# دراسة بكتيريولوجية وسريرية للمرضى المصابين بتضخم البروستات الحميد أما أو التهاب البروستات المزمن

رسالة

مقدمة الى كلية الطب في جامعة بابل
كجزء من متطلبات نيل درجة الماجستير
في علم الأحياء المجهرية الطبية

أعدت من قبل

**بان حسين كاظم علوش**

**بكالوريوس طب وجراحة عامة**

١٤٢٦هـ ٢٠٠٦ م

# A Bacteriological & Clinical Study of Patients with Benign Prostatic Hyperplasia & or Chronic Prostatitis

A Thesis
Submitted to the College of Medicine - Babylon University In Partial Fulfillment of the Requirements
For the Degree of Master of Science
In Medical Microbiology

*By*


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# List of Abbreviations

| | |
|---|---|
| BPH | Benign Prostatic Hyperplasia |
| UTI | Urinary Tract Infection |
| AUA | American Urological Association |
| AP | Acute Prostatitis |
| CP | Chronic Prostatitis |
| NIH | National Institutes of Health |
| DRE | Digital Rectal Examination |
| EPS | Expressed Prostatic Secretion |
| PSA | Serum Prostatic Specific Antigen |
| DHT | Dihydrotestosterone |
| TUMT | Transurethral Microwave Thermotherapy |
| LUTS | Lower Urinary Tract Symptoms |
| CPPS | Chronic Pelvic Pain Syndrome |

| | |
|---|---|
| GUE | General Urine Examination |
| HPF | High Power Field |
| WBCs | White Blood Cells |
| RBCs | Red Blood Cells |
| CFA | Colonization Factor Antigen |
| TMP-SMX | Trimethoprim-Sulfamethoxazole |
| MR | Methyl Red Reagent |
| VP | Voges-Proskauer Reagent |
| TSI | Triple Sugar Iron |
| EMB | Eosin Methylene Blue |
| MRSA | Metheyline Resistant *Staphylococcus aureus* |
| CFU | Colony Forming Unit |

## *Certification*

**We certify that this thesis was prepared under our supervision at the College of Medicine, University of Babylon as partial fulfillment of the requirements for the Degree of Master of Science in Medical Microbiology.**

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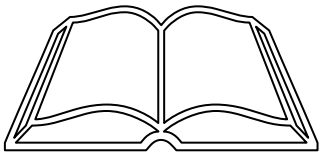

بسم الله الرحمن الرحيم

وَمَا أَنزَلْنَا عَلَيْكَ الْكِتَابَ إِلَّا لِتُبَيِّنَ لَهُمُ الَّذِي اخْتَلَفُوا فِيهِ وَهُدًى وَرَحْمَةً لِّقَوْمٍ يُؤْمِنُونَ

صدق الله العظيم

﴿سورة النحل \ الآية ٦٤﴾

## الخلاصة

شملت هذه الدراسة ( ١٥٠ ) مريضاً يعانون من تضخم البروستات الحميد أما أو التهاب الغدة المزمن راجعوا استشارية الجراحة البولية في مستشفى الحلة التعليمي وكانت أعمارهم تتراوح بين الثلاثين والتاسعة والتسعين ( ٣٠ – ٩٩ ) سنه من العمر وكان متوسط أعمارهم ( ٦٣,٩ ) . كان ( ٧٨ % ) منهم يعانون من تضخم البروستات الحميد, ( ١٣.٣ % ) يعانون من التهاب البروستات المزمن و ( ٨.٧ % ) كان لديهم التهاب البروستات المزمن والتضخم الحميد .

من الناحية السريرية كانت اهم الاعراض التي عانى منها هؤلاء المرضى هي تكرار التبول ( ٩٨ % ) ، التبول الليلي ( ٩٠ % ) ، الحرج البولي ( ٨٢ % ) ، التلكؤ البولي ( ٥٣ % ) ، حرقة البول ( ٥١.٣ % ) ، ضعف المجرى البولي ( ٤٦.٧ % ) وتقطير البول ( ٢٢ % ) . أما بقية الأعراض فقد تضمنت ألم مثل ألم البطن ، أسفل الظهر ، المنطقة التناسلية والعجانية ( ٢٢ % ) .

المرضى الذين كان لديهم حجم باق بعد التبول كانت نسبتهم ( ٢٠.٧ % ) و ( ١٠ % ) من المرضى كان لديهم تاريخ وضع أنبوب بزل الإدرار و ( ٤ % ) خضعوا لعملية تنظير المثانة .

وكانت نتائج فحص الإدرار العام هي خلايا قيحية ( ٥٤ % ) وكريات الدم الحمراء ( ٢٠.٧ % ) ، أما الخلايا البكتيرية فقد مثلت ( ٨ % ) وخلايا قيحية نظيفة ( ١٢ % ) الناتجة من الزرع السالب .

أما بالنسبة لنتائج فحص سوائل البروستات المستخلصه بطريقة التدليك هي خلايا قيحية ( ٦٦.٦ % ) وكريات الدم الحمراء ( ١٢.١ % ) .

فيما يخص نتائج زرع الادرار من المرضى المصابين بتضخم البروستات الحميد أما أو التهاب البروستات المزمن فقد نمت البكتيريا بنسبة ( ٤٣.٣ % ) معظمها من نوع *E. coli* حيث مثلت ( ١٤.٧ % ) ، *Staphylococcus epidermidis* ( ٦ % ) ، *K. pneumoniae* و *Staphylococcus aureus* مثلت كل واحده منهما ( ٤ % ) ، أنواع *Acinetobacter* ( ٣.٣ % ) ، بينما أنواع *Enterobacter* و*Pseudomonas aeruginosa* مثلت كل واحدة منهما ( ٢.٧ % ) من العزلات . *Proteus mirabilis* ( ٢ % ) ، بالإضافة إلى *Staphylococcus saprophyticus*، أنواع *Corynebacterium* وأنواع *Enterococcus* مثلت كل واحدة ( ١.٣ % ) .

أما فيما يتعلق بنتائج زرع سوائل البروستات فقد لوحظ إن نسبة النمو البكتيري وصلت إلى ( ٤٥.٥ % ) وكانت *Staphylococcus aureus* هي الأكثر حيث مثلت ( ١٢.١ % ) ، *Staphylococcus epidermidis* و*Staphylococcus saprophyticus* و*E. coli* و*Klebsialla pnumoniae* كل واحدة مثلت ( ٦.١ % ) بينما انواع *Enterobacter* وأنواع *Acinetobacter* وأنواع *Corynebacterium* كل واحدة مثلت ( ٣ % ) .

أما بالنسبة لتأثير بعض المضادات الحيوية على العزلات البكتيرية فقد ظهرت أعلى نسبة مقاومة للأموكسلين ( ٧٣.٨ %)،النالدكسيك أسيد( ٧٠.٨ %)،الجنتمايسين ( ٦٠ %)،السيفالكسين ( ٥٥.٤ %)،التراي مثبيريم–سالفاميثوكساسول ( ٥٠.٨ %) بينما المقاومة لبقية المضادات فكانت بنسبة أقل للدوكسيسايكلين ( ٤٠%)،السيفوتاكسيم ( ٣٢.٣ %) ،السيبروفلوكساسين( ٢٧.٧%)،للأموكسلين–كلافيولانيك أسيد( ١٨.٥%)والأميكاسين( ٧.٧%).

الزنك له تأثير في تثبيط النمو البكتيري خصوصا في التراكيز الأعلى من ( ١.٠٥ ملغم/مل) من الوسط الزرعي وفيها كان التأثير على البكتيريا السالبة لصبغة كرام أكثر من البكتيريا الموجبة لصبغة كرام ، ووجد أنه يزيد من التأثير القاتل للمضادات الحيوية على العزلات بالإضافة إلى تأثيره في اختزال محفظة البكتريا .

كما شملت هذه الدراسة بعض الإنزيمات المنتجة من قبل العزلات البكتيرية فبالنسبة لإنزيم الفوسفاتيز وجد أن كل من Enterobacteriaceae ومجموعة *Corynebacterium* و*S. aureus* و*S. epidermidis* وعزلة واحده *P. aeruginosa* لها القدرة على أنتاج أنزيم الفوسفاتيز ، بينما ولا واحده من أنواع *Enterococcucs* وأنواع *Acinobacter* و *S. saprophyticus* منتجه لهذا الإنزيم .

من جهة أخرى العزلات المنتجة لأنزيم البروتيز خارج الخلية هي *E. coli* ، *P.aeruginosa* ، *S. aureus* و*S. epidermidis*. كذلك عزلة واحده فقط من *P.mirabis* ،أنواع *Acinetobacter* ، أنواع *Corynebacterium* و*Enterococcus* منتجة لهذا الإنزيم ، بينما *K. pneumoniae* ،أنواع*Enterobacter*، *S.saprophyticus* وأنواع *Enterococcus* غير منتجة لهذا الإنزيم.

We, the examiner committee, certify that we have read the thesis entitled ***(A Bacteriological & Clinical Study of Patients with Benign Prostatic Hyperplasia & or Chronic Prostatitis)*** and have examined the student ***(Ban Hussein Kadhum Alwash)*** in its contents, and that in our opinion it is accepted as a thesis for the degree of Master of Science in Medical Microbiology.

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# Dedication

# To . . .

# My Mother And Father

# My Brothers

My Husband

# My Kids:

# Rawan, Ali & Jaber

**Ban**

# *Acknowledgment*

Praise to "**ALLAH**" and to his prophet "**Mohammed**". This research has been completed under their benediction.

I acknowledge with thanks and gratitude the valuable advice, assistance, cooperation, and encouragement of **Dr. Mohammed Sabri Abdul-Razak** and **Dr. Emmad Hassan Al-Jaff** throughout the course of preparing my thesis. They devoted much of their time in going through every detail in their work which helped in accomplishing it.

I express my sincere gratitude to my family (especially to my mother and father) for their encouragement and support during the period of preparing this work.

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BAN

# ABSTRACT

This study included (١٥٠) patients with benign prostatic hyperplasia & or chronic prostatitis visited Al-Hilla Teaching Hospital-Department of Urology. Patients age ranged from (٣٠-٩٩) years with mean age of (٦٣.٩) years. It was found that (٧٨٪) of them had benign prostatic hyperplasia ١٣.٣٪ had chronic prostatitis and ٨.٧٪ had benign prostatic hyperplasia and chronic prostatitis.

The clinical features were frequency (٩٨٪), nocturia (٩٠٪), urgency (٨٢٪), hesitancy (٥٣٪), dysuria (٥١.٣٪), poor stream (٤٦.٧٪), dribbling of urine (٢٢٪). Other clinical features were pain (٢٢%) such as suprapubic pain, lower backache, groin and perineal pain.

(٢٠.٧٪) of patients had post voiding residual urine, while (١٠٪) had history of catheterization and cystoscopy was done to (٤٪).

Results of general urine examination were pyuria (٥٤٪), RBCs (٢٠.٧٪), bacteruria (٨٪) and (١٢٪) had sterile pyuria with urine culture and sensitivity negative.

Results of expressed prostatic secretion examination were pus cells (٦٦.٦ %), RBCs (١٢.١٪).

Regarding the results of urine cultures in patients with benign prostatic hyperplasia & or chronic prostatitis, (٤٣.٣%) had positive culture for bacteria. *E.coli* was the most common type of bacterial isolates (١٤.٧٪), *Staphylococcus epidermidis* (٦٪), *Klebsiella pneumoniae* and *Staphylococcus aureus* and each of which represented (٤٪), *Acinetobacter* spp. (٣.٣٪), *Enterobacter* spp. and *Pseudomonas aeruginosa* represented (٢.٧٪) each, *Proteus mirabilis* (٢٪).

In addition, *Staphylococcus saprophyticus*, *Corynebacterium* spp. and *Enterococcus* spp. represented (١.٣%) each.

As far as prostatic secretions cultures are concerned, (٤٥.٥٪) had positive results for bacteria. The most common isolates were *Staphylococcus aureus* were (١٢.١٪). *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *E.coli* and *Klebsiella pneumoniae* represented (٦.١٪) each. *Enterobacter* spp., *Acinetobacter* spp. and *Corynebacterium* spp. represented (٣٪) each.

The effect of some antibiotics on bacterial isolates showed that the isolates had high rate of resistance to amoxicillin (٧٣.٨%), naldixic acid (٧٠.٨٪), gentamycin (٦٠٪), cephalexin (٥٥.٤٪), trimethoprim-sulfamethoxasole (٥٠.٨٪), while the resistance to others was lower as doxycycline (٤٠٪), cefotaxim (٣٢.٣٪),

ciprofloxacin (٢٧.٧٪), amoxicillin-clavulanic acid (١٨.٥٪) and amikacin (٧.٧٪).

Zinc had inhibitory effect on the growth of bacteria especially at concentrations more than (١.٠٥) mg/ml of broth culture in which there was more effect on the Gram-negative bacteria than Gram-positive bacteria and it increased the bactericidal effect of antibiotics. In addition, it had an effect in the loss of the capsule of the bacteria.

Some enzymes produced by bacterial isolates were also studied, and the results showed that all isolates of Enterobacteriaceae, *Corynebacterium* spp., *S.aureus* and *S.epidermidis*, and one isolate of *P.aeruginosa* produced phosphatase enzyme while none of *Enterococcus* spp., *Acinetobacter* spp, and *S.saprophyticus* produced this enzyme.

On the other hand, the isolates produced extracellular protease enzyme included *E.coli, P.aeruginosa*, *S.aureus,* and *S.epidermidis*. Also, one isolate of each of *P.mirabilis, Acinetobacter* spp., and *Corynebacterium* spp. produced this enzyme, while *K.pneumoniae, Enterobacter* spp., *Enterococcus* spp. and *S.saprophyticus* did not produce this enzyme.

# ١.١ Introduction

**Chronic bacterial prostatitis usually is the result of partial blockage of male lower urinary tract, which occurs with benign prostatic hyperplasia. Such blockages promote the harboring of bacteria from a previous infection and reduce circulation, thereby preventing both the body's natural immune mechanisms and medication from getting to the site (Floxin *et.al.*, ٢٠٠٦).**

**Benign prostatic hyperplasia and prostatitis cannot be distinguished according to symptoms, and some believe that they**

**may be the same disease (Goran, ٢٠٠١). The line between them is blurred; the prevalence of histological signs of prostatitis increased with age and was highest when BPH was also present, so prostatitis as a histological lesion was found in ٩٨٪ of patients with benign prostatic hyperplasia (Lee, ٢٠٠٠).**

**Benign prostatic hyperplasia is a non malignant neoplastic process secondary to increased cellular growth and it is the age related disease (Jack *et.al*., ٢٠٠٣). The majority of men with BPH present with lower urinary tract symptoms only such as nocturia, frequency, urgency, incomplete bladder emptying, hesitancy, weak stream and straining to void (Donovan *et.al*., ١٩٩٧; Saldden, ٢٠٠٠).**

**Prostatitis is an inflammation of the prostate gland that must be excluded from other causes of lower urinary tract symptoms, chronic prostatitis is possibly the most common infectious disease in middle-aged men and sometimes caused by bacterial infection of prostate, However, most men with CP complain of variable irritative and voiding obstructive symptoms such as dysuria, urgency, frequency, nocturia, hesitancy and poor stream, In addition, pain perceived in various sites within the pelvis and genitalia (Stimac *et.al*., ٢٠٠١). The hallmark of chronic bacterial prostatitis is recurrent urinary tract infection caused by the same pathogen (Naber *et.al*., ٢٠٠٥).**

**Elderly men are at risk for UTIs because prostatic enlargement can lead to urinary obstruction and retention, providing an excellent medium for bacterial growth. Zinc antibacterial factor, a bactericidal substance is normally found in prostatic fluid, which declines with age. In older men, prostatic fluid becomes more alkaline. All these factors put older men not only at risk for UTIs but for prostatitis as well (Judith, ١٩٩٦; Lipsky, ٢٠٠٣).**

**The commonest uropathogens identified in complicated urinary tract infection is *E. coli* as the main uropathogen, other bacteria such as *Klebsiella* spp., *Proteus mirabilis, Enterobacter* spp., *Serrtia* spp., *Enterococcus* spp., *Pseudomonas aeruginosa* and *Staphylococcus* spp. are also identified (Romolo *et.al*., ٢٠٠٤). Recently, *Corynebacterium* group D٢ and *Acinetobacter* spp. may occur in hospital–acquired infection as opportunistic pathogens. Coagulase-negative *Staphylococcus* might represent an important agent of UTI (Schrier and Gottschall, ١٩٩٦).**

**Furthermore, the causative organisms of bacterial prostatitis by culture of the expressed prostatic secretion or post prostatic message urine sample (VB٣) are similar in type and incidence to those responsible for UTI; common strains of *E. coli* clearly predominate. Infections caused by species of *Klebsiella, Enterobacter, Proteus and Serratia*. *Pseudomonas* and other less**

**common Gram-negative organisms occur less frequently (Jiao *et.al*., ٢٠٠٢).**

**Traditional dogma states that the role of Gram-positive bacteria which are commensal in the anterior urethra is controversial, whereas *Enterococci* are accepted as a cause of bacterial prostatitis and the UTIs associated with it (Antonio, ١٩٨١). While Bergman, (١٩٩٤) suggested that coagulase-negative *Staphylococci* are involved in the pathogenesis of chronic prostatitis, and did not conclusively demonstrate that these bacteria were actually causing the inflammation and symptom complex rather than simply colonizing the prostate.**

**On the basis of the previous introduction, the aims of this study are:**

- **To assess bacteriologically and clinically the patients with benign prostatic hyperplasia &or chronic prostatitis.**
- **To study in vitro antimicrobial sensitivity pattern of bacterial isolates from those patients.**
- **To detect some enzymes produced by those bacterial isolates.**
- **To detect the effect of zinc sulfate alone and combination of some antibiotics with zinc sulfate on bacterial growth in vitro.**

# ١.٢ LITRATURE REVIEW

## ١.٢.١ Anatomy

**The prostate is ovoid in shape and walnut size gland weighs ١٨ gm measure (٣-٤) cm in length and (٤-٦) cm in width and (٢-٣) cm in depth. It is traversed by the prostatic urethra; and surrounded by a fibrous capsule. It has a base, an apex, an anterior, a posterior surface, and two lateral surfaces and incompletely divided into five lobes, anterior, middle, posterior, right and left lateral lobes which are rich in glandular tissue which produce a milky fluid that liquefies semen. In addition, smooth muscle cells which contract during sex and squeeze the fluid from the glandular cells into the urethra, where it mixes with sperm and other fluids to make semen (Patrick *et.al.*, ١٩٩٧).**

**Three distinct zones have been identified, peripheral account for ٧٠٪, transitional ٥٪ and central ٢٥% of volume of prostate. (McNeal, ١٩٩٠). So, because of the anatomic configuration of the prostate, it is considered as reservoir for recurrent infections (Sunil *et. al.*, ٢٠٠٤).**

## ١.٢.٢ Benign prostatic hyperplasia (BPH) and chronic prostatitis

### ١.٢.٢.١.١ *Benign prostatic hyperplasia*

**Benign prostatic hyperplasia is a medical condition closely related to aging and it is a microscopic diagnosis characterized by cellular proliferation of stromal and epithelial elements in the transition zone of the prostate produces histological BPH, thus contributing to the bladder outlet obstruction that leads to clinical BPH (Strandberg , ٢٠٠٠).**

**The clinical manifestation of BPH includes lower urinary tract symptoms, poor bladder emptying, urinary retention, detrusor instability, urinary tract infection, hematuria and renal insufficiency. However, the majority of men with BPH are presented with LUTS only (Herbert, ٢٠٠٤). There is a relatively low correlation between urinary symptoms, prostate size and urinary flow rate (Girman, ١٩٩٥).**

**The self-administration questionnaire developed by AUA is reliable in identifying the need to treat patients and in monitoring their response to therapy. A symptom score of ٠-٧ is considered**

**mild, ٨-١٩ is considered moderate, and ٢٠-٣٥ is considered sever (Miller, ١٩٩٦).**

### *١. ٢. ٢. ١. ٢ Etiology of benign prostatic hyperplasia*

**The cause of BPH is not well understood. It mainly occurs in older men and does not develop in men whose testes were removed before puberty. So, factors related to aging and the testes may spur the development of BPH.**

**Throughout their lives, men produce testosterone, an important male hormone, and small amounts of estrogen, a female hormone. As men age, the amount of active testosterone in the blood decreases, leaving a higher proportion of estrogen that promotes cell growth (Jack *et.al*., ٢٠٠٣).**

**Another theory focuses on dihydrotestosterone, a substance derived from active testosterone in the prostate, which may help control its growth. Some research has indicated that even with a drop in the blood's testosterone level, older male continues to produce and accumulate high levels of DHT in the prostate; this accumulation of DHT may encourage the growth of cells (Walsh *et.al.,* ١٩٩٠; Roehborn and McConnell, ٢٠٠٢).**

