TURKISH REPUBLIC OF NORTH CYPRUS
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

ANTIBIOTIC UTILIZATION PATTERN AND THE DRUG-RELATED PROBLEMS DETECTED IN URINARY TRACT INFECTION PATIENTS IN JORDAN

HAMZA TAYSEER AQEL U'WAIS

MASTER THESIS

A THESIS SUBMITTED TO THE GRADUATE INSTITUTE OF HEALTH SCIENCES NEAR EAST UNIVERSITY

DEPARTMENT OF CLINICAL PHARMACY

SUPERVISORS:

ASSOC. PROF. DR. ABDIKARIM MOHAMED DAUD

ASSOC. PROF. DR. HANEEN AHMED AMAWI

Northern Cyprus, Nicosia
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DEDICATION

All praises go first to God who brought down faith and patience on my heart. Then I dedicate this work mostly for those who were the source of motivation and support, whose words of encouragement and push for tenacity ring in my ears, so they are the reason of all my success. My dad and mom, I hope that I make you very proud. To my brother and sisters, for your endless love and help. To my friends who always supported me.

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LIST OF ABBREVIATIONS

Abbreviation	Description
UTI	Urinary Tract Infection
ASHP	American Society of Health-System Pharmacists
VUR	Vesicoureteral Reflux
BPH	Benign Prostatic Hyperplasia
USD	Urinary Stone Disease
E. coli	Escherichia Coli
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
TMP/SMX	Trimethoprim / Sulfamethoxazole
CDC	The Centers For Disease Control and Prevention
WHO	World Health Organization
ED	Emergence Department
US	United State
PSA	Prostate Specific Antigen
IDSA	Infectious Diseases Society of America
CVD	Cardiovascular Disease
FDA	Food and Drug Administration
SCI	Spinal Cord Injury
AIDS	Acquired Immune Deficiency Syndrome
CKD	Chronic Kidney Disease
DM	Diabetes Mellitus
MS	Multiple Sclerosis

Abbreviation	Description
CAUTI	Catheter - Associated UTI
ESWL	Extracorporeal Shock Wave Lithotripsy
GI	Gastrointestinal
RBC	Red Blood Cell
WBC	White Blood Cell
CBC	Complete Blood Count
PAC	Proanthrocyanidins
IV	Intravenous
IM	Intermuscular
ESBL	Extended – Spectrum Beta – Lactamase
MRSA	Methicillin-Resistant Staphylococcus Aureus
AMR	Antimicrobial Resistance
MDR	Multi-Drug Resistance
TB	Tuberculosis
OTC	Over – The – Counter
DRP	Drug – Related Problems
PCNE	Pharmaceutical Care Network Europe
ACCP	American College of Clinical Pharmacy
KAUH	King – Abdullah University Hospital
IRB	Institutional Review Bord
MENA	Middle East and North Africa
ESCMID	European Society of Clinical Microbiology and Infectious Diseases

Antibiotic Utilization Pattern and The Drug-Related Problems Detected In Urinary Tract Infection Patients In Jordan

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ABSTRACT

Introduction: UTIs are one of the most common infections seen by health care providers. Women are usually more susceptible to UTIs with more severe complications. Antimicrobial agents usually are the first-line treatment for UTIs. Choosing antibiotics depends on patient diagnosis, medication allergies, compliance history, cost, availability, and local antibiograms. Worldwide, irrational use of antibiotics is escalating, both in developed and developing countries.

Aim: The study aims to evaluate the rational of antimicrobial prescription in the treatment of urinary tract infections in Jordan and highlight the prevalence of drug-related problems, the patient's adherence towered their antibiotic usage, and the most common microorganisms causing UTIs and their antibiotic sensitivities.

Method: A prospective, descriptive study was conducted in two major health institutions in two cities of Jordan, Irbid and Amman for six months from September/ 2019 till - March/ 2020. The study population involved the patients admitted and diagnosed with UTIs at King Abdullah University Hospital (KAUH) and Al Bashir hospital from the inpatient and outpatient settings. Patients' information was collected from both patient's interview based on a questionnaire and the patient's files. The data was collected and analyzed using Microsoft Excel 2016 and Statistical Package for the Social Sciences (SPSS) software version 25.0.

Results: A total of 273 patients from the inpatient and outpatient settings were included in the analysis, in which 56.4% of them were women. Urine culture was done to 84.6% of the patients included in this study, which showed that E. coli is the most common causative pathogen in these patients (46.8%), followed by K. pneumonia

(10%). The susceptibility results showed a high resistance rate to cefazolin (87.5%) and ticarcillin (84.2%) out of the parenteral antibiotics. Related to the patients' adherence and education toward their previous usage of antibiotics, 42.5% of patients showed non-adherence to previously used antibiotics, and only 33.7% reported that they received a previous education on who and when to use the antibiotics. Ciprofloxacin (24.3%) was the most commonly used, followed by TMP/SMX (11.9%). Related to DRPs, 58.2% of the patients had at least one DRP.

Conclusion: This study indicates a high percentage of resistance to currently prescribed antibiotic agents for UTIs. Also, the DRPs were relatively high in investigated patients, due to the long duration of antibiotic use, inappropriate antibiotic selection, lack of prophylaxis, and the over-prescription of antibiotics.

Keywords: UTI, drug-related problems, antimicrobial resistance, antibiotics, infections, pharmacist, Jordan

Ürdün'de İdrar Yolu Enfeksiyonu Hastalarında Tespit Edilen Antibiyotik Kullanım Modeli ve İlaçla İlgili Sorunlar

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ÖZ

Giriş: İYE'ler, sağlık hizmeti sağlayıcıları tarafından görülen en yaygın enfeksiyonlardan biridir. Kadınlar genellikle ciddi komplikasyonları olan idrar yolu enfeksiyonlarına daha duyarlıdır. Antimikrobiyal ajanlar genellikle idrar yolu enfeksiyonları için birinci basamak tedavidir. Antibiyotik seçimi, hasta teşhisine, ilaç alerjilerine, uyum geçmişine, maliyete, bulunabilirliğe ve yerel antibiyogramlara bağlıdır. Dünya çapında, hem gelişmiş hem de gelişmekte olan ülkelerde uygun olmayan antibiyotik kullanımı artmaktadır.

Amaç: Bu çalışma, Ürdün'de idrar yolu enfeksiyonlarının tedavisinde antimikrobiyal reçetenin mantığını değerlendirmeyi ve ilaçla ilgili sorunların yaygınlığını, hastanın antibiyotik kullanımına olan bağlılığını ve idrar yolu enfeksiyonlarına neden olan en yaygın mikroorganizmaları ve antibiyotik duyarlılıklarını vurgulamayı amaçlamaktadır.

Yöntem: Ürdün'ün iki şehri Irbid ve Amman'daki iki büyük sağlık kurumunda Eylül / 2019'dan Mart / 2020'ye kadar altı ay süreyle ileriye dönük, tanımlayıcı bir çalışma yürütülmüştür. Çalışma popülasyonu, yatılı ve ayakta tedavi ortamlarından King Abdullah Üniversite Hastanesi (KAUH) ve Al Bashir Hastanesi'nde İYE tanısı alan ve kabul edilen hastaları içermektedir. Hastaların bilgileri hem ankete dayalı olarak hasta görüşmesinden hem de hastanın dosyalarından elde edilmiştir. Veriler, Microsoft Excel 2016 ve Sosyal Bilimler için İstatistik Paketi (SPSS) 25.0 yazılım sürümü kullanılarak toplanmış ve analiz edilmiştir.

Bulgular: Analize yatılı ve ayakta tedavi merkezlerinden %56.4'ü kadın olan toplam 273 hasta dahil edilmiştir. Çalışmaya dahil edilen hastaların %84,6'sına idrar kültürü yapılarak bu hastalarda E. coli'nin (%46,8) en sık nedensel patojen olduğunu ve bunu K. pneumonia (%10) takip ettiği belirlenmiştir. Duyarlılık sonuçları, parenteral antibiyotiklerden sefazolin (%87.5) ve tikarsiline (% 84.2) yüksek direnç oranı göstermiştir. Hastaların önceki antibiyotik kullanımına olan bağlılığı ve eğitimi ile ilgili olarak, hastaların %42,5'i daha önce kullanılan antibiyotiklere uyumsuzluk göstermiş ve sadece %33,7'si antibiyotikleri kimin ve ne zaman kullanacakları konusunda önceden eğitim aldıklarını bildirmiştir. En sık kullanılan siprofloksasin (%24,3) olurken, onu TMP / SMX (%11,9) izlemiş ve DRP'lerle ilgili olarak, hastaların %58,2'sinde en az bir DRP olduğu sonucuna varılmıştır.

Sonuç: Bu çalışma, idrar yolu enfeksiyonları için halihazırda reçete edilen antibiyotik ajanlara karşı yüksek bir direnç yüzdesini göstermektedir. Ayrıca, uzun süreli antibiyotik kullanımı, uygun olmayan antibiyotik seçimi, profilaksi eksikliği ve aşırı antibiyotik reçetesi verilmesi nedeniyle DRP'lerin araştırmaya dahil edilen hastalarda nispeten yüksek olduğu belirlenmiştir.

Anahtar Kelimeler: İYE, ilaçla ilgili sorunlar, antimikrobiyal direnç, antibiyotikler, enfeksiyonlar, eczacı, Ürdün

1. INTRODUCTION

Urinary tract infections (UTIs) are one of the most common infections seen by health care providers worldwide (Foxman et al. 2000). It can be classified into lower UTI (cystitis, urethritis, and prostatitis) and upper UTI (pyelonephritis) based on the site of the infection, or as uncomplicated or complicated infections according to the grade of severity (Najar, Saldanha and Banday, 2009).

Generally, UTIs are more prevalent in women than men due to differences in the anatomy of the urinary tract and the hormonal changes during pregnancy and menopause. Many risk factors can contribute to the prevalence of UTIs include aging, urinary retention, suppressed immune system, urologic instrumentation, benign prostatic hyperplasia (BPH) in men, vesicoureteral reflux (VUR), neurogenic bladder, urinary stone disease (USD), and recent urinary procedures (Fatima et al. 2018).

Previous studies showed that Escherichia coli (E. coli) is the most common causative pathogen of UTIs, followed by Klebsiella and Proteus species (Das et al. 2009). These uropathogens can invade the urinary tract by three main mechanisms include ascending, hematogenous, or lymphatic route (Niall and Davis 2011).

The diagnosis of UTI is usually made based on a combination of clinical presentation and laboratory findings. Signs and symptoms of UTI include fever, dysuria, urgency, frequency, nocturia, incontinence, macroscopic or gross hematuria, abdominal pain, suprapubic tenderness, and costovertebral angle tenderness (Schmiemann et al. 2010). However, urine culture is still considered the gold standard diagnostic tool in UTIs. Other advanced investigations might be necessary in some cases including a computerized tomography (CT) scan, a magnetic resonance imaging (MRI), and an ultrasound (Chu and Lowder, 2018).

Antimicrobial agents are usually the first-line treatment for UTIs. Choosing antibiotics depends on the patient's diagnosis, medication allergies, compliance history, cost, availability, and local antibiograms (Wawrysiuk et al. 2019; Johnson and Russo 2018). Commonly used antimicrobial agents in the management of UTIs include nitrofurantoin, trimethoprim/sulfamethoxazole (TMP/SMX), fluoroquinolones (ciprofloxacin or levofloxacin), fosfomycin, cephalosporins, penicillins, and

carbapenems (Hryniewicz et al. 2001). Generally, the ability of these antibiotics to achieve the appropriate concentration in urine to efficiently eradicate the bacteria is the reason to prefer these agents (Leekha, Terrell, and Edson 2011). As the landscape of infectious disease changes with growing concerns over the development of resistance, the choice of antibiotic becomes more challenging (Sedor and Mulholland 1999). A recent study in USA showed that the economic burden of UTIs is approximately five billion U.S. dollars annually (Gajdács et al. 2019).

The role of clinical pharmacist in the management of infectious diseases is vital. Clinical pharmacists identify and resolve drug-related problems while collaborating with physicians and other health care providers to develop a personalized therapeutic scheme for each patient. This contribution reduces the use of inappropriate drugs, dosing errors, interactions as well as improves the provided care for each patient (Viktil and Blix, 2008).

1.1 The aim of the study

This study was conducted to evaluate the rationality of antimicrobial prescription in the treatment of urinary tract infections in Jordan and highlight:

- The prevalence of drug - related problems.
- The most common microorganisms causing UTIs and their antibiotic sensitivities.
- The patient’s adherence towered their antibiotics usage.

2. LITERATURE REVIEW

2.1 Urinary tract infections

2.1.1 Definitions and epidemiology of UTIs

Infections are diseases caused by pathogenic microorganisms such as bacteria, viruses, yeast, fungi, or parasites ('Infectious diseases'). Many organisms live in and on our bodies. Usually these organisms are harmless or even helpful, but are capable of causing infections under certain conditions ('Infectious Diseases. Also called: Communicable diseases' 31 August 2016). If the host's immune system is compromised, or the infectious agent overcomes the immune system, an infectious disease result (Kotra, 2007). Some of these infectious diseases are contagious, passed from person to person; others can be zoonotic diseases spreading from animals to humans('Infectious diseases.').

UTIs are very common infectious disease in both inpatient and outpatient settings worldwide. Further, UTIs are the most common hospital-acquired infections, accounting for about 40% of all nosocomial infections (Saint et al. 2008).

A UTI is defined as the presence of greater than or equal to 10^5 bacteria CFU/mL (10^8 CFU/L) in the urinary tract. It affects approximately 150 million people each year (Waller et al. 2018a). In USA, UTIs account for nearly 8.3 million office visits and more than 1 million hospitalizations annually (Kumar et al. 2015). The Centers for Disease Control and Prevention (CDC) reports that UTIs contribute to 13,000 deaths every year (Kumar and Das 2017). The economic burden for the management of UTIs has been estimated to be between $1.6 and $2.14 billion each year (Cardwell et al. 2016). A study in the United State (US) reported a significant increase in UTI visits to the emergency department (ED) between 2007 and 2010, from 2.3 million to 3 million, respectively, with more than 80% of these visits were made by women (Flores-Mireles et al. 2015; Takhar and Moran 2014). In Jordan there are not enough studies focused on the prevalence of UTIs or their financial burden on the healthcare system.

Generally, women are twice more likely to be affected by UTIs than men in all age groups, with approximately 50- 60% of women experiencing at least one infection during their lifetime (Abou Heidar et al., 2019).While the prevalence of UTIs increase

with age, a spike is found in young women aged 14−24. On the other hand, women over 65 have a nearly 20% prevalence rate, compared with approximately 11% in the overall population. Close to 10% of postmenopausal women indicate that they had a UTI in the previous year (Medina and Castillo-Pino, 2019). On the other hand, men demonstrate lower rates of UTIs, with 5- 8 cases per 10,000 in young and middle-aged men. However, men older than 50 years demonstrate a higher risk of UTI due to prostate enlargement, debilitation, and potential urinary tract instrumentation (Long and Koyfman 2018). The significant increase in the incidence of UTIs in women is attributed to many factors, including a shorter urethra and the different hormonal changes during pregnancy and menopause. In men, the dryer environment at the urethral opening and the antibacterial activity of the prostate-specific antigen (PSA) has recently been found to enhance the innate prostate defences, contributing to clearance as well as the direct killing of E. coli (Wagenlehner et al. 2014; Townes et al., 2013).

2.1.2 Classifications of urinary tract infections

There are many UTI classification systems, the most widely used are those developed by the CDC, Infectious Diseases Society of America (IDSA), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) along with the U.S. Food and Drug Administration (FDA) (G. Bonkat (Co-chair) 2018). Most of which frequently classify UTI depending on the infection site and grade of severity (Öztürk and Murt, 2020).

2.1.2.1 Site of infection

UTIs can be anatomically classified into lower and upper urinary tract infections. Lower infections involve the bladder (cystitis), the urethra (urethritis), and the prostate (prostatitis in men). An upper tract infection is referred to as pyelonephritis and it involves the renal parenchyma and collecting system (Foxman, 2002).

2.1.2.2 Grade of severity

Depending on the severity, UTIs can be categorized in to uncomplicated and complicated infections. Uncomplicated UTIs are limited to non-pregnant, premenopausal women with no known relevant anatomical or functional abnormalities

within the urinary tract or any comorbidities ('Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry' August 2019). Complicated UTIs can be defined as any infection where the previous criteria do not apply. Accordingly, complicated UTIs encompass all men, pregnant women, patients with relevant anatomical or functional abnormalities of the urinary tract, urologic instrumentation, urolithiasis, renal diseases, and/or with other concomitant immunocompromising diseases such as diabetes ('Complicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry', 2018).

2.1.3 Risk factors of urinary tract infections

The normal urinary tract typically is resistant to infection and colonization by pathogenic bacteria. Deafens mechanisms in the immune system act effectively to protect against these infections. However, these mechanisms can be compromised in some patients with certain risk factors. Risk factors can be modifiable behavioural factors, while others are more inherent to the patient's overall health (Girard et al., 2017).

