INVESTIGATION OF THE PATTERNS OF ANTIBIOTIC USE AND BACTERIAL RESISTANCE IN PATIENTS WITH UTI IN BURAIDAH CENTRE HOSPITAL, SAUDI ARABIA

BY

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ABSTRACT

Urinary tract infections (UTIs) are one of the most common bacterial infections in hospital and community settings requiring antimicrobial treatment. Antimicrobial resistance (AMR) reduces the effectiveness of antimicrobial agents, leading to difficulties in the treatment of patients with the potential of prolonging the duration of illness and increasing mortality in patients. The misuse of antibiotics could result in public health problems, including the high prevalence of antibiotic resistance. This study aims: to determine the most common antimicrobial drugs resistance in regards to bacteria in UTI patients in Buraidah Centre Hospital (BCH), Saudi Arabia; to investigate the relationship between demographic data, bacteria, and antimicrobial drugs resistance; to investigate the relationship between the empirical and final treatments with regard to bacteria, antimicrobial drugs resistance, and diseases; to explore the background knowledge of physicians regarding antimicrobial drugs resistance in UTI patients; and, to measure the attitudes of physicians towards antimicrobial drugs resistance in UTI patients. Our study is divided into two phases: 1) retrospective analysis of UTI cases at BCH from August 2016 to January 2017; 2) quantity and quality studies were conducted on the BCH's physicians to measure their knowledge, attitude, and practice. In Phase I, 104 (14.7%) of the 709 patients who met the criteria for UTI diagnosis had a positive urine culture (55.8%, female and 44.2%, male; mean [SD] age 53.3 [21.51] years) were reviewed. Forty-one (39.4%) admitted during the winter, and 44 (42.3%) were to the Medical ward. Gram-negative bacilli (GNB) were the most frequent bacteria, followed by *E-coli*. Phase II has two categories—quantitative and qualitative. Of the 110 participants, 103 (93.6%) returned the questionnaires. Their attitudes did not differ across speciality or level of training. Wide-spread antibiotic use was believed by more than 85% of the participants to be a very important general cause of resistance, and inappropriate empirical choices were believed by 73.8% of the participants to be a very important general cause of resistance. About 68% of participants said that the lack of guidelines on antibiotic use is a very important general cause of resistance. A total of 16 doctors were interviewed regarding antibiotic choices in the case scenario of uncomplicated cystitis. A majority (50.2%) of participants recommended ciprofloxacin as the first-mentioned antibiotic. Fluoroquinolones were chosen as the first-line agent rather than trimethoprim-sulfamethoxazole or nitrofurantoin, for controlling UTI symptoms. It was unknown whether forfomycin is a familiar first-line treatment option for uncomplicated cystitis to the participants. Urine cultures are (20.2%) obtained from hospitalised patients, even in the absence of urinary symptoms. The appropriateness of treatment was higher in the empirical treatment compared to the final treatment. Meanwhile, the final treatment had more drug resistance than empirical treatment. The physicians acknowledged that among the most significant factors of AMR is antimicrobial misuse, either by over-prescribing or providing inappropriate drugs. By adhering to local guidelines, continuous education, and other practical interventions, the burden of resistance can be alleviated.