**Some researchers suggest that BPH may develop as a result of "instructions" given to cells early in life. According to this theory, BPH occurs because cells in one section of the gland follow these**

**instructions and "reawaken" later in life. These "reawakened" cells then deliver signals to other cells in the gland, instructing them to grow or making them more sensitive to hormones that influence growth (McNeal, ١٩٩٠).**

**The increase in cells number may be the result of epithelial and stromal proliferation or of impaired programmed cell death leading to cellular accumulation. Androgens, estrogens, stromal-epithelial interactions, growth factors, and neurotransmitters may play a role, either singly or in combination, in the etiology of the hyperplastic process (Kathy, ٢٠٠٤).**

### ١. ٢. ٢. ٢ *Prostatitis*

**Prostatitis is an inflammation of the prostate associated with urinary tract infection. In clinical practice, the term prostatitis encompasses multiple diverse disorders that cause symptoms related to prostate gland, it can be caused by bacterial infection (Stimac *et.al.,* ٢٠٠١).**

**The most common form of prostatitis is non bacterial depending on the microbiology of expressed prostatic secretion (EPS) or segmented urine samples. The limitations of the traditional diagnostic algorithm and traditional classification system led to the National Institutes of Health (NIH) consensus meeting on prostatitis which can be classified by (Jiao *et.al.*, ٢٠٠٢) into the following:**

**Category I – Acute bacterial prostatitis (ABP).**

**Category II – Chronic bacterial prostatitis (CBP).**

**Category III – Chronic pelvic pain syndrome (CPPS)-discomfort or pain in pelvic region.**

**A- Inflammatory CPPS.**

- **More than ١٠ of WBC in semen or expressed prostatic secretion (EPS) or urine specimen after prostate massage (VB٣).**

**B- Non-Inflammatory CPPS.**

- **Less than ١٠ of WBC cells in semen or expressed prostatic secretion (EPS) or urine specimen after prostate massage (VB٣).**

**Category IV – Asymptomatic inflammatory prostatitis (Histological prostatitis): by definition, does not cause symptoms. The patients may present with infertility, BPH or prostate cancer (an elevated prostate-specific antigen level) and histological examination of BPH chips, prostate cancer specimens, or prostate biopsies disclose evidence of prostatic inflammation (the presence of significant leukocytes or bacteria or both in prostate biopsies).**

**Chronic prostatitis is very common, ٩.٧٪ of male respondents aged (٢٠-٧٤) years, reported pain or discomfort in the perineum or with ejaculation or both, plus a total pain score (possible ٠ to ٢١) of ٤ or greater, this location and level of pain would be sufficient to lead most physicians to make a diagnosis of chronic prostatitis, in this age group, ٦.٦٪ of men reported similar symptoms over the previous week with a pain score of ٨ or greater, which would place them in the moderate or severe category (Floxin *et.al.*, ٢٠٠٦).**

### ١. ٢. ٢. ٣ *Epidemiology*

**Benign prostatic hyperplasia is a common chronic disease that can be found in approximately ٣٧ million men in USA aged more than ٥٠ years (Jack *et.al.*, ٢٠٠٣). The Histopathology of this disease characterized by hyperplastic stromal and epithelial cells within the prostate which can be observed in approximately ٥٠٪ of men aged more than ٦٠ years and up to ٩٠٪ by the age ٨٥ years (Mark *et.al.*, ٢٠٠٥).**

**In addition, Roger and Kirpy, (٢٠٠٤) found that pathologic evidence of BPH are present in ٨٪ of men between ٣١ and ٤٠ years of age, with a marked increase to more than ٧٠٪ in men aged ٦١ to ٧٠ years. Similarly, analysis of Logie *et.al.*, (٢٠٠١) demonstrated that the occurrence of lower urinary tract symptoms suggestive of BPH increased linearly between the ages (٤٥-٨٥) years.**

**The prevalence of lower urinary tract symptoms increased from ٣.٥٪ in men at their late ٤٠s to ٣٥٪ in men at their late ٨٠s (Huges, *et.al.*, ٢٠٠٠). Worldwide BPH is a common problem as epidemiolologic studies show that ٣٨٪ of American men and ٥٦٪ of Japanese men aged (٤٠-٧٩) years experience moderate to severe LUTS attributed to BPH (Jacks *et.al.*, ٢٠٠٣).**

**Prostatitis is the most common urologic diagnosis in men under ٥٠ years of age, and the third most common in older men who are more than ٥٠ years old (after BPH and prostate cancer), representing ٨٪ of urology consultation and epidemiologic studies described in this section confirm that prostatitis affects men of all ages, unlike BPH which is predominantly diseases of older men (Collines and Barry, ١٩٩٩). Furthermore, (١٠-٣٠) % of men will have had a diagnosis of prostatitis by ٧٩ years of age (Goran, ٢٠٠١).**

**The histolopathologic prevalence of prostatitis ranges from (thirty five to ninety eight percent as summarized by (Vanden, ٢٠٠٠) or from six to forty four percent according to (Roberts, ١٩٩٨). Usually, up to ٥٠٪ of all men experience symptoms of prostatitis during the lifetime (Stimac, ٢٠٠١).**

*١.٢.٢.٤.١ Host factors that prevent UTI*

**The important host factors in preventing UTI include the mucosal secretions of soluble compounds that can bind to the glycoprotein or glycolipid receptors on the epithelial cell surfaces may provide competitive inhibition of bacterial adherence and colonization, blood group antigens may constitute the soluble compounds responsible for decreasing the availability of receptor sites for bacterial adherence (Holmberg, ١٩٨٦; Emil *et.al*., ٢٠٠٤).**

**The normal flora of periurethral area forms a defense against the colonization of pathogenic bacteria. Periurethral gland secretion and urine flow are flushing of the prostatic urethra by emptying the bladder (Ghiro *et.al*., ٢٠٠٢; Thomas, ٢٠٠٥).**

**Zinc has been identified as an important component of prostatic fluid that carries potent bactericidal properties, men with chronic bacterial prostatitis exhibit absent or reduced amounts of zinc in their prostatic fluid and normal serum zinc levels; they are also most likely to suffer recurrent infections of urine (Fair *et.al*.١٩٧٩).**

**Spermine and spermidine also are natural host defences in prostatic fluid and their antibacterial activity is directed mainly at gram-positive bacteria (Sunil *et.al.,* ٢٠٠٤).**

**Other factors like low pH, urinary antibodies, polymorphonuclear neutrophils, cytokines and urinary osmolarity can be inhibitory to**

**bacterial growth. In addition, salts, urea, and organic acids present in urine can reduce survival of bacteria within the urinary tract, so alterations in any of these factors may predispose to bacterial colonization. Also, lactoferrin within urine can scavenge essential iron away from bacteria (Judith, ١٩٩٦).**

### ١. ٢. ٢. ٤. ٢ *Altered prostatic host defense*

**Risk factors that allow bacterial colonization or infection of the prostate with potentially pathogenic bacteria include intraprostatic ductal reflux, phimosis, unprotected penetrative anal rectal intercourse, UTI, acute epididymitis, indwelling urethral catheters and condom catheter drainage and transurethral surgery especially in men who have untreated infected urine (Mears, ١٩٩٧).**

## ١. ٢. ٢. ٥ *Diagnosis of patients with benign prostatic hyperplasia or chronic prostatitis*

### ١. ٢. ٢. ٥. ١ *Digital rectal examination (DRE)*

**A DRE has to be formed to determine the size, consistency and shape of the prostate gland. Hyperplasia usually produces a smooth, firm elastic enlargement of the prostate; however, the size**

**of the prostate on rectal examination does not permit one to estimate the degree of bladder outlet obstruction or severity of symptoms. DRE allowing the physician to exclude the possibility of other pathologies, such as prostate cancer and prostatitis (Bruskewitz, ٢٠٠٤).**

### ١. ٢. ٢. ٥. ٢ *Laboratory findings*

- Urinalysis:

A- Pyuria**: is a number of white blood cells (WBCs) greater than ٥/ HPF, it was ٨٥٪ sensitive for urinary tract infection (David *et.al.,* ٢٠٠٠). While, other authors have reported greater than ١٠ (WBCs)/ HPF was a more reliable breakpoint making the diagnosis (Stamm and Hooth, ١٩٩٣).**

**It is more important than bacteriuria because the patients may be presented with cystitis secondary to chronic non specific prostatitis occasionally produces pus without bacteriuria, pus cells are present in urine of normal subjects if there are no more than (٢-٣) WBCs / HPF (Spencer, ٢٠٠٤).**

B- Red Blood Cells (RBCs): **There should be only an occasional red blood cell in the urine (٢-٣/HPF) and positive presence of these is most commonly associated with sever infection such as cystitis and pylonephrities but is rarely seen in urithritis, hematuria can be**

**present with BPH patients (Hamburger *et.al.,* ١٩٧٨; Jean *et.al.,* ٢٠٠١).**

C- Reaction**: The pH of urine and EPS is measured by dipstick that normal pH is between (٥.٥-٦.٥), 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 (Woolth *et.al.,* ١٩٨٩).**

D- Bacteriuria**: means the present of one bacteria/oil field in which equal or more than $١٠^{٥}$ (Dulawa *et.al.,* ٢٠٠٣).**

- Urine culture**: To detect causative microorganism, the culture may be negative (David *et. al.,* ٢٠٠٠).**
- Expressed prostatic secretion tests**: These tests are used to rule out prostatitis. Since prostatic infection is a focal process and sampling errors are inevitable, false negative results do occur. Two or more bacterial localization tests may then be required to identify the pathogenic bacteria. If no organisms can be cultured, and the prostatitic fluid has an increased leukocyte count more than (١٠/HPF), a diagnosis of chronic pelvic pain syndrome (inflammatory type) can be made, negative routine culture results occur for various reasons, including initiation of antibiotics prior to obtaining an EPS and the presence of fastidious organisms, these patients often have symptoms improvement after antibiotics treatment (Weidner *et.al.,* ١٩٩١).**

- Blood sample**: To assess the renal function including blood urea and serum creatinine to exclude renal insufficiency caused by the presence of obstructive uropathy. (Gerber *et.al.,* ١٩٩٧).**
- Serum Prostatic Specific Antigen (PSA)**: is moderately elevated in (٣٠-٥٠) % of patients with benign prostatic hyperplasia depending on prostate volume and degree of obstruction (Lepor, ١٩٩٩).**

### ١. ٢. ٢. ٥. ٣ *Ultrasound*

**It gives an accurate picture of the size and shape of the prostate gland; also it may be used for detecting kidney damage, stones, and post voiding residual urine volume (Byun, ٢٠٠٣).**

### ١. ٢. ٢. ٥. ٤ *Uroflowmetry*

**It is the electronic recording of the urinary flow rate throughout the course of micturition; an abnormally low flow rate may be caused by bladder outlet obstruction such as that in benign prostatic hyperplasia (Abrams and Grifit, ١٩٩٥).**

### ١. ٢. ٢. ٥. ٥ *Urethrocystoscopy*

**It is the standard endoscopic procedure used for evaluating the lower urinary tract (urethra, prostate, and bladder), it can provide information as to the cause, size and severity of obstruction, patency of bladder neck, prostatic occlusion of urethra and estimated prostate size (Herbert, ٢٠٠٤).**

## ١.٢.٣ Bacterial agents

**The important bacteriological agents in patients with chronic prostatitis due to organisms persist in prostatic fluid, they do not readily respond to usual antibiotics (Britton and Carson, ١٩٩٨). Bacteria may exist in aggregated biofilms adherent to the prostatic ductal walls or within the obstructed ducts in the prostate. Nickel, (٢٠٠٠) cultured urine specimens and transperineal prostate biopsies specifically for commensal and fastidious organisms. Prostatitis may be caused by undocumented infections with *Chlamydia trachomatis*, *Ureaplasma urealiticum and Mycoplasma hominis* (Plotti *et.al*., ١٩٨٥).**

### ١.٢.٣.١ *Gram-negative bacteria*

*A- Enterobacterieceae*

**They are Gram-negative, non-spore-forming bacilli that grow both aerobically and facultative anaerobically on ordinary laboratory media and are oxidase test negative (MacFaddin, ٢٠٠٠). The most common cause of bacterial prostatitis is the Enterobacteriaceae family of gram-negative bacteria which originate in the gastrointestinal flora (Weidner *et.al*., ١٩٩١).**

- *Escherichia coli*

**It is a member of Enterobacteriaceae and it is the most common cause of urinary tract infections , predominantly, strains of *E. coli* that have been identified in ٦٥٪ to ٨٠٪ of chronic bacterial prostatitis as the cause of cultural prostatitis (Lipsky,٢٠٠٣). The majority of community acquired UTIs are caused by uropathogenic *E. coli* and which caused recurrent infection (Joel *et.al.,* ٢٠٠٢ ; Al-Amedi, ٢٠٠٣).**

**Many strains of *E.coli* uropathogens belong to limited number of O, K, and H serogroups mainly O٢, O٤, O٦, O٧, O٨ and O١٥٧, also production of CF/I, CF/II and CF/III, they increased adherence properties to uroepithelial cells (Blance *et.al.,* ١٩٩٦).**

**Uro-virulence factors play a significant role in the pathogenesis of bacterial prostatitis, for instance, bacterial P-fimbriae binds to the uroepithelial receptors, and this subsequently facilitates ascent into the urinary tract as well as establishing deep infections in the prostate gland itself (Roberry *et.al*., ١٩٩٧). These are observed in ٩٠٪ of *E.coli* strains causing pyelonephritis but less than ٢٠٪ of the strains causing lower urinary tract infection (Svenson *et.al.*, ١٩٨٣).**

**Colonization of the lower urinary tract by *E. coli* is also facilitated by the presence of the type ١ fimbriae, also known as**

**mannose-sensitive fimbriae which bind to glycolipids or glycoproteins receptors on the surface membrane of uroepithelial cells, help bacteria to adhere to bladder and prostatic mucosa and to be important in the development of cystitis and prostatitis in humans, and its presence in prostatitis has also been documented (Marty *et.al*., ٢٠٠٠).**

**Most uropathogenic *E. coli* strains produce hemolysin, which initiates tissue invasion and makes iron available for infecting pathogens (Huges, ١٩٩٦). The presence of K antigen on the invading bacteria protects them from phagocytosis by neutrophils. These factors allow the infecting pathogens to escape the various host defenses (Svanborg *et.al*., ١٩٩٦).**

**Some strains are urease-producing *E.coli* and they are commonly present in the complicated UTI (Falkow and Collinins, ١٩٩٠).**

- *Klebsialla pneumoniae*

***Klebsiella* is a non-motile member of Enterobacteriaceae. *Klebsiella* spp. are usually capsulated, mucoid colonies on laboratory medium, especially if it has high sugar content (Collee *et.al.,* ١٩٩٦). *Klebsiella pneumoniae*, accounts for a significant proportion of chronic prostatitis and hospital-acquired urinary tract infections which account for ٣-٧٪ of all nosocomial bacterial infections**

**and it is primarily attack immunocompromised individuals (Diancourt *et.al.*, ٢٠٠٥).**

**The virulence of *Klebsiella* is not well understood, but it is antiphagocytic capsule plays a role in the infections by preventing phagocytosis. It is thought that it secretes enterobactin and aerobactin (iron-binding proteins), CFA/I, CFA/II and CFA/III as adhesive factors with urinary tract epithelium and it produces β-lactamase enzyme which contributes to pathogenicity and antibiotic resistance of bacteria (Al-Saedi, ٢٠٠٠ ; Spanu *et.al.*, ٢٠٠٢).**

**Some strains of *Klebsiella* produce hemagglutinins (may be mannose-sensitive phenotype) and they may be associated with pathogenicity in addition of endotoxins which have an important role in virulence and antibiotic resistance of bacteria (Podschun and Ullmann, ١٩٩٨). It is generally sensitive to cephalothin (Moland *et.al.*, ٢٠٠٣).**

- *Enterobacter* spp.

***Enterobacter* is a motile-member of Enterobacteriaceae, mucoid on sheep blood agar, some of which are encapsulated, they also posses flagella. In contrast to *Klebsiella,* organisms are motile. *Enterobacter* species, particularly *E. cloacae* and *E. aeregenes,* are important nosocomial pathogens responsible for a variety of urinary tract infections especially in patients having anatomical**

**defects or indwelling catheters also isolated from patients with chronic prostatitis (Lipsky, ٢٠٠٣). *E. cloacae* was the fourth most frequently isolated non fastidious Gram-negative rode in rate of (٦٪) in the microbiology lab and are observed most frequently in neonates and in elderly individuals, reflecting the increased prevalence of severe underlying diseases at these age extremes (Christian *et.al*., ٢٠٠٣).**

**The important virulence factors seem to be largely due to an endotoxin that it produces community-acquired infections which are sometimes observed. The *Enterobacter* species are resistant to cephalothin due to β-lactamase enzymes production, so, strains that cause hospital-acquired infection are more frequently antibiotic resistant than other strains due to β-lactamase enzymes production (Pitout *et.al*., ١٩٩٨).**

- *Proteus* and related group

**It is a part of the Enterobacteriaceae family. The *Proteus* species include *P. vulgaris, P. mirabilis, Providencia* and *Morganella*. They are small Gram-negative bacillus and a facultative anaerobe, *Proteus* is characterized by its swarming motility; it's able to ferment maltose, and its non lactose fermenters, in addition, the outer membrane contains a lipid bilayer, lipoproteins, polysaccharides, and lipopolysaccharides,**

***P.mirabilis*** **is indole negative while** ***P.vulgaris*** **is indole positive (Senior, ١٩٩٨).**

***P. mirabilis*** **causes ٩٠٪ of proteus infections and after** ***E.coli*** **it is considered as the commonest cause of urinary tract infections of young males as in patients suffered from prostatitis, and the elderly of both sexes (Ahmed, ٢٠٠٥). Patients with recurrent infections, those with structural abnormalities of urinary tract, those who had urethral instrumentation, those with chronic prostatitis and whose infections were acquired in the hospital, have increased frequency of infection caused by** ***Proteus*** **(Jone, ٢٠٠٥).**

**The important virulence factors of** ***P. mirabilis*** **is the flagella which is crucial to it's motility, a characteristic that helps the organism colonize and form biofilms, aiding in the bacteria's resistance to defenses of the host and selected antibiotics (Cus *et. al.,*٢٠٠٣). It relies on its pili for adhesion to avoid being flushed out of the urinary tract system (Murry *et.al.,* ٢٠٠٢).**

**The ability of** ***P. mirabilis*** **to produce urease, responsible for raising the pH and alkalinize the urine by hydrolyzing urea to ammonia and consequently making it easier to thrive, increased pH allows stone formation (Ligx *et.al*., ٢٠٠٢). The endotoxins of** ***Proteus*** **responsible for induction of the inflammatory response system and performing hemolysins (Micheal *et. al*., ٢٠٠٣).**

***P. mirabilis*** **infections can be treated with broad-spectrum pencillins or cephalosporins (Kouda *et.al.,* ١٩٩٩). It is not susceptible to tetracycline or nitrofurantion (Resistance does not appear to be a significant clinical factor, but (١٠-٢٠)% of strains can acquire resistance to ampicillin, first-generation cephalosporin and ciprofloxacin (Janicka *et.al.*, ١٩٩٩; Khon and Lue, ٢٠٠٤).**

**Other Enterobacterieceae include *Serratia* spp. which represent opportunistic pathogens and can be isolated from patients with bacterial prostatitis (Lopez and Bostwick, ١٩٩٠).**

*B- Pseudomonas aeruginosa*

**It is Gram-negative bacterium that is noted for its environmental versatility, ability to cause disease in particular susceptible individuals, and it's resistant to antibiotics (Passador *et.al.*, ١٩٩٣). It is opportunistic pathogen causes ١٢٪ of hospital acquired urinary tract infection and rarely causes community acquired infections in immunocompetent patients (Murry *et.al*., ٢٠٠٢). *Pseudomonas* with *Proteus, Serratia* and *Klebsiell*a account for (١٠-١٥) % of bacterial prostatitis (Goran, ٢٠٠١). Furthermore, bacterial infection of the genitourinary tract in immune-compromised host was recurrent *P.aeroginosa* infection (Ohi *et.al.*, ١٩٩٤).**

**The virulence factors of it have both cell associated (flagellum, pilus, non pilus adhesins, lipopolysaccharide, alginate slime) ,and extracellular virulance factor (proteases, exotoxin A, exoenzyme S, pyocyanine and hemolysin), these are extracellular products that after colonization can cause extensive tissue damage, blood stream invasion and dissemination (Jaffar- Bandjee *et.al.*, ١٩٩٥ ; Pellegr *et.al.*, ٢٠٠٤).**

**In addition, the siderophore production under low iron condition helps the growth of pathogen (Pollack *et.al.*, ٢٠٠٠).**

