurred in presence of Tannic acid instead of D-mannose as following:

- Bacterial solution was prepared separately for each isolate as in above.
- ٣٪ RBC solution was prepared from the human blood (group A) after centrifuged it at least ٣ times with adding sterilized phosphate buffer saline to it. Then added to sediment of blood sterilized phosphate buffer saline to complete the preparation of the solution (vol/vol).
- ٠.١M of Tannic acid was prepared, then on clean slide, mixed a one drop of bacterial suspension was mixed with one drop of ٠.١M of Tannic acid on one side and to a one drop of ٣٪ RBC suspension on another side.

The agglutination of RBC with bacteria was detected after ١-٢ min (Symth, ١٩٨٢).

٣.١. Clinical Study

٣.١.١. Sex Related Disease

This study included (١٠٢) patients suffering from chronic pyelonephritis who were admitted to Hilla teaching hospital-Department of Urology. The incidence of this disease was found to be higher in females than in males as shown in table (٣.١) as ٦١.٨٪ are females and ٣٨.٢٪ are males with ratio of female**:** male is ١.٦ **:** ١.

Table (٣.١): Numbers and Percentage of Sex Distributed Disease.

Sex	Numbers	Percentage
Female	٦٣	٦١.٨%
Male	٣٩	٣٨.٢%
Total	١٠٢	١٠٠٪

The results were agreed with the results obtained by Sakran *et.al.* (٢٠٠٣) who showed that ٧٩٪ of patients with kidney infection were females. In addition, the prevalence of recurrent UTI was increased from twofold to sixfold in female than in male (Kosakai *et.al.*,١٩٩٠). However, Ghiro *et.al.* (٢٠٠٢) pointed that ٣٦٪ of children with pyelonephritis were males and the remaining were females. In general, the females are more susceptible to UTI than males because the urethra is shorter and nearer to anus more in females leading to be more prone to infected with enteric bacteria; in addition, the vaginal pathogens may invade the urinary tract causing UTI (Mims *et.al.*, ٢٠٠٤).

٣.١.٢. Age Related Disease

The age of the patient is an important factor in the study of the epidemiology of chronic pyelonephritis as shown in figure (٣.١). The more affected age group in female was between ٤٠-٦٠ years old (٣١.٥٪) while in male, the more affected age group was between ٥٠-٧٠ years old (٢٠.٥٪). In patients below ١٩ years, only ٥.٦% was affected and most of them are females (٣.٧٪). The age group between ٣٠-٤٠ years (young adults) was equally affected in both sexes (٦.٨٪). As regards the older age (more than ٧٠ years), the males were more affected than female (٤.٧٪ and ٣.٧٪ respectively).

These results are agreed with the results obtained by Bryan and Reynolds (١٩٨٤) who showed that in the patients with upper UTI, males were usually affected between ٦٠-٨٠ years and the females were usually between ٢٠-٦٠ years and that means the elderly age group was most common for males. In addition, Winberg *et.al.* (١٩٨٢) showed that ٥٪ of chronic pyelonephritis were children below ١٠ years with VUR and these results were in accordance with the results gained in this study but VUR might represent more than ٥٠٪ of causes of chronic pyelonephritis. On other hand, Tepmongkol *et.al.* (٢٠٠٢) obtained that ٥٩.٢٪ of children below ١٢ years with VUR have developed chronic pyelonephritis. Generally, the middle age group was the peak in both males and females that may be due to its predisposing factors which most of them occurred in adult age group except in VUR which occurred in young children.

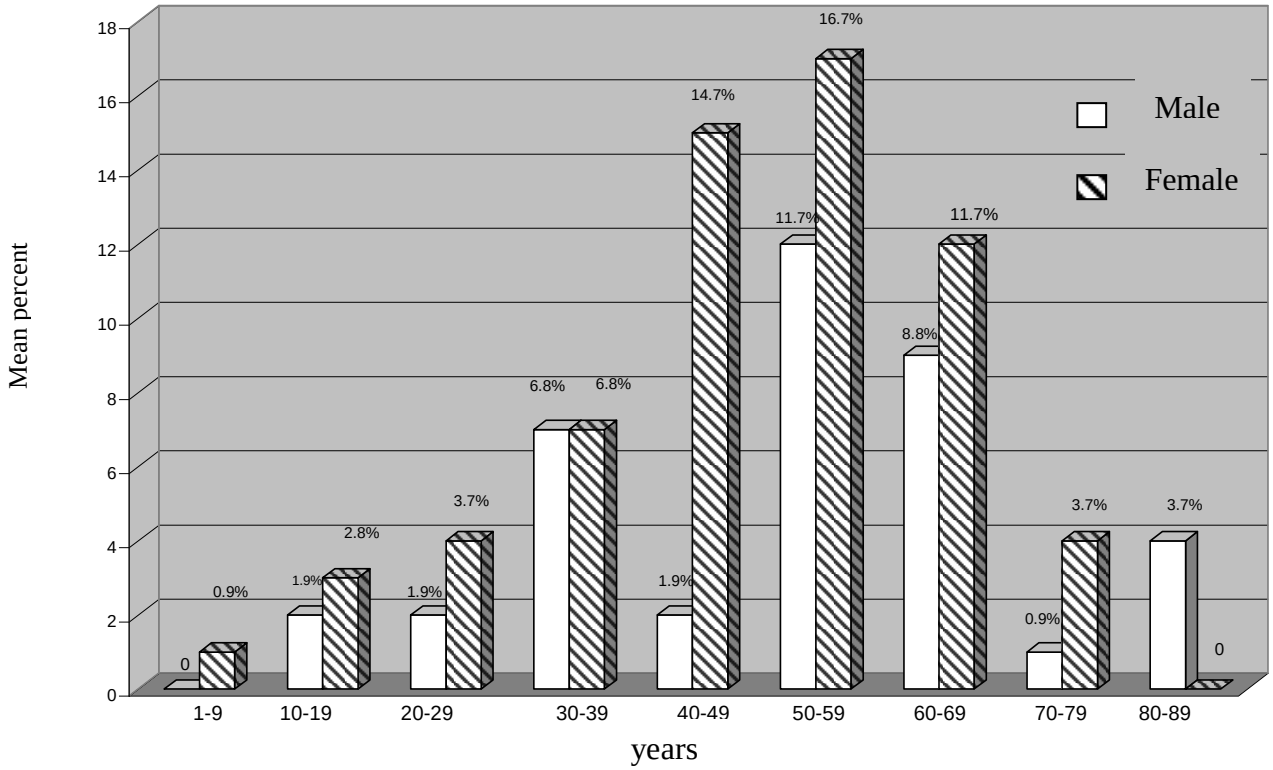

Figure (٣.١): A histogram demonstrate age related to sex of patients with chronic pyelonephritis**.**

٣.١.٣. Clinical Features Related to Disease

Regarding the clinical features as shown in table (٣.٢ a and b), most of the patients were presented with classical symptoms of chronic pyelonephritis including loin pain (٩٨.٢٪), low grade fever (٤٤.٨%) and urinary symptoms that including frequency (٨٣.٣٪), dysuria (٧٩.٤٪), nocturia (٧٥.٥٪), polyuria (٦٧.٦٪), nausea or vomiting (٣١.٤٪), loss of appetite (٢٧.٥٪) and loss of weight (١٧.٤٪). These differences in the presentation are attributed to many factors like age, sex, predisposing factors, regime of therapy and response to treatment. In regard to other results obtained by Huland and Busch (١٩٨٤) who showed that the loin pain was a common clinical features of pyelonephritis accompanied by

urinary symptoms. The variation in the presentation of urinary symptoms may be due to the severity of accompanying lower UTI.

Others were presented as a complicated cases (١٣.٧٪ with hypertension and ٩.٨٪ with chronic renal failure or ureamia) and these results were shortly extended with other results obtained by Gower (١٩٨٦) and Huland and Busch (١٩٨٢) respectively who showed that ٤٠٪ of women with chronic pyelonephritis had hypertension and ٢٠٪ of adult with chronic pyelonephritis ended with chronic renal failure. This differences in the comparison of presentation of complicated cases are attributed to improvement of investigating methods leading to early diagnosis and proper management of disease with reducing of complications. In general, the hypertension is a major complication of renal disease but rarely the hypertension cause renal disease that might only happened in malignant hypertension. The renal failure is commonly a late complication of renal disease and it is associated with bad prognosis (Walsh *et.al.*, ١٩٩٧).

On the other hand, only two cases presented asymptomatically (١.٨٪) and this agreed with results obtained by Gaymans *et.al.* (١٩٨٦) who found out that ٣٪ of females with upper UTI were asymptomatic in the first presentation. The asymptomatic cases may be seen in elderly people with long standing catheterization or due to the underlying disease like diabetic, VUR and renal stones leading to asymptomatic bacteriuria.

Table (٣.٢): Numbers and Percentages of presentation of patients with chronic pyelonephritis.

Presentation	Numbers	Percentages
Symptomatic	١٠٠	٩٨.٢ %
Asymptomatic	٢	١.٨ %
Total	١٠٢	١٠٠%

Table (٣.٣): Numbers and Percentages of clinical feature of ١٠٢ chronic pyelonephritic patients.