خلاصة البحث

إلتهابات المسالك البولية تعد من أكثر الإلتهابات البكتيرية وفرة في المستشفيات والمجتمعات التي تتطلب وصف المضادات الحيوية. الميكروبات المقاومة للمضادات الحيوية تقلل من فعالية العوامل المضادة للجراثيم، وتؤدي الى صعوبات في معالجة المرضى، مع القدرة على إطالة فترة المرض وزيادة معدل الوفيات. الأستخدام الخاطى للمضادات الحيوية قد يؤدي إلى مشاكل في الصحة العامة، التي تتضمن إرتفاع معدل إنتشار مقامة المضادات الحيوية. أهداف هذه الإطروحة هي: تحديد أكثر المضادات الميكروبية إستخدامًا وخصوصًا البكتيرية لدى مرضى المسالك البولية في مستشفى البريدة في المملكة العربية السعودية. لإيجاد العلاقة بين البيانات الديموغرافية والبكتيريا وأدوية المضادات الحيوية التي لديها مقاومة. لإيجاد العلاقة بين العلاجات المبدئية والعلاجات النهائية فيما يتعلق بالبكتيريا ومقاومة الأدوية المضادة للميكروبات والأمراض. لإستكشاف مدى معرفة الأطباء فيما يتعلق بمقاومة الأدوية المضادة للميكروبات لدى مرضى اللذين عندهم الإلتهابات البولية. ولإستكشاف مواقف الأطباء للأدوية المقاومة للمضادات الميكروبية لدى مرضى الإلتهابات البولية. تنقسم الدراسة الحالية إلى قسمين: حالات الإلتهابات البولية قد جمعت من المرضى الداخلين (المنومين) في المستشفى من أغسطس 2016 إلى يناير 2017، وتم إجراء دراسة استقصائية للأطباء في مستشفى البريدة. (القسم الأول) مئة و أربعة (14.7%) من أصل سبعة مئة و تسعة مرضى الذين استوفوا معايير تشخيص الإلتهابات البولية واللذين كان فحص البول عندهم إيجابي (55.8% نساء و 44.2% رجال، المعدل الوسطي للأعمار 53.3 سنة). أغلب المرضى الذين أدخلوا للمشفى للمبيت كانوا في فصل الشتاء حيث كانوا 41 مريض (39.4%) و 44 (42.3%) مريض كانوا في الجناح الطبي. العصيات سلبية الجرام كانت أكثر البكتيريا تواجدا في الدراسة الحالية، حيث آتت قبل الإشريكية القولونية حيث آتت في المرتبة الثانية. (القسم الثاني) 103 طبيب من أصل 110 قبلوا و جاوبوا على الإستمارات الإستبيانية. لم تختلف مواقفهم عبر التخصص أو مستوى التدريب. يعتقد أكثر من 85٪ من المشاركين أستخدموا المضادات الحيوية على نطاق واسع حيث أنه يعد سبب مهم جدًا للمقاومة، ويعتقد أكثر من 73% من الأطباء أن الخيارات العلاجية التجريبية (الأولية) غير ملائمة للمرضى و هي تعد سبب عام مهم للغاية لمقاومة المضادات الحيوية. أكثر من 65٪ من المشاركين قالوا إن عدم وجود إرشادات حول استخدام المضادات الحيوية هو سبب عام مهم جدًا لمقاومة المضادات الحيوية. عملية زرع البول تتم بشكل متكرر للمرضى في المستشفيات، حتى في حالة عدم وجود أيت أعراض للإصابة بمرض الإلتهابات البولية. يجب تنفيذ الاستراتيجيات الفعالة لتحسين توعية الإطباء من ناحية طلب زرع البول للمرضى وإستعمال المضادات الميكروبية في المستشفيات. هناك بعض الإختلافات بين العلاج التجريبي (الأولي) و بين العلاج النهائي للمرضى من ناحية مقامة المضادات الميكروبية. المضادات الميكروبية، عالميًا ومحليًا، تعتبر تهديدًا خطيرًا، و الأطباء في هذه الدراسة قد أكدوا ذلك. من بين العوامل الأكثر أهمية هو إساءة أستخدام المضادات الميكروبية، إما عن طريق الإفراط في وصف الأدوية غير الملائمة أو تقديم الأدوية غير الملائمة مع بعض التناقض بين وصف الأدوية والتشخيص، بالإضافة إلى أهمية فهم مضار المقاومة للمضادات الحيوية. من خلال الإلتزام بالمبادئ التوجيهية المحلية والتعليم المستمر والتدخلات العملية الأخرى، يمكن تخفيف معدل المقاومة، كما هو موضح في هذا الإستبيان.

