An-Najah National University

Faculty of Graduate Studies

ASSESSMENT OF ANTIBIOTIC PRESCRIBING AND COST IN PALESTINIAN HOSPITALS

By

Rufayda Dawood Manassrah

Supervisor

Prof. Rowa Al Ramahi

This Thesis is Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Clinical Pharmacy, Faculty of Graduate Studies, An-Najah National University, Nablus - Palestine.

2022

ASSESSMENT OF ANTIBIOTIC PRESCRIBING AND COST IN PALESTINIAN HOSPITALS

By

Rufayda Dawood Manassrah

This Thesis was Defended Successfully on 14/11/2022 and approved by

Prof. Rowa' Al Ramahi Supervisor	Signature
Dr. Hussein Hallak External Examiner	Signature
Dr. Adham Abu Taha Internal Examiner	Signature
Dr. Samah Jabi Internal Examiner	Signature

Dedication

I would like to dedicate this thesis to my parents and all my family members, who have supported me throughout my education. I appreciate how you encouraged me to see this adventure through to the end. Finally, I would like to thank God for guiding me through all the difficulties.

Acknowledgements

I would like to acknowledge and give my warmest thanks to my supervisor, Prof. Rowa Al Ramahi, who made this work possible. Her guidance and advice carried me through all the stages of writing my project. I would like to thank the Palestinian Ministry of Health for their permission to conduct this study. I would also like to thank my committee members for letting my defense be an enjoyable moment and for your brilliant comments and suggestions. Thanks to you

Declaration

I, the undersigned, declare that I submitted the thesis entitled:

ASSESSMENT OF ANTIBIOTIC PRESCRIBING AND COST IN PALESTINIAN HOSPITALS.

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student's Name: Rufayda Dawood Manassrah.

Signature: Rufayda

Date: 14 November 2022.

List of Contents

List of Tables

List of Figures

List of Appendices

ASSESSMENT OF ANTIBIOTIC PRESCRIBING AND COST IN PALESTINIAN HOSPITALS

By
Rufayda Dawood Manassrah
Supervisor
Prof. Rowa Al Ramahi

Abstract

Background: One of the largest problems facing the world today is the enormous morbidity and mortality caused by antibiotic resistance in bacterial infections. A major factor in antimicrobial resistance (AMR) is the irrational use of antibiotics. The objective of this study was to assess the prescribing and cost of antibiotics in two major governmental hospitals in the West Bank of Palestine.

Methods: A retrospective cohort study was conducted on 428 inpatient prescriptions containing antibiotics from two major governmental hospitals in the West Bank of Palestine, from December 2020 to March 2021, they were evaluated by some drug use indicators. Descriptive statistics were performed using IBM-SPSS version 21.

Results: The mean ± SD number of drugs per prescription (NDPP) was 6.72 ± 4.37. Of these medicines, 38.9% were antibiotics. The mean ± SD number of antibiotics per prescription (NAPP) was 2.61 ± 1.54. The average ± SD cost per prescription (CPP) was 392 ± 744 USD. The average ± SD antibiotic cost per prescription (ACPP) was 276 ± 553 USD. The most commonly prescribed antibiotics were ceftriaxone (52.8%), metronidazole (24.8%), and vancomycin (21.0%). About 19% of the antibiotics were prescribed for intra-abdominal infections; followed by 16% used as prophylactics to prevent infections. Almost all antibiotics prescribed were administered intravenously (IV) 94.63%. In general, the average duration of antibiotic therapy was 7.33 ± 8.19 days. The study indicated that the number of antibiotics per prescription was statistically different between the hospitals ($p = 0.022$), and it was also affected by other variables like the diagnosis ($p = 0.006$), the duration of hospitalization ($p < 0.001$), and the NDPP ($p < 0.001$). The most commonly prescribed antibiotics and the cost of antibiotics per prescription were significantly different between the two hospitals ($p < 0.001$); The cost was much higher in the Palestinian Medical Complex.

Conclusion: The practice of prescribing antibiotics in Palestine's public hospitals may be unnecessary and expensive. This has to be improved through education, adherence to recommendations, yearly immunization, and stewardship programs; intra-abdominal infections were the most commonly seen infection in inpatients and ceftriaxone was the most frequently administered antibiotic.