Clinical feature		Numbers	Percentages
Loin Pain		١٠٠	٩٨٪
Frequency		٨٥	٨٣.٣٪
Dysuria		٨١	٧٩.٤٪
Polyuria		٧٧	٧٥.٥٪
Nocturia		٦٩	٦٧.٦٪
Low grade fever		٤٥	٤٤.٨٪
Nausea or vomiting		٣٢	٣١.٤٪
Loss of appetite		٢٨	٢٧.٥٪
Loss of weight		١٨	١٧.٤٪
Symptoms of complications	Hypertension	١٤	١٣.٧٪
	Ureamia	١٠	٩.٨٪

٣.١.٤. Previous History of Other Diseases

The previous history of urinary tract infections in table (٣.٣) showed that ٨٦.٣٪ of patients had history of UTI but only ٦٢.٧٪ of them had history of UTI with stone, ٢٣.٥٪ of patients had history of surgery for removal of stone and these results were agreed with results obtained by Ng *et.al.* (٢٠٠٣) who showed that the majority of patients with chronic

pyelonephritis had history of UTI and ٧٧٪ of them had history of renal stone. ٤.٨% of patients had history of surgery for VUR repair. These results were in accordance with results obtained by Winberg *et.al.* (١٩٨٢) who showed that only ٥٪ of patients with chronic pyelonephritis were due to VUR.

Table (٣.٤): Numbers and Percentages of Previous history related to ١٠٢ chronic pyelonephritic patients.

Previous History		Numbers	Percentage
UTI	With stone	٦٤	٦٢.٧٪
	Without stone	٢٤	٢٣.٥%
Surgery to remove stone		٢٤	٢٣.٥٪
Surgery of (VUR)		٥	٤.٩٪

٣.١.٥. Ultrasound Results

The findings of Ultrasound for patients with chronic pyelonephritis was a small size kidney, thin cortical thickness with irregular outline. It is either unilaterally or bilaterally affected as shown in table (٣.٤) that revealed ٦٥.٧٪ of patients were one side affected (unilateral) and ٣٤.٣٪ were both kidneys affected (bilateral).

These results were correlated with the results obtained by Gower (١٩٨٦) who showed that ٧٧% of women with chronic pyelonephritis were unilateral affected and ٢٣% were bilaterally affected that means they commonly presented with one side affected and that returned to the underlying causes like renal stones in one side or unilateral VUR. The bilateral cases are occurred either due to neglected unilateral cases or rarely they were bilateral from beginning (bilateral renal stones or

bilateral VUR). In addition, the unilateral cases had a normal life span with less complications but the bilateral cases commonly ended with impaired renal function and renal failure with bad prognosis (Feldberg, ١٩٨٢).

Table (٣.٥): Numbers and Percentages of Sides affected associated disease.

Sides affected	Number	Percentage
Unilateral	٦٧	٦٥.٧٪
bilateral	٣٥	٣٤.٣٪
Total	١٠٢	١٠٠٪

٣.١.٦. Results of Abnormal Parameters of General Urine Examination (GUE)

Results of abnormalities of parameters in General Urine Examination (GUE) as shown in table (٣.٥).The examination was done to each patient included pH of urine that was ٧٠.٨٪ of patients had normal pH (acidic) and the remainder (٢٩.٢٪) were alkaline. The result of alkaline pH may reflect the type of pathogens which appeared in the study like *P.mirabilis, Corynebacterium* and other urease-producing pathogens (Woolhandler *et.al.*, ١٩٨٩).

The pyuria (pus cells more than ٥/HPF) which was presented in ٩٤.١% of patients means that majority of patients have pyuria and this pyuria was usually associated infection or inflammation of urinary tract (Hamburger *et.al.*, ١٩٧٨). RBC was presented in ٦٩.٦% of patients that the presence of RBC concluded the presence of stone or may associated with severe infection of urinary tract (Nemoy and Stamey, ١٩٨١).

The albumin in urine was presented in ٣٧.٢٪ of patients and sometimes it was accompanied with sever infection or renal impairment but the presence of casts in the urine was usually associated with impaired renal function (Wagner *et.al.*, ١٩٨٦) that the casts were seen in ١٩.٥% of patients with albuminuria. These results were agreed with other results obtained by Dayan and Smith (١٩٨٦) and Nuutiuen *et.al.* (١٩٩٩) who showed that the majority of pyelonephritic patients complicated with albuminuria and half of them ended with renal failure and because of the casts accompany with renal dysfunction that means the half of albuminuria positive patients had casts in their urine. Furthermore, WBC casts were ٦٠% and this agreed with Massey (٢٠٠٤) who found that most of patients with chronic pyelonephritis had WBC casts in their urinalysis. Granular casts were ٣٠% while hyaline casts were ١٠%.

In regard to the crystals which were found in ٨٤.٣٪ of patients. The urate crystals were found in ٤٥.٣٪, the phosphate crystals were presented in ٤١.٨٪ and oxalate were found in ١٢.٨٪. The crystals are commonly associated with severe infection or presence of stones like the phosphate crystals that accompanied with struvite stones and urease-producing bacteria (Ryan and Murray, ١٩٩٤).

Table (٣.٦): Numbers and Percentages of abnormal parameter of GUE results to ١٠٢ chronic pyelonephritic patients**.**

Items of GUE		Number		Percentage	
Pus cell		٩٦		٩٤.١٪	
RBC		٧١		٦٩.٦٪	
Albumin		٣٨		٣٧.٢٪	
Alkaline pH		٣٠		٢٩.٦٪	
Cast	**WBC cast**	١٢	٢٠	٦٠٪	١٩.٥٪
	Granular	٦		٣٠٪	
	Hyaline	٢		١٠٪	
Crystal	**Urate**	٣٩	٨٦	٤٥.٣٪	٨٤.٣٪
	phosphate	٣٦		٤١.٨٪	
	oxalate	١١		١٢.٨٪	

٣.٢. Isolation of Bacteria Associated with Disease

The results of urine culture in table (٣.٦) showed that ٧٩.٥% of patients had positive culture and ٢٠.٥٪ of them had negative culture. These results was agreed with other result obtained by Leblebicioglu and Esen (٢٠٠٣) who showed that ٧٨.٤٪ of patients with hospital-acquired UTI had positive culture and those with negative culture may be associated with *Mycoplasma* or *Chlamydial* infections.

Table (٣.٧): Number and Percentages of urine culture results**.**

Culture	Number	Percentage
Culture positive	٨١	٧٩.٤٪
Culture negative	٢١	٢٠.٦٪
Total	١٠٢	١٠٠٪

٣.٢.١. Types of Bacterial Isolates

Table (٣.٧) showed that ٢٩.٦٪ of isolates revealed *E.coli* which is the most common bacteria in our study, while coagulase-negative *staphylococci* represented ٢٨.٤% of isolates, ٢٥.٩٪ of them were *Staphylococcus epidermidis* and ٢.٥٪ were *Staphylococcus saprophyticus*. *Klebsiella pneumoniae* represented ١٢.٣٪ of isolates. Both, *Corynebacterium spp.* and *Proteus mirabilis* were represented ٧.٤٪ of isolates. In addition, *Pseudomonas aeruginosa*, *Enterobacter spp.* and *Acinetobacter spp*. were represented ٣.٧٪ of isolates, *Enterococcus spp*. were ٢.٥٪, and lastly, one isolate of *Staphlococcus aureus* obtained (١.٣٪).

These results can be compared with other results obtained by Gordon and Jones (٢٠٠٣) to patients with hospital-acquired UTI, who showed that *E.coli* was ٤٧%, *K.pneumoniae* ١١%, *Proteus mirabilis* ٥٪, *P.aeruginosa* ٨٪, *Enterobacter spp.* ٤٪, *Enterococcus spp*. ١٢٪ and coagulase-negative *Staphylococci* ١٣%. In addition, Guirguitzova *et.al.* (٢٠٠٢) showed that ٢٣٪ of complicated UTI was due to coagulase-negative *Staphylococcus spp.*, ٧٥% of them were *S.epidermidis* and the remainder were other types of coagulase-negative *Staphylococcus spp.* and Sakran *et.al.* (٢٠٠٣) showed that Enterococcus represented ٣٪ from recurrent UTI. As for *Acinetobacter* and *Corynebacterium,* Joshi *et.al.* (٢٠٠٣) showed that *Acinetobacter spp.* represented ٢٢% from hospital-acquired UTI and Nebreda-Mayoral *et.al.* (١٩٩٤) obtained that *C.urealyticum* represented ٠.٣٪ of patient with recurrent UIT.

Table (٣.٨): Numbers and Percentages of Bacterial isolates in urine cultures.

Type of Bacteria		Number	Percentage
Gram Negative	***E.coli***	٢٤	٢٣.٥٪
	K.pneumoniae	١٠	٩.٩٪
	P.mirabilis	٦	٥.٩٪
	P.aeruginosa	٣	٢.٩٪
	Enterobacter spp.	٣	٢.٩٪
	Acinetobacter spp.	٣	٢.٩٪
Gram Positive	***S.epidermidis***	٢١	٢٠.٨٪
	Corynebacterium spp.	٦	٥.٩٪
	S.saprophyticus	٢	١.٩٪
	Enterobacter spp.	٢	١.٩٪
	S.aureus	١	٠.٩٪
No Growth		٢١	٢٠.٦٪
Total		١٠٢	١٠٠٪

٣.٣. Identification of Bacteria

٣.٣.١ *Enterobacterieceae, P.aeruginosa and Acinetobacter*

The isolation of these bacteria was depended on the difference in specific biochemical tests like catalase, oxidase, lactose fermented, indol, MR, VP, urease, citrate, motility, growth on TSI agar and production of H٢S gas (Macfaddin, ٢٠٠٠).