APPROVAL PAGE

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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LIST OF ABBREVIATIONS

ACSQH	Australian Commission on Safety and Quality in Health
AMDR	Antimicrobial Drugs Resistance
AMR	Antimicrobial Resistance
CCG	Clinical Commission Group
CDC	Centers for Disease Control and Prevention
CPSG	Clinical Prescribing Subgroup
DSS	Dextran Sulfate Sodium
ECDC	European Centre for Disease Prevention and Control
ESMID	European Society for Microbiology and Infectious Diseases
GPs	General Practitioners
HAI	Healthcare-Associated Infection
HCPs	Healthcare Professionals
IDSAG	Infectious Diseases Society of America Guidelines
IDSG	Interdepartmental Steering Group
IMS	Intercontinental Marketing Service
KAP	Knowledge, Attitudes and Practices
KPC	*Klebsiella pneumoniae carbapenemase*
MDR	Multi-Drug Resistant
NICE	National Institute for Health and Clinical Excellence
OTC	Over-the-Counter
RCGP	Royal College of General Practitioners
TARGET	Treat Antibiotics Responsibly, Guidance, Education, Tools
TLRs	Toll-Like Receptors
TNFα	Tumor Necrosis Factor Alpha
UTI	Urinary Tract Infection
UPEC	Uropathogenic *Escherichia coli*
WAAW	World Antibiotic Awareness Week
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

1.1.1 Urinary Tract Infection

Although infrequently serious unless affecting the kidneys, lower urinary tract infections (UTIs) are common. Treatment of UTIs in daily practice is largely empirically based. The identity of the causative agents is generally predictable, and clinical practice guidelines state that cultures are not necessary (Hooton, 2001; Hooton & Stamm, 1997). Antimicrobial prescribing for UTIs represents 12% of overall antimicrobial prescribing, in the fourth place after lower respiratory tract infections (18%), sore throat (16%) and upper respiratory tract infections (14%) (I. Petersen & Hayward, 2007). The diagnosis of UTIs is suggested by the presentation of classic symptoms, such as frequency of urination, dysuria, and by the presence of white blood cells and nitrates in the urine. Meanwhile, empirical therapy for UTIs is a rational and cost-effective approach for individual treatment if used appropriately on a macro level (DeAlleaume & Tweed, 2006). Antimicrobials are sometimes prescribed to patients even in the absence of infection, while in some cases patients with an infection may be prescribed an inappropriate antibiotic. Prudent and appropriate antimicrobial use should be informed by the changing trends in antimicrobial resistance in the community (Teoh et al., 2014). Microbiology laboratories are also responsible for collating susceptibility data to facilitate the analysis for monitoring resistance prevalence and incidence and the possible detection of resistance trends. They are the initial sources for identification of

emerging antimicrobial resistance (AMR) patterns (Cantón, 2005; Reller et al., 2001). The availability of urine samples due to the high incidence of UTIs, the importance of adequate empirical antimicrobial therapy, standard methods for diagnosing UTIs, the general acceptance of a consistent approach to laboratory diagnosis, and the high levels of antimicrobial used, render UTIs a suitable condition to study antimicrobial resistance in the community. Additionally, UTIs are recurrent infections, which are more likely to be associated with resistant organisms because of the exposure to antimicrobial agents in the treatment of a previous episode (Coyle & Prince, 2009; Hooton, 2001). Culture and susceptibility test results and antimicrobial treatment of previous episodes of UTI may also be able to guide empirical therapy in subsequent episodes.

UTIs remains a significant health problem worldwide, constituting around 25% of all patients. The cellular architecture of the urinary tract (UT), which is enforced with tight epithelial barriers, is designed to oppose pathogen invasion. Additionally, the mild antiseptic properties of urine contribute to the inhibition of microbial growth. Although most microorganisms do not survive, a few could colonise and cause infection in the UT (Hamilton, Tan, Miethke, & Anand, 2017). However, the urothelium is the first line of defence against UTIs, as epithelial cells afford both a physical and an immunological barrier to avoid infection and trigger activation of the innate immune system. Given the variety of pathogens that can infect the UT, an understanding of the immune response during the establishment and clearance of UTIs is important to comprehend the mechanisms of recurrent infections, and also identify alternative treatment strategies in light of increasing antimicrobial resistance (C.-R. Lee, Cho, Jeong, & Lee, 2013). Interactions between the innate and adaptive immune responses to pathogens colonising the UT have been extensively investigated. Inflammasomes are part of the innate immune defence system and can respond rapidly to infectious insult. The assembly of