Keywords: Antibiotics, Antimicrobial resistance, Cost analysis, Prescribing, Rational use of medicine.

Chapter One

Introduction and Theoretical Background

1.1 Introduction and literature review

Antibiotics are pharmacological substances that were first created by bacteria or fungus but are now frequently created synthetically. They either inhibit bacterial growth or kill them (1).

Antibiotics were heralded as miracle drugs when they were initially released in the mid-twentieth century. The apparently miraculous impact of these medications on serious bacterial infections astounded both patients and clinicians. For the past fifty or sixty years, doctors have grown to expect antibiotics to heal practically all of their patients' bacterial infections, and patients expect the miracle treatments to continue to work. Surgical drainage, antiseptics, silver compounds, arsenicals, or tinctures of time were all used to treat infections before 1940. Bacterial endocarditis was almost always lethal, and a diagnosis of pneumonia or meningitis was virtually always fatal. The fast development of antibiotics in the latter half of the twentieth century was really amazing, providing clinicians with a plethora of alternatives for successfully treating a wide range of bacterial infections. We can fairly question whether the miracle has ended only six decades later. Staphylococci quickly developed resistance to penicillin after the first few years of usage. Furthermore, in the early 1960s, Kislak and Finland reported a single strain of *Streptococcus pneumoniae* that was penicillin-resistant (2).

Antibiotics are one of the most cost-effective and life-saving treatments, and they also help people live longer lives; according to studies, billions of people have been rescued worldwide in the seven decades since the discovery, mass manufacture, and therapeutic usage of antibiotics, but, due to the rapid spread of antibiotic resistance in bacteria, many antibiotics that were formerly highly effective have become useless in recent decades (3, 4). Unfortunately, when bacteria become more resistant to the antibiotics widely used to treat them, it becomes impossible to treat single-drug resistant bacteria. That increases the cost of treating diseases in both economic terms and in quantity and quality of human life (1). Furthermore, antimicrobial resistance (AMR) would jeopardize successful treatments for other diseases such as cancer chemotherapy, human immunodeficiency virus (HIV) treatment, and malaria treatment (5).

Clinicians are familiar with the various antibiotic classes. Sulfonamides are commonly used in conjunction with trimethoprim to treat urinary infections, nocardial infections, and community-acquired MRSA infections. Penicillin is still the antibiotic of choice for treating syphilis and Group A beta-hemolytic streptococcal infections, but penicillin resistance among pneumococci has spread in most countries. Cephalosporins are still beneficial in some community and nosocomial infections, but methicillin-resistant *Staphylococcus aureus* (MRSA) and several gram-negative bacilli have developed resistance to a variety of these medications. Carbapenems show antibacterial action against a wide range of gram-positive and gram-negative microorganisms, including *Pseudomonas aeruginosa* (ertapenem excepted). The aminoglycosides are key bactericidal injectable antibiotics used to treat gram-negative bacterial sepsis as well as tuberculosis and enterococcal infections in conjunction with other medicines. Macrolides, azalides, streptogramins, and ketolides play a role in the therapy of respiratory tract infections caused by susceptible strains of pneumococci, such as *Haemophilus influenzae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, and others. Clindamycin is now largely used to treat anaerobic infections or as a supplementary therapy for some streptococcal and staphylococcal toxin-mediated illnesses. The new fluoroquinolones have efficacy against a wide range of gram-positive and gram-negative organisms; however, resistance to several of these drugs is rising. Vancomycin and teicoplanin are well-known glycopeptides that are effective against MRSA, but hetero-resistant strains and a low minority of vancomycin-resistant bacteria have been identified. Linezolid is an oxazolidinone that is effective against gram-positive cocci such as MRSA and vancomycin-resistant enterococci, as well as other "atypical" respiratory pathogens (6).

The current antibiotic network and infrastructure are insufficient to combat the global rise in resistance, particularly among gram-negative bacteria. If antibiotic research continues at its current pace, the antibiotic era will be over in a few decades, at least for many gram-negative infections (7).

Unfortunately, one of the most underappreciated issues is antibiotic resistance. This is most likely due to the fact that there are still only a small number of people living in industrialized nations who regularly encounter resistance. Furthermore, it is challenging to convince people that a great crisis is approaching as long as there are still a few effective antibiotics available, doctors eager to prescribe them, and people willing to sell them (1).