*C- Acinetobacter spp.*

**This genus often capsulated Gram negative bacilli or coccobacilli (often diplococco-bacilli), some strains have gelatin liquefaction (Brooks *et.al.,* ٢٠٠١). They are one of acknowledged prostate pathogens with other gram-negative uropathogens (Goran, ٢٠٠١).**

**The virulance factors of it produce hemolysin or siderophore, some species produced lipase, and they have no adhesive agents like that of *E. coli* (Bonnet, ٢٠٠٤). In addition, Al-shukri, (٢٠٠٣) mentioned that *Acinetobacter* spp. produced CFA/III, sidrophor and extracellular protease enzymes but did not produce CFA/I, CFA/II and hemolysin.**

*D- Neisseria gonorrhea*

**It has been shaped as typical Gram-negative intracellular diplococci, fastidious, oxidase positive and appears on microscopical examination of a smear of urethral exudates (men), as a pinkish-brown after incubation for ٤٨h it grows on specialized media such as Thayer-Martin medium (Baron *et.al*., ١٩٩٦). It is an important cause of sexually transmitted disease so as a man with gonococcal urethritis presented with dysuria and purulent discharge (Evangelista and Beilstein, ١٩٩٣). In addition, prostatitis is an infection of prostate gland usually caused by organisms that are sexually acquired such as *N.gonorrhoe* (Knapp, ١٩٨٨).**

### ١. ٢. ٣. ٢ *Gram-positive bacteria*

**The significance of Gram-positive cocci in patients with chronic prostatitis is:**

*A- Staphylococcal spp.*

**They are Gram-positive spherical, non-motile, non-spore-forming, occasionally capsulated bacteria usually arranged in grape like irregular clusters, they have many species but the main three species are *S.aureus, S.epidermidis* and *S.saprophyticus* (MacFaddin, ٢٠٠٠).**

***S.aureus*** **is considered as one of the probable prostate pathogens in cases with chronic prostatitis, the pathogenesis of *S.aureus* in CP is attributed to combined effects of extracellular factors and toxins together with invasive properties such as adherence, biofilm formed by MRSA have become resistant to most available antimicrobial agents and phagocytosis (Goran, ٢٠٠١; Eiichi *et. al.,* ٢٠٠٤). Other virulence factors of *S.aureus* include hemolysin, CFA/III, protein A, polysaccharide capsule (some strains), and cell wall that protect it from lysis by osmotic condition and aid the bacteria to attach to mucosal surfaces (Al-Saigh, ٢٠٠٥).**

**Typically, Coagulase-negative *Staphylococcus* may colonize the anterior urethra (Adam *et.al*., ٢٠٠٢). The predisposing factors for primary *staphylococcal* bacteriuria include nosocomial (indwelling catheters, surgery, and instrumentation) and obstructive disease such as prostatic hyperplasia (Arpi and Rennerg, ١٩٨٤; Tenover *et.al.*, ٢٠٠٥). Nickel and Costeron, (١٩٩٢) suggested that coagulase-negative *staphylococci* are involved in the pathogenesis of chronic prostatitis, but did not conclusively demonstrate that these bacteria were actually causing the inflammation and symptom complex rather than simply colonizing the prostate. The role of the *S.epidermidis* and *S.saprophyticus* in chronic prostatitis is still controversial and a matter of dispute (Lee, ٢٠٠٠).**

**The virulence factors of Coagulase - negative *Staphylococcus* following initial colonization, a copious amount of extracellular polysaccharide or slime which may correlate with pathogenicity and bacterial adherence and can be the reservoir for antibiotic resistant genes which can be transferred to other bacteria (Eiff *et.al.*,٢٠٠٢; Novick,٢٠٠٣; Heikens *et.al.*, ٢٠٠٥).**

*B- Enterococcus* spp.

**They are Gram-positive cocci, facultative anaerobe, catalase negative, non-capsulate, hydrolyze esculin and they grow readily on ordinary nutrient media and on MacConkey agar (Collee *et.al.,* ١٩٩٦). It is opportunistic pathogens capable of causing invasive disease in the presence of immunosuppression, structural anatomical abnormalities and broad-spectrum antimicrobial therapy (Robin, ٢٠٠٥).**

***Enterococci* are believed to account for ٥-١٠٪ of documented prostate infections. It is now generally agreed that *Enterococcus faecalis* may cause chronic bacterial prostatitis and related recurrent *Enterococcal* bacteruria (Bergman, ١٩٩٤; Meares, ١٩٩٧).**

**Virulence of *Enterococci* is not well understood but adhesin; hemolysin, hyalurindase, bacteriocin, proinflammatory wall and gelatinase are putative virulence factors (Weinstein *et.al.*, ١٩٩٦).**

*C- Corynebacterium* spp.

**They are Gram-positive, club-shaped, non-spore forming rods, may also contain metachromatic granules, non-motile, non-capsulate, non-acid-fast, and aerobic or facultative anaerobic (Collee *et.al.*, ١٩٩٦).**

***Corynebacterium* species have usually been acknowledged as prostate non pathogens but have been suggested as potential etiologic agents in this disease (Reiger and Ruimy١٩٩٥). The polymerase chain reaction techniques were able to identify a bacterial signal (phylogenetically Gram-positive organisms with predominance of *Corynebacterium* species) in ٦٥٪ of patients with chronic prostatitis, approximately, half of these patients tended to respond to antimicrobial therapy, whereas patients in whom molecular signals for these bacteria could not be identified did not (Tanner *et.al.,* ١٩٩٩).**

**The commonest species that cause UTI in human being is *C.urealiticum* (group D٢) that is isolated from patients with complicated UTI and it has been implicated as a cause of alkaline-encrusted cystitis and urinary tract struvite calculi (Ryan and Murray, ١٩٩٤). This bacterium is characterized by its ability to produce urease and can tolerate a high value of pH (alkaline pH), these conditions enable *C.urealiticum* to grow and colonize in urinary tract (Bsci, ٢٠٠٠).**

## ١.٢.٤ Zinc in prostatic secretion

**Zinc is an essential mineral, and the normal prostate contains a higher concentration of zinc than other human tissues, zinc deficiency may be more common because poor dietary intake or excessive body loss and may be associated with enlargement of prostate (Schater, ١٩٩٥).**

**Zinc is important to maintain prostatic health by reducing the blood level of circulating prolactine which promotes the uptake of testosterone by the prostate. This in turn leads to activation of the enzyme ٥-alpha-reductase, which catalyzes the formation of dihydrotestosterone so a high concentration of zinc will tend to reduce DHT and reduce BPH (Reed and Stich, ١٩٧٧). The studies support the concept that the prostate cells express a unique hormone-responsive, plasma membrane-associated, rapid zinc uptake transport gene associated with their unique ability to accumulate high zinc levels (Lopez and Bostwick, ١٩٩٠).**

**In healthy men, prostatic secretions contain a significant amount of zinc, which has antibacterial activity and is a key factor in the natural resistance of the male urinary tract infection (Fair *et.al.,* ١٩٧٩). In vitro studies of free zinc ions at concentrations normally found in prostatic fluid have confirmed the bactericidal**

**activity of zinc to most common pathogens that commonly cause genitourinary tract infections (Parrish *et.al.,* ١٩٨٣).**

**Zinc is found predominantly more than ٩٥٪ bound to high molecular weight lignads such as metalloenzymes, metalloproteins, nucleoproteins, and relation to its function of producing, accumulating, and secreting extremely high levels of zinc (Chandler *et.al.,* ١٩٧٩).**

**The mean value of zinc in the prostatic secretion was approximately ٣٠٠ µg/ml, with a wide range of (١٥٠-١٠٠٠) µg/ ml. In CBP and NBP these zinc levels are significantly reduced; however, it is not clear whether this indicates a predisposition to, or is the result of prostatic infection (Neal *et.al.,* ١٩٩٣). Zinc supplements increased semen levels of zinc in men with prostatitis in study by (Marmar *et.al.,* ١٩٧٥). Zinc supplements have been associated with improvement of BPH, according to one preliminary report; no research has examined their effectiveness for prostatitis and nonetheless, many doctors of natural medicine recommend zinc for this condition (Byar, ١٩٧٤). Zinc deficiency is usually accompanied by decreased urine zinc excretion (Lipasky, ٢٠٠٣).**

**Zinc can also be taken as a nutritional supplement in one of many forms as Zinc citrate, zinc acetate, and zinc sulfate may be the best absorbed, copper is an important cofactor of zinc for prostatic health and enzyme function, because zinc competes with copper**

**for absorption so copper supplementation is recommended when zinc is taken as a dietary (Bush *et.al.,* ١٩٧٤).**

**In semen, the gel proteins semenogelins I and II are digested by PSA resulting in liquefaction and release of motile spermatozoa, semen contains a high concentration of zinc, which is known to inhibit the protease activity of PSA, so the binding of zinc to semenogelins I and II that regulate the activity of PSA (Magnus *et.al*., ٢٠٠٤).**

## ١.٢.٥ Phosphatase production

**Phosphatase activity was measured as the ability of the sample to release *p*-nitrophenol from *p*-nitrophenyl phosphate (PNP), which either acid (pH ٤ to ٦) or alkaline (pH ٨ to ١١), acid phosphatase activity is higher than ٢٠٠ times abundant in prostatic tissue than in any other tissue and it is activity was dependent on divalent metal ions, specifically Co (II) and Mg (II) (Cheryl *et. al.*, ٢٠٠٢).**

**Phosphatase usually found in all living cells especially prostatic cells and are one of the master control switches that regulate virtually all types of cellular activity, to turn cellular**

**activity on enzyme called kinase attaches or tags a phosphate molecule to a specific aminoacid in the cell. To turn cellular activity off, another enzyme called protein tyrosine phosphatase, removes or snips off the phosphate molecule (Dixon, ١٩٩٩).**

**Alkaline phosphatase catalyzes the non specific hydrolysis of phosphonoesteres and is determined with enzymes isolated from prokaryotic organisms such as *E. coli* isolated from infected prostate (Holtz and Kantrowitz, ١٩٩٩).**

**It is believed that the parasitic phosphatases have a role in infection, because they are produced during human infection as in prostatic infection. Molecular cloning and characterization of addition of phosphatases have expanded our appreciation of their roles in cell activation, development, migration and adhesion (Miniatis *et.al*., ١٩٨٢).**

**In *K.pneumoniae* biofilms and colonies, alkaline phosphatase expressed in the region of biofilm immediately adjacent to the carbon and energy source (Podschun and Ullemann, ١٩٩٨). Futhermor, phosphatase enzyme was required for identification of uropathogens *S.aureus* and *S.epidermidis* which they produced this enzyme while *S.saprophiticus* did not produce it (MacFaddin, ٢٠٠٠; Ching *et.al*., ١٩٩٨).**

## ١.٢.٦ Exteracellular protease production

**Proteolytic enzymes or proteases enzymes represent a class of enzymes catalyse important proteolytic steps in tumor invasion or in infection cycle of number of pathogenic microorganism and viruses, divided as endopeptidases or proteinases and exopeptidases, these assist the hydrolysis of large polypeptides in smaller peptides and aminoacids (Beynom and Bond, ١٩٨٩).**

**It is present in the prostatic secretion causing the liquefaction of ejaculate after clotting (Aummuller *et.al*., ١٩٩٠ ; Lilja, ١٩٩٨).**

**The extracellular protease enzyme produced by *E. coli* isolated from infected prostate is responsible for degradation of damaged proteins (Pinaki *et.al*., ٢٠٠٢). This enzyme also contribute to *Staphylococcus* pathogenicity (Raksha *et.al*., ٢٠٠٣).**

**Microbial proteases account to approximately ٤٠٪ of the total worldwide enzymes sale. Proteins are degraded by microorganisms, and they utilize the degradation products as nutrients for the growth. The degradation is initiated by proteinases (endopeptidases) secreted by microorganisms and further hydrolysis by exopeptidases (Maeda and Yamamoto, ١٩٩٦; Khan and James, ١٩٩٨).**

## ١.٢.٧ Treatment of benign prostatic hyperplasia

### ١.٢.٧.١ *Medical treatment*

**Alpha blockers are widely prescribed for the treatment of benign prostatic hyperplasia, they relax smooth muscles; specifically affect muscles in the urinary tract and prostate such as tamsulosin, serum PSA is not affected (Narayan and Moon, ٢٠٠٣).**

**٥-alpha-reductase inhibitors are the drugs that block the conversion of testosterone to dihydrotestosterone such as finasteride, serum PSA is reduced (Gormley *et.al.,* ١٩٩٢). They improved voiding parameters (especially in older patients with BPH and prostatitis) and reduced intraprostatic ductal reflux (Nickel, ٢٠٠٠).**

**Combination treatment of alpha blockers and ٥-alpha-reductase inhibitors are effective in the treatment of BPH (Kathy, ٢٠٠٤).**

**Plant extracts are also reviewed because these agents are widely used in some parts of the world despite the lack of properly designed clinical trials, because plant extracts are not classified as**

**drugs, the marketing and claims are not critically scrutinized by regulatory agencies (Emil *et.al.,* ٢٠٠٤).**

### ١. ٢. ٧. ٢ *Minimally invasive therapy*

**TUMT, Laser therapy, transurethral electrovaporization of prostate, transurethral needle ablation of prostate and high-intensity focused ultrasound. These therapies used to heat the prostatic tissue results in a coagulative necrosis and induction of apoptosis; in addition, transurethral balloon dilation of the prostate is performed with specially designed catheters that enable dilation of prostatic fossa alone or with bladder neck (Blute and Lason, ٢٠٠١).**

### ١. ٢. ٧. ٣ *Surgical treatment*

**Transurethral resection of prostate (TURP) is the most common surgical procedure for BPH,complication after TURP can be high such as bleeding , urinary tract infections, sexual dysfunction, scarring in the bladder and urethra which cause obstruction, other surgical treatment include simple open prostatectomy and transurethral incision of prostate (Lim *et.al.,* ٢٠٠٤).**

## ١.٢.٨ Treatment of chronic prostatitis

### ١.٢.٨.١ *Medical treatment*

**Antimicrobial therapy of patients with chronic prostatitis depends on it's penetration into the prostate gland, their sensitivities and patients characteristics (Lee, ٢٠٠٠). The efficacy is limited, a long duration of treatment is required, and failure rates are high (٣٠-٤٠) %, infection often persists because antibiotics do not penetrate easily and no active transport mechanism exists, whereby antibiotics can enter the prostatic ducts by passive diffusion and enter the epithelial-lined prostatic glandular acini(Kalpana *et.al.,* ٢٠٠٥).**

**The epithelial cells do not allow the free passage of antibiotics unless they meet certain criteria, non-ionized, lipid-soluble and not firmly protein-bound (Dan, ٢٠٠٥). Another inhibiting factor is that prostatic fluid is acidic (pH equal to ٦.٤) compared to plasma (pH equal to ٧.٤) thus creating a pH gradient further inhibiting diffusion of acidic antibiotics into the prostatic fluid (Cox and Childs, ١٩٩٢). The objectives of therapy for chronic bacterial prostatitis are to eradicate uropathogenic microorganisms, to normalize parameters of inflammation, and to relieve symptoms (Sunil *et.al.*, ٢٠٠٤).**

**B-Lactam drugs such as amoxicillin, ampicillin, amoxicillin-clavulanic acid and cephalosporin had bactericidal activity against gram-positive and gram-negative bacteria causing prostatitis; In addition, carbenicillin which for years was the only antibiotic approved for treatment of prostatitis (Britton and Carson, ١٩٩٨).The third generation cephalosporins have broader spectrum and are reliable in sever cases of prostatitis (Curtis *et.al.,* ٢٠٠٠).**

**Trimethoprim-sulfamethoxazole (TMP-SMX) has broad-spectrum activity against most common prostatic and urinary tract pathogens and sexually transmitted pathogens like *Chlamydia* and *Gonorrheal* organisms, it is ineffective against *Pseudomonas* spp. and *Enterococcus* spp. (Kalpana *et.al.,* ٢٠٠٥). Trimethoprim achieves high concentrations in the acidic pH of the normal prostate. However, the natural or alkaline pH often encountered in prostatic secretion from patients with chronic prostatitis means that prostatic fluid trimethoprim concentration can be expected to be negligible, which may explain why clinical studies show TMP-SMX cure rates less than ٥٠٪ in patients with chronic bacterial prostatitis; Hence, (TMP-SMX) are generally not first line choices for chronic prostatitis (Chesley and Dow, ١٩٧٣). In addition, Lept and Miller, (٢٠٠١) reported that the microbial resistance to TMP-SMX exceed (١٠-٢٠) %.**

**Flouroquinolones are first line in the treatment chronic bacterial prostatitis, because they have excellent pharmacodynamic properties, good prostate tissue penetration, high bioavailability, equivalence between oral and parenteral forms, and little proclivity for promoting bacterial resistance (Schaeffer and Darras, ١٩٩٠). Flouroquinolones like naldixic acid, norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, gatifloxacin demonstrated improved therapeutic results, especially in chronic prostatitis caused by *E. coli* and other members of the Enterobacteriaceae (Donnell and Gelone. ٢٠٠٠; Nabert *et.al.,* ٢٠٠٤). Ciprofloxacin achieves concentrations in seminal fluid up to nine times more than the plasma and choice for greater than ٩٠٪ of chronic prostatitis (Riemon, ١٩٨٩).**

**Aminoglycosides are bactericidal action and the most important newer one is amikacin which is more effective than gentamycin in the treatment of chronic prostatitis (Sunil *et.al*., ٢٠٠٤). Aminoglycosides have good activity against Gram-negative uropathogens, such as *Pseudomonas* spp. When combined this group with β-lactame antibiotic including newer penicillins and third generation cephalosporins, they provide a synergic effect against certain bacterial species like *Enterococci* (Warren *et.al*., ٢٠٠٤). It can be in combination with TMP-SMX against Gram-positive uropathogens (Ghiro *et.al.,* ٢٠٠٢).**

**Tetracyclines are broad-spectrum bacteriostatic antibiotic. They are active against a wide range of Gram-positive and Gram-negative bacteria in chronic bacterial prostatitis, they are also used as alternative antibiotic when penicillin is contraindicated (Yu *et.al.,* ١٩٩٩). Doxycycline is a semisynthetic tetracycline with lower side effect, both minocycline and doxycycline have good penetration into the prostate but doxycycline is preferred because it is less toxic than minocycline and resistance to minocycline can be high in urinary tract pathogens (Paulson *et.al*., ١٩٨٦). Furthermore, doxycycline is effective for treatment of chronic bacterial prostatitis caused by *Staphylococcus* or *Pseudomonas* spp. (Saber, ٢٠٠٢).**

**Alpha blockers diminish intraprostatic ductal reflux. A combination treatment of alpha-blockers and antibiotics are reported to have a higher cure rate than antibiotic alone in inflammatory chronic pelvic pain syndrome (Barbalies *et.al*., ١٩٩٨).**

**Anti-inflammatory agents and immune modulators such as non steroidal anti-inflammatory drugs, steroids, and immunosuppressive drugs theoretically should improve the inflammatory parameters within the prostate and possibly result in a reduction of symptoms (Nickel, ٢٠٠٠).**

**Skeletal muscle relaxants combined with adjuvant medical and physical therapies have been advocated and promoted (Britton and Carson, ١٩٩٨).**

**The allopurinol groups had lower levels of serum urate, urine urate, and EPS urate and xanthine (Bishop *et.al.,* ٢٠٠٥).**

### ١.٢.٨.٢. *Transurethral microwave thermotherapy*

**It is believed that the heat applied to the prostate gland by the microwave process could shorten the natural resolution of the inflammatory process, perhaps by accelerating the process of fibrosis or scar formation in the area of chronic inflammation and it may be even kills cryptic bacteria (Mears, ١٩٩٧).**

## ٢.١ Patients & Materials

### ٢.١.١ Patients

One hundred fifty (١٥٠) male patients whose ages ranged between (٣٠-٩٩) years underwent the study from (October) ٢٠٠٤ to (May) ٢٠٠٥; these patients visited Hilla teaching Hospital-Department of Urology.

All patients underwent full history and complete physical examination by the urologist. (١٥٠) urine samples collected from all

patients. (٣٣) prostatic secretions were taken. Investigation was sent for general urine examination, urine culture and sensitivity, EPS examination, culture and sensitivity, blood urea, serum creatinine and abdominal ultrasound.

## ٢.١.٢ Specimens collection

### *A-Urine sample*

Midstream urine sample was collected which allowed the first drops of urine to pass; the samples of urine were collected in the sterilized screw-cap container.

### *B-Expressed prostatic secretion sample*

Samples were taken after prostatic massage by urologist in classical way under sterile condition.

## ٢.١.٣ Laboratory instruments

The Laboratory instruments used in this study are shown in (Table ٢.١).

Table (٢.١): Laboratory instruments used

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

## ٢.١.٤ Chemical &biological materials

### *A-Chemical materials*

The Chemical & Biological materials used in this work are shown in Table (٢.٢).