multi-protein inflammasome complex activates caspase-1, processes pro-inflammatory cytokines interleukin IL-18, IL-1β, IL-6, tumor necrosis factor (TNFα), and toll-like receptors (TLRs) (particularly TLR4, TLR5, and TLR11 (in mice)), and induces pyroptosis. These effector pathways, in turn, act at different levels to either resolve or prevent infection or to eliminate the infectious agent itself. In certain instances, inflammasome activation promotes tissue pathology; however, the precise functions of inflammasomes in UTIs remain unexplored. Despite the pivotal role of inflammasomes in fighting infection, our understanding of the effects of inflammasome assembly in specific infections is imperfect and mainly limited to a few well-studied microorganisms. Although UTI is the main cause of morbidity and mortality worldwide, the function of inflammasome signalling in UTIs has only recently been suggested (Hamilton et al., 2017). The most common cause of both complicated and uncomplicated UTIs is uropathogenic *Escherichia coli* (UPEC) (Foxman, 2014; Levison & Kaye, 2013), which is estimated to cause up to 80% of all UTIs (Flores-Mireles, Walker, Caparon, & Hultgren, 2015). Other common infectious agents include *Enterococcus faecalis, Klebsiella spp, Staphylococcus saprophyticus, Group B Streptococcus (GBS), Staphylococcus aureus, Pseudomonas aeruginosa, and Candida spp* (Flores-Mireles et al., 2015; Foxman, 2014).

Autophagy is an intracellular degradation system that allows the cell to recycle cytosolic components such as proteins and damaged organelles. Previously, data have suggested autophagy as the main mechanism for the removal of intracellular pathogens, additional to its role in the adaptive immune response and the inflammatory process (Anand et al., 2011; Deretic, Saitoh, & Akira, 2013; Kuballa, Nolte, Castoreno, & Xavier, 2012; Levine, Mizushima, & Virgin, 2011; Lupfer et al., 2013). However, autophagy activation (macroautophagy) is a multistage process that starts with the

formation of the phagophore, a membrane that elongates to a preautophagosomal structure and finally matures into an autophagolysosome. Every stage of autophagosome elaboration requires the concerted effort of a number of autophagy-related proteins. Particularly, defective autophagy was shown to increase susceptibility to bacterial infection and worsened dextran sulfate sodium (DSS)-induced acute colitis (Anand et al., 2011; Lassen et al., 2014; Saitoh et al., 2008). Consequently, the role of autophagy in UPEC colonisation might be specific to the pathogen and the experimental model used. Another argument favouring the detrimental role of autophagy in UPEC infection is supported by the apparent function of autophagy in promoting UPEC persistence (Hamilton et al., 2017).

1.1.2 Antimicrobial Resistance

The use of antimicrobials combined with the improvements in nutrition, housing and sanitation, and the introduction of widespread immunisation programmes have caused a dramatic decline in morbidity and mortality due to previously untreatable bacterial infections. Nowadays, the benefits of antibiotics are jeopardised by another development: the emergence and spread of microbes that are resistant to these, once described, "wonder drugs" (Leung, Weil, Raviglione, & Nakatani, 2011). The emergence and spread of antimicrobial resistance (AMR) is a complex phenomenon involving antimicrobial agents, bacterial species, resistance genes and their horizontal and or vertical transfer, and the various mechanisms of resistance (Guardabassi & Courvalin, 2006). Clinically, a microbial strain is defined as resistant when it survives antimicrobial therapy. This resistance can be intrinsic due to a structural or functional trait, which diminishes the effect of a particular drug on all members of a bacterial species (tolerance). On the other hand, acquired resistance is a major threat to health