From a microbiological perspective, there are various approaches to define antibiotic resistance (ABR). Resistance is defined as a phenotypic that makes the bacterium less sensitive than other members of the same species, regardless of the level of resistance. Contrarily, clinical resistance is defined as resistance that has reached a critical degree and is interfering with pharmacotherapy for a clinical issue caused by the bacterium (8). Bacteria that proliferate even in the presence of antibiotics are referred to as "resistant bacteria". Antibiotics inhibit key biological functions; however, bacteria can develop resistance through the acquisition of exogenous resistance genes or chromosomal changes. Resistance mutations are frequently found in genes that encode vital functions; these alterations are thus generally harmful in the absence of medications. Bacteria, on the other hand, can overcome this disadvantage by obtaining extra mutations known as compensatory mutations. Genetic interactions (epistasis) with the background or between resistances (in multi-resistant bacteria) have a significant impact on the survival cost of antibiotic resistance and its compensation, hence determining the spread of antibiotic resistance mutations (9).

AMR is a natural phenomenon, but how quickly it happens depends on how frequently organisms are exposed to medications. There have been many well-publicized cases of pathogens evolving into AMR, including methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant tuberculosis, and antibiotic-resistant gonorrhoea, all of which are significantly more dangerous strains than the original pathogens. This is a critical public health issue because bacteria control is heavily reliant on our ability to treat infection adequately (10, 11). For example, one study found that enteric microorganisms in Thailand had developed resistance to practically all antibiotics used to treat non-cholera diarrhea (sulfamethoxazole and trimethoprim (TMP-SMZ), ampicillin, and tetracycline), as well as the latest fluoroquinolone and macrolide families of medications (12). Methicillin was the initial semisynthetic penicillinaseresistant penicillin to attack strains of penicillinase-producing Staphylococcus aureus when it was introduced in 1961. Unfortunately, resistance to methicillin was identified shortly after the drug's introduction (13). *Staphylococcus aureus* specimens from intensive care units and blood culture isolates around the world are becoming highly resistant to a wider range of antimicrobial drugs. As a result, there are fewer effective bactericidal medicines available to treat these often fatal illnesses. Staphylococci have developed efficient ways to resist new antibiotics as quickly as they are introduced. Furthermore, vancomycin was widely used to treat infections caused by methicillin-resistant staphylococci (both coagulase-positive and coagulase-negative), *Clostridium difficile*, and enterococcal infections before vancomycin-resistant staphylococci emerged. A clinical isolate of *Staphylococcus haemolyticus* was the first to show vancomycin resistance. The first case of vancomycin-intermediately resistant S. aureus (VISA) was reported in Japan in 1997, and subsequent instances from various countries were reported. The MRSA isolates from VISA were all non-clonal. Many of the patients had MRSA infections and had undergone vancomycin therapy (14).

One of the most serious issues confronting the world today is the massive morbidity and mortality caused by antibiotic resistance in bacterial diseases. Multidrug-resistant Gram-positive and Gram-negative bacteria are difficult to treat with regular antibiotics and may be untreatable (15). A study released in 2021 found considerable national and subnational disparities in antibiotic consumption in low- and middle-income countries (LMICs), with sub-Saharan Africa having the lowest levels and Eastern Europe and Central Asia having the highest. They estimated that worldwide antibiotic usage increased by 46%. They also discovered significant increases in the use of fluoroquinolones and third-generation cephalosporins across North Africa, the Middle East, and South Asia(16). The current dearth of viable therapies, efficient preventative measures, and new antibiotics is due to the difficulties associated with bacterial infection and related illnesses, which necessitate the creation of fresh therapeutic alternatives and alternative antimicrobial drugs. The availability of up-to-date epidemiological data on antibiotic resistance in commonly occurring bacterial infections will be helpful not only in determining treatment techniques but also in developing an effective antimicrobial stewardship program in hospitals to decrease bacterial resistance (15).