*Table (٢.٢): Chemical & biological materials used*

| No. | Chemicals | Company |
|---|---|---|
| ١ | NaCl, $MgSO_4$, $KH_2PO_4$, $Na_2HPO_4$, $CaCl_2$, KOH, $K_2HPO_4$. | Merk-Darmstad |
| ٢ | α-naphthol, esculin, Trichloroacetic acid, Tetramethyl-***p***-paraphylenediamine dihydrochloride | B.D.H. |
| ٣ | *p*-nitrophenyl phosphate (PNP). | Randox Laboratories |
| ٤ | Citrate buffer | LTd., (USA) |
| ٥ | $ZnSO_4$ | Alhavi ( Iran) |
| ٦ | $H_2O_2$, Glucose, ٩٩٪ alcohol (Ethanol), Urea solution, Kovac's reagents. | Fluka chemika-Switzerlan. |
| ٧ | Amoxicillin powder | S.D.I. – IRAG. |
| ٨ | Cefotaxim powder | Mauritius (Ajanta) |

| | | |
|---|---|---|
| ٩ | Ciprofloxacin and Amikacin powder | Reyoung,Pharma Naraina (India) |
| ١٠ | Antibiotics discs | OXIOD-England |

## B- Culture media

The culture media used in this work are shown in (Table ٢.٣).

**Table (٢.٣): Culture media used**

| No. | Media | Company |
|---|---|---|
| ١ | Blood base agar, Brain heart infusion agar, agar-agar, Muller-Hinton agar, MacConkey agar, Mannitol salt agar, Peptone broth. | Mast |
| ٢ | Nutrient agar media, Nutrient broth. | Oxiod |
| ٣ | Urea base agar, Simmon citrate agar, Triple sugar iron agar, MR-VP broth | Diffco-Michigan |

# ٢.٢ Methodology

## ٢.٢.١ The preparation of reagents

### ١. Oxidase reagent:

It was prepared directly by dissolving ٠.١gm of Tetra-*p*-paraphenylene diamine dihyhydrochloride in ١٠ ml of distill water and stored in a dark container (Baron *et.al.*, ١٩٩٦).

### ٢. Catalase reagent:

It was prepared by adding ٣% of $H_2O_2$ solution and was stored in dark container (Collee *et.al.*, ١٩٩٦).

### ٣. 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).

### ٤. Voges-Proskauer reagent:

A. ٥ gm of α-naphthol was dissolved in ١٠٠ ml of ٩٩٪ ethanol then stored in a dark container away from light.

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

**٥. Kovac's reagent:**

It was prepared by dissolving ٥gm of (*p*-dimethylaminobenzaldyde) in ٧٥ ml Amyl alcohol, and then ٣٥ ml of HCl was added. This reagent used for detection of indole (MacFaddin, ٢٠٠٠).

## ٢.٢.٢ The preparation of media

**١. M٩ media:** ٦gm of Na٢HPO٤, ٣gm of KH٢PO٤, ٠.٥ gm of NaCl and ١gm of NH٤Cl are dissolved in ٩٥٠ ml of distill water with ٢٪ agar & then they were sterilized into autoclave after cooling the mixture to ٥٠ C°, ٢ ml of ١M of MgSO٤, ١٠ ml of ٢٠٪ glucose & ٠.١ ml of ١M of CaCl٢ (all of them were 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 (Holt *et.al.*, ١٩٩٤). This media was made from preparation of nutrient agar with ٠.٤ gm ferric citrate & ٤ gm esculin added to it & volume was completed to ١٠٠٠ ml. After that the media was poured into tubes & all were sterilized into autoclave then a slant of media was formed (MacFaddin *et.al.*, ٢٠٠٠).

## ٢.٢.٣ The preparation of solutions

**١. The preparation of p-nitrophenyl phosphate solution:** ٠.١gm of *p*-nitrophenyl phosphate powder was dissolved in ٠.٩ ml of citrate buffer at pH (٥-٥.٥) then all of them were dissolved in ٩٩ ml of sterile distill water in which the volume was completed to ١٠٠ ml (Penny and Huddy, ١٩٦٧).

**٢. Antibiotics solutions:**

**A. Amoxicillin solution:** ١ gm from amoxicillin powder was dissolved in ٩٠ ml of sterile distill water then the volume was completed to ١٠٠ ml to obtain total concentration (١٠mg/ml) (Miniatis *et.al.*, ١٩٨٢).

**B. Cefotaxim solution:** ١ gm from cefotaxim powder was dissolved in ٩٠ ml of sterile distill water then the volume was completed to ١٠٠ml to obtain final concentration (١٠mg/ml) (Miniatis *et.al.*, ١٩٨٢).

**C. Amikacin solution:** ١gm from amikacin powder was dissolved in ٩٠ ml of sterile distill water then the volume was completed to ١٠٠ml to obtain final concentration (١٠mg/ml) (Miniatis *et.al.*, ١٩٨٢).

**D. Ciprofloxacin solution:** ٠.٢ gm of ciprofloxacin powder was dissolved in ٩٠ ml of sterile distill water, then the volume was

completed to ١٠٠ml to obtain final concentration (٢mg/ml) (Miniatis *et.al.,* ١٩٨٢).

## ٢.٢.٤ Stains

١- **Grams stain:** This stain was used to differentiate Gram-negative from Gram-positive bacteria.

٢- **Albert stain:**This stain was used to diagnose *Corynebacterium*

- A heavy smear of bacterial isolate was prepared on glass slide and allowed to dry without fixing.
- Albert stain was applied for (٣-٤) minutes then it was washed with water and Albert iodine was applied for one minute

It was washed with water allowed to dry in air and later it was examined under the microscope showed bacilli with numerous metachromatic granules (Benson, ١٩٩٨).

٣- **Capsule stain:**

- A heavy smear of bacterial isolate was prepared on glass slide and allowed to dry.
- ١٪ Crystal violet was applied to fixed smear and waited for about ٥ minutes.

The smear was washed with ٢٠٪ copper sulfate solution as counter stain then it was allowed to dry in air and later it was

examined under the microscope in which the capsule appeared as a light blue in contrast to a deep purple of the cell (Cruickshank *et.al.*, ١٩٧٥).

## ٢.٢.٥ General urine examination

It was done as the following:

The urine spine in centrifuged to allow sediments then examined microscopically for the presence of pus cells (WBC) and red blood cells (RBC) as method of (Graham, and Galloway, ٢٠٠١).

## ٢.٢.٦ Expressed prostatitic secretion examination

It was done as the following:

EPS was examined microscopically for the presence of pus cells (WBC) and red blood cells (RBC) as method of (Cruickshank *et.al.*, ١٩٧٥).

## ٢.٢.٧ Identification of bacteria

A single colony was taken from each primary positive culture and it was identified depending on its morphology then examined microscopically after staining it with gram-stain or other specific

stain such as Albert stain for diagnosis of *Corynebacterium*. After staining, the other biochemical tests were done to each isolate according to (MacFaddin, ٢٠٠٠).

## ٢.٢.٨ Biochemical tests

### ١. Catalase test:

A colony of the organism was transferred to drop of ٣٪ H٢O٢ on a microscope slide, by using sterile wooden sticked colonies on the slide, the presence of catalase meant that the formation of gas bubbles had occurred which indicated the positive result (Collee *et.al*., ١٩٩٦).

### ٢. Oxidase test:

A piece of filter paper was saturated in a petridish with oxidase reagent then a small portion of the colony of bacteria was spread on the filter paper by wooden stick, when the color around the smear turned from rose to purple that mean the oxidase test was positive (Baron *et.al*., ١٩٩٦).

### 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 was incubated at ٣٧ C° overnight**.** The test was read

by tilting the tube and observing clot formation in the plasma. Negative test results in the plasma remained free-flowing with no evidence of a clot (Collee *et.al.,* ١٩٩٦).

## ٤. Indol test:

١٪ of tryptophane broth solution was prepared in the tubes then it was sterilised into autoclave, the tubes were inoculated with several bacterial colonies by the loop and it was incubated for (٤٨-٧٢) hours at ٣٧ Cº, Indol test was done by adding ٦-٨ drops of Kovac's reagent, the positive reaction (red color ring) at top of broth while (yellow color ring) was indicated a negative result (MacFaddin, ٢٠٠٠).

## ٥. Methyl Red test:

The test was performed by preparing (MR-VP broth) with ٥ ml in each tube. The tubes were inoculated with bacterial colonies then they were incubated for ٢٤ hours at ٣٧C°. After that ٦-٨ drops of methyl red reagent were added. The change of color to orange-red indicated a positive result (MacFaddin, ٢٠٠٠).

## ٦. Voges - Proskauer test:

The test was performed by preparing (MR-VP broth) as ٥ ml in each tube. The tubes were inoculated with bacterial colonies then they were incubated for ٢٤ hours at ٣٧ C°. After that ١٥ drops of ٥٪ alpha-naphthol (reagent A) were added followed by ١٠ drops of

٤٠٪ KOH (reagent B) then shaken well and allowed standing up for ١٥ minutes before considering the reaction as negative. The change of color to red mean a positive result and this indicated partial analysis of glucose which produced (acetyl methyl carbonyl) (Collee *et.al.*, ١٩٩٦).

## ٧. Simmon Citrate test:

After the sterilization of Simon citrate slants by autoclave, the bacterial colonies were inoculated and incubated them for (٢٤-٤٨) hours at ٣٧C°. The change of color of media from green to blue indicated positive result. While the unchange of the color indicated negative reaction (Benson, ١٩٩٨).

## ٨. Urease test:

The urea base agar was sterilized by autoclave then it was cooled to ٥٠C°. The urea substrate was added to it and poured in sterile tubes; then inoculated by bacterial colonies and the tubes were incubated for (٢٤-٤٨) hours at ٣٧C°. The color changed to a deep pink which indicated positive result while unchanging of the color meant negative reaction (Benson, ١٩٩٨).

## ٩. 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 result (MacFaddin, ٢٠٠٠).

## ١٠. Triple Sugar Iron (TSI) test:

The aim is to differentiate Enterobacteriaceae according to carbohydrate fermentation and hydrogen sulfide production. The bacterial colonies were inoculated on TSI media slant by stabbing and streaking then they were incubated at ٣٧C° 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 bottom of slant. In addition, the formation of hydrogen sulfide was given a black color precipitation at bottom (MacFaddin, ٢٠٠٠).

## ١١. Eosin Methylene Blue (EMB) agar:

After culturing the bacteria on this media, bacterial colonies with lactose-fermented were either dark centers with transparent colorless peripheries or metallic sheen, while those that did not ferment lactose remain uncolored. This purple color was due to absorption of the eosin-methylene blue complex, which formed in the presence of acid. Certain members of the coliform group, especially *E. coli*, exhibited a greenish metallic sheen in reflected light (Baron *et.al*., ١٩٩٦).

## ١٢. Mannitol salt agar:

The medium was inoculated with bacterial colonies then incubated at ٣٧C° for ٢٤ hours. The color changed from pink to

bright yellow when the bacteria was lactose fermented and meant positive result, while unchanging color of the medium was negative result (MacFaddin,٢٠٠٠).

## ١٣. Motility Test:-

The semisolid media was dispensed in test tubes with ١٠ ml in each tube and leaving the set in vertical position then the bacterial colonies were inoculated by stabbing singly down the center of the tube to about half the depth of the medium. The cultured tubes were incubated at ٣٧C° and the tubes were examined after 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, while motile bacteria were typically given diffuse hazy growths that spread throughout the medium rendering it slightly opaque (MacFaddin, ٢٠٠٠).

## ٢.٢.٩ Antibiotics sensitivity test:

Antibiotic diffusion test (The Kirby- Bauer susceptibility test).

١. It was performed by 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 the streaked on a Muller-Hinton plate.

٢. 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 optimal time of ١٤ hours at ٣٧C°.

٣. Antibiotics inhibition zones were measured using a caliber; zone size was compared to standard zones to determine the susceptibility or resistance of organism to each antibiotic (MacFaddin, ٢٠٠٠).

Antibiotics discs potency was supplied from Oxiod Company (Table٢. ٢.٤).

Table (٢.٤): Antibiotics discs potency

| No. | *Antibiotics* | Discs potency µg/ml |
|---|---|---|
| ١ | AMX | ١٠ |
| ٢ | AMC | ٣٠ |
| ٣ | CTX | ١٠ |
| ٤ | CXN | ٣٠ |
| ٥ | GM | ٣٠ |

| | | |
|---|---|---|
| ٦ | AK | ٣٠ |
| ٧ | DOX | ٣٠ |
| ٨ | CIP | ٣٠ |
| ٩ | TMP | ٣٠ |
| ١٠ | NA | ٣٠ |
| ١١ | NOV | ٥ |

AMX: Amoxicillin; AMC: Amoxcillin-Clavulanicacid; CTX: Cefotaxim; CXN: Cephalexin; GM: Gentamicin AK: Amikacin; DOX: Doxycyclin; CIP: Ciprofloxacin; TMP-SMX: Trimethoprim-Sulfamethoxazole; NA: Naldixic acid; NOV: Novobiocin.

## ٢.٢.١٠ Effect of zinc on bacterial growth

The effect of zinc sulfate was tested by the following method (Al-Saeed, ١٩٩٧).

A. Nutrient broth was prepared in tubes and zinc sulfate was added to each tube at various volumes to gain the final concentration (٠.١٥, ٠.٣, ٠.٤٥, ٠.٦, ٠.٧٥, ٠.٩, ١.٠٥, ١.٢, ١.٣٥, and ١.٥) mg/ml.
B. Positive control was prepared by using nutrient broth free from zinc sulfate.

C. The tubes were inoculated with ٠.١ml of freshly grown bacterial suspension, then serial of tenth fold dilutions ($١٠^{-١}$, $١٠^{-٢}$, $١٠^{-٣}$, $١٠^{-٤}$, $١٠^{-٥}$) were used in sterile normal saline.
D. With the use of spreader the bacterial strains were streaked on the supplemented nutrient agar and incubated for ٢٤ hr. at ٣٧ C°.
E. After the period of incubation, the viable count of bacteria was estimated by multiply the number of colonies/plate by the dilution factor to obtain the viable count/ml in original suspension (Collee *et.al*., ١٩٩٦).

## ٢.٢.١١ Effect of combination of some antibiotics with zinc sulfate on bacterial growth

The effect of combination of antibiotics with zinc sulfate was tested by the following method (Al-Saeed, ١٩٩٧).

A. Nutrient broth was prepared in tubes as ٢ml in each tube.
B. The antibiotics solutions were added to each tube as ٠.٢mg of each of amoxicillin and cefotaxim, ٠.١mg of amikacin, lastly ٠.٠٤ mg of ciprofloxacin.
C. A different volume of zinc sulfate was added to each tube to get final concentration (٠.٩, ١.٠٥, ١.٢, ١.٣٥, and ١.٥) mg/ml.

D. A positive control was prepared by using nutrient broth with antibiotics only.
E. The tubes were inoculated with ٠.١ml of freshly grown bacterial suspension, then a serial tenth fold dilution ($١٠^{-١}$, $١٠^{-٢}$, $١٠^{-٣}$, $١٠^{-٤}$, $١٠^{-٥}$) in sterile normal saline in relation to antibiotics alone and antibiotics with zinc sulfate.
F. The colonies were streaked on the supplemented nutrient agar and incubated for ٢٤ hr. at ٣٧C°.
G. After incubation the viable count of bacteria was estimated as mentioned above (٢.٢.٩).

## ٢.٢.١٢ Phosphatase production

Phosphatase was prepared by procedure of (Penny and Huddy, ١٩٦٧). This procedure depends on the hydrolysis of *p*-nitrophenyl phosphate (PNP) as following:

١. About ٠.٥ml of ٠.١٪ PNP was added in each tube.
٢. Each tube was inoculated with a heavy inoculum from blood agar.
٣. The tubes were incubated for (٤) hours at ٣٧C°, if the color changed to yellowish that meant liberation of *p*-nitrophenol which indicated the positive result. While unchanged of the color indicated negative reaction.

### ٢.٢.١٣ Extracellular protease production

This method was carried out by using M٩ agar supplemented with ٢٪ agar. After sterilization in autoclave and cooling it at ٥٠C°, ٠.٢٥ gm/L glucose (sterilized by filtration) was added, and then the medium was supported by ١٪ Gelatin. After that this medium was inoculated with bacterial strain and was incubated for (٢٤-٤٨) hours at ٣٧C°, and then ٣ ml of Trichloroacetic acid (٥٪) was added to precipitate the protein. The formation of transparent area around the colony indicated the positive result (Benson *et.al.*, ١٩٩٨).

## ٣.١ Clinical Study

### ٣.١.١ Benign prostatic hyperplasia and chronic prostatitis

**One hundred fifty patients aged (٣٠ – ٩٩) years old suffered from lower urinary tract symptoms associated with benign prostatic hyperplasia& or chronic prostatitis.**

Clinically, this work included three variants of patients (Table ٣.١).

| Diagnosis | No. of patients | % |
|---|---|---|

| | | |
|---|---|---|
| **Benign prostatic hyperplasia** | ١١٧ | ٧٨٪ |
| **Chronic prostatitis** | ٢٠ | ١٣.٣٪ |
| **BPH and chronic prostatitis** | ١٣ | ٨.٧٪ |
| Total | ١٥٠ | ١٠٠٪ |

Table (٣.١): Distribution of patients with benign prostatic hyperplasia & or chronic prostatitis

**Seventy eight percent of patients were presented with benign prostatic hyperplasia only, while (١٣.٣٪) had chronic prostatitis and (٨.٧٪) had both CP and BPH. There was a significant difference between patients according to diagnosis (p<٠.٠١).**

**In fact, these groups of patients were selected according to age, symptoms, physical examination by urologist and investigation. Usually, BPH patients aged more than ٥٠ years, while chronic prostatitis patients, their ages less than ٥٠ years and both groups presented with lower urinary tract symptoms. Pain such as suprapubic pain, perneal and testicular pain) was presented in those who had chronic prostatitis. Third group of patients aged more than ٥٠ years old and presented with lower urinary tract symptoms associated with pain.**

**The results of this research agreed with those obtained by (Mittal *et.al.*, ١٩٨٩) and (Kaplan *et.al.*, ٢٠٠٠) who noticed that the prevalence of BPH was (٩٢.٩٧٪) and (٨٦.٣٪) respectively.**

Moreover, these findings matched those of (Joe *et.al.*, ٢٠٠٠) who reported that the prevalence of chronic prostatitis was ١١.٥٪ in men below ٥٠ years old and (٨.٥٪) in men over ٥٠ years of age.

## ٣.١.٢ Age related disease

The most affected age group presented with benign prostatic hyperplasia was between (٥٠-٧٩) years (٧٧.٣%) as in (Figure ٣.١). The highly affected age group between (٦٠-٦٩) years old (٣٤٪). This correlated with the results of Huges *et al.*, (٢٠٠٠) who determined that the prevalence of lower urinary tract symptoms in men whose age was between (٤٠-٨٠) years old suggestive of benign prostatic hyperplasia increased linearly from ٣.٥٪ in men in their late ٤٠s to ٣٥٪ in men in their late ٨٠s. Furthermore, Lukacs, (٢٠٠٥) found that benign prostatic hyperplasia was a common adenomatous hyperplasia of periurethral gland which affected at least ٦٥٪ of men over ٥٥ years old.