2.1.3.1 Age

As people age, they can be more susceptible for developing UTIs due to changes in immune function, exposure to nosocomial pathogens, an increasing number of comorbidities and several changes throughout the genitourinary tract (Nicolle, 2009). Through aging, the kidney function changes, about two-thirds of people undergo a gradual decline in the filtration rate after the age of 30. In addition, there is a significant decrease in kidney size due to the narrowing of the suppling arteries ('Aging changes in the kidneys and bladder' 2020). As for the urethra in older women, there is a significant decline in the maximum urethral closure pressure, detrusor contraction strength, and urine flow rate. Moreover, the lining becomes thinner. The trigger for these changes in a woman's urethra seems to be a declining level of estrogen after menopause (Pfisterer et al. 2006; Gopal et al., 2008).

Throughout life, sporadic contractions of the urinary bladder muscles occur separately from any need to urinate. In younger people, most of these contractions are blocked by central nervous system controls, but the number of contractions that

are not blocked rises with age, sometimes resulting in episodes of urinary incontinence (Vahabi et al., 2017).

Furthermore, with aging the amount of urine that remains in the bladder after urination increases (residual urine), which can cause urine retention (Asimakopoulos et al. 2016).In older men, the prostate gland tends to enlarge, gradually blocking the flow of urine. If untreated, blockage may become complete, causing urinary retention and possibly kidney damage (Griebling 2005). All these changes can lead to increased voiding frequency, nocturia, urgency, urge incontinence, and poor bladder emptying, which can increase the incidence of UTIs in the elderly population. Over 10% of women older than 65 reported having a UTI within the past 12 months (Foxman et al. 2000). This number increases to almost 20%-30% in women over the age of 80. On the other hand, for healthy men, a UTI is uncommon until over the age of 60 (Eriksson et al., 2010).

2.1.3.2 Incomplete bladder emptying

Urinary retention and incomplete emptying result from obstructive or nonobstructive conditions. Urethral obstructions can be mechanical resulting from benign prostatic hyperplasia and urethral stricture, or functional at the level of the external sphincter caused by shy bladder syndrome (Dray and Clemens, 2017).

For nonobstructive urinary retention, the bladder detrusor muscle areflexia or impaired centricity can be caused by neurologic conditions with the most common being spinal cord injury (SCI), multiple sclerosis, cerebral vascular events and Parkinson's disease. Gradual expansion of the bladder capacity due to sensory deficit seen commonly in patients with diabetic neuropathy is another possible cause. Also, some medications cause incomplete emptying of the urine, such as anticholinergic agents. If urinary retention is left untreated, it can lead to urinary tract infections and damage to the kidneys (Yoshimura and Chancellor, 2004).

2.1.3.3 Immunocompromised host

An immunocompromised host is a patient who cannot respond appropriately to infection because of an impaired or weakened immune system and consequently is more susceptible to UTIs. This impairment to fight infection may be caused by certain

diseases or conditions, such as Acquired Immune Deficiency Syndrome (AIDS), cancer, DM, chronic kidney diseases (CKD), malnutrition, organ transplant, and certain genetic disorders. It may also be caused by certain medications or treatments, such as chemotherapeutic agents, radiation therapy, and stem cell therapy (Bula-Rudas, 2020).

2.1.3.4 Diabetes mellitus

DM is a chronic, metabolic disease characterized by persistently elevated levels of blood glucose (or blood sugar). It is considered as one of the most significant emerging threats to health in the 21st century. Globally, around 422 million patients are diagnosed with DM ('Diabetes'). Along with the classical complications, DM has been associated with reduced T cell response, neutrophil function, and disorders of functional immunity (Casqueiro, Casqueiro, and Alves 2012). Related to UTIs, the altered immunity in diabetic patients cause increased adherence of the pathogens to the uroepithelial cells, granulocyte dysfunction, and altered intracellular calcium metabolism. Another significant urologic complication of DM is the diabetic bladder dysfunction which affects more than 50% of uncontrolled diabetic patients. Furthermore, some pathogens flourish well in the high glucose environment (Mama et al. 2018). All these factors contribute to the increased susceptibility to infections in diabetic patients; specifically, the urinary tract is considered the primary site of infection (Kumar et al., 2019).

2.1.3.5 Kidney transplantation

“Transplantation is the transfer (engraftment) of human cells, tissues or organs from a donor to a recipient with the aim of restoring function(s) in the body” ('Transplantation'). In a patient with end-stage renal disease, kidney or renal transplantation is the most clinically effective treatment (Giessing, 2012). However, in the first six months after kidney transplantation, UTIs occur in an estimated 38% of kidney transplant recipients, due to vesicoureteral reflux, underlying urologic diseases, urinary catheters, and comorbidities (Ten Doesschate et al., 2019). In conjunction with physical risk factors, the immunosuppressive agents that are needed in renal transplant patients to prevent graft rejection can further contribute to varying degrees of risk for infections (Hollyer and Ison, 2018). Many studies showed that the use of azathioprine,

mycophenolate mofetil and anti-thymocyte globulin are associated with higher rate of UTIs in the post-transplant patients (Fiorentino et al., 2019). Hence, UTIs remain the most common infectious complication in these patients.

2.1.3.6 Benign prostatic hyperplasia (BPH)

BPH is defined as a noncancerous enlargement of the prostate gland; it is the most common prostate problem for men older than 50 years of age. The exact cause of this enlargement is unknown, but it's believed to be linked to hormonal changes occurring during the aging process (Edwards, 2008). Clinical manifestations of BPH are caused by extrinsic compression of the prostate at the base or neck of the bladder which can reduce or stops the flow of urine into the urethra leading to urinary retention, impaired voiding, hematuria, hesitancy, weak stream, nocturia, and incontinence (Speakman and Cheng, 2014). Due to these complications, BPH patients have a higher tendency to UTIs. Many studies showed that BPH and genitourinary instrumentation were significant risk factors to UTI in men (Heyns, 2012).

2.1.3.7 Vesicoureteral reflux (VUR)

Normally urine flows in one-way from each kidney to the ureters and into the bladder then when the bladder is full, it squeezes and sends the urine out through the urethra. Nevertheless, in some people urine flows backwards from the bladder to one or both ureters and sometimes to the kidneys, this condition is called VUR, where it can be either congenital or acquired (Reflux nephropathy, 2019). VUR is usually ranked as grades from 1 to 5. Grade (1) is the mildest condition where grade (5) is the most serious. The incidence of this condition is higher among infants and children than adults (Carlos Roberto Estrada 2018). Many factors can increase the risk for UTIs, but over the last few years, no factor has received higher consideration than VUR. It affects 1% to 2% of all children, and approximately 30% to 45% of children with VUR will experience UTI (Keren et al., 2015).

2.1.3.8 Neurogenic bladder

Neurogenic bladder is a condition in patients who lack bladder control due to a brain, spinal cord or nerve problem. This nerve damage can result from diseases such as DM, multiple sclerosis (MS) or Parkinson's disease (Gill, 2018). Determined by the nerves

involved and the nature of the damage, the bladder becomes either overactive or underactive. Neurogenic bladder can lead to permanent urological alterations, such as recurrent UTI, hydronephrosis, reflux, stones, and it always inevitably leads to diminished patient quality of life (Amarenco et al., 2017). Multiple studies showed that UTIs are one of the most common infection in neurogenic bladder patients. Approximately 31 % of these patients were diagnosed with UTI within one year of diagnosis (Jahromi, Mure, and Gomez, 2014).

2.1.3.9 Urinary stone disease (USD)

USD or urolithiasis is defined as the presence of stones and calcification within the urinary tract caused by supersaturation. in USD, the concentration of some substances in the urine, such as calcium oxalate and calcium phosphate exceed the limits of their solubility (Kirkali et al., 2015). Furthermore, the majority of stones initially form in the kidneys. Nearly 10% of people will have USD during their lifetime (Schwaderer and Wolfe, 2017). Many studies have shown that UTI has a higher prevalence rate in patients with USD, reported in 21% to 34% (Nevo et al., 2019).

2.1.3.10 Instrumentation

2.1.3.10.1 Urinary catheterisation

Urinary catheterization is a procedure where a flexible tube is placed into the bladder that facilitates direct drainage of the urine (Sovrin and Shah ,2019). This procedure is indicated in patients with acute urinary retention, chronic urinary obstruction, urine incontinence, and other medical conditions such as MS, spinal cord injury, or dementia. The main four types of catheters are indwelling catheter (used for a short or long time), condom catheter (must be changed every day), intermittent self-catheter (can be done once or several times a day) and suprapubic catheter (changed every 1 to 3 months) (Anthony and Schaeffer, 2019). More than 50% of catheterized patients suffer from complications such as UTIs, bladder stones, blood infections (septicemia), blood in the urine (hematuria), kidney damage (usually only with long-term, indwelling catheter use), urethral strictures, and bladder cancer (only after long-term indwelling catheter) (Gil and Shlamovitz, 2016). Urinary catheterization is the single most crucial leading cause for the development of nosocomial UTI; approximately 75% of nosocomial UTIs are catheter-associated UTIs (CAUTIs) ('Catheter-associated

Urinary Tract Infections (CAUTI)' 2015). In the US, based on prospective surveillance data reported to the CDC, the incidence of CAUTIs in 2012 was up to 1.7 per 1,000 catheter days in inpatient adult and pediatric (Dudeck et al., 2013). The duration of catheterization is one of the most crucial risk factors for CAUTIs may be caused by extraluminal or intraluminal infections (Saint et al., 2016). Extraluminal infection occurs through the entry of bacteria into the bladder along with the biofilm that forms around the catheter in the urethra. On the other hand, intraluminal infection occurs as a result of urinary stasis caused by drainage failure, or due to contamination of the urine collection bag with subsequent ascending infection. Some studies showed that the extraluminal infections have a higher incidence rate than the intraluminal infections 66% to 34%, respectively (Tambyah, Halvorson and Maki, 1999).

2.1.3.10.2 Ureteric stent

Ureteric stent (also called a double-J stent) is a thin, flexible plastic tube which is placed temporarily into the ureter to allow the urine to pass from the kidney to the bladder ('Insights: Why Urologists Use Ureteral Stents' 2018). The double-J stent is mainly used for stabilization of the ureter after surgery such as extracorporeal shockwave lithotripsy (ESWL) to minimize blockage from multiple stone fragments that can clog and obstruct a ureter post-surgery. Also, it provides drainage through a ureter that may be leaking, dysfunctional, or strictured (Sajjad, 2019). However, the double-J stent is often associated with several complications, primarily when the stent left for longer duration in place. These complications include haematuria, dysuria, fever, suprapubic pain, urinary frequency, UTIs bacteremia and renal failure (Scotland et al. 2019). Bacterial colonization of ureteral stents that can lead to UTIs is a critical problem, colonization rates of ureteral stents in these patients vary between 42% to 90%, but not all affected patients are symptomatic for UTI. Some studies showed that only 38% of patients were symptomatic (Kehinde et al. 2002; Lange et al., 2015).

2.1.3.11 Pregnancy

During pregnancy, physiological changes of the urinary tract and immunologic alterations predispose women to infections (Gilbert et al., 2013). Physiologic changes of the urinary tract consist of ureteral dilation due to compression of the ureters from the gravid uterus. Hormonal effects of progesterone also induces smooth muscle

relaxation leading to dilation and urinary stasis, and VUR increases (Yan et al., 2018). The bladder also experiences progressive superior and anterior displacement, hypertrophy and smooth muscle relaxation, causing increased capacity and urinary stasis (Glaser and Schaeffer, 2015). Immune alterations with pregnancy may impair pathogen clearance. These changes may lead to sever maternal and fetal complications (Sappenfield, Jamieson, and Kourtis, 2013). UTI is considered one of the most common maternal infections, affecting up to 10% of pregnant women (Szweda and Jozwik, 2016). Untreated UTI in pregnancy can lead to perinephric cellulitis and abscess, septic shock, renal dysfunction (usually transient), hematologic dysfunction (e.g. anemia or thrombocytopenia), hypoxic fetal events, preeclampsia, preterm labor, and possible subsequent preterm delivery, leading to increased infant morbidity and mortality (Raisa and Platte, 2019).

2.1.3.12 Menopause

The risk factors for UTIs in women vary between premenopausal and postmenopausal women (Gupta and Trautner, 2013). In premenopausal women behavioural risk factors include frequency of sexual intercourse, using spermicidal agents and/or contraceptive diaphragm, condom use, a previous UTI history, recent antibiotic use and nonsecretor status (Stavridis, 2013). On the other hand, the predisposing factors in postmenopausal women include estrogen deficiency, cystocoele, urogenital surgery, high post-void residual volume, history of previous UTI, also some changes in the vaginal flora (Aydin et al., 2015). During postmenopausal period, the vaginal pH increases, lactobacilli disappear, and the vagina is predominantly colonized by many pathogenic bacteria, causing an increased prevalence of UTIs in postmenopausal women (Raz, 2011).

2.1.4 Etiology of urinary tract infections

A variety of bacteria can cause UTIs, but gram-negative bacteria is estimated to be the primary cause. E. coli is a gram-negative bacteria, and it is considered the most frequent uropathogen responsible for UTIs accounting for 85% to 90% of uncomplicated UTI cases (Mazzariol, Bazaj, and Cornaglia, 2017). Other enteric gram-negative bacteria can cause UTIs, including Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, Enterobacter cloacae, Serratia

marcescens, and Citrobacter spp. However, some of the gram-positive organisms also implicated in UTIs, such as Staphylococcus saprophyticus, Enterococcus faecalis, and (rarely) Staphylococcus aureus. Most of these uropathogens usually originate from bowel flora (fecal flora) of the host (Millner and Becknell, 2019). It has been shown that there is a relationship between the type of uropathogen and particular predisposing factors. For example, Klebsiella pneumoniae, group B Streptococci, and Enterococcus faecalis are more frequently observed in nosocomial UTI. On the other hand, E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus spp., Serratia spp., Enterococci, and Staphylococci are more common in spinal cord injury patients (Khorvash et al., 2009). Most UTIs are caused by a single organism. However, in patients with stones, indwelling urinary catheters, or chronic renal abscesses, multiple organisms may be isolated. Depending on the clinical situation, the recovery of multiple organisms may represent contamination, and a repeat evaluation should be done (Alastair and Hay, 2016).

2.1.5 Pathophysiology of urinary tract infections

In normal healthy individuals, several mechanisms attempt to prevent bacteria from invading the urinary tracts, these mechanisms usually work together to prevent UTIs. They include urination which washes most bacteria out of the urethra, bladder contraction leading to closes of the ureterovesical junction, thus preventing urine from ascending upwards into the upper urinary tract. In the distal urethra, the urethral sphincter prevents the upward movement of bacteria, mucus-secreting cells in the female urethra help trap bacteria so it cannot move upward (Abraham and Miao, 2015). In men, the length of the urethra in addition to the prostate and associated glands create secretions to shield bacteria from invading the urinary tract. Also, several factors work to create a bactericidal effect such as high osmolality and low pH of the urea, uromodulin presence, and the epithelial cells of the urinary tract (O'Brien et al., 2015). UTIs occur when one or more of these normal defences are disrupted or overwhelmed by the bacteria. Generally, three main mechanisms are responsible for UTI:

2.1.5.1 Ascending infection

Colonization with ascending spread is the most common route of infection, the ascension of bacteria from the urethra to the bladder. Many studies showed that the

uropathogenic E. coli originate from the fecal flora, spread across the perineum, and enter the bladder through the urethra causing UTI (Zanelotti, Barnes and Khaja, 2017).

2.1.5.2 Haematogenous infection

Hematogenous infection happens when the bacteria spread via the blood to other organs of the body, causing infections away from the original site of infection, such as prolonged bacteraemia. It often associated with a deep source of infection such as endocarditis or untreated pyelonephritis, especially emphysematous pyelonephritis (Walsh and Collyns, 2017). This route of infection is less prevalent than other mechanisms. Hematogenous UTIs are usually due to Staphylococcus species (particularly S. aureus) (Spencer et al., 2014).