Understanding the causes of antimicrobial resistance (AMR) requires understanding the numerous sequential stages required for a medicine to reach a patient and its eventual use—including production, distribution, prescription, dispensing, and ultimately consumption by the patient or use in animal production. As a result, any imprudent practice along this flow could lead to the development of resistance (17). In addition, antibiotics used in agriculture are frequently the same or comparable to antibacterial drugs used in medicine; however, overuse may lead to drug resistance. The food supply is the primary route by which antibiotic-resistant bacteria spread between animal and human populations. Antibiotics are given to animals in some affluent countries through their food, water, or parenterally, which may cause microorganism resistance to that specific antibiotic. For example, the use of antibiotics as growth boosters in cow feed increases antibiotic resistance. Recent research suggests that poultry or pork may be the source of quinolone-resistant Escherichia coli in Barcelona's rural areas, where one-fourth of youngsters were discovered to be fecal carriers of these germs. These children, however, had never been treated with quinolones (4, 18).

A major factor in antimicrobial resistance (AMR) is the irrational use of antibiotics. The World Health Organization (WHO) defines rational medicine use as patients receiving the appropriate medicines, for appropriate indications, in doses that meet their own individual requirements, for an adequate period of time, at the lowest cost both to them and society, and with appropriate information. When one or more of these requirements is not met, irrational or needless medication use occurs (19). A national drug strategy that addresses drug quality, safety, efficacy, availability, and cost is essential to achieving optimal medication availability and appropriate drug usage (20).

Understanding the primary causes of irrational antibiotic use is essential. These include a lack of information and awareness among the general people, unrestricted access to medicines, leftover antibiotics from previous prescriptions, insufficiently quick and accurate diagnostic procedures, a lack of local antibiotic susceptibility data, and pharmaceutical promotion; and insufficient training for prescribers, pharmacists, and medical professionals in terms of their understanding, attitudes, and practices around the use of antibiotics (21). There is widespread agreement that the key cause driving ABR development is antibiotic overuse; consequently, large-scale studies should be done to completely understand the prescribing pattern and identify the associated determinants, allowing relevant interventions to be designed and implemented (22).

Recent studies indicate that the COVID-19 pandemic has made AMR worse. As more patients are admitted to hospitals with severe COVID-19 infections, frequently as a result of worsening respiratory symptoms requiring ventilation, more patients are developing secondary bacterial infections that need antibiotic treatment. This worsens the current levels of resistance and frequently unnecessary empirical use of antibiotics in patients hospitalized with COVID-19 (23). So coordination at the national level is required to gather more data on the complicated effects of COVID-19 to limit the potential longer-term impact on AMR and access to effective antibiotics (24).

Both the decision to take antibiotics and the choice of antibiotic class are related to the prescriber. They are likely to have an effect on prescribing behavior through their knowledge, attitudes, and perceptions about antibiotic use and resistance. According to signs obtained from clinical practice, it has been stated that the attitude and expertise of physicians determine the quality of antibiotic prescribing. The studies showed that factors associated with general practitioners' (GPs') prescribing of antibiotics include concern of infection-related consequences, a careless attitude toward patients, and a lack of awareness about ABR (25).

Inappropriate antibiotic prescribing and awareness are issues among doctors in general and young doctors in particular, with doctors preferring to prescribe antibiotics even for viral diseases, according to a systematic study published in 2015 and a narrative review published in 2021. Many factors appear to influence prescription behavior, including patients' demands for maintaining patient satisfaction; diagnostic uncertainty; time pressure; pharmaceutical companies' marketing efforts; a lack of updated information sources; and physicians' fear of losing their patients. Improper antibiotic prescribing also seems to be associated with a physician's lack of motivation to learn more and develop their prescribing techniques. The majority of the medical professionals in the studies that were reviewed also wanted more feedback on their prescription decisions for antibiotics. The eventual prescription and consumption of antibiotics can also be affected by supply, healthcare infrastructure, and financial assistance, particularly in low- and middle-income nations (26, 27). According to research, clinical antibiotic use is also more common among private practitioners than among those in government service. Recently available broad-spectrum antibiotics like azithromycin and quinolones are more regularly recommended in private clinics. The uncontrolled private sector promotes incorrect diagnostic and prescribing methods, which promote the selection of antibiotic-resistant bacteria and increase antibiotic resistance (28).

Furthermore, a systematic review and proportion meta-analyses conducted in 2014 using the PubMed and Scopus scholarly databases revealed that increasing general community knowledge and attitudes concerning antibiotics and antibiotic resistance is recommended. Antibiotic knowledge was found to be lacking. In particular, 33.7% of the sample was unaware that antibiotics can treat bacterial illnesses, and 53.9% were unaware that antibiotics are ineffective against viruses. Moreover, while 59.4% of the sample was aware of antibiotic resistance, 26.9% were unaware that antibiotic overuse can contribute to the problem. Finally, 47.1% of respondents discontinue taking antibiotics once they feel better (29).