In this study, the mean age was (٦٣.٩) years. This result matched those of Kaplan *et.al.*, (٢٠٠٠) who reported that the mean age in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia was (٦٥.٩) years. In addition, Lim *et.al.*, (٢٠٠٤) stated that the mean age of patients with benign

**prostatic disorder from ١٩٧٠s, ١٩٨٠s and ١٩٩٩ were (٦٨.٨, ٦٩.٢ and ٦٩.٤) years respectively. Furthermore, Haidinger *et.al.*, (٢٠٠٠) pointed that the most important risk factor of the lower urinary tract symptoms was the age and the mean age in their study was (٥١.٣)years old.**

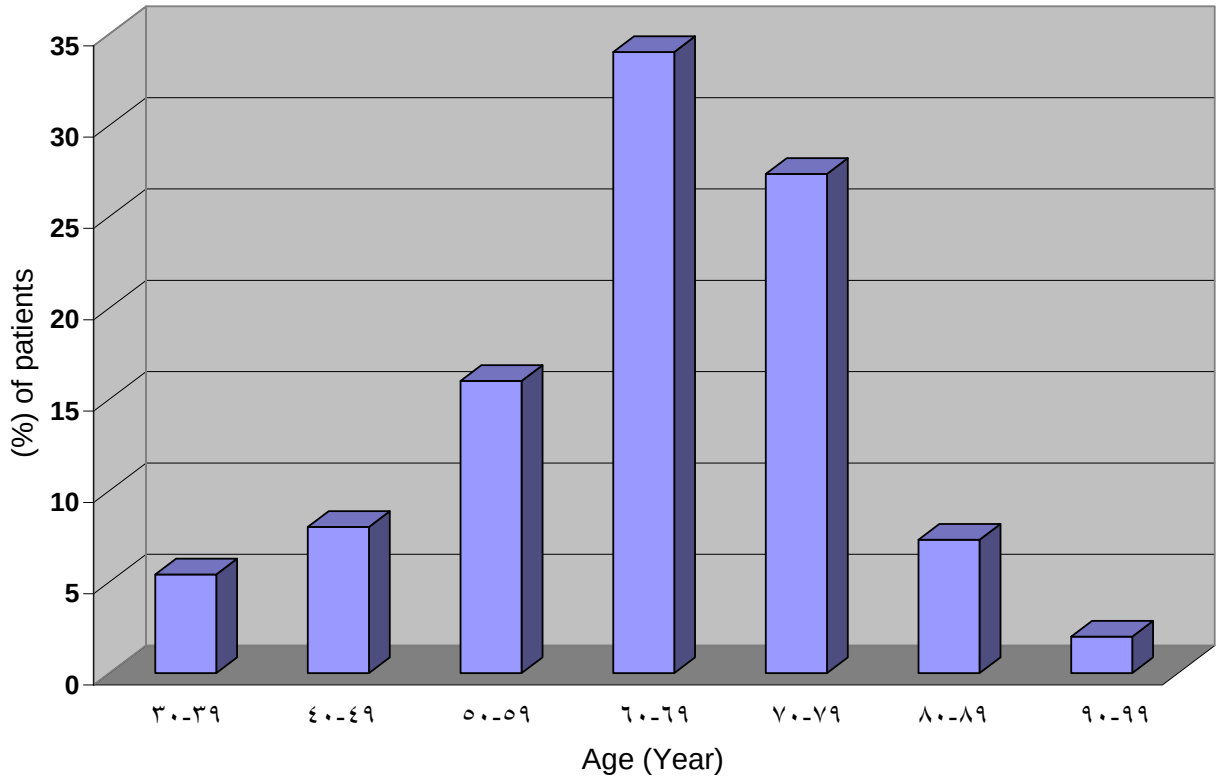



Figure (٣.١): Percentage of ages of patients with benign prostatic hyperplasia & or chronic prostatitis.

**On the other hand, the age group between (٣٠-٤٩) years old was (١٣.٣%) which diagnosed as chronic prostatitis. This result matched those of Jiao *et.al.*, (٢٠٠٢) who showed that the chronic prostatitis was a common prostatic disorder that affected the ages between (٢٠-٥٠) years old.**

## ٣.١.٣ Urinary tract infection

**Benign prostatic hyperplasia and chronic prostatitis cause urinary tract infection; In addition, the following factors may predispose to urinary tract infection in (١٥٠) study patients (Table ٣.٢).**

**Table (٣.٢): Number and percentage of factors predispose to UTI in patients with benign hyperplasia & or chronic prostatitis**

| Predisposing factors | N٠. of patients | % |
|---|---|---|
| **PVR*** | ٣١ | ٢٠.٧% |
| **History of catheterization** | ١٥ | ١٠٪ |
| **Cystoscopy** | ٦ | ٤٪ |

PVR* - Post Voiding Residual Urine volume

**The post voiding residual urine was found in ٢٠.٧%, while ١٠٪ had history of catheterization. Cystoscopy was done to ٤٪ of them.**

**Urinary tract infection is more common in elderly men because of significant residual bladder urine, poor emptying the bladder due to prostatic hyperplasia and increased use of instrumentation (Lipsky, ٢٠٠٣; David *et.al.,* ٢٠٠٠). The results of this work agreed with those of Steele *et.al*., (٢٠٠٠) who reported that ١٠٠٪ of normal men PVR less than ١٢ml, also noticed that chronic outflow obstruction associated with prostatic hyperplasia is believed to be accompanied by increasing post void residual urine volumes which demonstrated by ultrasound or catheter in which depending on the degree of urine obstruction, the tension in the detrusor wall rises with increasing bladder volume and varying degrees of urinary retention.**

**The important complication of benign prostatic hyperplasia is retention of urine which needs indwelling catheter in which the rates of catheter-associated UTIs range between (٩-٢٣) % (Jonson *et.al.*, ١٩٩٠).**

**Elevated post voiding residual urine considered as good media for bacterial growth which may cause infection. In addition, instrumentation increases the risk for UTI (Morten, ٢٠٠٤).**

## ٣.١.٤ Clinical features

**The highest lower urinary tract symptoms associated with (١٥٠) study patients were frequency which were presented in (٩٨٪) of patients, nocturia (٩٠٪), urgency (٨٢٪), hesitancy (٥٣٪), dysuria (٥١.٣٪), poor stream (٤٦.٧٪) and dribbling of urine (٢٢٪). Other symptoms included pain which presented in patients who had chronic prostatitis such as (suprapubic pain, lower backache, groin and perineal pain) in ٢٢% (Table ٣.٣).**

Table (٣.٣): Number and percentage of symptoms in patients with benign prostatic hyperplasia & or chronic prostatitis

| Symptoms | No. of patients | % |
|---|---|---|
| **Frequency** | ١٤٧ | ٩٨٪ |
| **Nocturia** | ١٣٥ | ٩٠٪ |
| Urgency | ١٢٣ | ٨٢٪ |
| **Hesitancy** | ٨٠ | ٥٣٪ |
| **Dysuria** | ٧٧ | ٥١.٣٪ |
| Poor stream | ٧٠ | ٤٦.٧٪ |
| **Dribbling of urine** | ٣٣ | ٢٢٪ |
| **Pain** | ٣٣ | ٢٢٪ |

These results correlated with those of Saldden, (٢٠٠٠) who reported that the important lower urinary tract symptoms in men aged between (٤٠-٨٠) years old are frequency ٧٢.٧٪, nocturia ٧٢.٧٪, urgency ٣٠٪, and dysuria ٧٦.٥٪, poor stream ٥٤.٥٪, dribbling of urine ٣٥٪.

**Obstruction-induced changes in detrusor function, compounded by age-related changes in both bladder and nervous system function, lead to urinary frequency, urgency, and nocturia, the most bothersome BPH-related complaints (Haidinger *et.al.,* ٢٠٠٠; Donovan *et.al.,* ١٩٩٧).**

**The predominant symptom in patients with prostatitis was pain, which was most commonly localized in the perineum, suprapubic area, and penis, but can also occur in the testes, groin, or low back, pain during or after ejaculation is a prominent feature in many patients. In addition, irritative and obstructive voiding symptoms including urgency, frequency, hesitancy, and poor interrupted urine flow are associated with many patients with prostatitis (Nickel, ٢٠٠٠).**

## ٣.١.٥ General urine examination

**Regarding the general urine examination of (١٥٠) samples submitted by study patients. Microscopically, it was found that pus cells was present in ٥٤٪, ١٢٪ of them had sterile pyuria with culture and sensitivity negative (Table ٣.٤).**

**Pyuria in male referred to WBC count over ١٠/HPF correlates well with significant leukocyte excretion rates and is considered the**

**standard for the determination of significant pyuria which is usually sufficient for a diagnosis of UTI in non hospitalized patients if standard symptoms, also is associated with infection or inflammation of urinary tract as in BPH (Graham, and Galloway. ٢٠٠١).**

Table (٣.٤): Number and percentage of microscopical urine examination in patients with benign prostatic hyperplasia & or chronic prostatitis

| Items of GUE | No. of samples | % |
|---|---|---|
| Pus cells | ٨١ | ٥٤٪ |
| RBC | ٣١ | ٢٠.٧٪ |
| Bacteruria | ١٢ | ٨٪ |

**Sterile pyuria is associated with a number of infectious and non-infectious causes, including *Chlamydia trachomatis*, *Ureoplasma urealyticum* and *Mycobacterium tuberculosis*, structural and physiological abnormalities of the genitourinary tract, and recent antibiotic treatment (Lammers *et.al.,* ٢٠٠١). RBC was represented in ٢٠.٧٪ which may be due to BPH or may be associated with severe infection of urinary tract (Barry, ٢٠٠٣).**

**Bacteruria was presented in ٨٪ of samples. These results were close to the results of Boscia *et. al*., (١٩٨٦) who pointed that**

**bacteruria is more common in elderly men because of increased susceptibility to UTI.**

## ٣.١.٦ Expressed prostatic secretion examination

**The microscopical examination of (٣٣) expressed prostatic secretion was done. It was found that pus cells ٦٠.٦ %, RBC ١٢.١% (Table ٣.٥). ٤٥.٤٪ of samples had pus cells associated with positive culture results (Table ٣.٧) which indicated bacterial prostatitis, while the remainder pus cells due to inflammatory type of chronic pelvic pain syndrome. While absent of pus cells meant non inflammatory CPPS.**

**Chronic pelvic pain syndrome is recognized as discomfort or pain in pelvic region and it is either inflammatory type which more than ١٠ of WBC in semen/expressed prostatic secretion (EPS)/urine specimen after prostatic massage (VB٣) or non inflammatory which less than ١٠ of WBC cells in semen/expressed prostatic secretion (EPS)/urine specimen after prostatic massage (VB٣)(Jiao *et.al.*,٢٠٠٢).**

**Table (٣.٥): Number and percentage of microscopical expressed prostatic secretion examination in patients with chronic prostatitis**

| Items of EPS | No. of samples | % |
|---|---|---|
| Pus cells | ١٨ | ٦٦.٦٪ |
| RBC | ٤ | ١٢.١٪ |

## ٣.٢ Bacterial isolation

### ٣.٢.١ Bacterial isolates from urine specimens in patients with benign prostatic hyperplasia& or chronic prostatits

**The results of (١٥٠) urine culture revealed that (٦٥) samples had resulted in positive culture for bacteria ٤٣.٣٪ (Table ٣.٦). Morten, (٢٠٠٤) showed that the prevalence of UTI in males increases with age, among ages ranging from (٣٦-٦٥) years old, the prevalence is ٢٠% and in more than ٦٥ years group is ٣٥٪. These infections are almost invariably complicated and relate to many causes such as prostatic hyperplasia, chronic prostatitis and catheterization.**

**In addition, Gilberts, (١٩٩٩) noticed that the prevalence of UTI in benign prostatic disorder were ٤٠٪.**

**In this study, *E. coli* was the most common type of bacterial isolates ١٤.٧٪, followed by *Staphylococcus epidermidis* ٦٪, *Klebsiella pneumoniae* and *Staphylococcus aureus* and each of which represented ٤٪, *Acinetobacter* spp. ٣.٣٪, *Enterobacter* and *Pseudomonas aeruginosa* and each of which represented ٢.٧٪, *Proteus mirabilis* ٢٪. In addition, *Staphylococcus saprophyticus*, *Corynebacterium* spp. and *Enterococcus* spp. represented ١.٣% each (Table ٣.٦).**

**These results can be compared with the results of Romolo *et. al*., (٢٠٠٤) who established that complicated UTIs involve a diverse spectrum of microorganisms, but the most common one is *E.coli* which is responsible for more complicated UTIs than any other single organism, it represented approximately (٤٠-٥٥)% of isolates from patients with complicated UTIs. *K. pneumoniae*, *Enterobacter* spp., *Proteus mirabilis* and *Enterococcus* spp. each one represented (٥-١٠) % of isolates. The remaining was due to *P. aeruoginosa* and *Staphylococcus* spp.**

**Furthermore, Graham and Galloway, (٢٠٠١); Ahmed, (٢٠٠٥) revealed that *E. coli* and *Enterobacter* were the main uropathogen in adolescent men while in elderly men *Psedomonas aeurginosa*, *Klebsiella* spp., *Enterobacte*r and *Proteus* spp. were increasingly prevalent. Moreover, Bouza *et.al*., (٢٠٠١) and Al-Amedi, (٢٠٠٣)**

**confirmed that *E. coli* was the commonest uropathogen (٣٨.١٪) and (٣٥.٦%) respectively.**

Table (٣.٦): Number and percentage of bacterial isolates from urine specimens in patients with benign prostatic hyperplasia & or chronic prostatitis

| Types of bacterial isolates | No. of isolates | % |
|---|---|---|
| ***E. coli*** | ٢٢ | ١٤.٧٪ |
| ***Staphylococcus epidermidis*** | ٩ | ٦٪ |
| ***Klebsiella pneumoniae*** | ٦ | ٤٪ |
| ***Staphylococcus aureus*** | ٦ | ٤٪ |
| ***Acinetobacter* spp.** | ٥ | ٣.٣٪ |
| ***Enterobacter* spp.** | ٤ | ٢.٧٪ |
| ***Pseudomonas aeroginosa*** | ٤ | ٢.٧٪ |
| ***Proteus mirabilis*** | ٣ | ٢٪ |
| ***Staphylococcus saprophiticus*** | ٢ | ١.٣٪ |
| ***Enterococcus* spp.** | ٢ | ١.٣٪ |
| ***Corynebacterium* spp.** | ٢ | ١.٣٪ |
| Culture positive | ٦٥ | ٤٣.٣٪ |
| Culture negative | ٨٥ | ٥٦.٧٪ |
| Total | ١٥٠ | ١٠٠٪ |

**In addition, (Jones *et.al.,* ١٩٩٩) noticed that in a survey of UTI pathogens, the top isolate was *E. coli* (٤٨.٦٪), *Enterococcus* spp. ١٣.٧٪, *Klebsiella* spp. *(*١٢٪), and *Pseudomonas aeruginosa* (٦.٢٪). These results are to some extent comparable to the results of this study. However, Mehdie, (٢٠٠٠) found that the common types of isolates in UTI were *Klebsiella* spp.**

**Furthermore, Guirguitzova *et.al.,* (٢٠٠٢) showed that ٢٣٪ of complicated UTI were due to Coagulase-negative *Staphylococcus* spp., ٧٥٪ of them were *S.epidermidis* and the remainder were other types of coagulase-negative *Staphylococcus*. Joshi *et.al*., (٢٠٠٣) found that *Acinetobacter s*pp. represented ٢٢٪ of hospital acquired UTI , Nebreda *et.al.,* (١٩٩٤) revealed that *C. urealyticum* represented ٠.٣٪ of patients with recurrent UTIs and (Sakran *et.al*., ٢٠٠٣) pointed that *Enterococcus* spp. represented ٣٪. The difference in pathogens may be related to factors such as using another stream sample other than midstream sample as from bladder catheter (the catheter associated UTIs may be caused by *S. epidermidis, Proteus* spp*., P.aeruginosa*), different ground of study other than the hospital as an out patients or community based, sex and age determined are different from one study to another.**

## ٣.٢.٢ Bacterial isolates from expressed prostatic secretions in patients with chronic prostatitis

**Thirty three patients had chronic prostatitis in which expressed prostatic secretions cultures were done. (٤٥.٥٪) of them had resulted in positive culture (table ٣.٦). This result was higher than those of Jiao *et.al.,* (٢٠٠٢) who expressed that the prevalence of bacterial prostatitis ranged from (٥-١٥) % in patients aged between (٢٠-٤٨) years, moreover Greenberg *et.al.*, (١٩٨٥) showed that the cultures results of males aged below ٥٠ years with the clinical diagnosis of chronic prostatitis were evaluated for bacterial etiology by the Stamey and Meares method (١٩٦٨) identified only ١٧٪ of patients with bacterial prostatitis.**

**In this study, from (١٥) isolates, (٦) isolates from expressed prostatic secretions of patients whose ages ranged from (٣٠-٥٠) years and the remainder isolates from those aged more than ٥٠ years and presented with benign prostatic hyperplasia. The different number of EPS which were taken from lesser number of patients because most of them refused to submit to this test.**

**According to (Table ٣.٧), the most isolates were *S.aureus* which represented ١٢.١٪ followed by *S. epidermidis*, *S.***

***saprophyticus*, *E. coli* and *K. pneumoniae* represented ٦.١٪ each. *Enterobacter* spp., *Acinetobacter* spp. and *Corynebacterium* spp. represented ٣٪ each.**

**In this study, there was no contamination which may occur due to other types of bacteria because prostatic message was done in aseptic sterilized condition by urologist.**

**Kriger and McGonagle, (١٩٨٩) had studied the patients with chronic prostatitis due to bacterial cause which included *E.coli., Enterococcus* spp. represented ٨٪ each. *Klebsiella pneumoniae* ٢.٧٪, each of *P. aeruginosa* and *Enterobacter cloacae* represented ٢.٥٪ and one isolate was *Staphylococcus saprophyticus*; Also, they noticed that chronic prostatitis should concentrate on the isolation and antimicrobial susceptibility testing of bacteria that have an established pathogenic potential in genitourinary tract.**

| Types of bacterial isolates | No. of isolates | % |
|---|---|---|
| ***Staphylococcus aureus*** | ٤ | ١٢.١٪ |
| ***E. coli*** | ٢ | ٦.١٪ |
| ***Klebsiella pneumoniae*** | ٢ | ٦.١٪ |

| | | |
|---|---|---|
| ***Staphylococcus epidermidis*** | ٢ | ٦.١٪ |
| ***Staphylococcus saprophyticus*** | ٢ | ٦.١٪ |
| ***Enterobacter* spp.** | ١ | ٣٪ |
| ***Acinetobacters* spp.** | ١ | ٣٪ |
| ***Corynebacterium* spp.** | ١ | ٣٪ |
| Culture positive | ١٥ | ٤٥.٥٪ |
| Culture negative | ١٨ | ٥٤.٥٪ |
| Total | ٣٣ | ١٠٠٪ |

Table (٣.٧): Number and percentage of bacterial isolates from expressed prostatic secretions in patients with chronic prostatitis

**In addition, Reiger and Ruimy, (١٩٩٥) and Carson and Szoke, (١٩٩٨) identified Gram-positive aerobes, such as coagulase-negative *Staphylococcus* as well as various Gram-positive and Gram-negative anaerobes in EPS cultures.**

**The identification of Gram-positive bacteria from expressed prostatic secretion and/or prostate tissue has also sparked debate. Some believe that these bacteria are involved in the pathogenesis of chronic pelvic pain syndrom (Stimac *et.al.,* ٢٠٠١). On histology, the Gram-positive *Staphylococci* were identified in focal colonies adherent to the prostatic duct walls (Lee, ٢٠٠٠). While, Bergman, (١٩٩٤) demonstrated that ٤٣٪ of patients with symptoms of prostatitis grew gram-positive bacteria in significant numbers. In addition, Joe *et.al.,*(٢٠٠٠) suggested that because patients with CPPS have had multiple series of long-term antibiotics, the bacterial flora of the prostate was disturbed, allowing the growth of Gram-positive bacteria, they treated these patients and found symptom eradication in ٤٠٪ and symptom improvement in ٢٥٪, suggesting that these Gram-positive bacteria were pathogenic.**

**Polymerase chain reaction (PCR) was used to detect microorganisms that were not found by standard means described by Krieger, (١٩٩٨) firstly. Similarly, Sunil *et.al*., (٢٠٠٤) expressed that the use of the reverse transcriptase (RT-PCR) showed the evidence of bacterial infection despite negative finding after urine or EPS culture.**

# ٣.٣ Identification of bacteria

## ٣.٣.١ Gram-positive bacteria

**In this study, the biochemical tests used for identification Gram-positive bacteria are performed according to (MacFaddin, ٢٠٠٠) (Table ٣.٨).**

Table (٣.٨): Biochemical tests for identification G+ve bacteria

| Tests | *S.aureus* | *S.epidermidis* | *S.saprophyticus* | *Corynebacterium* | *Enterococcus* |
|---|---|---|---|---|---|
| Gram stain | G+ve cocci (clusters) | G+ve cocci (clusters) | G+ve cocci (clusters) | G+ve cocci (chinees letter) | G+ve long cocci |
| Albert stain | – | – | – | + | – |
| Esculin test | – | – | – | – | + |
| Oxidase | – | – | – | – | – |
| Catalase | + | + | + | + | – |
| Coagulase | + | – | – | – | – |
| Hemolysis | + | – | – | – | – |
| Urease | – | – | + | + | – |
| Manitol ferment | + | – | + | – | + |
| Novobiocin resistance | – | – | + | – | – |
| Phosphatase | + | + | – | + | – |
| Motility | – | – | – | – | – |

## ٣.٣.٢ Gram-negative bacteria

**In this study, the biochemical tests used for identification Gram-negative bacteria are performed according to (MacFaddin, ٢٠٠٠) (Table ٣.٩).**