E.coli produced a lactose fermented colonies, it was metalic sheen on EMB agar. Its biochemical tests showed that catalase positive, oxidase negative, MR positive, VP negative, indol positive, on KIA agar :H٢S negative, motility positive, urease was negative in ٧٥٪ of isolates and citrate was negative in ٩١٪ of isolates and this agreed with results obtained by Collins and Falkow (١٩٩٠) that showed *E.coli* isolated from

patients with complicated UTI had urease producing gene (Benson, ١٩٩٨).

K.pneumoniae produced a mucoid lactose fermented colonies, it was centrally dark on EMB agar. Its biochemical tests showed that catalase positive, oxidase negative, MR negative, VP negative, indol negative, on KIA agar :H_2S negative, motility negative, urease positive and citrate positive for all (Mims *et.al.*, ٢٠٠٤).

P.mirabilis produced a non-lactose fermented colonies with swarming motility and urea smell on nutrient agar, it was pale on EMB agar. Its biochemical tests showed that catalase positive, oxidase negative, MR negative, VP negative, indol negative, on KIA agar :H_2S positive, motility positive, urease positive and citrate positive for all (Macfaddin, ٢٠٠٠).

Enterobacter spp. produced a mucoid weak lactose fermented colonies, it was centrally dark on EMB agar. Its biochemical tests showed that catalase positive, oxidase negative, MR negative, VP positive, indol negative, on KIA agar :H_2S negative, motility positive, urease negative in one out of three (٦٦.٦٪) and citrate positive for all (Baron *et.al.*, ١٩٩٦).

Pseudomonas aeruginosa produced a non-lactose fermented colonies with bluish green color on nutrient agar, it was pale on EMB agar. Its biochemical tests showed that catalase positive, oxidase positive, MR negative, VP negative, indol negative, on KIA agar :H_2S negative, motility positive, urease positive and citrate positive for all (Benson, ١٩٩٨).

Acinetobacter produced a non-lactose fermented colonies, it was pale on EMB agar. Its biochemical tests showed that catalase positive, oxidase negative, MR positive, VP negative, indol negative, on KIA agar :H_2S negative, motility negative, urease negative in one out of three (٣٣.٣٪) and citrate negative in all of them (Baron *et.al.*, ١٩٩٦).

Table (٣.٩): The diagnostic and biochemical tests of *Enterobacterieceae, P.aeruginosa and Acinetobacter*.

Test	***E.coli***	***K.pneumoniae***	***P.mirabilis***	***Enterobacter***	***P.aeruginosa***	***Acinetobacter***
EMB	Metallic	Centrally dark	pale	Centrally dark	pale	pale
Lactose ferm.	+	+	–	+	–	–
Catalase	+	+	+	+	+	+
Oxidase	–	–	–	–	+	–
Urease	– *	+	+	–***	+	–****
Citrate	– **	+	+	+	+	+
MR	+	–	+	–	–	+
VP	–	+	–	+	–	–
Indol	+	–	–	–	–	–
H_2S	–	–	+	–	–	–
motility	+	–	+	+	+	–

* Negative in ٧٥٪ of bacteria.
** Negative in ٩١٪ of bacteria.
***Negative in ٦٦.٦ % of bacteria.
****Negative in ٣٣.٣٪ of bacteria.

٣.٣.٢. *Staphylococcus Species*

They were gram positive cocci arranged in clusters. The main three species of *Staphylococcus* can be differentiated by the shape and color of their colonies on blood agar, coagulase test and fermentation of mannitol on mannitol salt agar (Mims *et.al.*, ٢٠٠٤).

Table(٣.١٠) The diagnostic and biochemical tests of *Staphylococcus species.*

Test	***S.aureus***	***S.epidermidis***	***S.saprophyticus***
Catalase	+	+	+
Oxidase	–	–	–
Urease	–	+*	+
Coagulase	+	–	–
Mannitol ferment	+	–	–
Resist to Novobiocin	†	–	+
motility	–	–	–

* Positive in (٥٢.٤٪) of isolates.

† Test used to distinguish between *S.epidermidis* and *S.saprophyticus*.

S.aureus produced a large hemolytic golden yellow colonies in appearance. Its biochemical tests were catalase positive, oxidase negative, urease negative, coagulase positive, mannitol fermentation positive and motility negative (Benson, ١٩٩٨).

S.epidermidis produced a small non-hemolytic white colonies in appearance. Its biochemical tests were catalase positive, oxidase negative, urease positive in ٥٢.٤٪ of isolates, coagulase negative, mannitol fermentation negative, sensitive to novobiocin and motility negative (Macfaddin, ٢٠٠٠).

S.saprophyticus produced a small hemolytic white color colonies in appearance. Its biochemical tests were catalase positive, oxidase negative, urease positive, coagulase negative, mannitol fermentation negative, resisted to novobiocin and motility negative (Mims *et.al.*, ٢٠٠٤).

٣.٣.٣. *Corynebacterium and Enterococcus Species*

Corynebacterium were gram positive rods. They produced a small non-hemolytic white colonies on blood agar. On Albert stain, the metachromatic granules were distinguishable. The best growth was on Tween ٨٠ media and their biochemical tests were catalase positive, oxidase positive, esculin negative, urease positive and motility negative (Mims *et.al.*, ٢٠٠٤).

Enterococcus produced gram positive cocci colonies arranged as small chains, grew on blood and MacConcky agars as faint colonies. The biochemical tests of them were catalase test negative, oxidase test negative, esculin test positive, urease test negative and motility negative (Baron *et.al.*, ١٩٩٦).

Table(٣.١١) The diagnostic and biochemical tests of *Corynebacterium* and *Enterococcus species.*

No.	**Test**	***Corynebacterium***	***Enterococcus***
١.	Catalase	+	–
٢.	Oxidase	+	–
٣.	Esculin	–	+
٤.	Urease	+	–
٥.	motility	–	–

٣.٤. Study Group (I): Comparative study between bacteria isolated from blabber samples and those from kidney samples in same patients:

In our study, two urine samples obtained from five patients, one was a bladder sample and the other was a kidney sample (either from nephrostomy or by ureteric catheter or direct from renal pelvis). All samples were identical in results of urine culture except one which had additional pathogen in the bladder sample than in kidney sample. These results were agreed with the results obtained by Watson *et.al.* (١٩٩٩) showed that among pyelonephritic patients, ٣٦.٨٪ had additional pathogens in their bladder sample than in nephrostomy sample. This additional pathogen might have resulted from lower UTI or due to accidental contamination of bladder sample.

Table (٣.١٢) Types of organisms in both bladder and kidney urine samples in ٥ chronic pyelonephritic patients

No. of bacterial isolate	Organism of bladder sample	Organism of kidney sample
١	***Enterobacter spp.***	***Enterobacter spp.***
٢	***K.pneumoniae***	***K.pneumoniae***
٣	***S.epidermidis***	***S.epidermidis***
٤	***S.epidermidis +P.mirabilis***	***P.mirabilis***
٥	***K.pneumoniae***	***K.pneumoniae***

٣.٥. Study Group (II): Pyuria with no bacterial growth in chronic pyelonephritic patients:

Sterile pyuria means the presence of significant number of pus cells but the routine urine culture is negative (Tanagho and McAninch, ٢٠٠٠).

There were ٢١ cases with negative culture, ١٥ of them were (٦٦.٦%) with pyuria and no bacterial growth in their urine. Eleven from those with sterile pyuria had renal stone and its one of causes of pyuria due to causing of inflammation in urinary tract (Kreder and Williams, ٢٠٠٠), in addition Al-Eisa *et.al.* (٢٠٠٢) showed that ٢٢٪ of Kuwaiti patients with renal stones presented with sterile pyuria.. The other ٢ had chronic renal failure while another one had diabetes. Subat-Dezulovic *et.al.* (٢٠٠٢) showed that some of patients with renal failure presented with sterile pyuria. The remaining ٢ cases might infected with other species that were not detected with ordinary methods of urine culture like *Mycoplasma*, *Chlamydia* and *Mycobacterium* (Klouman *et.al.*, ٢٠٠٢; Wong and Yuen, ١٩٩٥ and Reis *et.al.*, ١٩٩٥).

Table (٣.١٣) Numbers and Percentages of patients with sterile pyuria with their causes.

Cause of sterile pyuria	Number	Percentage
Renal stone	١١	٧٣.٤%
Renal failure	٢	١٣.٣٪
Unknown	٢	١٣.٣٪
Total	١٥	١٠٠٪

٣.٦. Study Group (III): Long standing catheterization associated bacteriuria:

There were six chronic pyelonephritic patients with long standing catheterization. The cause of catheterization was either due to BPH, bladder injury or urethral injury. Two of them were infected with

K.pneumoniae (٣٣.٣٪), one was with encapsulated *E.coli* (١٦.٦٪), one with encapsulated *Corynebacterium spp.* (١٦.٦٪), one with encapsulated *Acinetobacter spp.* (١٦.٦٪) and the last with *Enterobacter spp.* (١٦.٦٪). All of these strains had high resistance to the classical antibiotics used for treatment of UTI with high virulence properties. Carratala-Castellsague *et.al.* (١٩٩٩) showed that ١٠٪ of catheterized patients had *Corynebacterium* in their urine culture whereas, Ayan *et.al.* (٢٠٠٣) showed that the catheterization was a common associated factor for *Acinetobacter* infections. Tambyah *et.al.* (٢٠٠٢) showed that ١٣٪ of catheter associated UTI were caused by *E.coli* and ٢٥٪ of them were caused by *K.pneumoniae* and *Enterobacter*.