A three-year cohort study discussed the critical factors that influence antibiotic prescribing and have been identified as attitudes, workload, and working circumstances in emergency rooms (30). Another cross-sectional study conducted in 2018 among biomedical students revealed a need for more effective courses on prescribing antibiotics, and the students' inadequate knowledge of how to follow guidelines for antibiotic use highlighted the need for modifications to the current curricula (31). A systematic review and meta-analysis were conducted between 2005 and 2020 to evaluate and compare the prevalence, reasons, sources, and factors associated with self-medication with antibiotics (SMA) within Africa. SMA prevalence ranged from 12.1% to 93.9% in Africa, with a median incidence of 55.7% (IQR, 41-75%). Western Africa had the highest recorded frequency of 70.1% (IQR 48.3-82.1%), followed by Northern Africa, which had a prevalence of 48.1% (IQR 41.1-64.3%). Penicillins, tetracyclines, and fluoroquinolones were the most commonly prescribed antibiotics. 41% of these antibiotics are on the WHO Watch List. Upper respiratory tract infections, gastrointestinal problems, and febrile diseases were the most common causes of SMA. Community pharmacies, family and friends, leftover antibiotics, and prescription drug stores were common sources of antibiotics used for self-medication. No education or low educational status was the most often reported factor related with SMA (32). Another systematic study of the prevalence, possible reasons, and consequences of antibiotic self-medication (SMA) in the Middle East between 2000 and 2016 discovered that the prevalence ranged from 19% to 82%. SMA was mostly determined by age, gender, educational status, and economic status. The most often reported reasons for SMA were socio-cultural, economic, and regulatory considerations. Penicillins were the most commonly utilized antibiotics; the antibiotics were primarily obtained through stored unused medications, pharmacies without prescriptions, and friends and relatives. SMA was primarily used to treat upper respiratory tract issues. Relatives, friends, and previous successful experiences were the key sources of drug knowledge. Inappropriate medicine use was documented, including wrong indications, short and lengthy treatment durations, antibiotic sharing, and antibiotic storage at home for later use (33).

In Arabic countries, different factors were perceived as being very important causes of antibiotic resistance: using antibiotics when they are not necessary; not finishing the entire course of antibiotics; prescribing too many antibiotics; and using antibiotics without physician or pharmacist supervision (self-medication) (34). Misuse of antibacterials is also facilitated in developing countries by their availability over the counter, without a prescription, and through ungoverned supply chains, as well as a lack of effective and reliable surveillance systems and poor dissemination of research information. Healthcare providers in developing nations frequently lack up-to-date information on the AMR pattern in their communities (35).

Some of the factors that contribute to the emergence and spread of AMR in the Eastern Mediterranean Region (EMR) are the high prevalence of infectious diseases, weak health and surveillance systems, inadequate regulatory frameworks, poor infection prevention and control (IPC) in healthcare facilities, limited capacity of microbiology laboratories, lack of access to quality-assured antimicrobial drugs for humans and animals, poverty, and insufficient access to water, sanitation, and hygiene (36).

The abuse and overuse of antibiotics, ineffective infection management, and broad antibiotic use all lead to the acceleration of antibiotic resistance, according to a WHO survey from 2015: 76% of participants in Egypt had used antibiotics in the previous six months, compared to 65% across the 12 countries surveyed. Also the study evaluated the respondents' levels of awareness and understanding of the terms related to the issue. The findings suggest that three of the terms are well known (by more than two-thirds of respondents): antibiotic resistance, drug resistance, and antibiotic-resistant bacteria. It's also worth noting that 14% of those polled had never heard of any of these phrases. However, awareness of the phrases varies among the nations studied; for example, 89% of respondents in Mexico are familiar with them, while only 21% of those in Egypt are (37).