Table (٣.٩): Biochemical tests for identification G-ve bacteria

| Tests | *E. coli* | *K. pneumoniae* | *Enterobacter* | *P. mirabilis* | *P. aeruginosa* | *Acinetobacter* |
|---|---|---|---|---|---|---|
| Gram stain | G⁻ve, short rods | G⁻ve , short rods | G⁻rods | G⁻ve rods | G⁻ve rods | G⁻ve coccobacilli or diplococci |
| Lactose ferment | + | + | – | – | – | – |
| Hemolysis | – | – | – | –** | + | – |
| EMB | Metalic | Centrally dark | Centrally dark | pale | pale | pale |
| Oxidase | – | – | – | – | + | – |
| Catalase | + | + | + | + | + | + |
| MR | + | – | – | –* | – | – |
| VP | – | + | + | – | – | –*** |
| Indol | + | – | – | – | – | – |

| TSI | A/A/G | A/A /G | A/A/G | A/A orALK/A | ALK/ALK | ALK/ALK |
|---|---|---|---|---|---|---|
| $H^2S$ | – | – | – | + | – | – |
| Motility | + | – | + | + | + | – |
| Citrate | – | + | + | + | + | –*** |
| Urease | – | + | – | + | – | –*** |
| Swarming | – | – | – | + | – | – |

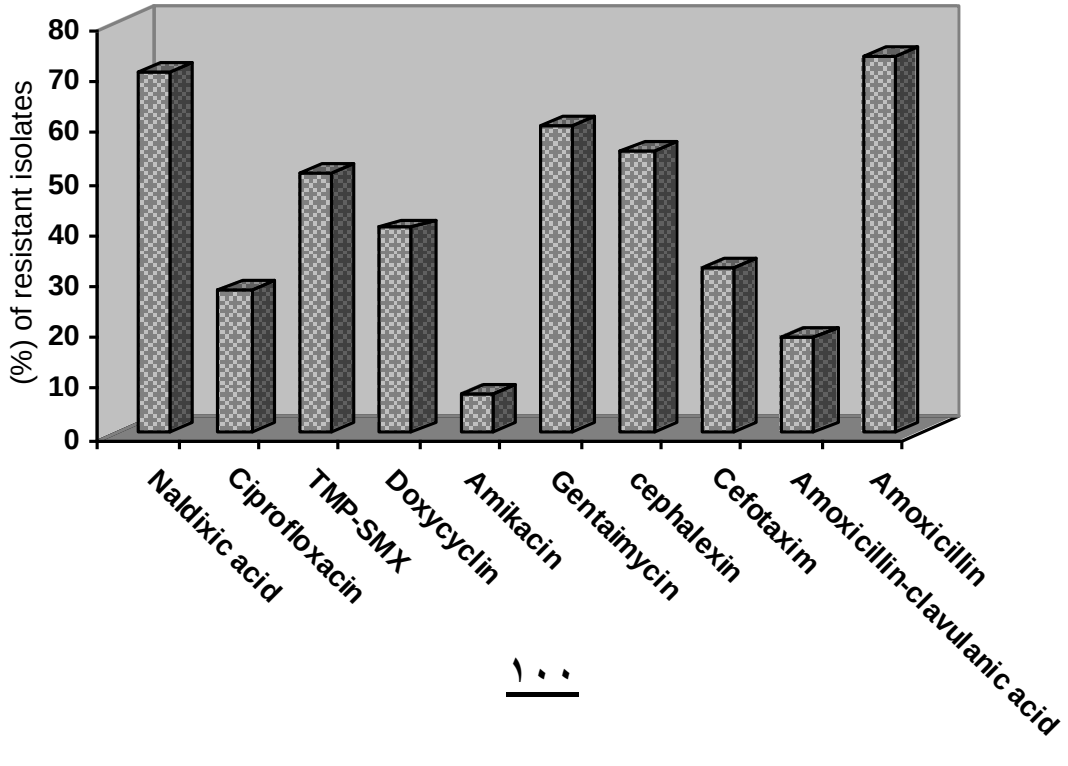
* Positive result in ٣٣.٣% of isolates

** Positive result in ٦٦.٧٪ of isolates

*** Positive result in ٤٠% of isolates

## ٣.٤ Effect of some antibiotics on the bacterial isolates

The effect of some antibiotics on isolated bacteria assessed by disk diffusion tests (Kirby-Bauer technique) are listed in (Figure ٣.٢).



Types of antibiotics

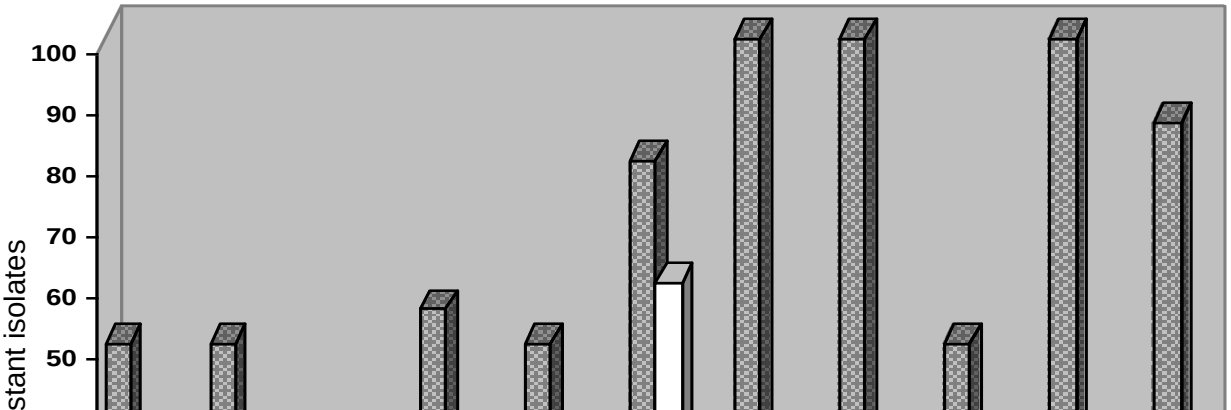
**Figure (٣.٢): Resistance of bacterial isolates to several antibiotics.**

**Regarding penicillin group, the total isolates resistance to amoxicillin was (٧٣.٨٪) while to amoxicillin-clavulanic acid was (١٨.٥٪). These results matched those obtained by Romolo *et.al.*, (٢٠٠٤) who pointed that the uropathogens resistance to amoxicillin was as high as to amoxicillin-clavulanic acid. The use of clavulanic acid decreased the resistance of bacteria to β-lactame drugs. The mechanism of this resistance is mostly due to either production of β-lactamases that hydrolyze β-lactame ring which is controlled by plasmid or chromosomal regulation, or lack of penicillin receptors on cell wall and/or alteration in their permeability to β-lactam antibiotics and preventing the uptaking of antibiotics by blocking the pores of outer membrane (Thomson and Amyes, ١٩٩٣). In addition, Gupta *et.al.,* (٢٠٠١) explained that over the past decade the utility of this class of antibiotics for treatment of UTIs and chronic prostatitis decreased due to increasing levels of resistance to β-lactam antibiotics.**

**(Figure ٣.٣) shows that the resistance of isolates to amoxicillin was significantly more than to amoxicillin-clavulanic acid (p<٠.٠٥). Among *E. coli*, the resistance rate to amoxicillin was ٨٦.٤٪ which was higher than to amoxicillin-clavulanic acid (٤٨.٢٪). This is comparable with Marre and schulz, (١٩٨٨) ; Wiedeman *et.al.*, (١٩٩١) who observed that upward trend in the resistance of *E. coli* to amoxillin/ampcillin and this resistance is predominantly caused by plasmid-encoded β-lactamase TEM-١; these enzymes preferentially hydrolyze penicillin, which is sensitive to β lactamase inhibitors such as clavulanic acid. It has become apparent that there are several mechanisms by which *E.coli* can be resistant to β-lactame-β-lactamase inhibitor combinations such as amoxicillin and clavulanic acid. The results of this study are higher than Paul *et.al.*, (١٩٩٥) who showed that in California over a five-years period demonstrated significant increases in the resistance of *E. coli* to ampcillin/amoxicillin (٣٠-٤٥٪) and to amoxicillin-clavulanic acid was ٥٪ and matched Huda *et.al.*, (٢٠٠١) disclosing that the prevalence of resistance rate of *E. coli* to amoxicillin more than ٥٠٪ and to amoxicillin-clavulanic acid was ١٩٪. Also, in this work *K. pneumoniae*, *P. mirabilis* and *P. aeruginosa* were completely resistant to amoxicillin (١٠٠٪) and (٨٠٪) of *Acinetobacter* were resistant while the resistance of other isolates to amoxicillin were significantly lesser than this percentage. This result is higher than those of Al-Shukri, (٢٠٠٣) who clarified that the resistance rate of uropathogenic *Acinetobacte*r to amoxicillin was ٦٣.٦٪ and correlates**

**with Al-Saedi, (٢٠٠٠) who noticed that most of *K.pneumoniae* was resistant to amoxicillin due to production of β-lactamases enzymes TEM and SHVS, so the addition of clavulanic acid can inhibit the action of these enzymes and only ٢٤.٤٪ are resistant to amoxicillin-clavulanic acid. Moreover, Dulawa *et.al*, (٢٠٠٣) and Aggarwal *et.al*., (٢٠٠٣) found that most of *E. coli* and *K.pneumoniae* isolated from recurrent UTI were resistant to amoxicillin. Furthermore, Clark, (٢٠٠٥) reported that the resistance mechanism in *P.aeruginosa* to β-lactame drugs resulted from the production of antibiotic modifying enzymes. Also, this work are close to Suareze *et.al*., (٢٠٠٢) who obtained that *C.urealyticum* had high resistance to amoxicillin.**

**Weinstein *et.al.,* (١٩٩٦) observed the *Enterococci* resistance to multiple antimicrobial agents such as β-lactam drugs. Dan, (٢٠٠٥) identified that more than ٥٠٪ of *S.epidermidis* isolated from patients with bacterial prostatitis were resistant to amoxicillin. In addition, Humphreys *et.al.,* (٢٠٠٤) achieved that the resistance of *S.epidermidis* to β-lactams is mediated by β-lactamase enzymes production under chromosomal control.**



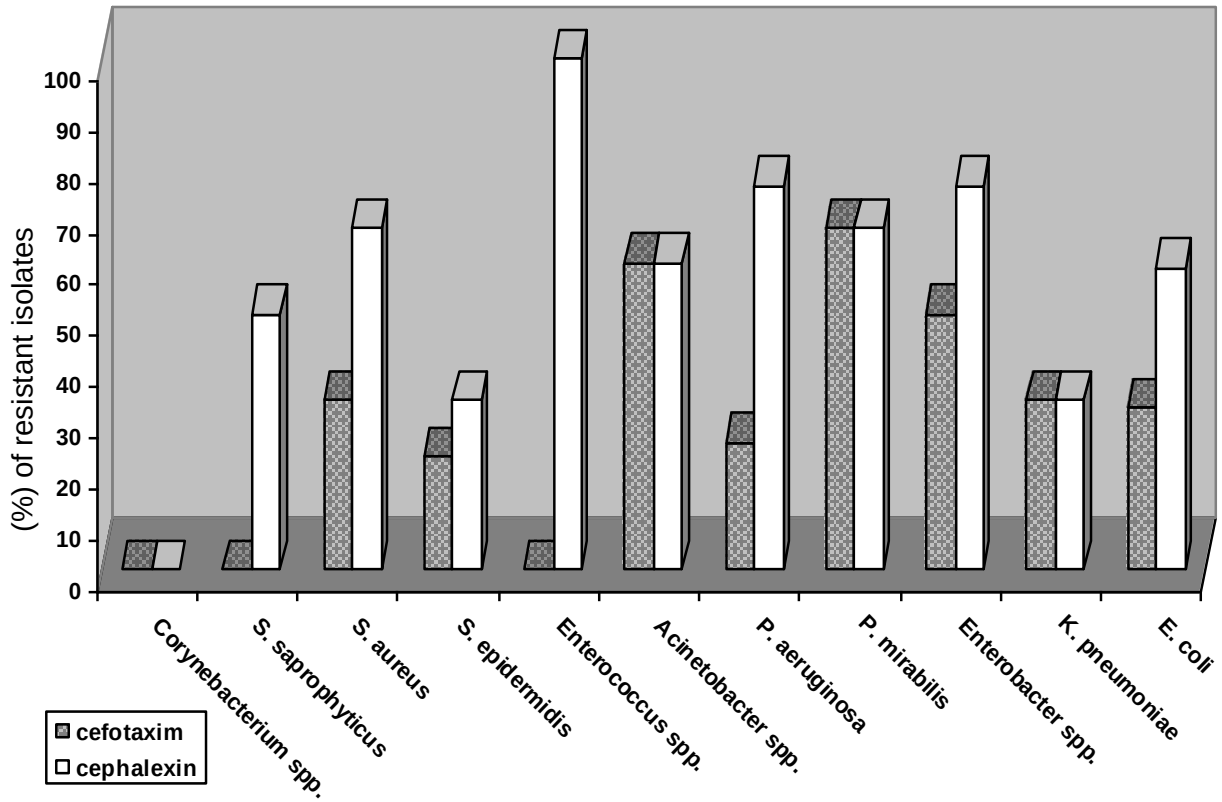
Type of bacteria

Figure (٣.٣): Resistance of bacterial isolates to penicillin group.

**In this work, *Enterococcus*, *S. epidermidis*, *S. saprophyticus* and *Corynebacterium* were significantly sensitive to amoxicillin-clavulanic acid and the resistance of other isolates to this antibiotic is shown in (Figure ٣.٣). These agreed with the results of Howared *et.al*., (٢٠٠٣) who showed that amoxicillin-clavulanic acid may be useful for UTIs caused by gram-positive organisms such as *Enterococcus* species and *S. saprophyticus*.**

**Regarding cephalosporins, the resistance of isolates to cephalexin was significantly higher than to cefotaxim (p<٠.٠٥) except *K. pneumoniae*, *P.mirabilis* and *Acintobacter,* (Figure ٣.٤). (٣٢.٣٪) of isolates were resistant to cefotaxim, (Figure ٣.٢). Two isolates of *Enterobacter* were resistant to it (٥٠٪). These results matched those of**

**Guibert *et.al.,* (١٩٨١) who reported that more than ٢/٣ patients with various UTIs were sensitive to cefotaxime, and found that only one isolate of *Enterobacter cloacae* was resistant to cefotaxim, while Hoffmann *et.al.*,(٢٠٠٣) showed that *Enterobacter* had high resistance to cefotaxime. In this research, the resistance of *P. mirabilis* to cefotaxim was (٦٦.٧٪), the resistance of other Enterobacteriaceae*, P. aeruginosa* , *S. aureus* and *S. epidermidis* to this antibiotic was less than (٥٠٪), while *S.saprophyticus*, *Corynebacterium* and *Enterococcus* were significantly sensitive (Figure ٣.٤). These results correlated with Leblebiciglu and Esen, (٢٠٠٣) who found that most of Enterobacteriaceae strains were sensitive to cefotaxim and lesser than the result of Micheal *et.al.*, (٢٠٠٣) who showed that ٩٠٪ of uropathogen *P. mirabilis* was sensitive to cefotaxim.**



Type of bacteria

**Figure (٣.٥): Resistance of isolates to cephalosporin group.**

**In addition, Al-Saedi, (٢٠٠٠) revealed that most of uropathogen *K. pneumoniae* was resistant to cefotaxim due to production of β-lactamase enzymes TEM-I. Jukka *et.al*., (١٩٩٥) identified that the resistance of *S. epidermidis* to cefotaxim was ٢٠٪. Simillary, Evangelos *et.al*., (١٩٩٨) stated that the prevalence of multiresistant *P.aeruginosa* isolates to cefotaxim increased over the last decade. In (Figure ٣.٤),(٦٠٪) of *Acinetobacter* were resistant to cefotaxim and this matched the finding of Hpa, (٢٠٠٣) who reported that in the past two years increment in the resistance of *Acinetobacter* spp. to cefotaxim was more than ٣٠٪.**

**As far as cephalexin is concerned, (٥٥.٤٪) of isolates were resistant, (Figure ٣.٢), this result is close to those of Martinez *et.al.,*(١٩٩٥) and Gupta *et.al.,* (٢٠٠١) who expressed that the usage of first generation cephalosporins is limited because of high resistance to it. ٥٩.١٪ of *E.coli* were resistant to cephalexin, (Figure ٣.٤), in contrast Collee *et.al*., (١٩٩٦) reports that all *E.coli* strains may still be sensitive to oral cephalosporin such as cephalexin, so increase resistance to it due to over usage in recent years.**

**In this study, *Enterococcus* spp. was completely resistant to cephalexin, while *Corynebacterium* spp. was sensitive. (٧٥٪) of *Enterobacter* spp. and *P. areuginosa* were resistant to this antibiotic, while the resistance of other isolates to it was lesser than this percentage. The resistance of *P. mirabilis* and *Acinetobacter* spp. to cephalexin was the same as with cefotaxim, (Figure ٣.٤). Similarly, Howard *et.al*., (٢٠٠٣) pointed out that most *Pseudomonas* and *Enterococcus* caused complicated urinary tract infection which was difficult to treat and might warrant more prolonged therapy. These findings correlated with the Eggman *et.al*., (١٩٩٧) and Brooks *et.al*., (٢٠٠١) who stated that the strains of *Enterobacter*, *Klebsiella, Proteus* and *Pseudomonas* isolated from hospitals had multiple antibiotic exposure were almost always resistant to oral cephalosporins because they possess inducible, chromosomally determined β-lactamases with high affinity for cephalosporins. Moreover, these results matched the reports of Riger, (٢٠٠٤) who showed that *Corynebacterium* was universally sensitive to β-lactam which is regarded as recommended drugs for the treatment of *Corynebacterium* infection. Zahac *et.al.,* (٢٠٠٣) asserted that *Enterobacter* resistance rate to cephalexin was ٩٨٪. This work results was higher than Micheal *et.al*., (٢٠٠٣) result who revealed that only (١٠-٢٠)% of *P. mirabilis* strains from urinary isolates can acquire resistance to first-generation cephalosporins. Antibiotic resistance phenomenon is widely common among clinical**

**isolates of *Acinetobacter* which are often inherently resistant to many antimicrobial agents including β-lactams, aminoglycosides and quinolones (Hpa, ٢٠٠٣). Add to that, Zhang *et al.,* (٢٠٠٣) mentioned that by forming biofilms, *S. epidermidis* is not only resistant to antibiotics, antibodies and phagocytosis but also can be the reservoir for antibiotic resistant genes which can be transferred to other bacteria.**

**Flouroquinolones resistant isolates especially to ciprofloxacin were (٢٧.٧٪), (Figure ٣.٢), these results matched those of Brahler *et.al*., (١٩٩٩) who showed that a bacteriological cure rate by ciprofloxacin treatment for UTIs especially for chronic bacterial prostatitis has increased within the recent years between (٧٠-٨٠) % higher than TMP-SMX (٤٠-٧١) % and both of them are considered as the first–and second line therapy in the management of chronic prostatitis. Furthermore, Kalpana *et.al.,* (٢٠٠٥) and Naber *et.al*.,(٢٠٠٤) asserted that flouroquinolone substituted trimethoprim-sulfamethoxasole as initial agents of choice in the treatment of chronic prostatitis.**

**Figure (٣.٥) shows that the resistance of isolates to naldixic acid was significantly higher than that to ciprofloxacin except *Enterococus* spp. (p<٠.٠٥). The resistance of *E. coli* to ciprofloxacin was (٣٦.٤٪) which differed from Donnell *et.al.,* (٢٠٠٠) and Klligore *et.al.*, (٢٠٠٤) who demonstrated that the resistance rate of**

**uropathogen *E. coli* to ciprofloxacin was ٠.٤٪, ١٣٪ respectively. There is a significant variance in resistance patterns which existed in different geographic regions. Additionally, the longer antibiotics are in use the greater the resistance ratio appears in time. In present study, the resistance of *Enterobacter* and *P. aeruginosa* to ciprofloxacin were (٢٥٪) which can be comparable to Zahac *et.al*., (٢٠٠٣) who showed that *Enterobacter* completely sensitive to ciprofloxacin and correlated with works of Karlowsky *et.al.,* (٢٠٠٣) who revealed that the effect of ciprofloxacin in the treatment uropathogen *P.aeruginosa* was with limited rate of resistance.**

**The resistance of *Acinetobacter* isolates is ٤٠٪, (Figure ٣.٥), which was higher than the results Howard *et.al*., (٢٠٠٣). Moreover, Al-Shukri, (٢٠٠٣) found that the uropathogen *Acinetobacter* was completely sensitive to ciprofloxacin. In this study, the resistance of *P. mirabilis* to ciprofloxacin was (٣٣.٣٪) which is lesser than the findings of Zerovs and Foch, (٢٠٠٣). Moreover, clinical studies supports that fluoroquinolones, such as ciprofloxacin are able to eradicate gram-negative bacteria from the prostate gland and from prostatic secretion in high percentage of patients and for long periods (Curtis *et.al*., ٢٠٠٠).**