Table (٣.١٣): Numbers of bacterial isolates associated to ٦ chronic pyelonephritic patients with long stand catheterization.

Types of bacteria	No. of isolates
K.pneumonia	٢
E.coli	١
Corynebacterium	١
Acinetobacter	١
Enterobacter	١

٣.٧. Effect of Antibiotics on Bacterial Isolates

The results of antibiotic sensitivity test that was done to the bacteria isolated from patients with chronic pyelonephritis had shown that these bacteria had high resistance to most common antibiotics used in treatment of pyelonephritis as shown in table (٣.١٣) and figure (٣.٢).

Regarding to amoxicillin, ١٠٠٪ of *Corynebacterium*, *P.mirabilis*, *Acinetobacter*, *P.aeruginosa* and *S.aureus* were resistant. These results

were correlated with results obtained by Suarez *et.al.* (٢٠٠٢), Orrett (١٩٩٩), Savov *et.al.* (٢٠٠٣) and Yamaguchi *et.al.* (١٩٩٩) who observed that these bacteria had high resistance to amoxicillin. In addition, ٧٩.١٪ of *E.coli*, ٩٠٪ of *K.pneumoniae* and two out of three of *Enterobacter* were resistant to amoxicillin and these were agreed with results obtained by Leblebicioglu and Esen (٢٠٠٣), Aggarwal *et.al.* (٢٠٠٣) and Zhou *et.al.* (٢٠٠٢) who found that ٧٣٪ of *E.coli*, ٨٧.٥٪ of *K.pneumoniae* and more than ٩٠٪ *Enterobacter aerogenes* strains isolated from recurrent UTI and pyelonephritis were resistant to amoxicillin respectively. In coagulase-negative *Staphylococci*, ٧٦.٢٪ of *S.epidermidis* and one out of two of *S.saprophyticus* were resistant to amoxicillin and this was in accordance with results obtained by Jureen *et.al.* (٢٠٠٣) who showed that the coagulase-negative *Staphylococcus* isolated from patients with upper UTI had high resistance to amoxicillin. Furthermore, one out of two of *Enterococci* was resistant to amoxicillin and this was in accordance with Sedlock *et.al.* (١٩٩٠) who found that *Enterococcus* had high resistance to β–lactam antibiotics.

Generally, ٨٢.٧٪ of bacteria isolated from patients in this study were resistant to amoxicillin and these results moderately extended with results obtained by Sakran *et.al.* (٢٠٠٣) who showed that ٥٢٪ of bacteria in upper UTI resisted to amoxicillin. The resistance of these bacteria is mostly due to either production of β-lactamase enzyme or lack of penicillin receptors on cell wall or even alteration in their permeability to β-lactam antibiotics (Yu *et.al.*, ١٩٩٩).

Regarding to nitrofurantoin, ١٠٠٪ of *Corynebacterium*, *P.mirabilis*, *P.aeruginosa* and *S.aureus* were resistant to it. These results were agreed with results obtained by Chiner *et.al.* (١٩٩٩), Echols *et.al.* (١٩٩٩) and Barrett *et.al.* (١٩٩٩) who showed that these bacteria had high resistant to nitrofurantoin. In addition, ١٦.٦% of *E.coli* and ٨٠% of *K.pneumoniae* were resistant to nitrofurantoin and these were in accordance with results obtained by Vromen *et.al.* (١٩٩٩) and Gupta *et.al.* (١٩٩٩) who showed that ١٠% of *E.coli* and ٥٢% of *K.pneumoniae* were resistant to nitrofurantoin respectively. One out of three of both *Enterobacter* and *Acinetobacter* were resistant to nitrofurantoin and these results were in accordance with those obtained by Zhou *et.al.* (٢٠٠٢) and Zeana *et.al.* (٢٠٠٣) who showed that most of *Enterobacter aerogenes* and *Acinetobacter banmanni* were sensitive to nitrofurantoin. In coagulase-negative *Staphylococcus*, ١٩% of *S.epidermidis* were resistant to nitrofurantoin and this was in accordance with results obtained by Guirguitzova *et.al.* (٢٠٠٢) who showed that only ١٠٪ of the coagulase-negative *Staphylococci* isolated from patients with upper UTI were resistant to nitrofurantoin. Furthermore, All isolates of *Enterococcus* and *S.saprophyticus* were sensitive to nitrofurantoin and these results agreed with those obtained by Sedlock *et.al.* (١٩٩٠) and Guirguitzova *et.al.* (٢٠٠٢).

In general, ٤١.٩% of bacteria isolated from patients in this study were resistant to nitrofurantoin while in Sakran *et.al.* (٢٠٠٣) showed that only ٤٪ of bacteria isolated from patients with recurrent UTI were resistant to nitrofurantoin.

Regarding to gentamicin, ١٠٠٪ of *Corynebacterium*, *Acinetobacter*, *S.aureus* and two out of three of *P.aeruginosa* had been resistant to it. These results were agreed with results obtained by De Briel *et.al.* (١٩٩١), Karlowsky *et.al.* (٢٠٠٣) and Deguchi *et.al.* (١٩٩٠) who showed that these bacteria had high resistance to gentamicin. In addition, ٣٧.٥% of *E.coli*, ٤٠% of *K.pneumoniae*, ٢٠٪ of *P.mirabilis* and one out of three of *Enterobacter* were resistant to gentamicin but Jones *et.al.* (٢٠٠٢) and Roosendaal *et.al.* (١٩٩١) showed that half of these bacteria susceptible to gentamicin. Blandino *et.al.* (١٩٩٠) showed that most of *Enterobacter aerogenes* and *P.mirabilis* were sensitive to gentamicin. In coagulase-negative *Staphylococci*, ٤٧.٦% of *S.epidermidis* and one out of two of *S.saprophyticus* were resistant to gentamicin and this was moderately extended with results obtained by Inamori *et.al.* (١٩٩٩) who showed that some coagulase-negative *Staphylococcus* were sensitive to gentamicin. All isolates of *Enterococcus* was sensitive to gentamicin and this agreed with that obtained by El-Kholy (٢٠٠٣).

Generally, ٤٦.٩% of bacteria isolated from patients in this study were resistant to gentamicin but Sakran *et.al.* (٢٠٠٣) who showed only ١١% of the bacteria isolated from patients with recurrent UTI were resistant to gentamicin. The production of aminoglycoside-modifying enzymes is the most important mechanism of its resistance commonly due to plasmid transfer but the alteration in cell wall permeability is another cause of the resistance (Mims *et.al.*, ٢٠٠٤).

Regarding to ciprofloxacillin, ١٠٠٪ of *Corynebacterium*, *P.aeruginosa*, and *S.aureus* were resistant to it. Madhusudhan *et.al.* (٢٠٠٣)

pointed that *P.aeruginosa* had high resistance to ciprofloxacillin but Sedlock *et.al.* (١٩٩٠) who observed that ٥٠٪ from both *P.aeruginosa* and *S.aureus* were sensitive to ciprofloxacillin. Martinez- Martinez *et.al.* (١٩٩٩) showed that *C.urealyticum* were resistant to ciprofloxacillin but Kuriyama *et.al.* (٢٠٠٢) observed that *C.urealyticum* were sensitive to fluoroquinolones. George *et.al.* (١٩٩٠) found out that *S.aureus* had high resistance to ciprofloxacillin. In addition, ٤٥.٨% of *E.coli*, ٣٠% of *K.pneumoniae*, ٣٣.٣٪ of *P.mirabilis* and one out of three of *Enterobacter* were resistant to ciprofloxacillin and these were correlated with results obtained by Miglioli *et.al.* (١٩٩٩), Roosendaal *et.al.* (١٩٩١) and Madhusudhan *et.al.* (٢٠٠٣) who found that these bacteria had good response to ciprofloxacillin but Jones *et.al.* (٢٠٠٢) showed *E.coli* and *K.pneumoniae* had high resistance to ciprofloxacillin. In coagulase-negative *Staphylococcus*, ٢٣.٨% of *S.epidermidis* were resistant to ciprofloxacillin but Sedlock *et.al.* (١٩٩٠) showed that ٤٥٪ of coagulase-negative *Staphylococcus* isolated from patients with upper UTI had resistance to ciprofloxacillin. All isolates of *Acinetobacter*, *Enterococcus* and *S.saprophyticus* were sensitive to ciprofloxacillin and these results correlated with those obtained by Seifert *et.al.* (١٩٩٣) and Guirguitzova *et.al.* (٢٠٠٢).

Generally, ٣٩.٥% of bacteria isolated from patients in this study were resistant/ to ciprofloxacillin but in Leblebicioglu and Esen (٢٠٠٣) observed that only ١٦% of bacteria isolated from patients with recurrent UTI were resistant to ciprofloxacillin and this increase of resistance may be due to abuse of antibiotics in our patients leading to transferring the

resistant through genetic factors such as plasmids and transposons or due to changing in cell wall permeability (Mims *et.al.*, ٢٠٠٤).