A systematic review and meta-analysis of antibiotic prescriptions in primary care in low- and middle-income countries (LMICs) discovered that the percentage of patients receiving antibiotic prescriptions in these settings frequently exceeds 50%. The high level of antibiotic consumption in LMICs is due to a number of factors, including a high prevalence of infectious diseases, a lack of restrictions to inhibit the over-the-counter sale of antibiotics, insufficient training of medical practitioners, and a lack of essential diagnostics, which favor empirical antibiotic use. These findings emphasize the critical need for immediate action to improve prescribing procedures (38). Another comprehensive survey conducted in Arabic countries in 2020 found that over one-third of healthcare professionals, adults in the community, and medical students all agreed that using antibiotics to treat fever is the primary reason for prescribing them. Additionally, about a quarter of the participants stated that viral infections are the main reason antibiotics are used. A quarter or so of those surveyed said the drug would always be successful in treating the same infection in the future. One-fourth of those polled said that between 21 and 50% of antibiotic prescriptions were unnecessary or inappropriate (34). When there is no definitive diagnosis or need for antimicrobial treatment, treatment may involve giving broad-spectrum antibiotics. In a Lebanese study, it was found that 63.7% of doctors prescribed antibiotics for the incorrect duration of therapy, and the prescription dose was improper in 52% of cases. Several variables could explain this, including a lack of simple and obvious guidelines for dose and therapy duration, an absence of clinical trials to determine the appropriate treatment duration, variability in medical expertise, and psychological issues involved in medical decision-making (39).

Data on bloodstream infections reported to the Global Antimicrobial Resistance Surveillance System during 2017–2019 in the Eastern Mediterranean Region was examined as part of a study that evaluated the capabilities of national infection prevention and control and antimicrobial stewardship programs. The median percentage of bloodstream infections ranged from 4.6% for carbapenem-resistant *Escherichia coli* to 70.3% for carbapenem-resistant *Acinetobacter spp.* Few nations have the resources for infection prevention and control and antimicrobial stewardship programs to stop the development and spread of AMR, according to the results of the regional assessments. In general, the severity of the issue and the limited ability to address it highlight the need for regional political leadership in combating AMR (40).

Locally, according to a study conducted in community pharmacies in the Nablus governorate, Palestine, to investigate the quality of prescription writing and prescribing trends, 46.9% of all prescriptions dispensed during the observation period contained antibacterial drugs, followed by analgesics and NSAIDs; this was evidence of poor prescribing procedures and overprescribing of specific drug classes, particularly modern antibiotics (41). Another cross-sectional study on community urinary isolates in Nablus, Palestine, between 2009 and 2010, found that *Escherichia coli* was the most common bacterium in the studied sample, with high resistance to first-line antibiotics such as trimethoprim/sulfamethoxazole (37%), nitrofurantoin (29%), ampicillin (65%), and nalidixic acid (37%) (42). Furthermore, a study conducted in the Gaza Strip in 2017 to analyze drug-prescribing practices in primary healthcare centers (PHCs), recognize deficiencies in prescribing, and investigate the prescription writing skills of physicians, regardless of the nature of their patients' conditions, clearly demonstrated that there is an irrational use of drugs, discovered that 67.5% of prescriptions contained an antibiotic, and recommended that there is a clear need to develop standards for drug prescribing and standard treatment guidelines for drug use (20).

One more study, conducted at a Central West Bank Hospital in Bethlehem, was a retrospective, cross-sectional study that investigated a cohort of 2,208 prescriptions ordered by outpatient clinics and the emergency room over one year and discovered a high proportion of outpatient prescriptions, irrational use of antibiotics (the rate was 30.3%), and the most prescribed antibacterial was broad-spectrum, highlighting the need for physician education programs regarding the rational use of antibiotics (43).

In addition, a study conducted in 2016 among Palestinian adults revealed significant knowledge and attitude gaps regarding the use of antibiotics and revealed that participants with a high family income and higher educational level were more likely to be aware of optimal antibiotic use. They advocated for continuing medical education, professional development, and training seminars on antibiotic stewardship and the health risks associated with antibiotic resistance for healthcare personnel. It is also critical to reduce non-prescription antibiotic use and raise public awareness about the health and economic dangers of antibiotic resistance (44).

WHO developed and implemented strategies to control irrational medication use, such as drafting and implementing standard treatment guidelines (STGs) for common illnesses and using essential medicine lists (EMLs) to guide purchase and training. To ascertain whether or not the use of antibiotics is reasonable, the percentage of antibiotic use has been considered as a critical indicator. When they discovered that the percentage of patients receiving antibiotic prescriptions is high in all countries and the injections are still widely prescribed, the WHO recommended that general outpatients in primary healthcare facilities have fewer than 30% of their encounters with one or more antibiotics prescribed (45).