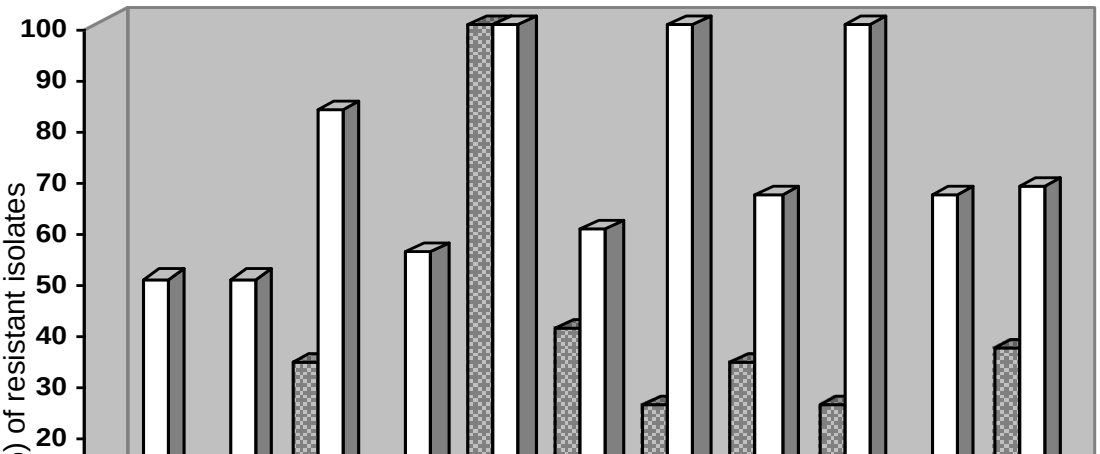


**Figure (٣.٥): Resistance of bacterial isolates to** flouroquinolone group.

**On the other hand, *Enterococcus* spp.were completely resistant to ciprofloxacin (١٠٠٪), this work results agreed with that of Robin, (٢٠٠٥) who noticed that an increase in the incidence of resistance of glycopeptide-*Enterococcus* associated with nosocomial UTI to fluroqunolones. *K. pneumoniae*, *Corynebacterium* spp. and *S.saprophyticus* were significantly sensitive to ciprofloxacin, (Figure ٣.٥), which matched the results of Judith, (١٩٩٦) who showed that microorganisms isolated from males with complicated UTIs and chronic prostatitis were sensitive to ciprofloxacin. This work showed that (٣٣.٣٪) of *S.aureus* and (١١.١٪) of *S.epidermidis***

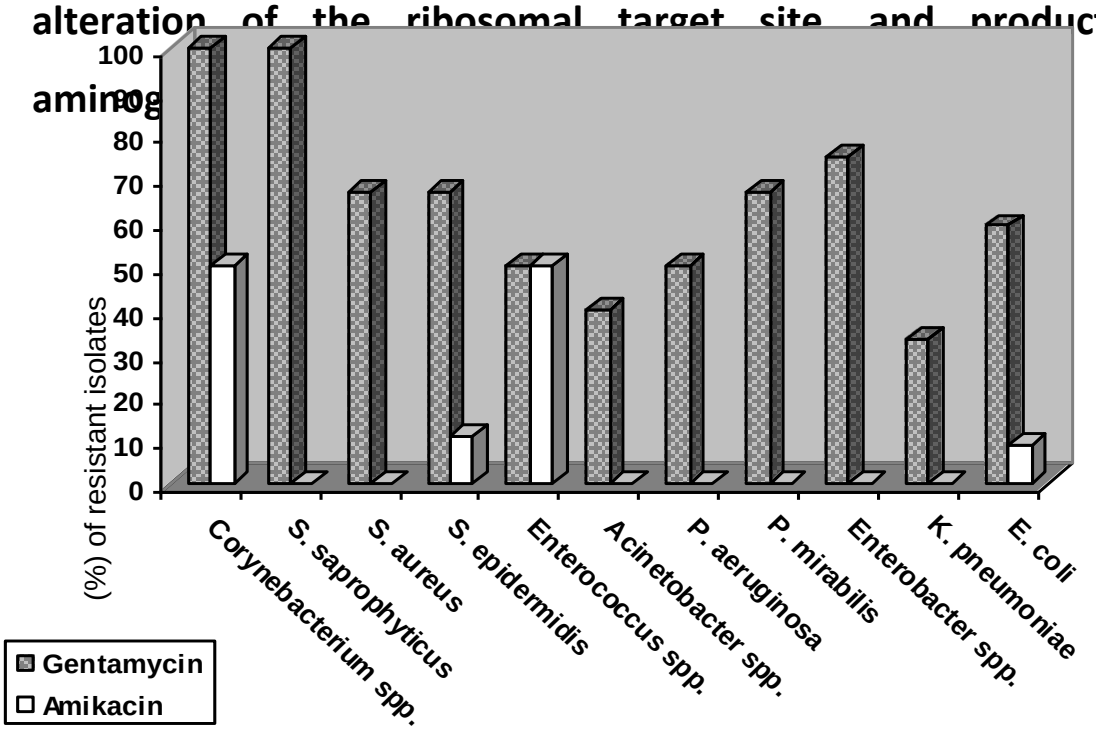
**isolates were resistant to ciprofloxacin. Similaraly, Rachid *et. al*., (٢٠٠٠) observed that in *Staphylococci*, there were increased numbers of strains resistant to ofloxacin and ciprofloxacin. In addition, Jukka *et. al*., (١٩٩٥) noticed that ٢٣% of *S.epidermidis* isolates were resistant to ciprofloxacin. Moroever, Donnell and Gelone, (٢٠٠٠) reported that the resistance to flouroquinolones is through chromosomal mutations or alterations affecting the ability of fluoroquinolones to permeate the bacterial cell wall. Fortunately, separate isomerases are required to produce this form of resistance (Romolo *et. al.,* ٢٠٠٤).**

**Regarding naldixic acid the isolates resistant were (٧٠.٨٪), (Figure ٣.٢), so half of *Corynebacterium* spp. and *S.saprophyticus* were resistance to it and the resistant of other isolates were more than ٥٠%. *Enterobacter* spp., *P. aeruginosa a*nd *Enterococcus* spp. were completely resistant to it (١٠٠٪) (Figure ٣.٥), these results are higher than those of Huda *et.al.,* (٢٠٠١). Flouroquinolones like ciprofloxacin and naldixic acid have broad spectrum of activity especially against gram-negative bacteria in which more effect against *Pseudomonas* species also have marginal activity against *Staphylococci* and *Streptococcal* species (Emil *et.al.,*٢٠٠٤). In addition, Christian *et. al.*, (١٩٩٨) explained that *P. aeruginosa* developed resistance to a variety of antibiotics due to the permeability barrier offered by its outer membrane**

**lipopolysaccharide; also its tendency to colonize surfaces in a biofilm form makes the cells impervious to therapeutic concentrations of antibiotics.**

**Regarding aminoglycosides, the bacterial isolates resistant to gentamycin and amikacin were (٦٠٪) and (٧.٧٪) respectively. Resistance of isolates to amikacin was least compared to other antibiotics, (Figure ٣.٢). The resistance of isolates to gentamycin was significantly much higher to amikacin except *Enterococus* spp. (p<٠.٠٥), (Figure ٣.٦). (٩.١٪) of *E. coli* were resistant to amikacin, while other Enterobacteriaceae, *P. aeruginosa*, *Acinetobacter* spp. were siginificantly sensitive, so it is used in the chronic bacterial prostatitis. These results are identical with Dulawa *et.al.,*(٢٠٠٣) who noticed that the effectiveness of parenteral amikacin in the treatment of UTI which has a good activity against gram-negative uropathogens. In addition, Huda *et.al*., (٢٠٠١) found that all strains of *E.coli* sensitive to amikacin and only ٤٪ of *Enterobacter* were resistant to it. Thomas, (٢٠٠٥) stated that in patients with chronic prostatitis in whom oral antibiotic therapy fails, other antibiotics should be used and these may include injection of gentamycin or amikacin directly into prostate and the anal submucosal injection of amikacin improved symptom scores with increase bacterial eradication rates better than intramuscular injection.**

**Ingreding gram-negative bacteria, *Enterobacter* spp. resistance to gentamycin was higher than the others (٧٥٪), (Figure ٣.٦). These results agreed with Zahac *et.al.,*(٢٠٠٣) who revealed that *Enterobacter* was resistant to gentamycin but it is sensitive to amikacin. Al-Shukri, (٢٠٠٣) observed that *Acinetobacter* was resistant to gentamycin and this resistance was produced through alteration of the ribosomal target site and production of amino**g**




# Figure (٣.٦): Resistance of bacterial isolates to aminoglycoside group.

**Moreover, Hpa, (٢٠٠٣) established that resistance of uropathogen *Acinetobacter* to gentamycin and amikacin were ٤٣٪ and**

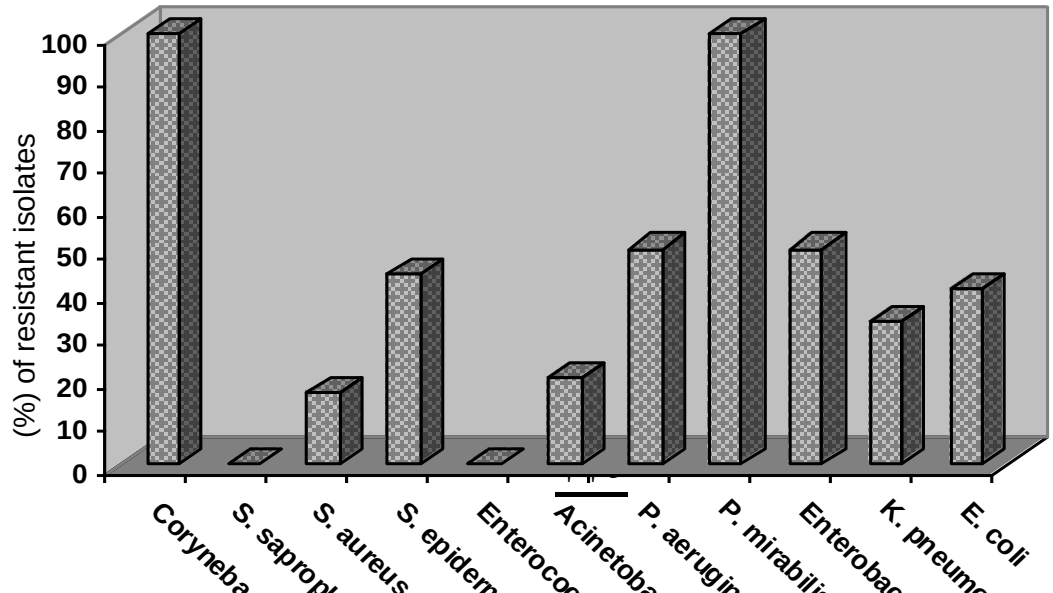
**٥٪ respectively. This work is close to Karlowsky *et.al*., (٢٠٠٣) who stressed that the resistance of *P.aeruginosa* to gentamycin was higher than to amikacin and this resistance is due to production of antibiotic modifying enzymes and previous exposure to antibiotics often leads to multidrug resistant *P. aeruginosa*.**

**In this work, (٦٦.٧٪) of *S. aureus* and *S. epidermidis* were resistant to gentamycin, but these isolates were sensitive to amikacin and only one isolate of *Enterococcus* spp. was resistant to these two drugs. *S. saprophiticus* and *Corynebacterium* spp. were resistant to amikacin (١٠٠٪), (Figure ٣.٦).**

**These results agreed with Moellering *et.al*., (٢٠٠٢) results who noticed that synergistic therapy of aminoglycosides in selected cases of *Staphylococcal* disease (*S.aureus* and Coagulase-negative *Staphylococcus*) and *Enterococcus*. This results are higher than those of Jukka *et.al*., (١٩٩٥) who pointed that uropathogens *S. epidermidis* resistance to gentamycin were ٤٦٪ also noticed that Multiresistant in *Staphylococcus* species in bacterial prostatitis was due to the distribution of the mecA gene among the *Staphylococcus epidermidis.* Similarly, Konino *et.al*., (١٩٩٥) showed that the endemic aminoglycoside-resistant MRSA strain persisted while new clones became endemic in hospitals, perhaps after changes in the use of aminoglycosides (decrease of gentamycin and increase of amikacin consumption), also Abernethy *et.al*., (٢٠٠٢) described that**

**synergism against *P.aeruginosa* and *Enterococci* may occur with β-lactam antibiotics and aminoglycosides.**

**Doxycycline resistant isolates were (٤٠٪), (Figure ٣.٢). It is used for patients allergic to quinolones in the treatment of chronic prostatitis (James *et.al.*, ٢٠٠٠). In this research, there was a significant difference between the resistance of isolates to this antibiotic (p<٠.٠٥). (٤٠٪) of *E. coli* was resistant to doxycycline (Figure٣.٧). The last five-year period demonstrated significant increases in the resistance of *E. coli* to tetracycline from (٢٩-٤٠) % (Romolo *et.al.*, ٢٠٠٤). (١٠٠٪) of *P. mirabilis* and *Corynebacterium* spp. were resistant to doxycyline while *Enterococcus* spp. *S.saprophyticus* were sensitive. (٥٠٪) of *Enterobacter* and *P. aeruginosa* were resistant to it. The resistance of the remainder isolates was lesser than ٥٠٪ (Figure ٣.٧). This work result was correlated with Marco and Parker, (١٩٩٧) result who declared that bacteria become resistant to tetracyclines by the transfer of DNA from a resistant cell to another, also Senior *et.al.,* (١٩٩٨) expressed that *P. mirabilis* was not susceptible to tetracycline.**



Type of bacteria

Figure (٣.٧): Resistance of bacterial isolates to doxycycline.

**Al-Sukri, (٢٠٠٣) reported that most of uropathogens *Acinetobacter* were sensitive to tetracycline. Contrarily, Weinstein *et.al.*, (١٩٩٦) observed that *Enterococci* species had high resistance to doxycycline. The difference in the results was due to the fewer numbers of *Enterococci* isolated than other studies. Kolar *et.al.*, (٢٠٠٢) expressed that in *Staphylococci* there were increased in number of strains resistant to tetracycline.**

**Regarding trimethoprim-sulfamethoxasole, (٥٠.٨٪) of isolates were resistant to it, (Figure٣.٢), and this result resemble those of Romolo *et.al.*, (٢٠٠٤) who observed that uropathogenis resistance rate to TMP-SMX has risen to as high as ٣٥٪. Mears,(١٩٩٧) stated that resistance of isolates from patients with chronic bacterial prostatitis to TMP-SMX were ٥٧.١٪. In this study, there was a significant difference between the resistance of isolates to TMP-SMX (p<٠.٠٥), (Figure ٣.٨). (٤٠.٩٪) of *E.coli* strains were resistant to this antibiotic. This result is similar to those of Huda *et.al.*, (٢٠٠١). *Enterococcus* species were significantly resistant to it (١٠٠٪), while *Corynebacterium* species were sensitive. The**

**resistance of *P. aeruginosa* to TMP-SMX was higher than other Gram-negative isolates (٧٥٪), (Figure٣.٨). Nowadays, there is a decrease in the use of TMP-SMX in the treatment of chronic prostatitis (James *et.al.,* ٢٠٠٠). However, Chesley and Dow, (١٩٧٣) ascertained that TMP-SMX is considered as a first–line antibiotic for chronic bacterial prostatitis caused by gram-negative bacteria. This work, agreed with Joshi *et.al.,* (٢٠٠٣) who ascertained that *Acinetobacte*r *baumannii* are resistant to TMP-SMX. Kalpan *et.al*, (٢٠٠٥) revealed that TMP-SMX active against most uropathogen except *Pseudomonas* spp. and *Enterococcus* spp. This research results were higher than Howard *et.al.,*(٢٠٠٣) study, who noticed that urinary *Acinetobacte*r resistance to trimethoprim was ٤٣٪ and matched the result of Bouza *et.al.,* (٢٠٠١) who expressed increase in the resistance of urinary *P. mirabilis* to trimethoprim. Furthermore, Bonnet, (٢٠٠٤) asserted that *Enterobacter* was completely resistant to TMP-SMX. (٧٧.٨٪) of *S. aureus* were resistant to TMP-SMX which was higher than the resistance of other *Staphylococcus* species to it, (Figure ٣.٨).**

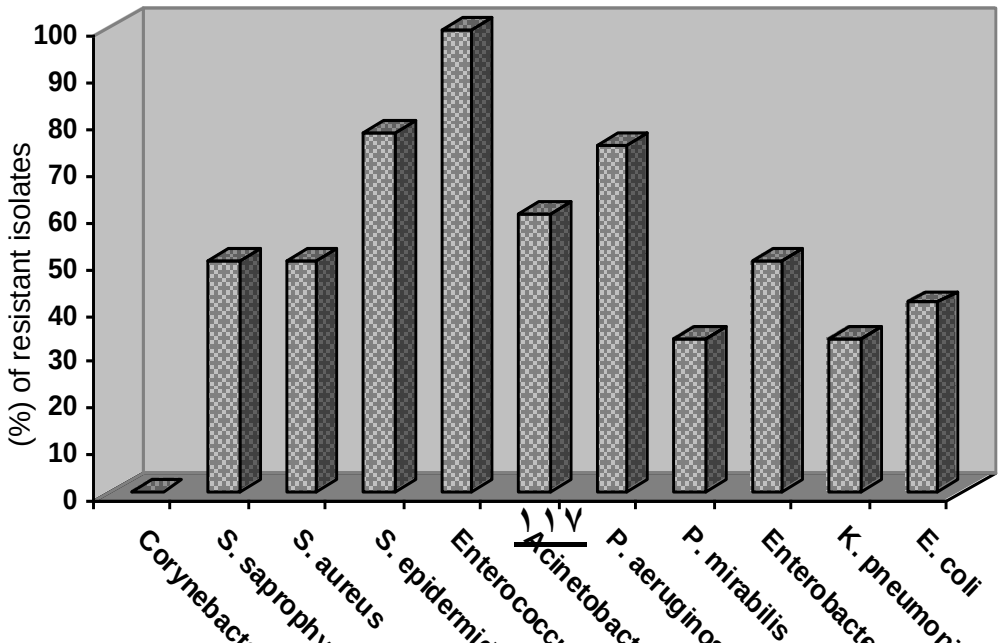


**Figure (٣.٨): Resistance of bactrial isolates to TMP-SMX.**

**This work results agreed with those of Jukka *et.al.,* (١٩٩٥) who suggested that half of *S. epidermidis* isolates were resistant to TMP-SMX. *S. epidermidis* exhibit resistance to many types of antibiotics attributed to R-plasmid acquired from pathogenic bacteria present at the site of infection (Rachid *et.al.*, ٢٠٠٠).**

**Antibiotic resistance increase in the ongoing years is due to irrational use which leads to multidrug resistant bacteria. Furthermore, chromosomal mutations, R-plasmid acquired from other pathogenic bacteria cause increased in rate of resistance to antibiotics, especially, the new ones, in time.**

**Results from recent studies show that bacterial ribosomal ribonucleic acid (rRNA), by a reverse transcriptase-polymerase chain reaction (RT-PCR), assist in predicting a successful response to antibiotic treatment in patients with chronic prostatitits (Sunil *et.al.*, ٢٠٠٤).**

## ٣.٥ Effect of zinc sulfate on the bacterial growth

**The effect of zinc sulfate at different concentration ranges between (٠.١٥-١.٥) mg/ml of broth culture (according to normal value of zinc concentration in prostatic secretion range of ١٥٠-١٠٠٠µg/ml) on some bacterial growth was investigated. It was observed that the addition of zinc sulfate to the culture media of isolates decreased the viable count of Gram-negative bacteria particularly at concentrations more than ١.٠٥ mg/ml of broth culture (Figure ٣.٩).**

**There was a relationship between zinc sulfate concentration and bacterial growth (Table ٣.١٠). The effect of zinc sulfate on the growth of *S. aureus* which represents Gram-positive bacteria was lesser than that on gram-negative bacteria in which the viable count reached to ٩×١٠$^{٧}$ cfu/ml at concentration ١.٥mg/ml. The zinc affected the capsule of gram negative and Gram positive bacteria which examined by capsular stain and demonstrated the loss of capsule. These findings agreed with (Sunil *et.al.*, ٢٠٠٤) who established that the presence of zinc in the prostatic secretion in high concentration which considered as antibacterial polypeptides is effective against Gram-negative and Gram-positive bacteria.**

**This work agreed with (Patrick *et.al.*, ١٩٩٧) who revealed that in vitro studies of free zinc ions at concentrations normally found in the prostatic fluid have confirmed the bactericidal activity of zinc against a variety of Gram-positive and Gram-negative bacteria.**