Regarding to cefotaxime, ٦٦.٦٪ of *Corynebacterium* were resistant and these results correlated with those obtained by Aspiroz-Sancho *et.al.* (٢٠٠٢) who found out that most of *Corynebacterium spp.* responded to cefotaxime. Furthermore, ١٠٠٪ of *P.aeruginosa* were resistant to it and these agreed with those obtained by Szabo *et.al.* (١٩٩٠) who showed that *P.aeruginosa* had high resistance to cefotaxime and cefixime whereas Gordon and Jones (٢٠٠٣) showed that only ٢٥٪ of *Pseudomonas* isolated from complicated UTI were sensitive to cefotaxime. In addition, ٤٥.٨% of *E.coli*, ٣٠% of *K.pneumoniae*, ٥٠٪ of *P.mirabilis* and two out of three of *Enterobacter* were resistant to cefotaxime and these were agreed with results obtained by Leblebicioglu and Esen (٢٠٠٣) and Thomson *et.al.* (١٩٩١) who stated that these bacteria were susceptible to cefotaxime. Chassagne *et.al.* (١٩٩٠) showed that most of *Enterobacter aerogenes* were resistant to cefotaxime but Blandino *et.al.* (١٩٩٠) showed that *P.mirabilis* were sensitive to cefotaxime. In coagulase-negative *Staphylococcus*, ٢٨.٥% of *S.epidermidis* were resistant to cefotaxime and this was in accordance with results obtained by Deguchi *et.al.* (١٩٩٠) who found that only ٢٥% of coagulase-negative *Staphylococci* isolated from patients with upper UTI were sensitive to cefotaxime. All isolates of *Acinetobacter*, *Enterococcus, S.saprophyticus* and *S.aureus* were sensitive to cefotaxime and these results agreed with those obtained by Irgbu *et.al.* (٢٠٠٣), Deguchi *et.al.* (١٩٩٠) and Sedlock *et.al.* (١٩٩٠).

In general, ٣٩.٥% of bacteria isolated from patients in this study were resistant to cefotaxime and this agreed with Gordon and Jones (٢٠٠٣) showed only ٢٠% of bacteria isolated from patients with recurrent UTI were resistant to cefotaxime. Some methicillin-resistant *Staphylococcus* and other strains of bacteria are resistant to third-generation cephalosporins due to production of extracellular materials with low affinity to β -lactam antibiotics (Katzung, ٢٠٠٢).

Regarding to cefixime, ٨٣.٣٪ of *Corynebacterium* were resistant and these correlated with those obtained by Aspiroz-Sancho *et.al.* (٢٠٠٢) who found that most of *Corynebacterium spp.* were less susceptible to cefixime. ١٠٠٪ of *P.aeruginosa*, and *S.aureus* were resistant to it. These results were agreed with results obtained by Szabo *et.al.* (١٩٩٠) and Gordon and Jones (٢٠٠٣) who pointed that these bacteria had high resistance to cefixime. In addition, ٤١.٦% of *E.coli*, ٣٠% of *K.pneumoni-ae* and two out of three of *Enterobacter* and *P.mirabilis* were resistant to cefixime and these were moderately extended with results obtained by Alonso-Sanz and Abad-Becquer (٢٠٠٣), Hoberman *et.al.* (١٩٩٩) and Zhou *et.al.* (٢٠٠٢) showed that ١٠٪ of *E.coli* and most of *K.pneumonia*, *Enterobacter aerogenes* and *P.mirabilis* isolated from recurrent UTI and pyelonephritis were resistant to cefixime. In coagulase-negative *Staphyl-ococci*, ٣٣.٣% of *S.epidermidis* were resistant to cefixime and this was in accordance with results obtained by Guirguitzova *et.al.* (٢٠٠٢) who showed that only ٢٥% of the coagulase-negative *Staphylococcus* isolated from patients with upper UTI had resistant to cefixime. All isolates of *Enterococcus* and *S.saprophyticus*

were sensitive to cefixime and these results agreed with those obtained by Guirguitzova *et.al.* (٢٠٠٢) and El-Kholy (٢٠٠٣).

Generally, ٤٣.٢% of bacteria isolated from patients in this study were resistant to cefixime but in Leblebicioglu and Esen (٢٠٠٣) showed that only ٤٪ of bacteria isolated from patients with recurrent UTI were resistant to cefixime. The resistance to third-generation cephalosporins was due to production of extracellular materials with low affinity to β - lactam antibiotics (Katzung, ٢٠٠٢).

Regarding to tetracycline, ١٠٠٪ of *Corynebacterium*, *P.mirabilis*, *P.aeruginosa*, *Enterobacter*, *Acinetobacter*, *S.saprophyticus* and *S.aureus* were resistant to it. These results were agreed with results obtained by Tauch *et.al.* (١٩٩٩), Orrett *et.al.* (١٩٩٩), Fernandez and Pizarro (١٩٩٩), Zhou *et.al.* (٢٠٠٢), Marques *et.al.* (١٩٩٧), Burriel (١٩٩٧) and Mlynarczyk *et.al.* (١٩٩٧) who showed that these bacteria had high resistance to tetracycline. In addition, ٨٧.٥% of *E.coli* and ٦٠% of *K.pneumoniae* were resistant to tetracycline and these were agreed with results obtained by Alonso-Sanz and Abad-Becquer (٢٠٠٣) and Aggarwal *et.al.* (٢٠٠٣) who showed that most of isolates of *E.coli* and *K.pneumoniae* were resistant to tetracycline. In coagulase-negative *Staphylococci*, ٨٥.٧% of *S.epidermidis* were resistant to tetracycline and this was in accordance with results obtained by Guirguitzova *et.al.* (٢٠٠٢) who showed that ٩٠٪ of coagulase-negative *Staphylococcus* isolated from patients with upper UTI had resistance to tetracycline. Furthermore, one out of two of *Enterococcus* were resistant to tetracycline and these results agreed with those obtained by Wu *et.al.*

(١٩٩٩) who found out that *Enterococcus* were susceptible to tetracycline.

In general, ٨٦.٤% of bacteria isolated from patients in this study were resistant to tetracycline. This resistance was partly due to widespread use of tetracycline in humans or their use as growth promoters in animal feed leading to synthesized a cytoplasmic protein to pump tetracycline out of resistant cell (Murray *et.al.*, ١٩٩٩)

Regarding to doxycycline which is one of tetracycline derivatives, ١٠٠٪ of *Corynebacterium*, *P.aeruginosa*, *Enterobacter*, *S.saprophyticus* and *S.aureus* isolates were resistant to it. These results were agreed with results obtained by Tauch *et.al.* (١٩٩٩), Fernandez and Pizarro (١٩٩٩), Zhou *et.al.* (٢٠٠٢) and El-Kholy (٢٠٠٣) who observed that these bacteria had high resistance to doxycycline. In addition, ٥٠% of *E.coli*, ٦٦.٦٪ of *P.mirabilis* and ٤٠٪ of *K.pneumoniae* were resistant to doxycycline and these were correlated with results obtained by Alonso-Sanz and Abad-Becquer (٢٠٠٣), Orrett *et.al.* (١٩٩٩) and Aggarwal *et.al.* (٢٠٠٣) who showed that half of isolates of *E.coli*, *P.mirabilis* and *K.pneumonia* were resistant to doxycycline. In coagulase-negative *Staphylococci*, ٤٢.٩% of *S.epidermidis* were resistant to doxycycline and these were moderately extended with results obtained by El-Kholy (٢٠٠٣) observed that most of coagulase-negative *Staphylococcus* isolated from patients with upper UTI were resistant to it. Two out of three of *Acinetobacter* were resistant to doxycycline and this accompany with Levin's results (٢٠٠٣) who said that *Acinetobacter* resisted to doxycycline. All isolates of *Enterococcus* were sensitive to doxycycline

and these results agreed with those obtained by Wu *et.al.* (١٩٩٩) who found that *Enterococcus* were susceptible to tetracycline and its derivatives.

In general, ٤١.٩٪ of bacteria isolated from patients in this study were resistant to doxycycline and this resistant is much less than in tetracycline in spite of their resistant was transported by a plasmid because it is a new drug with complete absorption and not affected by gut flora to increasing its resistance (Murray *et.al.*, ١٩٩٩).

Regarding to trimethoprim-sulfamethoxazole , ١٠٠٪ of *Corynebacterium*, *P.aeruginosa*, *Enterobacter*, *Acinetobacter*, *S.epidermidis*, *S.saprophyticus* and *S.aureus* were resistant to it. These results were agreed with those obtained by Gladin *et.al.* (١٩٩٩), Lindh *et.al.* (١٩٩٠), Barsic *et.al.* (١٩٩٧) and Guirguitzova *et.al.* (٢٠٠٢) who showed that these bacteria had high resistance to trimethoprim-sulfamethoxazole. In addition, ٦٢.٥% of *E.coli*, ٩٠٪ of *K.pneumoniae* and ٥٠٪ of *P.mirabilis* were resistant to trimethoprim-sulfamethoxazole and these were agreed with results obtained by Alonso-Sanz and Abad-Becquer (٢٠٠٣), Lin *et.al.* (٢٠٠٢) and Orrett *et.al.* (١٩٩٩) who showed that ٧٥% of *E.coli*, ٦٢٪ of *K.pneumoniae* and most of *P.mirabilis* isolated from upper UTI were less effective to trimethoprim-sulfamethoxazole. All isolates of *Enterococcus* was sensitive to trimethoprim-sulfamethox-zole and these results agreed with those obtained by El-Kholy (٢٠٠٣).