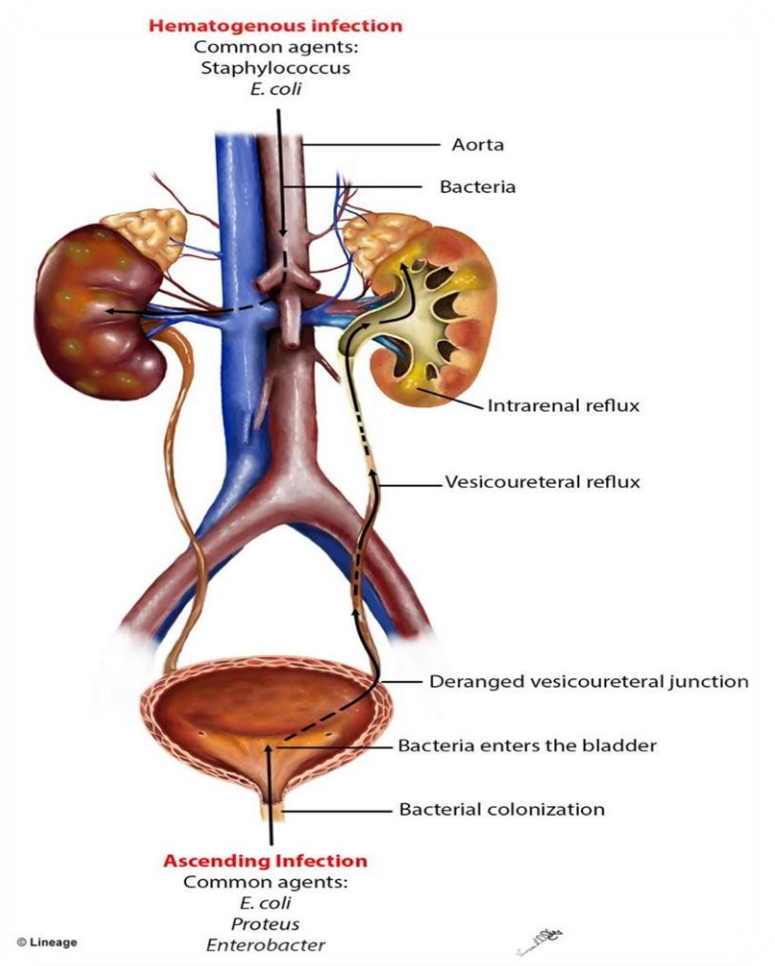

Figure 2.1.5: The Ascending and Hematogenous Mechanisms That Lead to UTIs (MD 2020).

2.1.5.3 Lymphatic infection

Lymphatic infection is an infection involving another organ in the genitourinary or gastrointestinal systems which may spread to affect the bladder through the lymphatic channels, causing UTIs. Conditions associated with the lymphatic route are retroperitoneal abscesses and severe bowel infections (McLellan and Hunstad, 2016).

2.1.6 Clinical presentation of urinary tract infections

In infants and young children, UTI may present with nonspecific signs and symptoms such as fever, irritability, poor feeding and poor weight gain. Other symptoms like foul-smelling urine, vomiting and diarrhea are generally not helpful in diagnosing UTI in young children (Leung et al., 2019). Fever may be the sole manifestation of UTI in infants and children younger than two years of age (Gauthier et al. 2012; Shaikh et al., 2007). On the other hand, the presenting signs and symptoms of UTIs in older children and adults are recognized easier include fever, dysuria, urgency, frequency, nocturia, incontinence, macroscopic or gross hematuria, abdominal pain, suprapubic tenderness, and costovertebral angle tenderness. The constellation of fever, chills, flank pain, nausea, vomiting, and malaise is suggestive for upper UTI ('Urinary tract infection (UTI)' 2019). Elderly patients may experience nonspecific urinary symptoms, for example, altered mental status, change in eating habits, lethargy, or gastrointestinal (GI) symptoms (McDermott, 2018). For a particular population with indwelling catheters or neurologic disorders usually will not present with lower urinary tract symptoms. Instead, they may present with foul or strong urine odor, abnormal urine color, cloudy urine, flank pain, chills and fever (Sovrin and Shah, 2018). The clinical presentation in male patients with acute prostatitis typically is high fever, chills, malaise, myalgia, localized pain (perineal, rectal, sacrococcygeal), frequency, urgency, dysuria, nocturia, retention, dribbling, hesitancy, pain or discomfort of the penis or testicles and painful ejaculation (John and Brusch, 2020). Patients with chronic prostatitis who have had symptoms for at least three months, these symptoms include voiding difficulties (frequency, urgency, dysuria), pain in and around the penis, testicles, anus, lower abdomen or lower back, and perineal or suprapubic discomfort (Prostatitis, 2020).

2.1.7 Diagnosis of urinary tract infections

Symptoms alone are unreliable for the diagnosis of UTIs. The key to the diagnosis of UTI is a combination of signs, symptoms and laboratory findings (Geerlings, 2016).

2.1.7.1 Dipstick test

Rapid urine test or dipstick test is a thin, plastic stick treated with chemicals; it placed in the urine to detect abnormalities. The chemical strips react and change color if certain substances are present in the urine or if their levels are above average (Rowe and Juthani-Mehta, 2014). A dipstick test is used to checks for the acidity (pH), protein, sugar, ketones, bilirubin, blood, nitrites or leukocyte esterase. However, multiple studies showed that urine dipstick test alone is not reliable in diagnosing UTIs, but it can be used in the outpatient clinic and primary health centers as a first-level screening test (Mambatta et al. 2015; Little et al., 2009).

2.1.7.2 Urine analysis

Urine analysis or urinalysis is a routine test done in the laboratory. During this test, a small amount of urine is examined under the microscope. Urine analysis can be used for the detection of red blood cells (RBCs), white blood cells (WBCs), crystals, protein, nitrites and bacteria (Schmiemann et al., 2010).

The pH level indicates the amount of acid in the urine, high pH levels it might be a signal for kidney or urinary tract disorder (kidney stones or UTIs). Elevated levels of protein in the urine (proteinuria) may indicate for many conditions such as diabetes, chronic kidney disease or pyelonephritis (Whiting et al., 2006). Any detection of sugar (glucose) or ketones in the urine usually calls for follow-up testing for diabetes. For bilirubin, normally, carried in the blood and passes into the liver, where it is removed and becomes part of the bile. However, the detection of bilirubin in the urine may indicate liver damage or disease (Staff, 2019). The presence of either nitrites or leukocyte esterase (product of WBCs) in the urine can be a sign of UTIs (White, 2011). Hematuria or the presence of the blood in the urine requires additional testing; it may be a sign for kidney damage, UTIs, kidney or bladder stones, kidney or bladder cancer, enlarged prostate (in men), or certain blood disorders (e.g. sickle cell anemia and cystic

kidney disease). Crystals in the urine are known as crystalluria; it can be indicators for the presence of urinary tract stones, or UTIs (Edgar and Lerma, 2015).

2.1.7.3 Urine culture

Urine culture is still considered the "gold standard" test in determining the presence of UTIs. It is a lab test to check for any organisms (such as bacteria) in the urine that can cause UTIs. A collected midstream urine specimen added to a substance that promotes the growth of organisms. A positive urine culture is the detection of greater than 10^5 CFU/mL (10^8/L) of a known uropathogen in urine (Ganzeboom et al., 2018). After identification and quantification are complete, the next step is to determine the susceptibility of the organism, which can lead to a better selection of an appropriate agent for the treatment (Price et al., 2016).

2.1.7.4 Complete blood count (CBC)

A CBC test is used to get information on the number of RBCs, WBCs and platelet cells in the blood. An abnormal WBCs count may be the results of an infection, inflammation, or other stress in the body. In patients with uncomplicated UTI, the WBCs count may or may not be elevated, although, it is usually elevated in patients with complicated UTIs (Lo et al., 2018).

2.1.7.5 Complications of urinary tract infections

UTIs usually do not cause complications, but if left untreated, it can lead to some severe consequences such as recurrent UTIs, permanent kidney damage (from acute or chronic pyelonephritis), urethral stricture (in men), and sepsis. Furthermore, in cases of pregnant women, an untreated or mistreated UTI can increase the risk of delivering low birth weight or premature infants (Staff).

Recurrent UTIs are considered either reinfections or relapses. Reinfection is an infection after complete treatment with another bacterial species and usually happens more than two weeks after the last UTI and is treated as a new uncomplicated UTI (Geerlings, Beerepoot and Prins, 2014). Relapse is an infection with the same bacteria that caused the initial infection and usually happens within two weeks of the original infection, and this relapse of the initial infection either because of unsuccessful

treatment of the original infection, a resistant organism, or anatomical abnormalities (Arnold, Hehn and Klein, 2016).

2.2 Management of urinary tract infections

2.2.1 Desired Outcomes

The goals of UTI treatments are to eradicate the invading organisms, prevent or treat any complications of the infection, reduce mortality, prevent the recurrence of UTI, and to decrease resistance to the antimicrobial agents.

2.2.2 Nonpharmacological treatment

Several nonpharmacological therapies have been suggested for the prevention of UTIs, such as:

2.2.3 Cranberry juice

Cranberry fruit and juices contain the compound proanthrocyanidins (PACs), which exerts antiadhesion characteristics against bacteria, especially E. coli. This antiadhesion interaction prevents bacteria from binding to the bladder epithelium and therefore rule out UTIs (Wang et al., 2012). However, the efficacy of cranberry is controversial. One study showed that the use of cranberry significantly reduced the occurrence of UTI by 55% in compered with placebo without significant adverse effects (Singh, Gautam and Kaur, 2016). Another study showed that the daily consumption of a cranberry juice for six months produced a 39% reduction in clinical UTI episodes (Maki et al., 2016). On the other hand, adhesion research and clinical trials show no significant effectiveness with cranberry juice in decreasing the incidence of another UTI (Barbosa-Cesnik et al., 2011).

2.2.3.1 Lactobacillus probiotics

Lactobacillus is a lactic acid bacterium used as vaginal suppositories for the prevention of UTI in women. Lactobacillus suppositories can helps keep the vaginal pH in the normal range (pH 4 - 4.5), produce lactic acid and bacteriocins that directly kill or inhibit any uropathogens, formation of microcolonies that adhere to the epithelial cell receptors and form a physical barrier against pathogen adhesion, and non-specific

stimulation of host defence mechanisms against pathogens (Ng et al. 2018; Akgül and Karakan, 2018).

2.2.3.2 Pharmacological treatment

Antimicrobial agents usually are the first-line treatment for UTIs. The choice and the duration of the medication prescribed depends on patient diagnosis, medication allergies, compliance history, cost, availability, local antibiograms and the available concentration of the different antimicrobial agents in the urine (Johnson and Russo, 2018).

2.2.3.3 Acute Uncomplicated Cystitis

The treatment for patients with uncomplicated UTIs is generally provided in the outpatient setting because these patients rarely presented with severe symptoms. Uncomplicated UTIs are usually preferred to be managed with a short course of antimicrobial agents involving single dose, three days or five days course depending on the diagnosis (Gupta et al., 2011a). This short course regimen may increase the adherence, decreased cost with fewer side effects, and less potential for the development of bacterial resistance. For the reason that urine culture results take several days to obtain, physician use the empirical treatment in the outpatient setting. The first-line antibiotic agents for empiric therapy in uncomplicated UTI are 100 mg orally 2 to 4 times daily of nitrofurantoin monohydrate/macrocrystals for five days (McKinnell et al., 2011), 160/800 mg orally twice daily of TMP/SMX for three days, or 3 grams of powder mixed in water as a single oral dose of fosfomycin (Gupta et al. 2007; Stein 1999). An alternative antimicrobial option can be used in certain conditions such as allergies or concern for the resistance of the above first-line antibiotics, oral beta-lactams such as pivmecillinam (400 mg orally twice daily), amoxicillin-clavulanate (500 mg twice daily), cefpodoxime (100 mg twice daily), cefaclor (250-500 mg 3 times daily), cefdinir (300 mg twice daily), and cefadroxil (500 mg twice daily), each given for 5 to 7 days (Kavatha et al., 2003; Hooton et al., 2005). If these agents cannot be utilized, a fluoroquinolone is reasonable alternative agents, ciprofloxacin (250 mg twice or 500 mg extended-release once daily) and levofloxacin (250 mg once daily), each for three days. Ofloxacin and norfloxacin are less commonly used but considered effective (Auquer et al. 2002;

Hooton, Roberts, and Stapleton, 2012). Other beta-lactams, such as cephalexin (250 to 500 mg 4 times daily) also can be considered. Ampicillin and amoxicillin should not be considered for empiric therapy due to the high prevalence of resistance to these agents (Kahlmeter 2003; Warren et al., 1999).

2.2.3.4 Asymptomatic Bacteriuria

Asymptomatic bacteriuria is defined as isolation of two consecutive urine cultures with more than 10^5 organisms/mL of the same organism in the absence of urinary symptoms (Stein and Fünfstück, 2000). In general, multiple studies suggest neither screening or treating for asymptomatic bacteriuria, except in a specific population such as pregnant women, patients undergoing urologic intervention, and recent renal transplant recipients. For example, in pregnant women with asymptomatic bacteriuria cephalexin or amoxiclav for 7 days can be used (Nicolle et al. 2019; Owens et al., 2019).

2.2.3.5 Acute pyelonephritis

Patients with acute pyelonephritis may be treated in outpatient or inpatient settings depends on the severity of signs and symptoms, and it should be individualized. Outpatient management is acceptable for patients with mild to moderate severity who can be stabilized with rehydration and oral antimicrobial agents. On the other hand, the indications for hospitalization are, patients with high fever (greater than 38.4°C/101°F), pain, inability to maintain oral hydration or take oral medications, patients suspected with urinary tract obstruction, or there are concerns regarding patient adherence (Ward, Jorden and Severance, 1991). Urine culture and susceptibility testing should be performed in all patients with complicated UTI, and the initial empiric therapy should be tailored appropriately to the susceptibility profile of the infecting bacteria. For patients in outpatient settings, oral fluoroquinolones can be used for empiric therapy. Ciprofloxacin 500 mg twice daily, ciprofloxacin 1000 mg extended-release once daily, or levofloxacin 750 mg once daily, each for 5 to 7 days (Talan et al. 2000; Peterson et al., 2008).

If the prevalence of resistant E. coli for fluoroquinolone is known to be higher than 10%, a single dose of ceftriaxone (1 gram intravenous (IV) or intramuscular (IM) once) before administering the fluroquinolone can be given. Ertapenem (1 gram IV or IM once) considered as an alternative for ceftriaxone; also, aminoglycosides such as

gentamicin or tobramycin (5 mg/ kg once IV or IM) can be used. Other options than fluoroquinolone following the parenteral agent are TMP/SMX (160 mg/800 mg orally twice daily) for 7 to 10 days, amoxicillin-clavulanate (875 mg orally twice daily) for 10 to 14 days, cefpodoxime (200 mg orally twice daily) for 10 to 14 days, cefdinir (300 mg orally twice daily) for 10 to 14 days, cefadroxil (1 g orally twice daily) for 10 to 14 days (Sanchez et al., 2002).

Hospitalized patients with complicated UTIs can be divided into critical illness or urinary tract obstruction, and patients who are not critically ill. For critical ill patients, a broad-spectrum antimicrobial regimen is suggested as empiric therapy such as imipenem (500 mg IV or IM 4 times daily), meropenem (1 gram IV or IM 3 times daily), to cover extended-spectrum beta-lactamase (ESBL)-producing organisms and Pseudomonas aeruginosa (Carmeli et al., 2016), in addition to vancomycin to cover methicillin-resistant Staphylococcus aureus (MRSA). An alternative to vancomycin is Daptomycin and linezolid (Singh et al., 2013). Besides, in patients who are not critically ill, ceftriaxone (1 gram IV once daily) or piperacillin-tazobactam (3.375 grams IV 4 times daily). Moreover, as alternative oral or parenteral fluoroquinolones (ciprofloxacin or levofloxacin) can be used ('Pyelonephritis (acute): antimicrobial prescribing' 2018).

2.2.3.6 Urinary tract infections in males

UTIs in men are uncommon and usually due to a structural or functional abnormality of the urinary tract. Therefore, they should not treat with a single dose or short course of antibiotics. However, the antimicrobial agents used are similar to that used in women with uncomplicated UTIs but with longer duration, usually 7 to 14 days (van Nieuwkoop et al., 2017).

2.2.3.7 Prostatitis

Prostatitis is classified as either acute or chronic, and it rarely occurs in males younger than 30 years of old. As many as 50% of all males develop some form of prostatitis at some period in their lifetimes (Coker and Dierfeldt, 2016). For patients with acute prostatitis who can take oral antibiotics, TMP/SMX (160 mg/ 800 mg orally twice daily), ciprofloxacin (500 mg orally twice daily), or levofloxacin (500 mg orally once daily) are considered as first-line empiric therapy, because they achieve high levels in

prostatic tissue. Acute prostatitis should be treated for at least 2 to 4 weeks (Brede and Shoskes 2011). In certain conditions, patients with acute bacterial prostatitis who cannot tolerate oral medication, demonstrate signs of severe sepsis or have bacteremia, may need to be hospitalized for IV or IM antibiotic therapy. In such cases, IV levofloxacin or ciprofloxacin may be given with or without an aminoglycoside (gentamicin or tobramycin 5 mg/kg daily) (Wagenlehner, Weidner, and Naber 2007). Alternative options for empiric treatment include IV carbapenem, broad-spectrum penicillins (e.g. amoxicillin/ clavulanate), or a cephalosporin (such as cephalexin or cefuroxime) with or without gentamicin. Patients initiated on parenteral antibiotics can be switched to oral antibiotics after 24 to 48 hours following improvement in symptoms (Lipsky, Byren and Hoey, 2010).

In chronic prostatitis, a prolonged antibiotic therapy at least 6 weeks up to 12 weeks is needed. Ciprofloxacin (500 mg orally twice daily) or levofloxacin (500 mg orally once daily) for four to six weeks, is generally the drug of choice for treatment of chronic prostatitis (Naber et al. 2008; Bundrick et al., 2003). TMP/SMX (160 mg / 800 mg orally twice daily) is an adequate alternative regimen. Other possibilities include macrolides (e.g. azithromycin), doxycycline, or cephalosporins (Perletti et al., 2013).