**Zinc is the mineral ion present in the prostate and prostatic fluid is higher than any organ. Zinc is bound to high molecular weight lignads such as metalloproteins (Byer, ١٩٧٤). In Gram-negative bacteria, zinc may bind to proteins inserted in lipopolysaccharide layer that act as water filled channels (porins) and its effect may be related to increasing diffusion of zinc into the bacteria through these channels, bind to the plasma membrane and disrupts its structure and permeability properties. The high concentration of zinc may lead to morphologic changes or lyses of susceptible bacteria. In Gram-positive bacteria, which have thicker cell wall (thicker murein coat), compared to Gram-negative bacteria, so the effect of zinc may lesser than the Gram negative bacteria. The presence of zinc in the prostatic fluid is very important to protect the prostate from many invaders. However, it's concentration in the prostatic fluid is important to carry out such task.**

## ٣.٦ Effect of combination of some antibiotics with zinc sulfate on bacterial growth

**The results of present study evaluated the activity of some antibiotics combined with zinc sulfate. The addition of zinc sulfate to antibiotics in different concentration (٠.٩, ١.٠٥, ١.٢, ١.٣٥ and ١.٥) mg/ml of broth culture increased the zinc-binding-antimicrobial aictivity of these antibiotics.**

**In fact, this experiment showed enhancement of susceptibility of *S.aureus* which exhibited resistance to amoxicillin and *E. coli* isolates which exhibited resistance to some antibiotics such as ciprofloxacin, cefotaxim, and amikacin. It was observed that the viable count of bacteria was ١٢٠×١٠^٦ cfu/ml for (AMX), ١٦٥×١٠^٦ cfu/ml for (CF), ١٥٤×١٠^٦ cfu/ml for (CTX) and ٩٨×١٠^٦ cfu/ml for (AK). The combination of each of those antibiotics with zinc sulfate affected on the bacterial growth which was characterized by decreasing the viable count of bacteria when zinc sulfate added at a concentration ٠.٩ mg/ml and more (Figure ٣.١٠).**

**In vitro, zinc sulfate appeared to enhance the bactericidal ability of β-lactam, fluroquinolones, and aminoglycosides. These results matched those of (Peter and Beth, ٢٠٠٠) who revealed that the number of *E. coli* isolates(CFU) in samples with either cefotaxim or ampicillin significantly decreased when zinc was added to the samples. ß-lactams are known to display bactericidal activity that is dependent on the rate of growth. Thus, it might be expected that this class of antibacterial agent would be more effective in vitro than in vivo (Cozens *et.al.*, ١٩٨٦). The antibacterial effect of zinc may be synergistic with β-lactam, flouroquinolones and aminoglycosides antibiotics. Zinc may alter the permeability of the bacterial cell, so it can facilitate entry of antibiotics that might not ordinary gain access to target sites, thus resulting in enhanced antimicrobial activity.**

**Presumably, the addition of zinc made the organisms more susceptible to the microbicidal activity of antibiotics.**

**Sohnle *et.al.,* (١٩٩٦) theorized that the substance responsible for antimicrobial effect is the calcium-and zinc binding protein called calprotectin, it appears to originate in cytoplasm of neutrophils and is then released at sites of infection so the cells die and lyse; this protein has bacteriostatic activity against a variety of bacterial and fungal microorganisms.**

Some antibiotics, particularly those of β-lactams, are most active against rapidly growing organisms and the microbistatic activity of calprotectin could interfere with the microbicidal activity of these antibiotics when they are used to treat complicated infections Clohessy and Golden, (١٩٩٥). Indeed, Bamberger *et.al*., (١٩٩٣) have demonstrated that prostatic fluid interferes with the ability of cefalozolin to kill *S. aureus* and *E. coli* but if zinc is added to reverse the growth-inhibitory effect of calprotectin, then killing proceeds normally. Thus, calprotectin appears to compromise the microbicidal effect of β-lactam antibiotics by suppressing growth of the target organisms. Quinolone antibiotics may relatively be more effective in killing microorganisms in bacterial prostatitis and its effect with zinc in microbial killing similar to β-lactam effect **(**Zeiler and Grohe, ١٩٨٤).

## ٣.٧ Phosphatase and Extra cellular protease production

**The isolates were tested for their ability to produce phosphatase, the production characterized by hydrolysis of *p*-nitrophenyl phosphate (PNP) and liberation of *p*-nitrophenol (yellowish color). The isolates that produced phosphataseenzymewere Enterobacteriaceae, *Corynebacterium, S. aureus* and *S. epidermidis* (Table ٣.١١). Furthermore, only one isolate of *P.aeruginosa* produced this enzyme, while none of *Enterococcus* spp., *Acinetobacter* spp., and *S. saprophyticus* produced this enzyme. This enzyme is important to differentiate between *S. aueus, S. epidermidis* and *S. saprophyticus* (MacFaddin, ٢٠٠٠).**

**Bacterial isolates from infected prostate like *E.coli, K.pneumoniae, S.aureus*, have developed the ability to inject a phosphatase and a few other bacterial virulence factors into mammalian cells. When these proteins enter a mammalian cell like a macrophage, they can rapidly disable the immune response. These bacteria use the phosphatase as a lethal weapon, and they are incredibly fast and effective (Thomas, ٢٠٠٥).**

**On the other hand, the ability of isolates to produce extracellular protease were investigated by using M٩ media which was supported by ٠.٢٪ glucose and gelatin and this study conducted to ability of bacterial isolates to produce this enzyme after ٢٤ hours. The transparent area around the colony after end incubation period and after added ٣ml (٥٪) of trichloroacetic acid**

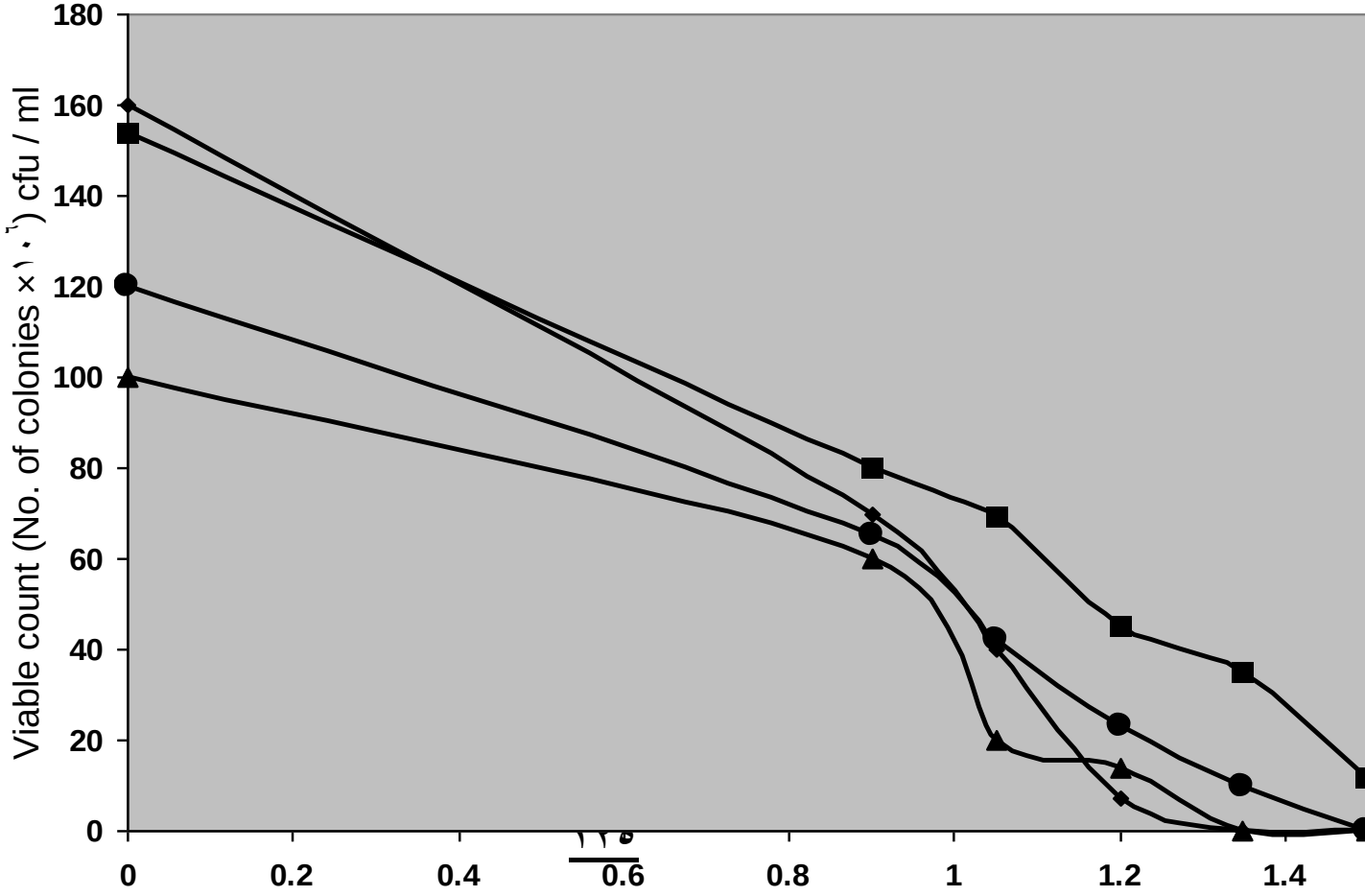
**indicated the positive result. The isolates which produced extracellular protease enzyme were *E.coli, P.aeruginosa*, *S.aureus, and S.epidermidis*. Also, one isolate of each of *P.mirabilis, Acinetobacter* spp. and *Corynebacterium* spp. produced this enzyme (Table ٣.١١). While *K. pneumoniae, Enterobacter* spp., *Enterococcus* spp. and *S. saprophyticus* did not produce this enzyme.**

Table (٣.١١): Number of isolates produced phosphatase and extracellular protease

| Bacterial isolates | No. of isolates (phosphatase) | No. of isolates (protease ) |
|---|---|---|
| ***E. coli*** **(٢٢)** | ٢٢ | ٢٢ |
| ***K. pneumoniae*** **(٦)** | ٦ | ٠ |
| ***Enterobacter*** **spp. (٤)** | ٤ | ٠ |
| ***Proteus mirabilis*** **(٣)** | ٣ | ١ |
| ***P. aeruginosa*** **(٤)** | ١ | ٤ |
| ***Acinetobacter*** **spp. (٥)** | ٠ | ١ |
| ***Enterococcus*** **spp. (٢)** | ٠ | ٠ |
| ***Corynebacterium*** **spp. (٢)** | ٢ | ١ |
| ***S. aureus*** **(٦)** | ٦ | ٦ |
| ***S. epidermidis*** **(٩)** | ٩ | ٩ |
| ***S . saprophiticus*** **(٢)** | ٠ | ٠ |
| Total | ٥٣ | ٣٤ |

**Extracellular protease enzyme which is produced by microorganisms is important for degradation of proteins and is involved in the virulence of gram-positive and gram-negative bacteria (Ching *et.al.*, ١٩٩٨; Beynom and Bond, ١٩٨٩; Raksha *et.al.*, ٢٠٠٣).**

**Numerous proteases are produced by microorganism owing to their broad biochemical diversity and their susceptibility to genetic manipulation and depending on the species of producer or strain even belonging to the same species. Several proteases are also produced by the same strain under various culture conditions (Pollack *et.al.*, ٢٠٠٠).**



Zinc sulfate concentration (mg/ml)

Figure (٣.١٠): Effect of some antibiotics with zinc sulfate on bacterial growth

Table (٣.١٠):- Effect of zinc sulfate on bacterial growth (cfu / ml)

| Conc.zinc sulfate (mg/ml) | *E.coli* | *K.pneumoniae* | *Enterobacter* | *Acinetobacter* | *S.aureus* |
|---|---|---|---|---|---|
| Control | ١٨×١٠$^{٧}$(١٠٠٪) | ١٦٤×١٠$^{٦}$ (١٠٠٪) | ١٧٦×١٠$^{٦}$(١٠٠٪) | ٢×١٠$^{٨}$(١٠٠٪) | ١٦×١٠$^{٧}$(١٠٠٪) |
| ٠.١٥ | ١٥×١٠$^{٧}$(٨٣.٣٪) | ١٤٥×١٠$^{٦}$(٨٨.٤٪) | ١٢×١٠$^{٧}$(٦٨.٢٪) | ١٥٩×١٠$^{٦}$(٧٩.٥٪) | ١٥٢×١٠$^{٦}$(٩٥٪) |
| ٠.٣ | ١٢×١٠$^{٧}$(٦٦.٧٪) | ١١٢×١٠$^{٦}$(٦٨.٣٪) | ٩×١٠$^{٧}$ (٥١.١٪) | ١٢٥×١٠$^{٦}$ (٦٢.٥٪) | ١٢٣×١٠$^{٦}$(٧٦.٩٪) |
| ٠.٤٥ | ١×١٠$^{٨}$(٥٥.٦٪) | ٩٣×١٠$^{٦}$(٥٦.٧٪) | ٧٥×١٠$^{٦}$ (٤٢.٦٪) | ١١٢×١٠$^{٦}$ (٥٦٪) | ١×١٠$^{٨}$(٦٢.٥٪) |
| ٠.٦ | ٨×١٠$^{٧}$(٤٤.٤٪) | ٨٢×١٠$^{٦}$(٥٠%) | ٦×١٠$^{٧}$ (٣٤.١٪) | ٩×١٠$^{٧}$(٤٥٪) | ١٠٢×١٠$^{٦}$(٦٣.٨٪) |
| | ٧×١٠$^{٧}$(٣٨.٩٪) | ٦٦×١٠$^{٦}$(٤٠.٢٪) | ٤٦×١٠$^{٦}$(٢٦.١٪) | ٧٧×١٠$^{٦}$(٣٨.٥٪) | ١×١٠$^{٨}$ (٦٢.٥٪) |
| ٠.٠ | ٦٥×١٠$^{٦}$(٣٦.١٪) | ٤٠×١٠$^{٦}$(٢٤.٤٪) | ٣×١٠$^{٧}$(١٧.١٪) | ٥٦×١٠$^{٦}$ (٢٨٪) | ٩٨×١٠$^{٦}$ (٦١.٣٪) |
| ١.٠٥ | ٥٣×١٠$^{٦}$(٢٩.٤٪) | ٢×١٠$^{٦}$(١٢.٢٪) | ٢×١٠$^{٧}$(١١.٤٪) | ٤×١٠$^{٧}$(٢٠٪) | ٩٦×١٠$^{٦}$(٦٠ %) |

| | | | | | |
|---|---|---|---|---|---|
| ١.٢ | ٢×١٠$^{٧}$(١١.١٪) | ٥×١٠$^{٦}$(٣.١٪) | ٠ | ٢٥×١٠$^{٦}$(١٢.٥٪) | ٦×١٠$^{٦}$(٦٠ %) |
| ١.٣٥ | ٨×١٠$^{٦}$(٤.٤٪) | ٠ | ٠ | ١٥×١٠$^{٦}$ (٧.٥٪) | ٩٥×١٠$^{٦}$(٥٩.٤ %) |
| ١.٥ | ٠ | ٠ | ٠ | ١٢×١٠$^{٦}$(٦٪) | ٩×١٠$^{٧}$(٥٦.٣ %) |
| r* | -٠.٩٨ | -٠.٩٨ | -٠.٩٥ | -٠.٩٨ | -٠.٨٤ |

r*: Correlation coefcient

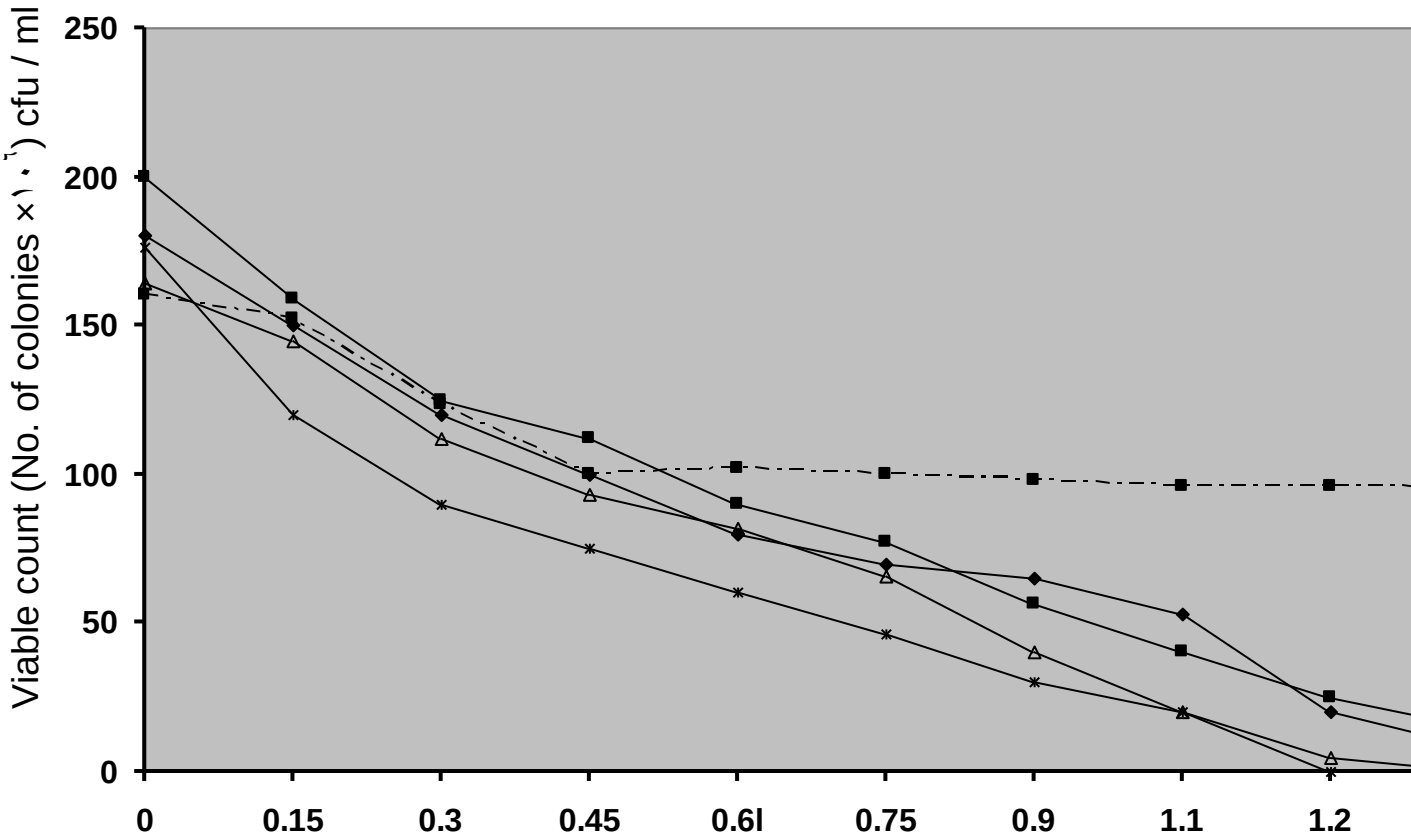


Figure (٣.٩): Effect of zinc sulfate on bacterial growth

## Conclusions

١. Benign prostatic hyperplasia affect older age men who are more than ٥٠ years old, while chronic prostatitis affect young men less than ٥٠ years, (BPH may hind CP as the same time).

٢. Most patients with benign prostatic hyperplasia and chronic prostatitis are presented with LUTS.

٣. The bacterial infection is associated with BPH and or CP including *E.coli, K.pneumoniae, Enterbacter* spp., *P.mirabilus, P.aeruginosa*, *Acinetobacter* spp., *Staphylococcus* spp., *Corynebacterium* spp., and *Enterococcus* spp.

٤. The isolates have showed multi-resistance to antibiotics and more sensitive antibiotics in the treatment of patients with benign prostatic

hyperplasia with chronic prostatitis or CP are amikacin, amoxillin-clavulanic acid and ciprofloxacin respectively.

٥. Important enzymes produced by some isolates from study patients are phosphatase and extracellular protease enzymes.

٦. Zinc sulfate had inhibitory effect on the growth of Gram-negative and Gram-positive bacteria especially when mixed with antibiotics.

# Recommendations

١. It is necessary to perform early diagnosis of cases with benign prostatic hyperplasia in the middle and elderly men followed by urine and expressed prostatic secretions cultures to ensure presentation of chronic prostatitis & or UTI and early treatment to avoid complication.

٢. Empirical treatment of antibiotics is better to avoided and continued surveillance of resistance rates among uropathogens is needed to ensure that appropriate recommendation can be made for treatment of infected patients.

٣. Current studies must be performed depending on the polymerase chain reaction (PCR) which helps to detect microorganisms that are not diagnosed by standard means.

٤. Addition of zinc to antibiotics for treatment of patients with prostatitis is suggested but the route of administration needs to be determined.

٥. Every prostatoctomiesed patients must send for histopathological examination for diagnosis asymptomatic chronic prostatitis with BPH.

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