because it is the source of the emergence and spread of resistance in normally susceptible bacterial populations, and consequently leads to therapeutic failures (Guardabassi & Courvalin, 2006). Higher prevalence of AMR in pathogenic bacteria can be primarily explained by the possible contribution of increased selective pressure by repeated exposure to therapeutic agents. Additionally, a strong relationship between resistance and virulence factors also likely contributes to the spread of antimicrobial resistance among pathogenic bacteria. There are some prominent factors influencing antibiotic usage, such as knowledge and expectations of patients and their interactions with the prescribers, economic incentives to the prescribers, followed by regulatory environments (D'Agata, Dupont-Rouzeyrol, Magal, Olivier, & Ruan, 2008). Antimicrobial agents are unique therapeutic agents as they treat more than just the individuals but also affect the pathogen population, and thereby the host population or society (Levy & Marshall, 2004). Optimising treatment success for the individual can lead to population level effects, which may substantially differ in magnitude or sometimes even go in the opposite direction (Lipsitch & Samore, 2002). Antimicrobial use affects resistance through direct individual effects and indirect population effects. One practical result of quantifying direct, individual-level antibiotic effects is to provide information on the short-term risk of infection with a resistant organism to a person about to initiate antibiotic treatment. This hazard needs to be taken into account when weighing the risks and benefits of the use of antimicrobial agents in individual patients. The underlying processes contributing to the long-term problem involve a chain of low probability events, such as mutation, genetic linkage or intra- and inter-species transfers (Magee, Heginbothom, & Mason, 2005). Standard statistical analytic approaches assume that the outcomes in different subjects are independent, but in the case of AMR, this assumption is violated (Halloran & Struchiner, 1991). In addition, observational

studies with antimicrobial prescribing data for a population and aggregated individual surveillance data on antimicrobial susceptibility are prone to ecological fallacy. Understanding the mechanisms by which antimicrobial use selects for AMR in treated patients and in the population requires methods that take into account the direct individual effects as well as the indirect effects of population level selection. Few studies have adequately addressed the issues of individual and group level interactions, and until the complexities of the spread of AMR are better understood, the design of effective interventions is rather difficult.

In recent decades, the infections caused by multidrug-resistant bacteria have dramatically increased by roughly 70% in all parts of the world. Moreover, for several decades AMR has been a rising threat to the effective treatment of an ever-increasing range of infections caused by bacteria. AMR results in reduced efficiency of antibacterial therapy, making the treatment of patients difficult or even impossible. The effect on particularly vulnerable patients is most obvious, resulting in increased mortality and prolonged sickness. The magnitude of the problem worldwide and the impact of AMR on human health for the health-care sector, as well as the wider societal impact, are still largely unknown (Exner et al., 2017; WHO, 2001). Over the last two decades, the development of antimicrobial resistance resulting from the agricultural use of antibiotics that could have an impact on the treatment of diseases affecting the human population, which require antibiotic intervention has become a significant global public health concern (Oliver, Murinda, & Jayarao, 2011; Rahimi & Nayebpour, 2012). AMR is a complex global public health challenge, and no single or simple strategy will suffice to fully contain the emergence and spread of infectious organisms that become resistant to the available antimicrobial drugs. The development of AMR is a natural phenomenon in microorganisms and is accelerated by the selective pressure exerted by the overuse

and misuse of antimicrobial agents in animals and humans. The recent lack of new antimicrobials of the necessary scope to replace those that have become ineffective brings added urgency to the need to protect the efficacy of existing drugs (WHO, 2014). Antimicrobial abuse is an important cause of antibiotic resistance and is a compelling target for attention. “Antimicrobial abuse” is an umbrella term for a wide range of breaches including overuse, inappropriate choice, incorrect dosage, incorrect duration of therapy, incorrect dosing intervals, and suboptimal route of delivery (Hamilton-Miller, 1984; Ventola, 2015).

A large body of evidence from hospitals in the United Kingdom and the United States reported that 30% to 40% of asymptomatic bacteremia cases received antibiotic regimen. A qualitative study with junior doctors in Switzerland reported that injudicious antibiotic use is an interplay of overdependence on biochemical parameters, distress overthinking about unacceptable patient outcomes, perceived pressure from peers and patients, and problems in understanding and explaining symptoms. Likewise, another qualitative research, after in-depth interviews with hospital clinicians, found that the use of urinary dipsticks were unreflective the misdiagnosis of UTIs (Eyer, Läng, Aujesky, & Marschall, 2016; M. J. Lee et al., 2015).