2.2.3.8 Recurrent urinary tract infections

Management strategies in recurrent UTIs depend on predisposing factors, the number of episodes per year, and the patient's preference. There are three main options for the treatment of recurrent UTIs include self-administered therapy, postcoital prophylaxis, and continuous low-dose prophylaxis (Aydin et al., 2015). Self-administered short-course therapy is appropriate in patients with less than three episodes of UTI per year, in which every episode may be treated as a separately occurring infection (Dason, Dason and Kapoor, 2011). In a patient with more frequent episodes, continuous low-dose prophylaxis is preferred. If continuous prophylaxis is chosen before its initiated, patients should be treated completely with an appropriate agent. Mainly the antimicrobial agents used for continuous low-dose prophylaxis therapy are TMP/SMX (40 mg/200 mg once daily), nitrofurantoin (50 or 100 mg once daily), trimethoprim (100 mg once daily), cephalexin (125 to 250 mg once daily), cefaclor (250 mg once daily), and ciprofloxacin (125 mg once daily) (Fisher et al. 2018). These agents are prescribed for six months; urine cultures are followed monthly during this period. If

any symptomatic episodes of UTIs develop, the patient should receive a full course of therapy with the appropriate agent and then resume prophylactic (Ahmed et al. 2017). In women who experience recurrences of infection associated with sexual intercourse, a single-dose prophylactic therapy (postcoital prophylaxis) of TMP/SMX (40 mg/ 200 mg to 80 mg/ 400 mg), nitrofurantoin (50 or 100 mg), trimethoprim (100 mg), or cephalexin (125 to 250 mg), taken after intercourse reduces the incidence of recurrent infection significantly (Albert et al., 2004).

2.2.3.9 Urinary tract infections in pregnancy

UTIs in pregnancy may cause some sever complications including prematurity, low birth weight, and stillbirth, and to avoid possible complications routine screening tests for bacteriuria is preferred. In pregnant women with significant bacteriuria, symptomatic or asymptomatic, treatment with antimicrobial agents is recommended (Schnarr and Smaill 2008). For asymptomatic and lower UTIs in pregnant women, the empiric therapy suggested are cefpodoxime (100 mg orally twice daily) for 5 to 7 days, amoxicillin-clavulanate (500 mg orally three times or 875 mg orally twice daily) for 5 to 7 days, and fosfomycin (3 g orally as a single dose) (Kazemier et al. 2015). Other agents such as amoxicillin (500 mg orally three times or 875 mg orally twice daily) for 5 to 7 days, or cephalexin (250 to 500 mg orally four times daily) for 5 to 7 days (Tan and File 1992). Nitrofurantoin (100 mg orally twice daily) for 5 to 7 days is another option during the 2nd or third trimester. TMP/SMX (160 mg/ 800 mg twice daily) for three days, can be used, but it should be avoided in the 1st trimester (Szweda and Jóźwik, 2016).

Pregnant women with acute pyelonephritis have a higher risk for complications, so they are treated with hospitalization and parenteral antibiotics until they are symptomatically improved for 24 to 48 hours then can be switched to oral therapy depends on culture susceptibility results (Wing et al., 1998). The drug of choices for initial empiric therapy in this population is parenteral, broad-spectrum beta-lactams. In mild to moderate pyelonephritis ceftriaxone (1 g once daily), cefepime (1 g twice daily), or aztreonam (1 g 3 times daily) are the drugs of choice. Also, ampicillin (1-2 g 4 times daily) + gentamicin (1.5 mg/kg 3 times daily) may be used, but this regimen should only use if intolerance precludes the use of less toxic agents because aminoglycosides have been associated with fetal ototoxicity (Glaser and Schaeffer,

2015). For severe pyelonephritis piperacillin-tazobactam (3.375 g 4 times daily), meropenem (1 g 3 times daily), ertapenem (1 g once daily), or doripenem (500 mg 3 times daily) are the suggested therapy (Wing et al., 1999). The oral options for acute pyelonephritis in pregnant women are mainly limited to beta-lactams or, if the patient in the second trimester, TMP/SMX can be used. The duration for oral antibiotics in this population is between 10 to 14 days (Wing et al., 1998).

2.2.3.10 Catheterized patients

The primary treatment for CAUTIs is the removal of the catheter if it is possible. However, for symptomatic CAUTI, they should be treated according to the recommendations for complicated UTI (Shuman and Chenoweth, 2018). Nevertheless, before initiating any antimicrobial therapy, urine culture and suitability testing should be obtained for presumed CAUTI due to the broad spectrum of potential infecting organisms and the increased likelihood of antimicrobial resistance. 7 to 14 days of therapy is the duration suggested for CAUTIs (Hooton et al., 2010).

2.2.1 Antimicrobial resistance:

Antimicrobial resistance (AMR) happens when microorganisms such as bacteria evolve some mechanism to avoid killing by antimicrobial agents. In 2014 the World Health Organization (WHO) warned that AMR is considered one of the most critical public health threats of the 21st century (WHO, 2014). The CDC reported that more than 2.8 million people are infected with antibiotic-resistant bacteria or fungi, and more than 35,000 people die each year in the U.S. alone, with a yearly cost estimated to be 21 to 34 billion dollars (CDC, 2020).

Bacteria have evolved multiple mechanisms of drug resistance includes alteration or destruction of the antimicrobial molecule, decreasing penetration or actively extruding the antimicrobial compound which can prevent the antibiotic to reach its target, protection and /or modifications of the target sites, and resistance by global cell adaptive processes (Munita and Arias, 2016).

Examples of this multi-drug resistant (MDR) bacteria are MRSA, which are responsible for more deaths in the US every year than emphysema, HIV/AIDS, Parkinson's disease and homicide combined (Llor and Bjerrum, 2014).

MDR Mycobacterium tuberculosis (M. tuberculosis) can develop resistance to isoniazid and rifampicin the two most antimicrobial agents effective against tuberculosis (TB), globally, 3.7% of new cases and 20% of previously treated cases of TB are estimated to be caused by these strains of bacteria (Davies and Davies, 2010). Gram-negative bacteria especially E. coli and K. pneumonia are one of the leading causes for UTIs, these bacteria can produce an enzyme called ESBLs that can hydrolyze extended-spectrum beta-lactam antibiotics like penicillin and cephalosporins (Ghafourian et al., 2015). In 2010, 7.8% of the E. coli urinary strains were ESBL producers, and this percentage increased to 18.3% in 2014 at the U.S. hospitals. For K. pneumoniae, 16.3% were ESBL producers between 2011 and 2013 across U.S. hospitals (Doi, Iovleva and Bonomo, 2017). Recent research studies in the MENA region reported a high prevalence of ESBL rate among E. coli isolates ranging from 38.2% to 39.4% among community-acquired UTI and from 50.5% to 70% among nosocomial UTI patients (Al-Mijalli 2016; Al-Assil, Mahfoud, and Hamzeh 2013a). In Jordan, between 2012–2015, a high rate of ESBL-producing E. coli (43–54%) was reported among patients with the community and hospital-acquired UTI. Generally, ESBLs are inhibited by clavulanic acid and tazobactam (Hayajneh et al. 2015; Nimri and Ba, 2012).

Many causes can drive the evolution of AMR such as the overuse of antibiotics (in many countries, antibiotics are unregulated and available over the counter (OTC) without a prescription), and inappropriate prescription. Other alternative causes such as extensive agriculture use (antibiotics are widely used in livestock as growth supplements, and approximately 80% of antibiotics sold in the U.S. are used to promote growth and to prevent infection in animals), and the availability of few new antimicrobials (due to economic and regulatory obstacles) (Ventola, 2015).

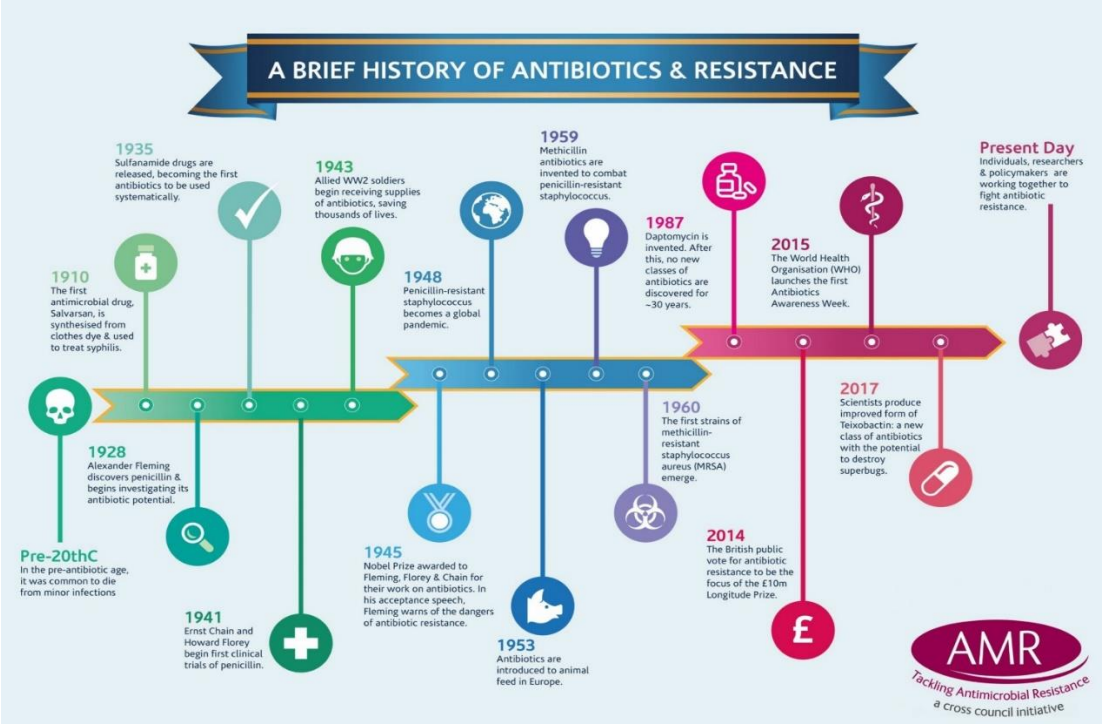

Figure 2.2.4: Comparison Between The Development of Antibiotics and The Appearance of Antibiotic Resistance ('EAM: a complex solution to the AMR crisis is possible ' 16/3/2020).

2.3 Drug - related problems (DRPs) and The Rational Antibiotic Use

2.3.1 Drug – related problems

According to the Pharmaceutical Care Network Europe (PCNE), DRPs can be defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" ('PCNE-DRP classification' 2019). Many classification systems are available for DRPs, such as PI-Doc, PCNE Classification, Apoteket, Granada-II, Westerlund, Hepler and Strand, and DOCUMENT system (Williams et al. 2012; Björkman, Sanner and Bernsten, 2008).

DRPs may affect both the patients and society by increasing the morbidity and mortality rate, as well as health care expenditure (Ruths, Viktil, and Blix 2007). The identification and prevention of DRPs are fundamental to the process of pharmaceutical care where a pharmacist, doctor and other health care professionals work together with the patient, to improve the therapeutic outcomes and quality of life (Basger, Moles and Chen, 2014).

PCNE system, which is one of the most frequently used systems consists of 6 primary domains of problems. These include adverse reactions (toxic, allergic, or non-allergic side effects), drug choice problem (inappropriate drug, drug form, or duplication, as well as contra-indication for drug or no clear indication), dosing problem (dose too low or too high, dosage regime not frequent enough, or too frequent, duration of treatment too short or too long), drug use problem (wrong or no drug taken/administered), interactions (manifest or potential drug-drug or drug-food interaction), and other problems (patient dissatisfied with therapy, insufficient awareness, unclear complaints, or therapy failure) (Eichenberger et al., 2010).

2.3.2 Rational antibiotics use

According to the WHO, antibiotics are used rationally "when patients receive the appropriate drug, for appropriate indications, in doses and duration that meet their requirements, at the lowest cost both to the patient and the society, and with appropriate information. Irrational or unnecessary use of antibiotics occurs when one or more of these conditions is not met" (Machowska and Stålsby Lundborg, 2018). Worldwide, irrational use of antibiotics is escalating, both in developed and developing countries. It is estimated that up to 80% of all antibiotics are used without a prescription, especially in developing countries where policies and regulations are often not implemented despite being in place (Gelband et al., 2015; Van Boeckel et al. 2014). Multiple studies in Southern and Eastern Europe recorded the prevalence of irrational use of antibiotics as approximately 30% and 19% respectively. In the Middle East, the prevalence of irrational antibiotic use varies significantly between countries, being as high as 39% in Jordan and Saudi Arabia (Morgan et al., 2011; Borg and Scicluna, 2002). Any use of antibiotics might contribute to the development of antimicrobial resistance, which occurs through genetic mutations of bacteria (Moxon and Paulus, 2016). However, the overuse and misuse of these medications may aggravate this process (Arthur Chioro, 2014). Therefore, local resistance patterns are usually influenced by local prescribing patterns, in which the place or settings where antibiotics are highly prescribed have higher rates of resistance toward prescribed antibiotics ('World Antibiotic Awareness Week' 16-22 November 2015; 'Global action plan on antimicrobial resistance' 2015).

2.4 The role of clinical pharmacist in the management of urinary tract infections

The American College of Clinical Pharmacy (ACCP) defines clinical pharmacy as "an area of pharmacy concerned with the science and practice of rational medication use, in which pharmacists provide patient care that optimizes medication therapy and promotes health, and disease prevention" (accp).

Clinical pharmacists are pharmacists who work directly with physicians, other health professionals, and patients to provide many services. These services include optimized the prescribed medications with the health problems of the patients, assess the appropriateness and effectiveness of the patient's medications, follow the patient's progress to determine any side effects of their medications, consult in selecting the appropriate therapy for the patient with the physicians and other health care providers, and educate the patient how and when to take the medications. These services can be provided with advanced training, knowledge, and experiences (Morgan et al. 2018; Dunn et al., 2015).

Multiple studies showed that 20% to 70% of the hospitalized patient has medications discrepancy on discharged (these patients are twice as likely to be re-hospitalized within 30 days), and 12% to 17% suffer from discharge-related adverse drug events. However, post-hospitalization clinical pharmacist interventions significantly improve medication discrepancy resolution and decrease the incidence of 30-day ED visits and rehospitalization (Hawes et al. 2014; Shcherbakova and Tereso 2016). One study in the U.S. reported that in only 14 consecutive days, 71 clinical pharmacists from inpatient and outpatient settings submitted 779 complete medication errors (Kuo, Touchette, and Marinac 2013). In the management of UTI clinical pharmacists can help to facilitate appropriate antibiotic selection, and developing specific antibiogram to help guide the treatment. Several studies have demonstrated that pharmacist monitoring of antimicrobials prescription has been associated with decreased costs and improved compliance with guidelines in outpatient and inpatient settings. In another study, pharmacists in the ED were able to identify all cases of inappropriate selection of antibiotics for UTI patients treated as outpatients and successfully make interventions for 83% of them (Lingenfelter et al. 2016).

In Jordan, the benefit of the implementation of clinical pharmacy appears obviously in multiple studies; one study involved hyperlipidaemic patients who were followed by clinical pharmacists for six months. After the six-month study period, 94.5% of the intervention group reached the treatment goal compared to 71.2% of the control group (Tahaineh et al. 2011). Another study was carried to reflect the effect of clinical pharmacists' contribution to the care of patients with chronic obstructive pulmonary diseases (COPD) by making an intervention focusing on patient education about COPD, counseling patients about their medications and the proper use of inhalation technique. Also, an assessment of patients' willingness to adhere to their medication was made, and the patients were referred to smoking cessation programs if necessary. The results showed significant improvement in COPD knowledge and medication beliefs and a significant decrease in patient's admission rates compared with controls (Jarab et al. 2012). A study was conducted to estimate the impact of clinical pharmacists' services on the cost of drug therapy for patients admitted to the intensive care units at Al-Hussein Hospital in Amman. The results showed that the total reduction in drug cost in the 10-month duration after implementation of clinical pharmacy practice was JD149,946.80 (US$211,574.90), representing a 35.8% average drug saving (Aljbouri et al. 2013).

3. METHODOLOGY

3.1 Study Design

This prospective, descriptive study of antibiotic utilization patterns and the drug-related problems in UTI patients was conducted between September 2019 and March 2020. Patient information and data were obtained from a patient's interview based on a questionnaire and from the patient archives and electronic records at King Abdullah University Hospital (KAUH) and Al Bashir hospital.

3.2 Settings and Subjects

This study was carried out at King Abdullah University Hospital (KAUH) and Al Bashir hospital in two cities in Jordan (Irbid and Amman). These tertiary hospitals are among the most visited hospitals and one of the most extensive leading medical facilities in Jordan. KAUH has fifteen floors with a total area of (95583 m^2) with an operational capacity of 678 beds, expandable to 819 beds in the event of an emergency. However, Al Bashir hospital has an area of (156000 m^2), and it currently holds 49 buildings and 80 departments with 1100 beds, it receives 7000 cases every day and up to 1.5 million visits annually.