In general, ٨١.٥% of bacteria isolated from patients in this study were resistant to trimethoprim-sulfamethoxazole and this was in accordance

with results obtained by Ashkeuazi *et.al.* (١٩٩١) who showed that ٧٠% of uropathogens were resistant to trimethoprim-sulfamethoxazole. The increasing in resistant rate of trimethoprim-sulfamethoxazole was due to the long using of it leading to pump it out of resistant cell (Murray *et.al.*, ١٩٩٩).

Regarding to vancomycin, all gram negative bacteria were resistant to vancomycin. ٣٨% of *S.epidermidis* were resisted to vancomycin but *S.saprophyticus* were sensitive and in compared with results obtained by Garrett *et.al.* (١٩٩٩) showed that decreasing the susptability of coagulase-negative *Staphylococcus* to vancomycin. In addition, ٣٣.٣% of *Corynebacterium* were resistant to vancomycin but Suarez *et.al.* (٢٠٠٢) and Tauch *et.al.* (١٩٩٩) showed that most of *C.urealytium* isolated from complicated UTI sensitive to vancomycin. All isolates of *Enterococcus* were sensitive to vancomycin and this agreed with that obtained by El-Kholy (٢٠٠٣).

Generally, ٧٤.١% of bacteria isolated from patients in this study were resistant to vancomycin because all gram negative bacteria were resistant to vancomycin which was represented ٦٠.٥٪ from all bacteria that because it had too large molecules to move through the outer membrane of their cells (Greenwood, ٢٠٠٠). In spite of that the resistance to vancomycin was high, in addition, there was only ٤٥.٥٪ of gram positive bacterial isolates sensitive to vancomycin and the resistance were commonly due to transferring the resistant factors and rarely it chromosomally founded. The resistance in coagulase-negative

Staphyloc-occus might be due to thicking in the cell wall leading to impairment of penetration of vancomycin (Gilbert *et.al.*, ٢٠٠٢).

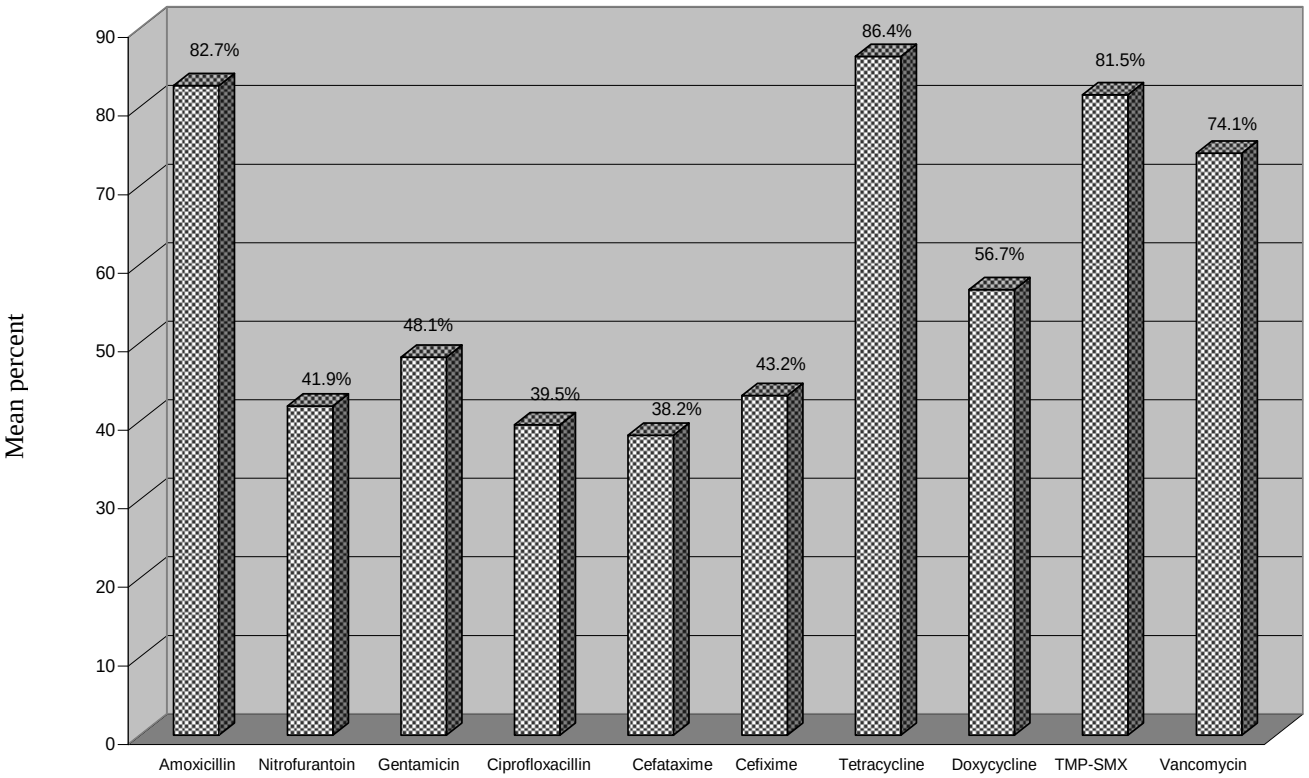

Figure (٣.٢): The percentages of resistance of bacterial isolates to antibiotics.

٣.٨. Detection of Virulence Factors

The virulence factors of bacteria are important to know the pathogenesis of the disease by these bacteria leading to infection as shown in table (٣.١٤).

In regard to the capsule that the capsular acid polysaccharide antigen was associated with ability to cause pyelonephritis which protect the bacteria from phagocytosis and aid it to adhere with host cells (Mims *et.al.*, ٢٠٠٤). The encapsulated isolates represented ٦٧.٩٪ including all isolates of *Corynebacterium*, *P.aeruginosa*, *K.pneumoniae*, *S.saprophyticus* and *S.aureus*. These results were in accordance with results obtained by Esteban *et.al.* (١٩٩٩), Bals *et.al.* (١٩٩٩), Meno and Amako

(١٩٩١) and Ammendolia *et.al.* (١٩٩٩) respectively who saw that these bacteria were encapsulated in their properties and some time they produced a slime layer. In addition, ٧٦.٢٪ of *S.epidermidis* and two out of three of *Acinetobacter* and *Enterobacter* were encapsulated. Mack *et.al.* (١٩٩٩) showed that *S.epidermidis* were encapsulated with a mucoid slime which appeared an important virulence factor of it. Furthermore, Garcia *et.al.* (٢٠٠٠) and Andersen *et.al.* (١٩٩٩) showed that *Acinetobacter* and *Enterobacter* had a polysaccharide capsule as one of its virulence factors.

In addition, ٤٥.٨% of *E.coli* were encapsulated and these agreed with Osterberg *et.al.* (١٩٩٠) who showed that in urinary tract infection, the non-fimbriated *E.coli* were more aggressive than P-fimbriated *E.coli* and they were usually encapsulated and associated with nosocomial UTI. Ebel and Trempy (١٩٩٩) observed that some isolates of *E.coli* were encapsulated.

Only one from six isolates of *P.mirabilis* were encapsulated and these agreed with those obtained by Rahman *et.al.* (١٩٩٩) who observed that some of *P.mirabilis* isolates which isolated from complicated UTI had capsular polysaccharide. *Enterococcus* isolates had no capsule and these results correlated with those seen by Obana and Nishino (١٩٩١) who pointed that *Enterococcus fecalis* were non-encapsulated.

Regarding to the hemolysis of blood, which the hemolysin affected on smooth muscle of blood vessels and heart with damaging of platelets that important in protection from phagocytosis, there was only ١٤.٨% from all isolates produced hemolysin (including α and β-hemolysis). β-

hemolysin was seen in all isolates of *P.mirabilis*, *S.saprophyticus* and *S.aureus* isolates. In addition, ١٢.٥% of *E.coli* produced α-hemolysin but Okeke *et.al.* (٢٠٠٢) showed that hemolysin produced by ١٠٠٪ of *E.coli* isolated from complicated UTI with capacity to cause kidney damage. Mims *et.al.* (٢٠٠٤) showed that most of *P.mirabilis*, *S.saprophyticus* and *S.aureus* produced β-hemolysin as one of their virulence factors. Other bacterial isolates in our study didn't produced hemolysin on blood agar and this associated with their properties (Mims *et.al.*, ٢٠٠٤)

In regard to extracellular protease production, which is an important to promote the bacterial attachment and inactivate the host defense mechanism, was seen in ١٠٠٪ of *P.aeruginosa* and *S.aureus*. Anderson *et.al.* (١٩٩٩) and Wu *et.al.* (١٩٩٩) showed that the *P.aeruginosa* and *S.aureus* produced elastase respectively. In addition, ٥٠٪ of *P.mirabilis* and ٦٦.٦٪ of *Corynebacterium* produced extracellular protease and that agreed with Walker *et.al.* (١٩٩٩) and Knipfer *et.al.* (١٩٩٩) who said that *Corynebacterium* and *P.mirabilis* had ability to produce extracellular protease (metalloproteases). Other bacterial isolates in our study didn't produced extracellular protease and this associated with their properties (Mims *et.al.*, ٢٠٠٤) but Agapova *et.al.* (١٩٩٩) and Mayer *et.al.* (١٩٩٩) observed that some strains of *E.coli* and *Klebsiella* produced gelatinase as part of their virulence properties but in our study, they did not produce this enzyme.