1.1.3 Physicians Knowledge and Attitudes towards Antimicrobial Resistance

Globally, the use of antibiotics has increased by around 36% in humans between the year 2000 and 2010 (Van Boeckel et al., 2014). Antibiotics are used in healthcare-settings from 20% to 80% in primary care (with or without a prescription) worldwide (Kotwani & Holloway, 2011). Half of the antibiotic provision in the community, globally, is inappropriate and leads to the resistance of antibiotics (Gelband et al., 2015). An inappropriate provision of antimicrobials fuels over-consumption. Furthermore,

inappropriate prescribing and dispensing can lead to misuse and overuse of antimicrobials. For example, in the United States, an antibiotic was prescribed in 221 prescriptions per 1000 population for acute respiratory infection, but only half of these prescriptions were appropriate treatment (Fleming-Dutra et al., 2016). More than eight million patients visit for UTIs each year, and the Centers for Disease Control and Prevention (CDC) reports that UTIs contribute to 13,000 deaths yearly (Waller, Pantin, Yenior, & Pujalte, 2018). Forms of inappropriate use include over-prescription of antibiotics by physicians, abuse of antibiotics by patients, use of antibiotics in animals for growth promotion, and use of antibiotics in nursing homes and long-term care facilities (Mah & Memish, 2000). Physicians should be aware of the most common bacteria causing UTIs and their propensity for resistance, and all physicians should seek out their local resistance patterns by accessing the antibiograms typically created by the local hospital (Waller et al., 2018). In hospital settings, strict infection prevention and control can restrict the spread of resistance. Health providers must preserve antimicrobial agents and improve their rational use. Also, health providers should encourage and educate the patients to assure their understanding of antimicrobial resistance issues and how to use antimicrobials appropriately (WHO, 2015a). Hospital surveillance systems and microbiology to inform about drug therapy are keys to improving medical treatment and feeding into resistance database (Uchil, Kohli, KateKhaye, & Swami, 2014). Physicians appear to recommend antibiotics to members of the public who use these communication practices as an indication of expectation and a desire for antibiotic treatment. However, these individuals might not always intend to communicate their pressure or expectation for antibiotic use, and inappropriately recommending antibiotics in this scenario may result in antibiotic resistance (Stivers, Mangione-Smith, Elliott, McDonald, & Heritage, 2003). For

countries in the Middle East, including Saudi Arabia, to obtain antibiotics is not difficult, and they are often considered an over-the-counter drug (OTC). There are no restrictions in using such medications, and they are easily accessible without a prescription (Awadh, Raja, Mahdi, & Khalid, 2017; Khalil et al., 2013; Morgan, Okeke, Laxminarayan, Perencevich, & Weisenberg, 2011). Numerous studies conducted to explore the knowledge, attitude, and practice (KAP) of the Saudi population towards antibiotic use in order to enhance the population general awareness; hence, reducing the undesirable effects of antibiotic misuse (Alumran, Hou, & Hurst, 2013; Awadh et al., 2017; Costelloe, Metcalfe, Lovering, Mant, & Hay, 2010; Nafisah et al., 2017).

Antimicrobial stewardship is an approach to promote and monitor the appropriate use of antimicrobial (NICE, 2015). The main objectives of antimicrobial stewardship are to achieve the most effective clinical outcome with reduced toxicity and adverse reactions, and to reduce multidrug-resistant bacteria by improving the awareness of the problem and helping clinicians to make smart choices with antibiotic prescribing (Waller et al., 2018). The first line of treatment in uncomplicated cystitis are nitrofurantoin, trimethoprim-sulfamethoxazole, and fosfomycin (Colgan & Williams, 2011). However, improper preferences and periods of antibiotic therapy for UTI are common problems, and providers often recommend fluoroquinolones as a first-line agent for uncomplicated cystitis and prescribe antibiotics for longer than the guidelines' recommended treatment duration. Its use is one of the possibility that has steered to the development of multidrug-resistant *E-coli* strain sequence type 131. In addition, the US Food and Drug Administration (FDA) published black box warnings for fluoroquinolones in 2016 and 2018 that fluoroquinolones should not be used for uncomplicated UTIs in patients who have other therapeutic choices. These FDA