The study population was the inpatients and the outpatients admitted and diagnosed with UTIs at these hospitals taking into consideration the inclusions and exclusions criteria:

Inclusion criteria:

All patients diagnosed with UTI at outpatient or inpatient settings of KAUH or Al Bashir hospital during the study duration who accepted to participate in the study.

Exclusions criteria:

Critical care patients.

3.3 Study tools and Data Collection

Patients' data, including their demographics, comorbidities, clinical presentation, and clinical outcomes, were collected from both patient's interviews based on a

questionnaire filled by the researcher, while other data, such as laboratory results and medical management, were collected from the patient's files. Our data collection form (Appendix B) consisted of multiple sections; section one focuses on the participant's demographic information, section two concentrates on the clinical presentation and the type of infection of the participant, and section three focuses on the past medical history and the medication history. In section four, the laboratory results were collected. Furthermore, section five focuses on the management of the patient include the treatment plan. In section six, the adherence of the patient was assessed using the Morisky scale. In section seven, the DRPs were documented and classified using the PCNE DRP classification tool (version 9.00). The study tools were safe validated by an expert panel including two urology physicians, one family physician and two clinical pharmacists. A pilot study was followed to asses the internal consistence of the study tools.

The DRP was assessed using the PCNE classification systems, which consists of 6 primary domains of problems. These include adverse reactions (toxic, allergic, or non-allergic side effects), drug choice problem (inappropriate drug, drug form, or duplication, as well as contra-indication for drug or no clear indication), dosing problem (dose too low or too high, dosage regime not frequent enough, or too frequent, duration of treatment too short or too long), drug use problem (wrong or no drug taken/administered), interactions (manifest or potential drug-drug or drug-food interaction), and other problems (patient dissatisfied with therapy, insufficient awareness, unclear complaints, or therapy failure). This classification system is validated and adapted regularly by 20-30 pharmacists (or doctors) with a clinical pharmacy/pharmaceutical care background.

The participants' adherence was assessed using the Morisky medication adherence scale, which considered the most accepted and widespread scale self-reported medication adherence measures, recommended to serve as screening tools in a clinical setting. Initially started in 1986 as a four-item scale, it was expanded into a structured eight-item scale, which is used for chronic conditions. However, in the case of antibiotic adherence, a short Morisky scale considered the best option, and it is valid for measuring adherence to antibiotic treatments (Treibich and Ventelou, 2017).

Further, the patients were defined as non-adherent when answering positively to at least one item.

The rationality of antibiotic prescriptions was analyzed using the IDSA guidelines, CDC guidelines, and UpToDate. The rationality of antibiotic prescriptions analyzed by a clinical pharmacist and a researcher step by step looking to the drug selection, dose, route of administration, duration of therapy, lab tests and cultures each case individually. An independent clinical committee assessed the clinical significance of the identified DRPs by the clinical pharmacist, the committee involved two clinical pharmacist and one pharmacologist.

3.4 Statistical Analysis

The collected and analyzed data were conducted using Microsoft Excel 2016 and Statistical Package for the Social Sciences (SPSS) software (version 25.0). Descriptive statistics for quantitative variables were used to analyse the results of the study. Categorical data are reported as frequencies and percentages (%). The associations between categorical variables were analyzed using Fisher's exact test and Pearson's Chi-square test, and the level of significance was set to (P-value < 0.05). Raosoft software (version 2.3) was used to determine the minimum required sample size. Cronbach's alpha was calculated using the SPSS and was showed internally consistence ($\boldsymbol{\alpha}$ = 0.901) and pilot study subjects were included in the study.

3.5 Ethical Consideration

An oral informed consent form was obtained from all the patients after they were informed about the study's objectives. Also, they were informed that all the data provided would be treated in a completely confidential manner.

Ethical approval of this study was attained from the Institutional Review Board (IRB) of King Abdullah University Hospital and Jordan University of Science and Technology (KAUH-JUST). The IRB reference is 107/18/3476. Additionally, the ethical approval was also obtained from the IRB of Al- Bashir Hospital - Ethics Committee. The IRB reference is Moh/REC/2020/7.

4. RESULTS

4.1 Participants' Characteristics

A total of 281 patients were approached, out of them, eight refused to participate, and 273 patients agreed were recruited in this study. The patient's characteristics are presented in Table (4.1.1).

Table 4.1.1: Participating Patients' demographics and characteristics

Demographics	**N = (273)**	**%**
Gender:		
Male	119	43.6 %
Female	154	56.4 %
Age:		
0 – 18	69	25.3 %
19 – 40	58	21.2 %
41 – 60	67	24.5 %
61 – 80	65	23.8 %
> 80	14	5.1 %
States:		
Single	88	32.2 %
Married	185	67.8 %
Smoking		
Yes	72	36.4 %
No	191	70 %
Ex-smoker	10	3.67 %
BMI		
Underweight	30	11 %
Normal	45	16.5 %
Overweight	38	13.9 %
Obese	34	12.5 %
None	126	46.2 %
Treatment setting:		
Inpatient	130	47.6 %
Outpatient	143	52.4 %

As shown in Table 4.1.1, approximately 56.4% of the patients were female, while 43.6% were males. More than half (67.8%) of the sample were married. The patients were classified into five age groups, patients within the age range of (≤ 1 month – ≤

18 years), (≤19 years – ≤ 40 years), (≤ 41 years - ≤ 60 years), (≤ 61 years – ≤ 80 years), and older than 80. These age groups accounted for 25.3%, 21.2%, 24.5%, 23.8% and 5.1% of the study sample, respectively. In this study, the outpatient and the inpatient settings were included. Out of a total of 273 patients, 52.4% were outpatients, and 47.61% were inpatients. Approximately 2.9% and 1.5% of the patients reported an allergy to penicillin and cephalosporin, respectively. More descriptive details related to demographic variables are summarized in Table (4.1.1).

Regarding patients' comorbidities, 30% had hypertension (HTN), 28.9% DM, 13.9% BPH, and 12.8% had cardiovascular diseases (CVD). However, 14.7% of the study sample had urethral catheterization, and only 6.2% had urological instrumentation. Table 4.1.2 shows other details about the comorbidities.

Table 4.1.2: The past medical history of the patients included in the study

Past medical history:	N = (273)	%
HTN	82	30 %
DM	79	28.9 %
BPH	38	13.9 %
CVD	35	12.8 %
Cancer	9	3.3 %
CKD	16	5.9 %
Urologic instrumentation	17	6.2 %
Urethral catheterization	40	14.7 %
Urinary tract obstruction	8	2.9 %
Vesicourethral reflux	19	7 %
Neurogenic bladder	24	8.8 %
Stones	18	6.6 %
Hydronephrosis	15	5.5 %
Botox injection (Bladder)	8	2.9 %

Patient's adherence to their medications:

In this study, the Morisky-scale was used. This five-item scale was used to examine the patient's adherence to antibiotics in general. The patient's responses to adherence questions are presented in the table (4.1.3).

Table 4.1.3: The General Shape of The Patient's Adherence to Antibiotic Use

Morisky-scale for adherence	**N = (273)**	**%**
1. Did you ever **forget** to take your antibiotic?	65	23.8 %
2. Did you have difficulty **remembering** to take your antibiotics?	28	10.3 %
3. Did you ever **stop** taking your antibiotic because you felt **better**?	94	34.4 %
4. Did you ever **stop** taking your antibiotic because you felt **worse**?	31	11.5 %
5. Are you **careless** at times about taking your medicines?	30	11 %

Among the total sample, non-adherence to antibiotic therapy in general was reported in 42.5% of the patients. As shown in table (4.1.3), approximately 34.4% of the patients have reported that they stop their antibiotics when start to feel better, 23.8% forget to take their antibiotics for many reasons, 11.4% stop if they felt worse after taking antibiotics, 11% are careless concerning the antibiotics, and 10.3% of them have difficulty remembering their antibiotics.

4.2 Disease Characteristics

4.2.1 Classification of Urinary Tract Infection

As shown in Table 4.2.1.1 below, the class of UTI based on the site of infections was tracked. However, the diagnosis in the outpatient's clinic did not specify the site of infections in most of the patients (73.6%). Only, 9.2% were diagnosed with upper UTI (pyelonephritis), and 1.2% with cystitis. Chi-square test was performed to examine the prevalence of upper UTIs among gender groups. Upper UTIs was significantly higher in females than males (P-value < 0.01). Of male patients, 41 patients diagnosed with prostatitis accounted for 34.5% of the total males included in this study. Prostatitis was significantly associated with age (P-value < 0.01), in which patients between the age of 30 and 80 were the most affected.

Table 4.2.1.1: Diagnosis distribution related to the type of UTI

Type of UTI:	N = (273)	%
Pyelonephritis	25	9.2 %
Cystitis	4	1.5 %
Prostatitis	41	15 %
Not specified	201	73.6 %

4.2.2 The Reported Clinical Presentation

As presented in table 4.2.2.1, dysuria was the most reported symptoms accounting to 66.3% of the patients, followed by frequency 53.5%, cloudy urine 52%, bad smiling urine 49%, and urgency 42.5%. Moreover, females' patients significantly reported more sign and symptoms than males include (urgency (P-value < 0.001), flank pain (P-value < 0.001), vomiting (P-value < 0.001), discharge (P-value < 0.001), pelvic pain (P-value < 0.001), nausea (P-value < 0.01), bad-smelling urine (P-value < 0.01), high fever (P-value < 0.01), nocturia (P-value < 0.05), cloudy urine (P-value < 0.05), and chills (P-value < 0.05)). In association with age, symptoms such as high fever (P-value < 0.001), bad-smelling urine (P-value < 0.001), vomiting (P-value < 0.001), cloudy urine (P-value < 0.05), and nausea (P-value < 0.05) were more common in younger patients (age <=18), others include testicular pain in men (P-value < 0.001), incontinence (P-value < 0.001), dribbling (P-value < 0.01), flank pain (P-value < 0.01), frequency (P-value < 0.05), and lower back pain (P-value < 0.05) were more common in older adults (age > 40). Other signs and symptoms are shown in table 4.2.2.1 below.

Table 4.2.2.1: The presented signs and symptoms reported

Sign and symptoms:	Yes		No	
Urgency	116 (42.5%)		157 (57.5%)	
Dysuria	181 (66.3%)		92 (33.7%)	
Frequency	146 (53.5%)		127 (46.5%)	
Cloudy	142 (52%)		131 (48%)	
Blood or color changing	113 (41.4%)		160 (58.6%)	
Bad-smelling	134 (49%)		139 (50.9%)	
Pelvic pain	99 (36.3%)		174 (63.7%)	
Flank pain	106 (38.8%)		167 (61.2%)	
	Yes	**Yes (not documented)**	**No**	
High fever	69 (25.3%)	18 (6.6%)	186 (68.1%)	
Chills	89 (32.6%)		184 (67.4%)	
Nausea	58 (21.2%)		215 (78.8%)	
Vomiting	59 (21.6%)		214 (78.4%)	
Nocturia	105 (38.5%)		168 (61.5%)	
Discharge	43 (15.8%)		230 (84.2%)	
Dribbling	27 (9.9%)		246 (90.1%)	
Lower back	28 (10.3%)		245 (89.7%)	
Urinary incontinence	34 (12.5%)		239 (87.5%)	
Suprapubic pain	21 (7.7%)		252 (92.3%)	
Poor stream	8 (2.9%)		265 (97%)	
	Yes		**No**	**Not applicable**
Testicular pain	29 (24.4%)		90 (75.4%)	154 (56.4%)

4.2.3 Recurrent urinary tract infections

About, 187 patients (68.5%) reported more than one episode of UTI, 128 (46.9%) of these patients fit the definition of recurrence which is more than 2 episodes of UTI in one year. Most of the recurrent patients (58.3%) were not classified as relapses or reinfection. However, 24.5% were diagnosed as relapse bacterial UTIs and 14.4% cases as reinfections. The details of recurrent UTI are shown in table 4.2.3.1.

Table 4.2.3.1: Recurrent episodes of UTI

	Yes	**%**
Not the 1st episode this year	187	68.5 %
Recurrent (more than 2 episodes)	128	46.9 %
The 1st or the 2nd episode/s	59	21.6 %
Reinfection	27	14.4 %
Relapse	51	27.3 %
Not specified	109	58.3 %

4.3 Diagnosis and Treatment Patterns

4.3.1 Urinalysis

A total of 229 urine analysis test have been done, which accounted for 83.9% of the sample size. Pyuria was the most reported result, which accounted for 64% of the total sample, followed by bacteriuria (49.8%) and mucus threads (45.4%). On the other hand, the appearance of the urine samples showed 32.6% with hazy appearance, 29.7% turbid, 23.1% clear, 13.1% cloudy, and only 1.3% with a slightly hazy appearance. Other details can be showed in table 4.3.1.1 below.

Table 4.3.1.1: Urine analysis results for 273 patients approached the inpatient and outpatient settings

	Yes			**No**	
Urinalysis:	229 (83.9%)			44 (16.1%)	
	N = (229)				**%**
Pyuria	149			65.1%	
Haematuria	79			34.5%	
Proteinuria	59			25.8%	
Bacteriuria	114			49.8%	
Crystals	19			8.3%	
Mucus threads	104			45.4%	
EP. Cells	68			29.7%	
	Hazy	**Clear**	**Turbid**	**Cloudy**	**Slightly hazy**
Appearance	75 (32.8%)	53 (23.1%)	68 (29.7%)	30 (13.1%)	3 (1.3%)

4.3.2 Urine culture and susceptibility testing

Figure 4.3.2.1 below shows the details on urine culture tests. Initially, the urine culture tests were done in 231 patients (84.6%). In this study, E. coli was the most prevalent bacteria diagnosed in UTI cases (46.8%) of the total sample, followed by K. pneumoniae (10%) and P. aeruginosa (3.5%). However, about 22.9% resulted in no bacterial growth, and only 7.8% have shown mixed bacterial growth. Further, a total of 81 tests (61.8%) showed a positive extended-spectrum beta-lactamase (ESBLs) producing bacteria. More details are demonstrated in figure 4.3.2.1 below. Generally, no association between the pathogenic bacteria caused the UTIs and patients age or gender, except K. pneumoniae, was significantly higher in patients younger than 18 years of age (P-value < 0.01).

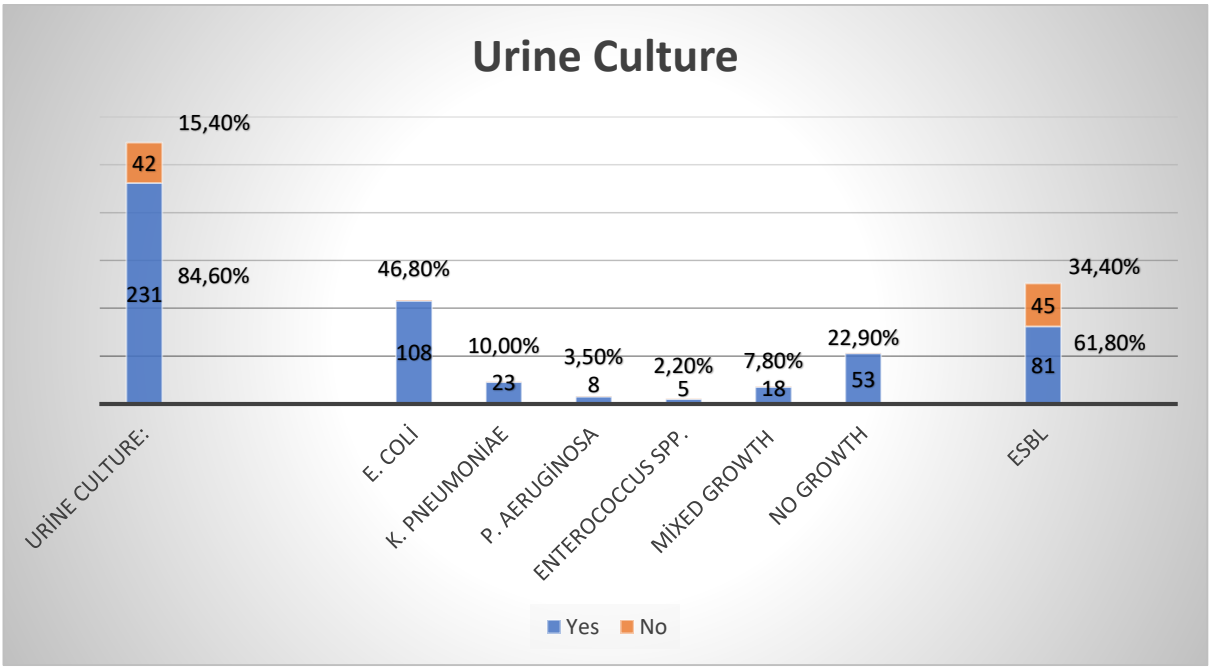

Figure 4.3.2.1: Urine culture results of 273 patients obtained from two health care institutes in Jordan. E. coli: Escherichia coli, K. pneumonia: Klebsiella pneumoniae, P. aeruginosa: Pseudomonas aeruginosa, Enterococcus spp: Enterococcus species, ESBL: Extended spectrum beta-lactamase

Regarding the susceptibility of E. coli isolates, out of the preantral antibiotics, imipenem and colistin showed the lowest resistance rate (0%), followed by amikacin (1%), meropenem (2%), tigecycline (3%), and ertapenem (4%). On the other hand, out of the oral antibiotics, nitrofurantoin (11%) and fosfomycin (13%) showed the lowest resistance rate. Figure 4.3.2.2 demonstrates further details.