Concerning to siderophores which were high efficient low molecular weight iron chelating agents. They were important in the bacterial growth that found in all isolates of *Corynebacterium* and *P.aeruginosa*

and these were in accordance with that obtained by Pohl *et.al.* (١٩٩٩) and Kerr *et.al.* (١٩٩٩) respectively who found that these species of bacteria produced iron chelating agents (siderophore). In addition, ٨٧.٥٪ of *E.coli*, ٨٠٪ of *K.pneumonia* and two out of three of *P.mirabilis*, *Enterobacter* and *Acinetobacter* isolates produced siderophores and these results correlated with that results seen by Vartivarian and Cowart (١٩٩٩) and Walker *et.al.* (١٩٩٩) who observed that most of these bacteria produced siderophores as part of their virulence.

Furthermore, ٧١.٤٪ of *S.epidermidis* and one out of two of *S.saprophyticus* produced siderophores but *S.aureus* did not produce them. These results were agreed with results obtained by Inamori *et.al.* (١٩٩٩) who pointed out that some of coagulase-negative *Staphylococcus* produced siderophores. One isolate of *Enterococcus* produced siderophores and this agreed with Huebner *et.al.* (١٩٩٩) who found that some of *Enterococcus* had siderophores-producing gene .

Regarding the adhesion factors of bacteria related to the human being, that the bacterial pilli bind to carbohydrate polymer on renal cells and aiding in attachment of the bacteria with host cell that ٣٣.٣% of isolates had CFA/I and ٥٣.١% of them had CFA/III.

In addition, ٧٩.٢% of *E.coli* isolates had CFA/I and ٥٠% of them had CFA/III and this results were agreed with other results obtained by Matsumoto *et.al.* (١٩٩٠) who showed that P-fimbriated *E.coli* had high binding capacity to uroepithelial cells in patients with chronic pyelonephritis and Smyth (١٩٨٢) showed also that some of *E.coli*

isolates possessed mannose-resistant fimbriae as one of their virulence factors.

Furthermore, ٦٦.٦٪ of *S.epidermidis* had CFA/III and ١٩٪ of them had CFA/I that means the majority of *S.epidermidis* had adhesion factors, in addition, one out of two of *S.saprophyticus* had CFA/III . These results were agreed with other results obtained by both Fey *et.al.* (١٩٩٩), van-Leeuwen *et.al.* (١٩٩٩) and Mack *et.al.* (١٩٩٩) who showed that coagulase-negative *Staphylococcus* had mannose-resistant fimbriae with positive haemoagglutination test.

In regard to the *P.mirabilis*, ٣٣.٣% of them had CFA/I and ٦٦.٦% had CFA/III and this was agreed with Li *et.al.* (١٩٩٩) who found out that *P.mirabilis* had a mannose-resistant fimbriae aiding in their attachment.

Furthermore, ٦٦.٦٪ of *Corynebacterium* had CFA/I and ٣٣.٣٪ of them had CFA/III and these results were agreed with other results obtained by Luna *et.al.* (١٩٩٩) who showed that *Corynebacterium urealyticum* had adhesion factors as one of its virulence factors.

Regarding to *Enterobacter*, two out of three of them had both CFA/I and CFA/III and this agreed with Dekitsch *et.al.* (١٩٩٩) who saw that the *Enterobacter* had fimbriae for attachment to the epithelial cells.

In addition, only ٤٠٪ of *K.pneumoniae* had CFA/III and no one had CFA/I. This result was agreed with those obtained by Podschun and Sahly (١٩٩١) who showed that *K.pneumoniae* had type III mannose resistant fimbriae mostly with nephropathogenic one. Moreover, one isolates of *P.aeruginosa* and *Acinetobacter* and had CFA/III and these correlated with other results obtained by Pasloske *et.al.* (١٩٨٥) and Joshi

et.al. (٢٠٠٣) who stated that some of these bacteria had mannose-resistant fimbriae. *S.aureus* isolate had only CFA/III and this correlated with those obtained by Fey *et.al.* (١٩٩٩) who pointed out that *S.aureus* had mannose-resistant fimbriae with positive haemoagglutination test. *Enterococcus* isolates had no adhesion factors and these results correlated with those seen by Franz *et.al.* (١٩٩٩) who pointed out that *Enterococcus fecalis* had no adhesin in their properties.

The production of urease enzyme and the ability to be motile were represented an important virulence factors in chronic pyelonephritis (Vrane *et.al.*, ٢٠٠١) that ٥٨٪ of isolates were positive urease production and ٤٤.٤٪ were motile.

Table(٣.١٥): The numbers and percentages of the virulence factors of bacteria isolated from patients with chronic pyelonephritis.

Type of bacteria	Capsule	hemolysin	exprotease	siderophore	CFA/I	CFA/III
E.coli(٢٤)*	١١(٤٥.٨ %)	٣ (١٢.٥٪)	٠	٢١ (٨٧.٥٪)	١٩ (٧٩.٢%)	٧(٢٩.٢%)
S.epidermidis(٢١)*	١٦ (٧٦.٢٪)	٠	٠	١٥(٧١.٤%)	٤ (١٩٪)	١٤ (٦٦.٦%)
K.pneumonia(١٠)*	١٠ (١٠٠٪)	٠	٠	٨ (٨٠٪)	٠	٧ (٧٠٪)
Corynebacterium (٦)*	٦ (١٠٠٪)	٠	٤ (٦٦.٦٪)	٦ (١٠٠٪)	١ (١٦.٦٪)	٤ (٦٦.٦%)
P.mirabilis(٦)*	٢ (٣٣.٣%)	٦ (١٠٠%)	٣ (٥٠٪)	٢ (٦٦.٦%)	٢ (٣٣.٣٪)	٤ (٦٦.٦%)
P.aeruginosa(٣)*	٣ (١٠٠٪)	٠	٣ (١٠٠٪)	٣ (١٠٠٪)	٠	١ (٣٣.٣٪)
Enterobacter (٣)*	٢ (٦٦.٦%)	٠	٠	٢ (٦٦.٦٪)	١ (٣٣.٣٪)	٢ (٦٦.٦٪)
Acinetobacter (٣)*	٢ (٦٦.٦%)	٠	٠	٢ (٦٦.٦٪)	٠	١ (٣٣.٣٪)
Enterococcus (٢)*	٠	٠	٠	١ (٥٠%)	٠	١ (٥٠%)
S.saprophyticus(٢)*	٢ (١٠٠٪)	٢ (١٠٠٪)	٠	١ (٥٠٪)	٠	١ (٥٠%)
S.aureus(١)*	١ (١٠٠٪)	١ (١٠٠٪)	١ (١٠٠٪)	٠	٠	١(١٠٠٪)
Total	٥٥(٦٧.٩ %)	١٢ (١٤.٨%)	١١ (١٣.٦%)	٦١ (٧٥.٣%)	٢٧ (٣٣.٣%)	٤٣(٥٣.١%)

* No. of isolates

Table (٣.١٤): The numbers and percentages resistance of bacterial isolates to several antibiotics.

Type of bacteria	AMX*	TF*	GM*	CF*	CE*	CXM*	TE*	DXY*	TMX*	VAN*
*E.coli(٢٤)**	١٩ (٧٩.١)%	٤ (١٦.٦٪)	٩ (٣٧.٥%)	١١ (٤٥.٨٪)	١١ (٤٥.٨٪)	١٠ (٤١.٦٪)	٢١ (٨٧.٥٪)	١٢ (٥٠%)	١٥ (٦٢.٥%)	٢٤ (١٠٠٪)
*S.epidermidis(٢١)**	١٦ (٧٦.٢٪)	٤ (١٩٪)	١٠ (٤٧.٦٪)	٥ (٢٣.٨٪)	٦ (٢٨.٥٪)	٧ (٣٣.٣٪)	١٨ (٨٥.٧٪)	٩ (٤٢.٩٪)	٢١ (١٠٠٪)	٨ (٣٨٪)
*K.pneumonia(١٠)**	٩ (٩٠٪)	٨ (٨٠٪)	٤ (٤٠٪)	٣ (٣٠٪)	٣ (٣٠٪)	٣ (٣٠٪)	٦ (٦٠٪)	٤ (٤٠٪)	٩ (٩٠٪)	١٠ (١٠٠٪)
*Corynebacterium (٦)**	٦ (١٠٠٪)	٦ (١٠٠٪)	٦ (١٠٠٪)	٦ (١٠٠٪)	٤ (٦٦.٦٪)	٥ (٨٣.٣٪)	٦ (١٠٠٪)	٦ (١٠٠٪)	٦ (١٠٠٪)	٢ (٣٣.٣٪)
*P.mirabilis.(٦)**	٦ (١٠٠٪)	٦ (١٠٠٪)	١ (٢٠٪)	٢ (٣٣.٣٪)	٣ (٥٠٪)	٢ (٦٦.٦%)	٦ (١٠٠٪)	٤ (٦٦.٦٪)	٣ (٥٠٪)	٦ (١٠٠٪)
*P.aeruginosa(٣)**	٣ (١٠٠٪)	٣ (١٠٠٪)	٢ (٦٦.٦٪)	٣ (١٠٠٪)	٣ (١٠٠٪)	٣ (١٠٠٪)	٣ (١٠٠٪)	٣ (١٠٠٪)	٣ (١٠٠٪)	٣ (١٠٠٪)
*Enterobacter (٣)**	٢ (٦٦.٦٪)	١ (٣٣.٣٪)	١ (٣٣.٣%)	١ (٣٣.٣%)	٢ (٦٦.٦%)	٢ (٦٦.٦٪)	٣ (١٠٠٪)	٣ (١٠٠٪)	٣ (١٠٠٪)	٣ (١٠٠٪)
*Acinetobacter (٣)**	٣ (١٠٠٪)	١ (٣٣.٣٪)	٣ (١٠٠٪)	٠	٠	٢ (٦٦.٦٪)	٣ (١٠٠٪)	٢ (٦٦.٦٪)	٣ (١٠٠٪)	٣ (١٠٠٪)
*Enterococcus (٢)**	١ (٥٠٪)	٠	٠	٠	٠	٠	١ (٥٠٪)	٠	٠	٠
*S.saprophyticus(٢)**	١ (٥٠٪)	٠	١ (٥٠٪)	٠	٠	٠	٢ (١٠٠٪)	٢ (١٠٠٪)	٢ (١٠٠٪)	٠
*S.aureus(١)**	١ (١٠٠٪)	١ (١٠٠٪)	١ (١٠٠٪)	١ (١٠٠٪)	٠	١ (١٠٠٪)	١ (١٠٠٪)	١ (١٠٠٪)	١ (١٠٠٪)	١ (١٠٠٪)
Total	٦٧ (٨٢.٧٪)	٣٤ (٤١.٩٪)	٣٨ (٤٦.٩%)	٣٢ (٣٩.٥%)	٣٢ (٣٩.٥%)	٣٥ (٤٣.٢٪)	٧٠ (٨٦.٤٪)	٤٦(٥٦.٧٪)	٦٦ (٨١.٥٪)	٦٠ (٧٤.١٪)