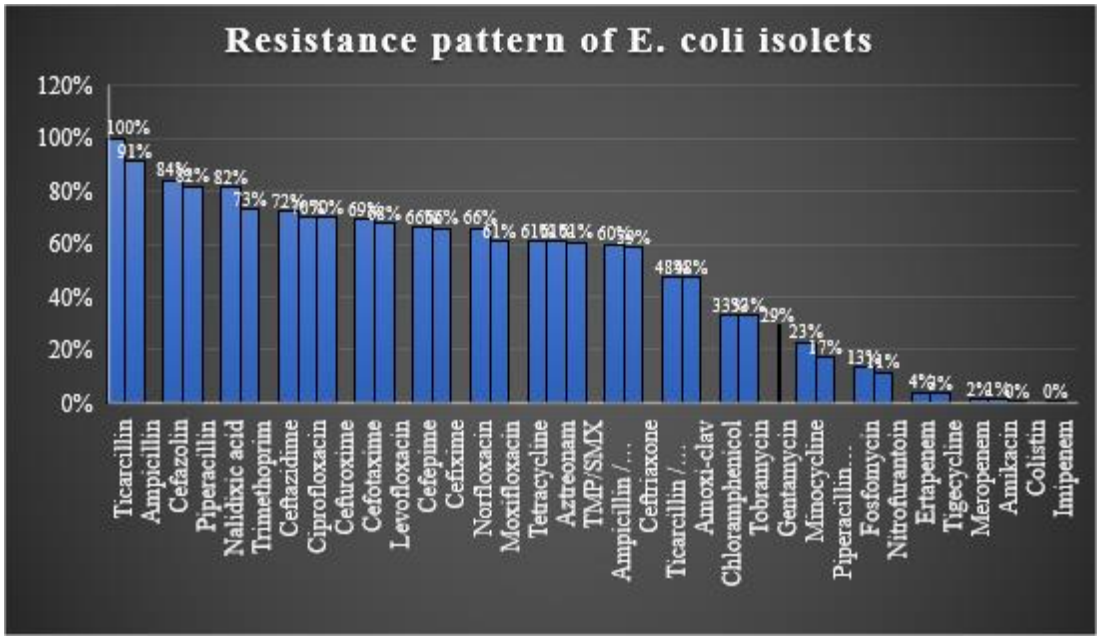

Figure 4.3.2.2: The resistance rate of the E. coli isolates collected form inpatient and outpatient setting in Jorden. TMP/SMX: Trimethoprim / sulfamethoxazole, Amoxi-clav: Amoxicillin/ clavulanic acid.

Table 4.3.2.3 shows the susceptibility results for all the bacterial species. Regarding the parenteral antibiotics, bacteria were most susceptible to colistin (100%), meropenem (98.1%), imipenem (97.2%), and ertapenem (95.5%). Also, amikacin (94.2%) and tigecycline (94.2%) showed relatively high susceptibility rates. On the other hand, bacteria were mostly resistant to cefazolin (87.5%), and ticarcillin (84.2%). For oral antibiotics, bacteria were most susceptible to fosfomycin (85.7%) and nitrofurantoin (78.5%). While, the highest resistance was observed in ampicillin (87.7%), cefuroxime (68%) and cefixime (67.2%), followed by trimethoprim (61.4%), ciprofloxacin (60%), norfloxacin (60.3%), TMP/SMX (59.6%), levofloxacin (56.6%), and amoxiclav (50%). More detailed descriptive results of the antimicrobial sensitivity pattern are presented in Table (4.3.2.3).

Table 4.3.2.3: Antimicrobial sensitivity pattern

Antibiotics (N = 231)	S	R	I	Total number of tests
Extended spectrum of beta- lactamase	55 (59.1%)	33 (35.5%)	5 (5.4%)	93
Ampicillin	9 (12.3%)	**64 (87.7%)**	0 (0%)	73
Ampicillin / Sulbactam	10 (23.3%)	29 (67.4%)	4 (9.3%)	43
Piperacillin tazobactam	73 (77.7%)	15 (16%)	6 (6.4%)	94
Cefazolin	4 (25%)	**28 (87.5%)**	0 (0%)	32
Ceftazidime	34 (36.2%)	60 (63.8%)	0 (0%)	94
Ceftriaxone	38 (40%)	57 (60%)	0 (0%)	95
Cefepime	56 (38.9%)	88 (61.1%)	0 (0%)	144
Ertapenem	**63 (95.5%)**	3 (4.5%)	0 (0%)	66
Imipenem	**139 (97.2%)**	1 (<1%)	3 (2%)	143
Amikacin	**97 (94.2%)**	6 (5.8%)	0 (0%)	103
Gentamycin	71 (67%)	34 (32%)	1 (<1%)	106
Tobramycin	36 (63.2%)	19 (33.3%)	2 (3.5%)	57
Ciprofloxacin	33 (38.8%)	**51 (60%)**	1 (1.2%)	85
Levofloxacin	39 (39.4%)	**56 (56.6%)**	4 (4%)	99
Nitrofurantoin	**106 (78.5%)**	24 (17.8%)	5 (3.7%)	135
Trimethoprim / Sulfamethoxazole	36 (40.4%)	**53 (59.6%)**	0 (0%)	89
Ticarcillin	3 (15.8%)	**16 (84.2%)**	0 (0%)	19
Ticarcillin / Clavulanate	36 (49.3%)	32 (43.8%)	5 (6.8%)	73
Piperacillin	17 (22.4%)	59 (77.6%)	0 (0%)	76
Cefuroxime	31 (31%)	**68 (68%)**	1 (1%)	100
Cefixime	22 (32.8%)	**45 (67.2%)**	0 (0%)	67
Nalidixic acid	22	77	2	101

	(21.8%)	(76.2%)	(2%)	
Aztreonam	28 (40%)	41 (58.6%)	1 (1.4%)	70
Meropenem	**104 (98.1%)**	2 (1.9%)	0 (0%)	106
Norfloxacin	29 (37.2%)	47 (60.3%)	2 (2.6%)	78
Moxifloxacin	20 (39.2%)	28 (54.9%)	3 (5.9%)	51
Tigecycline	**49 (94.2%)**	1 (1.9%)	1 (1.9%)	52
Trimethoprim	22 (38.6%)	**35 (61.4%)**	0 (0%)	57
Chloramphenicol	7 (63.6%)	4 (36.4%)	0 (0%)	11
Tetracycline	13 (40.6%)	19 (59.4%)	0 (0%)	32
Minocycline	19 (59.4%)	9 (28.1%)	4 (12.5%)	32
Colistin	**18 (100%)**	0 (0%)	0 (0%)	18
Fosfomycin	**18 (85.7%)**	3 (14.3%)	0 (0%)	21
Cefotaxime	19 (38.8%)	30 (61.4%)	0 (0%)	49
Amoxi-clav	7 (25%)	**14 (50%)**	7 (25%)	28

4.3.3 Characterization of care

The patients were asked about the education provided for them related to the antibiotic use as well as the source of this education. Out of the total participants, only 33.7% reported that they received an education about antibiotics in general. However, as shown in the figure (4.3.3.1) below, 55.5% of them received it from an unreliable source (internet, students, relatives, and friends), 22.8% from pharmacists, 14.1% from doctors, and 7.6% reported that they read the leaflet of the medications before start taking it.

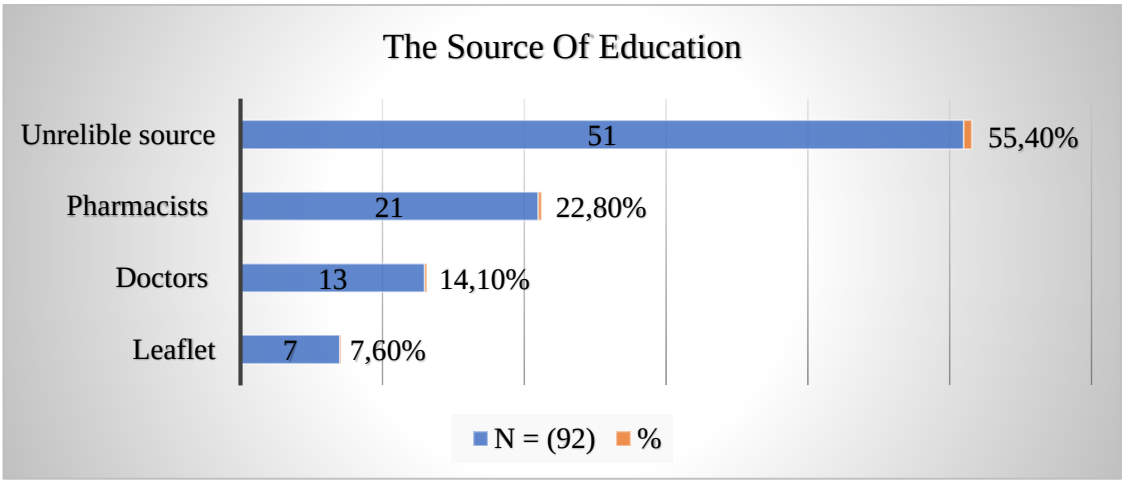

Figure 4.3.3.1: The education source about the antibiotics reported from the patients in two health institutes in Jordan. N: the number of patients who reported that they received an education.

4.3.4 Pharmacological treatment

Out of the 273 participants, only six patients (2.2%) did not receive any antibiotics waiting for the urine culture results. However, 267 (97.8%) received an empirical antimicrobial agent, although 16.1% of the patients do not have any urine analysis, 50.2% of those with urine analysis showed no bacteriuria, and 22.9% of the patients had negative urine culture results. As shown in figure (4.3.4.1) below, out of the oral antimicrobial agent ciprofloxacin (24.3%) was the most commonly used, followed by TMP/SMX (11.9%). On the other hand, for parenteral antibiotics, ceftriaxone (18.7%) and imipenem + cilastatin (15.7%) used the most. For patients with prostatitis, 19.5% of them have received a combination therapy between ciprofloxacin and doxycycline. Further details are demonstrated in figure (4.3.4.1).

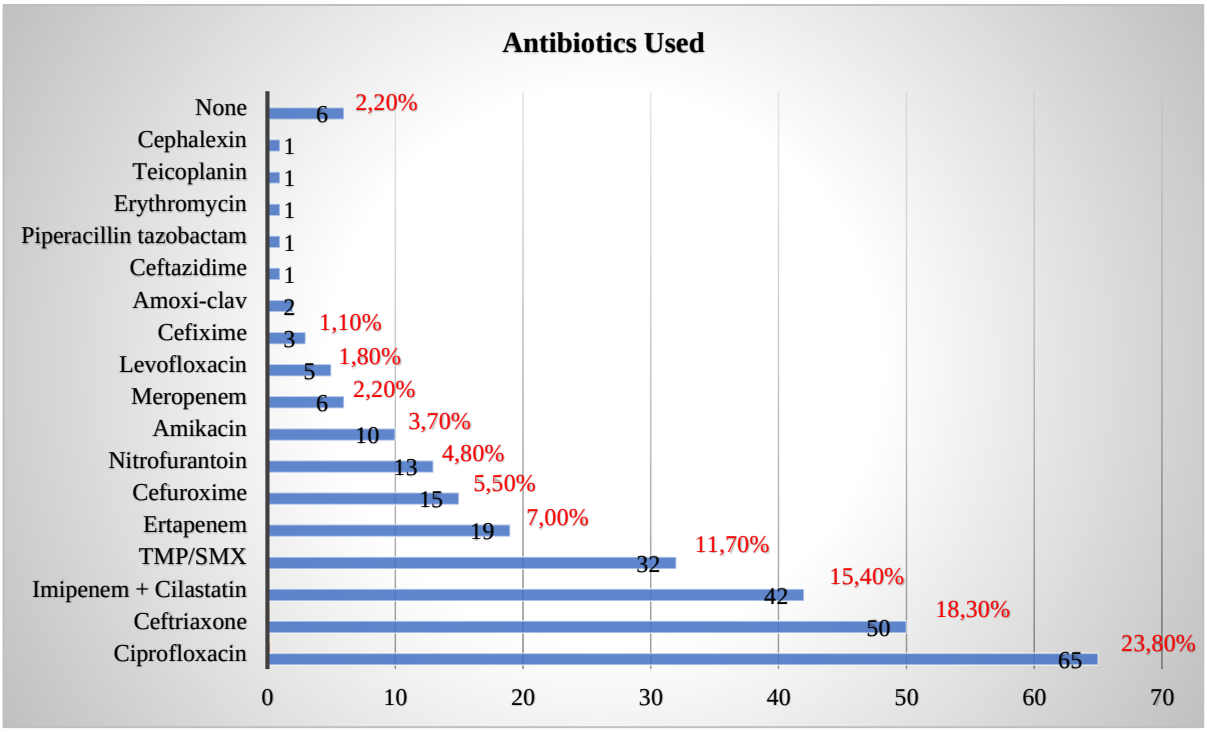

Figure 4.3.4.1: The Antimicrobial Agents Prescribed in Outpatient and Inpatient Settings in Two Health Institutes in Jordan. None: The Patients Who Did Not Receive an Antibiotic, Amoxi-clav: Amoxicillin / Clavulanic acid, TMX/SMX: Trimethoprim / sulfamethoxazole.

On discharge for inpatients the most prescribed antimicrobial agent was ciprofloxacin (30%), followed by TMP/SMX (16%), nitrofurantoin (8%), and cefuroxime (7%). However, 29.3% had no antibiotics prescribed. Other details are presented in figure (4.3.4.2).

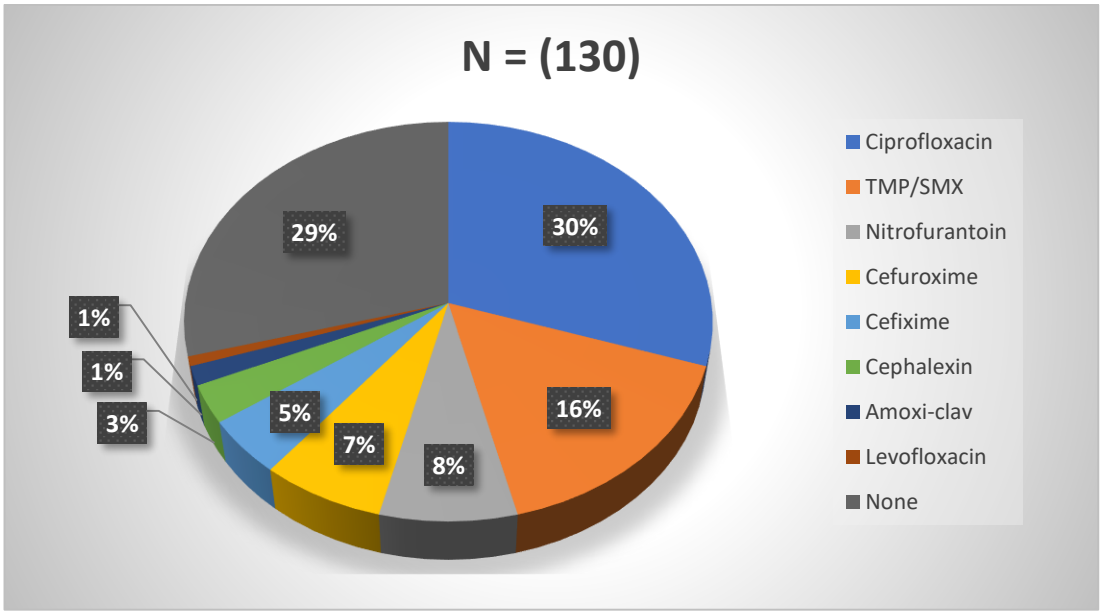

Figure 4.3.4.2: The Antibiotics Prescribed on Discharged Inpatients on Discharge in Two Health Institutes in Jordan. N: The Number of Patients Who Received an Antibiotic on Discharged, TMP/SMX: Trimethoprim / Sulfamethoxazole, Amoxi-clav: Amoxicillin / Clavulanic acid.

As mentioned above, recurrent episodes of UTIs accounted for 46.9% of the total participants; only 24 patients (18.8%) have received a prophylaxis antibiotic. In which, TMP/SMX prescribed for 5.5%, nitrofurantoin (4.7%), cephalexin (4.7%), and cefixime for 3.9% of these patients.

Out of 273 patients included in this study, 84.2% reported that they had taken one or more antibiotics in the last six months of their visit. Clinical pharmacist contributed to the management plan of only 10.62% cases of the total sample.

4.4 Drug - related problems

In this study, the PCNE classification system (version 9.00) was used to assess the DRPs. More than half of the participants included in this study had at least one DRP 58.2% (N = 159). In which, 85 (31.1%) of the patients had one problem; 57 (20.9%) had two problems; 15 (5.5%) had three problems and only two patients with more than four DRPs. Figure (4.4.1) below represents the DRPs detected in the participants. The most commonly observed problem was the long duration of the prescribed antibiotics (36.3%) which was significantly higher in patients 40 to 60 years of age (P-value < 0.001). This was followed by the inappropriate choice of antimicrobial agents

according to the guidelines and the over-prescription of antibiotics, which accounted for 21.2% and 12.5%, respectively. Figure (4.4.1) demonstrate more details of the DRPs.