- * No. of isolates.

- AMX* – Amoxicillin, GM* – Gentamicin, CF* – Ciprofloxacillin, TE* – Tetracycline, TMX* – Trimethprim-Sulfamaxazole, VAN* – Vancomycin, CE* – Cefotaxime, CXM* – Cefixime, DOX* – Doxycycline, TF* – Nitrofurantoin.

٤.١. CONCLUSIONS

- The chronic pyelonephritis is presented more commonly in middle age group and it is more in females than males. The unilateral uncomplicated cases are the most presentation.
- The symptomatic patients are commonly presented with urinary symptoms and less commonly with complications like hypertension and ureamia.
- The nosocomial bacterial infection is increased like *Proteus*, *Corynebacterium*, *Pseudomonas*, *Enterobacter* and coagulase-negative *Staphylococci*.
- Resistance rates among common uropathogens continue to evolve and appear to be increasing to many antibiotics commonly used for treatment of the chronic pyelonephritis.
- Ciprofloxacillin and cefotaxime were the most sensitive antibiotics for treatment the chronic pyelonephritis.
- The capsule, siderophore and colonization factor antigens were an important virulence factors to produce pyelonephritis by the causative bacteria.

٤.٢. RECOMMENDATIONS

- Continued surveillance of resistance rates among uropathogens is needed to ensure that appropriate recommendations can be made for treatment of infected patients.
- Further studies addressing the clinical and bacteriological outcomes of patients infected with a resistant pathogen are needed.
- Introduction of new molecular techniques for detection of fastidious microorganisms associated with pyelonephritis other than bacteria is recommended.
- Search for other member of quinolones and third generation cephalosporins that are used to treat chronic pyelonephritis is suggested.

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دراسة لبعض الجوانب السريرية و البكتيرية للمرضى المصابين بالتهاب الكلية المزمن في مستشفى الحلة التعليمي

رسالة مقدمة الى

مجلس كلية الطب في جامعة بابل كجزء من متطلبات نيل درجة الماجستير في علم الاحياء المجهريه

من قبل

رفل جليل جبار الصائغ

بكالوريوس في الطب والجراحة العامة

الخلاصة

١٤٢٥ هـ **٢٠٠٥م**

ان هذه الدراسة قد ضمت ١٠٢ مريضا كانوا مصابين بالتهاب الكلية المزمن و زاروا مستشفى الحله التعليم- وحدة الجراحة البوليه وكانت اعمارهم تتراوح ما بين ٧-٨٨ سنه، ٦١,٨٪ منهم نساء و٣٨,٢٪ منهم رجال. الفئة العمرية الاكثر اصابة بين النساء كانت بين ٤٠-٦٠ سنة و بين الرجال فكانت بين ٥٠-٧٠ سنة أما الاعمار التي هي اكثر من ٧٠ سنة فكانت الرجال فيها اكثر من النساء وكانت تمثل الاعمار التي هي اقل من ١٩ سنة ٥,٩٪ فقط.

ومن الناحية السريرية فانه يوجد هناك حالتان فقط مصابة بالمرض ولكن بدون اعراض اما الباقي فقد كانوا أما يعانون من آلالم الخاصره (٩٨,٢٪) مع او بدون الاعراض الاخرى لالتهابات المجاري البولية كتكرار التبول (٨٣,٣٪) و صعوبة التبول(٧٩,٤٪) والسلس الليلي (٧٥,٥٪) وكثرة البول (٦٧,٦٪) والرغبة في التقيء او التقيء(٣١,٤٪) وفقدان الشهية (٢٧,٥٪) وفقدان الوزن (١٧,٤٪). كذلك كان هناك بعض المرضى يعانون من مضاعفات المرض كارتفاع ضغط الدم (١٣,٧٪) والفشل الكلوي (٩,٨٪). بالاضافة الى ذلك فقد كان غالبية المرضى مصابون بالتهابات المجاري البولية المتكررة قبل الاصابة بالمرض(٨٦,٣٪) وان ٦٢,٧٪ من هؤلاء كانوا قد اصبوا بالحصى الكلوي. أما المصابون بالارتداد البولي المثاني الحالبي فقد كانت نسبتهم (٤,٨٪) فقط.

أما بالنسبة لنتائج السونار فقد كانت تشير الى ان(٦٥,٧٪) من الحالات عندهم كلية واحدة مصابة اما الباقي(٣٤,٣٪) فقد كانت الكليتان مصبتان بالمرض وكانت نتائج تحليل الادرار البسيط قد اشارت الى ان اغلب المرضى كان لديهم خلايا قيحية(pus cell) في الادرار وكانت نسبتهم (٩٤,١٪) مع او بدون وجود كريات الدم الحمراء (٦٩,٩٪). وان (٣٧,٢٪) من المرضى كان لديهم زلال في الادرار و (١٩,٥٪) لديهم قوالب كلوية في الادرار و كان هناك ايضا (٢٩,٧٪) من المرضى لهم ادرار قاعدي.

و كذلك فقد كانت نتائج زرع الادرار كانت موجبة ل٨١ مريض فقط و كانت انواع البكتيريا الظاهرة في الزرع و نسبها كما يلي: (٢٩,٦٪) *E.coli*

و(٢٥,٩٪)*Staphylococcus epidermidis* و (١٢,٣٪) *Klebsiella pneumonia* و(٧,٤٪) لمجموعة *Corynebacterium* و(٧,٤٪) *Proteus mirabilis* و (٣,٧٪)*Pseudomonas aeruginosa* و(٣,٧٪) مجموعة *Enterobacter* و(٢,٥٪)*Staphylococcus saprophyticus* واخيرا(١,٤٪) *Staphylococcus aureus*.

اما بالنسبة لتأثير بعض المضادات الحيوية على تلك العزلات االبكتيرية فقد اظهرت النتائج ان مقاومة هذه العزلات للتتراسايكليين (٨٦,٤٪) وللاموكسسليين (٨٢,٧٪) وللترايمثبريم-سلفاميثاكسازول (٨١,٥٪) وللدوكسيسايكليين (٥٦,٧٪) وللجنتمايسيين (٤٦,٩٪) وللسيفكزيم (٤٣,٢٪) وللنايتروفيورانتوين (٤١,٩٪) واخيرا فقد تساوت مقاومتهم للسبروفلوكساسليين وللسيفوتاكزيم بنسبة (٣٩,٥٪).

بالإضافة إلى ذلك فقد تمت دراسة بعض عوامل الضراوة التي تمتلكها البكتيريا ولكي تأهلها للتسبب بمرض التهاب الكلية المزمن وقد أظهرت النتائج ان (٧٥,٣٪) من العزلات ينتجون السايدروفورات و(٦٧,٨٪) يمتلكون المحفظة االبكتيرية. اما بالنسبة لعوامل الاستعمار فان (٦٠,٧٪) من العزلات يملكونها وان (٣٣,٣٪) منهم يملكون عامل الاستعمار الأول و(٥٣,١٪) يملكون عامل الاستعمارالثالث. وكان هناك (١٣,٦٪) من العزلات قادرة على انتاج الانزيم المحلل للبروتين و(١٤,٨٪) قادرة على انتاج الهيمولايسين.

كذلك فان بعض المصادر تعتبر القابلية على الحركة وانتاج اليوريز من عوامل الضراوة المهمة في التهاب الكلية المزمن حيث لوحظ ان ٥٨٪ من العزلات كانت منتجة لليوريز و(٤٤,٤٪) كانت لها القابلية على الحركة.