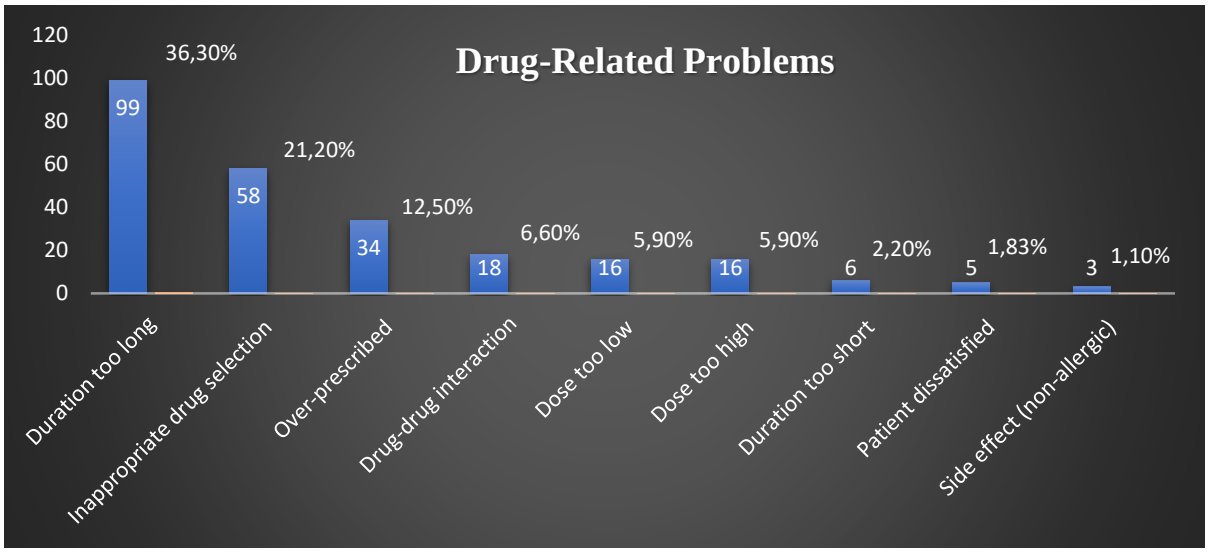

Figure 4.4.1: The Drug-Related Problems Detected in The Inpatient and Outpatient Settings in Two Health Sectors in Jordan

Generally, these DRPs were more commonly detected in outpatient (P-value < 0.05) than inpatient settings. In association with age, patients of age (40 – 60) had more distinguished DRPs (P-value < 0.01). On the other hand, females had higher DRPs (60.4%) than males (55.5%) but not statistically significant.

5. DISCUSSION, LIMITATION AND RECOMMENDATIONS

5.1 Discussion

UTIs are among the most common infectious diseases, affecting approximately 150 million people each year worldwide (Waller et al. 2018a). One study in the US showed that the economic burden of UTIs, including diagnosis and management, is nearly 3.5 billion dollars annually (Flores-Mireles et al. 2015). In addition, UTIs can lead to some severe complications if left untreated or inappropriately treated (Ailes et al. 2018). Additionally, the inappropriate prescriptions, over - prescription, and misuse of antibiotics in UTI patients are of the most common leading causes for accelerating the development of AMR (Waller et al. 2018b). Finally, patients with UTIs caused by drug-resistant bacteria are at higher risk for morbidities and mortality ('Multidrug-Resistant Gram-Negative Bacterial Infections in the Hospital Setting: Overview, Implications for Clinical Practice, and Emerging Treatment Options' 2016).

This descriptive study was conducted to evaluate the current antibiotic prescribing pattern for patients with UTI in outpatient and inpatient settings, the DRPs detected in those patients, and the incidence of resistant bacteria attributed to UTIs in two of the largest health institutions in Jordan.

The prevalence of UTIs in other studies showed that it's twice more likely to occur in women than in men (Foxman 2014; Guay 2009). In our study, 56.4% of the participants were women due to the fact that most of the sample was collected from urology clinics, where most of the patients are men, while women tend to visit general practitioners, gynaecologists, and the ED for an uncomplicated UTI. Related to the most common causative pathogens for UTIs, E. coil is considered the leading causative microorganisms for uncomplicated and complicated UTIs, which accounted for 80% and 50%, respectively (Marie A. Chisholm-Burns 2019). Similarly, in our study, E. coli is still the most common causative pathogen, accounting for 46.8%, which we found to be lower because it represents both uncomplicated and complicated UTI cases with no distinction. The prevalence of uropathogens dependent on the age groups was seen in one study, which showed that P. aeruginosa is more prevalent in children (< 9 years) and the elderly (<9 years and > 60 years) and K. pneumonia are more prevalent in the older age groups (>10 years) (Farajnia et al. 2009). However, in the current

study, we found that K. pneumonia was significantly higher (P-value < 0.01) in patients younger than 18. ESBL-producing bacteria are becoming increasingly frequent worldwide in these pathogens. In 2019 the CDC reported that the ESBL-producing E. coli is becoming a global threat. It was reported by the healthcare setting of the US in 2017 that the ESBL-producing E. coli accounted for 197,400 cases and 9,400 deaths (CDC 2019). Our results recorded that, 61.8% of E. coli and K. pneumonia isolates showed positive ESBL-production. Similarly, previous studies reported a high prevalence of ESBL- producing E. coli in the Middle East and North Africa (MENA) region (39.4 - 70%) in patients with community and nosocomial UTIs (Koksal et al. 2017; Al-Assil, Mahfoud, and Hamzeh 2013b). Our results is also in consistent with other studies in Jordan between 2012 – 2015 which reported (43-54%) ESBL-producing among these patients (Al-Jamei et al. 2019). On the other hand, these results are higher than reports from other parts of the world, including in the Canada (13%), US (18.3%), and Europe (Lob et al. 2016; Coque, Baquero, and Cantón 2008).

The AMR has been recognized as a worldwide threat to public health, which can influence the empiric antimicrobial choice in the treatment of UTIs (Pietrucha-Dilanchian and Hooton 2016). The IDSA guidelines for the treatment of UTIs, recommend a threshold of 20% as the resistance percentages of the causative pathogens at which the antibiotic is no longer suitable for empirical therapy of a lower UTI and must be below 10% for the treatment of an upper UTI (Gupta et al. 2011b). In this study, the resistance pattern was determined through the sensitivity tests, in which the resistance rate was very high for many parenteral and oral antibiotics, and this is an alarming finding that the whole local antibiogram should be re-evaluated. Regarding the parenteral antibiotics, bacteria showed the highest resistance rate to cefazolin and ticarcillin. While for oral antibiotics, the highest resistance was observed in ampicillin (87.7%), cefuroxime (68%) and cefixime (67.2%), followed by trimethoprim (61.4%), ciprofloxacin (60%), norfloxacin (60.3%), TMP/SMX (59.6%), levofloxacin (56.6%), and amoxiclav (50%). Other study conducted in 2015 in Jordan showed a consistent resistance rate for ampicillin (84 – 89%) but higher sensitivity for nitrofurantoin (89.6%) (Sohail et al. 2015). Similarly, one study in Saudi Arabia reported a high resistance rate to ampicillin (89.9%), amoxiclav (74.5%), and TMP/SMX (50.4%) (Al Wutayd et al. 2018). Another study conducted in Canada in 2016, showed high sensitivity to ertapenem (100%), fosfomycin (96%), and

nitrofurantoin (83%), while the resistance rate for ciprofloxacin and TMP/SMX were 86% and 44%, respectively (Ou and Nadeau 2017).

In the present study, the parenteral therapy that still has good selectivity include colistin, imipenem, meropenem, and tigecycline. Also, ertapenem and amikacin should be considered more in the future treatment of upper UTIs. On the other hand, for oral antibiotics, only fosfomycin and nitrofurantoin should be recommended for the future therapy of lower UTIs.

Nearly 98% of the participant included in this study received an antibiotic. More than half of them were prescribed irrationally. The diagnosis of UTI should generally be based on the presenting signs and symptoms in conjunction with urinalysis results. While waiting for the culture and susceptibility results, the patients should be started on empiric antibiotic therapy (Brittany N. Bates 2013). Based on our findings, 16.1% of the participants did not do a urinalysis, 50.2% of those with urine analysis showed no bacteriuria, 22.9% of the patients had negative urine culture results, and only 18.8% of the patients with recurrent UTIs have received a prophylaxis antibiotic, these results point to the irrational antibiotic prescriptions. One study reported that 43% of patients diagnosed in the ED did not have a positive urinalysis, and 95% of culture-negative patients received antibiotic therapy. UTI overtreatment increases the economic burden, antibiotic exposure, adverse reactions, AMR, and other complications, such as Clostridium difficile infections (Gordon et al. 2013).

In this study we found that 58% of participants who received an antibiotic had at least one DRP, “long duration of antibiotics use” was the most detected accounting for 36.3%, followed by the “inappropriate drug selection” with 18%. Compared to other recent studies reported an incidence of 40% DRPs in India, 84% in Norway, and 87.7% in Ethiopia. The most common detected DRP in India was “inappropriate drug selection” accounting for 20%, while in Norway, “no further need for the drug” was the most common DRP found (Blix et al. 2008; Madhu S, James, and Venu 2016). On the other hand, “the need for additional drug therapy” was the leading DRP identified in Ethiopia (25.2%) (Bizuneh et al. 2020).

Regarding the adherence to antibiotics, one global study was carried out in 11 countries showed that non-adherence to antibiotics was estimated to be 22.3%, but with a considerable variation between countries, in which the highest non-adherence was

seen in China (44%) and the lowest in the Netherlands (9%) (Pechère et al. 2007). In our study, 42.5% of the participant reported non-adherence to antibiotic therapy, which is almost as high as China. The Morisky-scale was used to detected the attitude of the patients towered the previous usage of antibiotics which reflect how they will deal with their antibiotic. Poor patient adherence is one of the leading causes to increase the recurrence of UTIs and accelerate the AMR; the WHO highlights the significance of patient education in improving antibiotic therapy adherence (Axelsson 2013). However, this education should come from a reliable source, in our study, 55.5% of the patients who reported receiving an education were from an unreliable source (internet, friends, relatives, and students).

In Jordan, the unique expertise of the clinical pharmacist is not employed to their maximum capabilities. The challenges that limit the implementation of clinical pharmacy services may include that clinical pharmacy services are relatively new in Jordan, with a lack of institutional policies that define the role, responsibilities, and clinical pharmacist position as a health care member. Additionally, the clinical pharmacist concept in Jordan is not fully developed and has limited communication with other professions (Alefan and Halboup 2016). According to the ACCP, clinical pharmacists should play a major role in proper drug education for patients (accp). A well-informed patient can be motivated to adhere to the medication plan customized by the clinical pharmacist in conjunction with other health care professionals, which leads to a decrease in the recurrence, complications, and AMR (Marianna Liaskou 2018). Also, the clinical pharmacist contributes significantly to closing the gap created by irrational antibiotic prescriptions. All of which reflect positively on proper antibiotics utilization in the treatment of UTIs and the reduction of DRPs. Multiple studies have reported the value of the clinical pharmacist in the treatment outcomes (Beahm et al. 2017; Sanii et al. 2016). Additionally, the community pharmacists can contribute in the management of uncomplicated UTIs which can lead to decrease the economic burden of UTI (Sanyal et al. 2019). Multiple studies showed that pharmacists could manage symptomatic uncomplicated UTIs in the community pharmacies, which reported that pharmacist management of UTI was highly efficient and reliable. Also, the patient's satisfaction with this clinical service was very high due to the accessibility of the community pharmacies and the trust in the care provided by

their pharmacists (Beahm, Smyth, and Tsuyuki 2018; Akers, Adams, and Klepser 2018).

5.2 Limitations

In respect to the limitations of this study, the number of recruited patients was relatively small. The adherence to the prescribed medications and other outcomes of therapy was not assessed on follow-up visits. Also, this study was conducted mainly in urology clinics in only two health institutions in Jordan. Patients usually approach other departments, including the emergency, private clinics, community pharmacies, and gynaecology clinics for their UTIs. Thus, the results of this prospective study can be used only as indicative of the current status of management of UTIs in Jordan. However, these results cannot be generalized and multi-centre studies with a more significant number of recruited patients in different regions of Jordan should be conducted in the future to give the exact picture of this issue.

5.3 Future Recommendations

- Future studies are needed to reflect the exact status of a microbial pattern, microbial resistance, patients' clinical outcomes, as well as the proper management of UTI infections according to these outcomes.
- Proper guidelines should be followed to add more restrictions on the prescribing and dispensing of antibiotics in Jordan. This especially needed to avoid inappropriate use and possible drug-related problems.
- Antibiograms should be developed for each institution to determine the proper management of UTI infections and the proper selection of antibiotics.
- The role of the clinical pharmacist should be activated in real practice. Clinical pharmacists should work with physicians and other health care providers to provide the best patients management.

6. CONCLUSION

This prospective study was conducted to describe the antibiotic utilization pattern and the DRPs in UTI patients in Jordan. The study showed high percentages of resistance to currently prescribed antibiotic agents for UTIs in both outpatients and inpatients settings with ampicillin, cefuroxime, cefixime, trimethoprim, ciprofloxacin, norfloxacin, and TMP/SMX showed the highest resistance rates among oral medications. Also, a high percentage of recurrent UTIs were reported. Different types of DRPs were prevalent in investigated patients, including long duration of antibiotic use, inappropriate antibiotic selection, and the over-prescription of antibiotics. Additionally, in spite 42% patients reported of non-adherence, which reflects a lack of proper use of antibiotics and only 33.7% received an education. The percentage of patients with recurrent UTIs was relatively high (46.9%), and only 18.8% were managed correctly. Patients also reported poor education about their antibiotics and the dependence on unreliable sources for their education. These results may explain the high rates of recurrence UTI and the development of resistance to many prescribed antibiotics.

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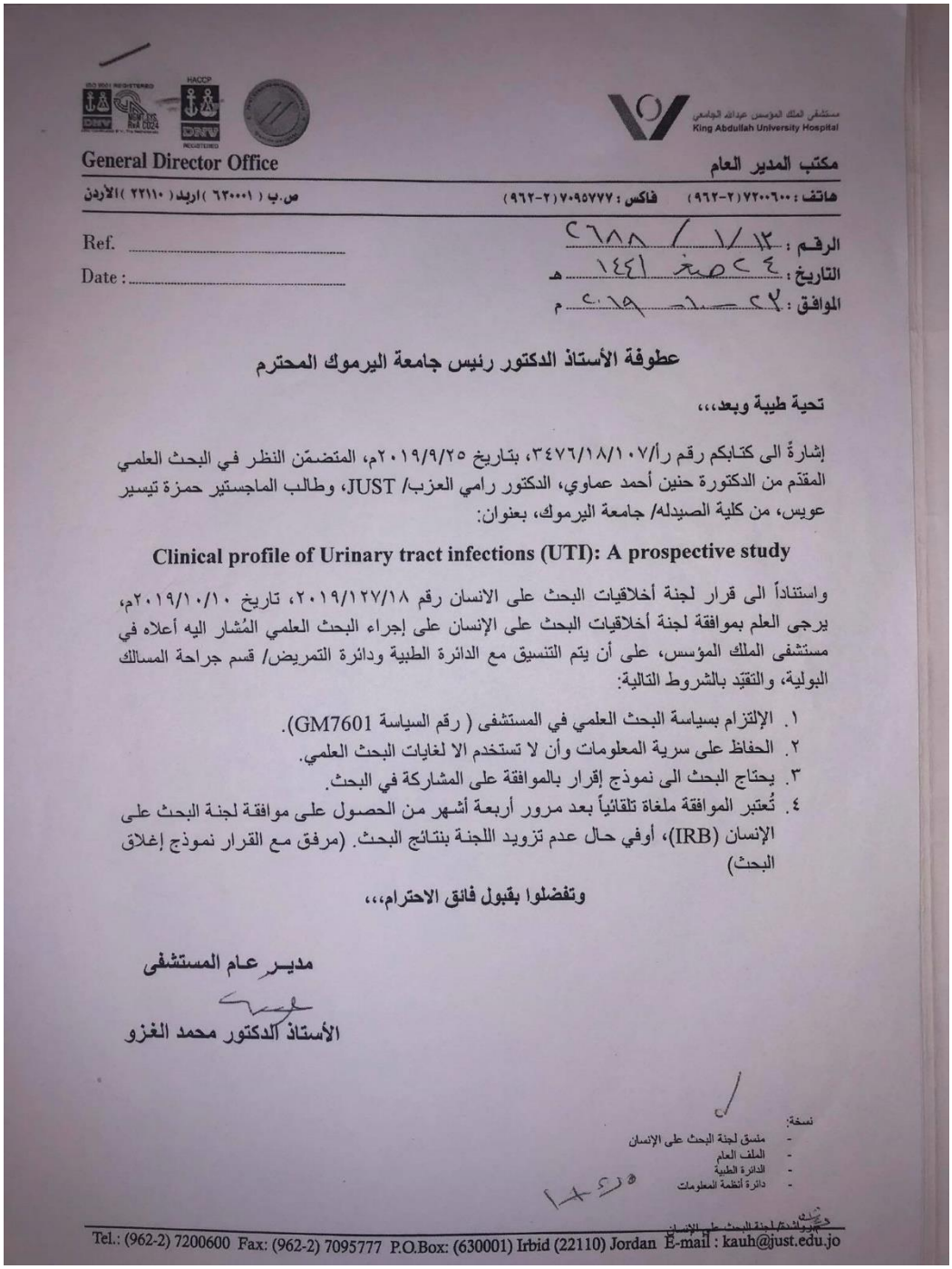
APPENDIX

Appendix A:

Institutional Review Board



مستشفى الملك المؤسس عبدالله الجامعي
King Abdullah University Hospital

General Director Office
مكتب المدير العام

ص.ب (٦٣٠٠٠١)اربد (٢٢١١٠)الأردن
فاكس : ٧٠٩٥٧٧٧ (٢-٩٦٢)
هاتف : ٧٢٠٠٦٠٠ (٢-٩٦٢)

Ref. ..... الرقم : ٦٨٨ / ١ / ١٢
Date : ..... التاريخ : ٤ صفر ١٤٤١ هـ
الموافق : ٢٢ / ١٠ / ٢٠١٩ م

عطوفة الأستاذ الدكتور رئيس جامعة اليرموك المحترم

تحية طيبة وبعد،،،

إشارةً الى كتابكم رقم رأ/٣٤٧٦/١٨/١٠٧، بتاريخ ٢٠١٩/٩/٢٥م، المتضمّن النظر في البحث العلمي المقدّم من الدكتورة حنين أحمد عماوي، الدكتور رامي العزب/ JUST، وطالب الماجستير حمزة تيسير عويس، من كلية الصيدله/ جامعة اليرموك، بعنوان:

Clinical profile of Urinary tract infections (UTI): A prospective study

واستناداً الى قرار لجنة أخلاقيات البحث على الانسان رقم ٢٠١٩/١٢٧/١٨، تاريخ ٢٠١٩/١٠/١٠م، يرجى العلم بموافقة لجنة أخلاقيات البحث على الإنسان على إجراء البحث العلمي المُشار اليه أعلاه في مستشفى الملك المؤسس، على أن يتم التنسيق مع الدائرة الطبية ودائرة التمريض/ قسم جراحة المسالك البولية، والتقيّد بالشروط التالية:

١. الإلتزام بسياسة البحث العلمي في المستشفى (رقم السياسة GM7601).
٢. الحفاظ على سرية المعلومات وأن لا تستخدم الا لغايات البحث العلمي.
٣. يحتاج البحث الى نموذج إقرار بالموافقة على المشاركة في البحث.
٤. تُعتبر الموافقة ملغاة تلقائياً بعد مرور أربعة أشهر من الحصول على موافقة لجنة البحث على الإنسان (IRB)، أوفي حال عدم تزويد اللجنة بنتائج البحث. (مرفق مع القرار نموذج إغلاق البحث)

وتفضلوا بقبول فائق الاحترام،،،

مديـر عـام المستشفى

الأستاذ الدكتور محمد الغزو

نسخة:
- منسق لجنة البحث على الإنسان
- الملف العام
- الدائرة الطبية
- دائرة أنظمة المعلومات

١٤٤١ هـ

رئيس لجنة البحث على الإنسان

Tel.: (962-2) 7200600 Fax: (962-2) 7095777 P.O.Box: (630001) Irbid (22110) Jordan E-mail : kauh@just.edu.jo

بسم الله الرحمن الرحيم

وزارة الصحة

الرقم تكليف/ط/١١٢٥

التاريخ

الموافق ١٦/١/٢٠٢٠

مدير مستشفى .....

تحية طيبة وبعد ،،،

أرفق طياً صورة عن كتاب مدير إدارة مستشفيات البشير / رئيس لجنة أخلاقيات البحث العلمي رقم م ب أ / لجنة أخلاقيات /١١٣٩ تاريخ ٢٠٢٠/١/١٦ بخصوص الموافقة للدكتورة **حنين احمد عماوي** عضو هيئة التدريس في كلية الصيدلة في جامعة اليرموك وفريقها البحثي إجراء بحث بعنوان :

(متابعة سريرية لحالات التهابات المسالك البولية)

وذلك عن طريق توزيع الاستبيان المرفق صورة عنه على المرضى المراجعين في المستشفيات الحكومية التابعة لوزارة الصحة.

أرجو التكرم بالإيعاز لمن يلزم تسهيل مهمة إجراء البحث أعلاه .

وتفضلوا بقبول فائق الاحترام ،،،

مدير مديرية التعليم وتطوير الموارد البشرية

الدكتورة رهام الحمود

هـ م

المملكة الأردنية الهاشمية
هاتف: ٩٦٢٦٥٢٠٠٢٣٠+ فاكس: ٩٦٢٦٥٦٨٨٣٧٣+ ص.ب: ٨٦ عمان ١١١١٨ الأردن . الموقع الإلكتروني: www.moh.gov.jo

بسم الله الرحمن الرحيم

وزارة الصحة

الرقم ٢٠٢٠/١/١٦

التاريخ م ب أ/ لجنة أخلاقيات / ١١٢٩

الموافق

مدير مديرية التعليم وتطوير الموارد البشرية

تحية طيبة وبعد،

اشارة لكتابكم رقم تطوير/خطط/ ٣٥١ تاريخ ٢٠٢٠/١/٥ بخصوص البحث العلمي المقدم من قبل الدكتوره / حنين أحمد عماوي .

أرفق بطيه قرار لجنة اخلاقيات البحث العلمي والمتضمن الموافقة على اجراء البحث العائد للمذكوره أعلاه.

للاطلاع واجراءاتكم لطفا.

واقبلو فائق الاحترام ،،،،

مدير ادارة مستشفيات البشير

الدكتور محمود سليمان زريقات

خ ع

وزارة الصحة

الرقم Moh/REC/2020/7
التاريخ .....
الموافق .....

قرار لجنة أخلاقيات البحث العلمي

اجتمعت لجنة أخلاقيات البحث العلمي بتاريخ ٢٠٢٠/١/١٣ لمناقشة ودراسة البحث العلمي المقدم من قبل الدكتورة /حنين أحمد عماوي .

بعنوان

"متابعة سريرية لحالات التهابات المسالك البولية"

وبناءاعليه قررت اللجنة الموافقة على اجراء البحث العائد للمذكوره اعلاه مع الالتزام بأخلاقيات البحث العلمي وحقوق المرضى،وتم التوقيع من قبل أعضاء اللجنة حسب الأصول.

مقرراللجنة/ رئيس وحدة تنمية الموارد البشرية خولة علاونة	**عضو** **مدير التمريض** الدكتور/نضال النسور	**عضو/مدير مستشفى** **الاسعاف والطوارئ** الدكتور/ عقاب الرواحنه	**عضو / مدير** **الشؤون الادارية والمالية** غالب عبدالرحيم القواسمي
عضو **المدير الطبي** الدكتور/ جمال حمدان	**عضو/ مدير مستشفى** **الباطني والسمعة علاجية** الدكتور / بشاره بقاعين	**عضو/ مدير مستشفى** **النسائية والأطفال** الدكتور/ محمود دولة	**عضو / مدير مستشفى** **الجراحة وج.التخصصية** الدكتور / قاسم عبيدات

رئيس اللجنة
مدير ادارة مستشفيات البشير
الدكتور/ محمود سليمان زريقات

Appendix B:

Questionnaire

<table>
<tr><th colspan="8">General Information</th></tr>
<tr><td>Patient ID</td><td colspan="7"></td></tr>
<tr><td>Age</td><td colspan="2"></td><td>Gender</td><td colspan="2">□ Male</td><td colspan="2">□ Female</td></tr>
<tr><td>Date of visit</td><td colspan="2">__/__/____</td><td>Status</td><td colspan="4">□ Single
□ Married
□ Divorced</td></tr>
<tr><td>Sign and symptoms</td><td colspan="7">□ A strong, persistent urge to urinate.
□ A burning sensation when urinating.
□ Passing frequent, small amounts of urine.
□ Urine that appears cloudy.
□ Urine that appears red, bright pink or cola-colored — a sign of blood in the urine.
□ Strong-smelling urine.
□ Pelvic pain, in women — especially in the center of the pelvis and around the area of the pubic bone.
□ Others:</td></tr>
<tr><td colspan="8">Vitals:</td></tr>
<tr><td>Temp</td><td></td><td>Pulse</td><td></td><td>RR</td><td></td><td>BP</td><td></td></tr>
<tr><td>Weight</td><td></td><td>Height</td><td></td><td>BMI</td><td></td><td></td><td></td></tr>
<tr><td>Smoking</td><td>□ YES</td><td>□ NO</td><td></td><td>Drug allergies</td><td colspan="2">□ NKA</td><td>□ Yes</td></tr>
<tr><td colspan="8">Type of UTI and its sign</td></tr>
<tr><td colspan="3">□ Kidneys (acute pyelonephritis)</td><td colspan="5">□ Upper back and side (flank) pain
□ High fever
□ Shaking and chills
□ Nausea
□ Vomiting</td></tr>
<tr><td colspan="3">□ Bladder (cystitis)</td><td colspan="5">□ Pelvic pressure
□ Lower abdomen discomfort
□ Frequent, painful urination
□ Blood in urine
□ Nocturia</td></tr>
<tr><td colspan="3">□ Urethra (urethritis)</td><td colspan="5">□ Burning with urination</td></tr>
</table>

	□ Discharge	
□ Prostate (prostatitis)	□ Difficulty urinating, such as dribbling or hesitant urination □ Pain in the abdomen, groin or lower back □ Pain or discomfort of the penis or testicles	
Recurrent UTI	□ **YES**	□ **NO**
	□ Reinfection □ Relapse	
	□ More than 2 or 3 infections per year □ Less than 2 or 3 infections per year	

Past Medical History/ Risk factors identification					
Hypertension	□ YES	□ NO	**Liver disease**	□ YES	□ NO
Diabetes	□ YES	□ NO	**COPD / Asthma**	□ YES	□ NO
Immunocompromised	□ YES	□ NO	**Congenital anomalies**	□ YES	□ NO
BPH	□ YES	□ NO	**Vesicourethral reflux**	□ YES	□ NO
CVD	□ YES	□ NO	**Bladder disease:**	□ YES	□ NO
Cancer	□ YES	□ NO	**Renal transplantation**	□ YES	□ NO
CKD / Kidney disease	□ YES	□ NO	**Neurogenic bladder**	□ YES	□ NO
Urologic instrumentation	□ YES	□ NO	**Other:**		
Urethral catheterization	□ YES	□ NO			
Urinary tract obstruction	□ YES	□ NO			

FOR WOMAN; USING BIRTH CONTROL:	□ Yes	□ No
Type of birth control:	□ diaphragms	
	□ spermicidal agents	
Pregnancy or postpartum <1 month	□ YES	□ NO

Drug History (BEFORE THIS UTI EPISODE)		

Tests	
Type of test	**Date of test**
□ Urine culture: □ E. Coli □ Staphylococcus saprophyticus □ Klebsiella pneumoniae □ Proteus spp. □ Pseudomonas aeruginosa □ Enterococcus spp. □ S. aureus □ Chlamydia trachomatis	
□ Urinalysis: □ Pyuria (elevated number of white blood cells in the urine) □ Haematuria □ Proteinuria □ Bacteriuria (presence of bacteria in the urine) □ Nitrites □ Crystals □ Others:	
□ Imaging**:** □ Computed tomography (CT) scan □ Magnetic resonance imaging (MRI) □ Cystoscopy □ Micturating cystourethrogram (MCUG) □ Abdominal x-ray (KUB) □ Intravenous pyelogram (IVU) □ Voiding cystourethrography (VCUG) □ Ultrasound □ Others:	

Lab Tests			
Hemoglobin		**PSA**	
WBC		**BUN**	
Na		**T4**	
K		**T3**	
Serum Creatinine		**TSH**	
Albumin		**HbA1C**	
Urine PH		**Urine Osmolality**	
ALP		**AST**	
GGT		**Urea**	

Non pharmacological treatment for UTI:	
□ Large volumes of cranberry juice □ Lactobacillus probiotics □ Phenazopyridine hydrochloride	
Pharmacological treatment for UTI	
Antimicrobial therapy	**Other treatment options (prophylactic treatment):**
□ Trimethoprim/sulfamethoxazole □ Nitrofurantoin □ Fosfomycin □ Ciprofloxacin □ Levofloxacin □ Cefpodoxime □ Cefdinir □ Cefaclor □ Cefuroxime □ Cefazolin □ Cefoxitin □ Ceftazidime □ Ceftriaxone □ Cefepime □ Cefixime □ Amoxicillin □ Amoxicillin/Clavulanic acid □ Tetracyclines □ Azithromycin □ Ampicillin □ Ampicillin/Sulbactam □ Piperacillin tazobactam □ Ertapenem □ Imipenem □ Amikacin □ Gentamycin □ Tobramycin □ Other:	□ A long course (6 months or more) of low-dose antibiotics □ Vaginal estrogen therapy for postmenopausal women □ A single dose of antibiotic after sexual intercourse if your infections are related to sexual activity. □ Others:

Duration of antibiotics	

Regarding the adherence to the antibiotics:		
1. Did you ever **forget** to take your antibiotic?	□ YES	□ NO
2. Did you have difficulty **remembering** to take your antibiotics?	□ YES	□ NO
3. Did you ever **stop** taking your antibiotic because you felt **better**?	□ YES	□ NO
4. Did you ever **stop** taking your antibiotic because you felt **worse**?	□ YES	□ NO
5. Are you **careless** at times about taking your medicines?	□ YES	□ NO

Any antibiotics in the last 6 months:	
□ Zinnat (Cefuroxime)	□ Amoclan (Co-amoxiclav)
□ Cefutil (Cefuroxime)	□ Augmentin (Co-amoxiclav)
□ Cefovex (Cefuroxime)	□ Clavodar (Co-amoxiclav)
□ Daroxime (Cefuroxime)	□ Curam (Co-amoxiclav)
□ Cefix (Cefixime)	□ Cipro (Ciprofloxacin)
□ Suprax (Cefixime)	□ Ciprodar (Ciprofloxacin)
□ Omnicef (Cefdinir)	□ Ciprolon (Ciprofloxacin)
□ Sefarin (Cefdinir)	□ Ciproflox (Ciprofloxacin)
□ Matador (Levofloxacin)	□ Balkatrin (Co-trimoxazole)
□ Uniflox (Levofloxacin)	□ Trimidar (Co-trimoxazole)
□ Avoxin (Levofloxacin)	□ Septrin (Co-trimoxazole)
□ Avicare (Levofloxacin)	□ Furolin (Nitrofurantoin)
	□ Monural (Fosfomycin)

Education about the antibiotics?

Drug-Related Problems	
Adverse reactions	□ Side effect suffered (non-allergic) □ Side effect suffered (allergic) □ Toxic effects suffered
Drug choice problem	□ Inappropriate drug (not most appropriate for indication) □ Inappropriate duplication of therapeutic group or active ingredient □ Contra-indication for drug (incl. Pregnancy/breast feeding)
Dosing problem	□ Drug dose too low or dosage regime not frequent enough □ Drug dose too high or dosage regime too frequent □ Duration of treatment too short □ Duration of treatment too long
Drug use problem	□ Wrong drug taken/administered □ Drug not taken/administered at all
Interactions (drug-drug or drug-food interaction)	□ Potential drug-drug interaction □ Potential drug-food interaction
Others	□ Patient dissatisfied with therapy despite taking drug(s) correctly □ Insufficient awareness of health and diseases (possibly leading to future problems) □ Unclear complaints. Further clarification necessary □ Therapy failure (reason unknown)

CURRICULUM VITAE

Name	Hamza	**Surname**	U'wais
Place of birth	Irbid – Jordan	**Date of birth**	7/8/1995
Nationality	Jordanian	**Tel**	+962796427808
E-mail	Hamza.t.owais@outlook.com		

Education level

	Name of the Institution where he/she was graduated	**Graduation year**
Postgraduate/Specialization		
Masters		
Undergraduate	Yarmouk university	2018
High school	Irbid modern school	2013

Job experience

Duty	**Institution**	**Duration (Year - Year)**
None	**None**	**None**

Foreign language

Foreign Languages	**Reading comprehension**	**Speaking***	**Writing***
English	Very good	Very good	Very good

Foreign Language Examination Grade

YDS	ÜDS	IELTS	TOEFL PBT	TOEFL IBT	TOEFL CBT	FCE	CAE	CPE
		6						

	Math	**Equally weighted**	**Non-math**
ALES Grade			
(Other) Grade			

Computer Knowledge

Program	**Use proficiency**
SPSS	Good
Excel	Very good
Word	Very good