There is a rapidly developing body of literature on strategies aiming to improve the quality of antibiotic prescribing and use for illnesses. Multifaceted initiatives, such as those involving physicians and pharmacists as well as patient education, are more likely to lower antibiotic prescribing rates while increasing the use of prescribed antibiotics and improving drug consumption. Reduced antibiotic dispensing in general offices can also reduce ABR and have a favorable influence on infection-seeking behavior (e.g., a change in expecting antibiotics). Several systematic evaluations have also found that various outpatient therapies can safely enhance or decrease antibiotic prescribing and use (46, 47) .In addition, pharmacists are actively involved in enhancing the appropriateness of antibiotic prescribing practice by general practitioners (GPs) by providing professional advice, training, and education, formulary linkages, susceptibility data sharing, increasing awareness of guideline adherence, and policy-guided antibiotic prescribing. Many nations are increasingly integrating these interventions at the healthcare system or practice level in order to achieve more collaborative care by physicians, pharmacists, and other health professionals in order to optimize antibiotic use (48). One such example is the model of practitioner-pharmacist partnership. According to studies, in order to improve antibiotic use in hospitals, pharmacists must be supported in their talks with doctors, have a greater presence on hospital wards, and be provided opportunity to share expert knowledge within multidisciplinary clinical teams (49). Other intervention systematic review findings support pharmacists' significant involvement in GPs' antibiotic prescribing norms and culture as a therapeutic adviser, trainer, academic detailer, medicine prescription reviewer, and feedback provider. The study clearly showed the importance of pharmacists in assisting general practitioners in promoting appropriate antibiotic prescribing practices. As a result, investigating the evidence for effective interventions in which pharmacists act as interventionists for GPs in order to improve the quality of antibiotic prescribing is critical (50).

Furthermore, the European Parliament's Directorate General for Internal Policies of the Union made a report that discussed antibiotic resistance; the report included a proposal for an action plan that included six policy choices based on information gleaned from recent publications and activities, especially in Europe. The term "policy options" is used broadly to describe both urgent action choices and research initiatives. The six policy alternatives are narrowly focused on steps that the European Union can begin in a short to medium time frame and where the projected benefits are most likely to outweigh the estimated costs. The working group has identified four areas in which the EU may help contain resistance: coordination, standardization, stimulation, and research. The six options are as follows: Policy option 1 (coordination): Expand the ECDC's function and scope in coordinating European antibiotic resistance initiatives. Policy option 2 (standardisation): Increased support for "prescription-only" regimes within Member States. Policy option 3 (standardisation): A Pan-European Accrediting System Create a voluntary accrediting program that combines and co-develops European and worldwide hygiene, health, childcare, and building requirements. Policy option 4 (Stimulation): Promote the use of quick diagnostics by investigating the feasibility of giving incentives to Member States to adopt reimbursement schemes that promote the use of rapid diagnostic tests in general practice. These incentives could take the form of a directive or direct subsidy, for example, in nations with reduced national incomes. Policy option 5 (Stimulation): Educational Campaign Fund-Matching Program: Begin the creation of a matched funding program, in which the EU matches a portion of the funding for national educational efforts. Policy option 6 (Research): To increase resistance control, more research money is essential. Instead of funding novel drug leads, research funds should be directed at limiting antibiotic resistance. Understanding cultural, contextual, and behavioral aspects of antimicrobial usage; providing evidence about the best ways to use various antimicrobial agents; developing methods to gather evidence and conduct analyses of the costs and benefits of containment strategies; and conducting evaluations of the costs and benefits of initiatives to reduce antibiotic consumption and to limit the spread of infectious diseases are all areas that require more attention and funding (1).

Through unneeded visits, antibiotic use, problems, and antibiotic resistance, incorrect antibiotic prescribing drives up expenses. Between $3 to $95 US may be the hidden societal cost of each ambulatory antibiotic prescription due to the rise in antibiotic resistance. As a result, the cost is significant and is taken into consideration when evaluating the performance of the practitioners' rational use of drugs, which raises concerns regarding the extent of misalignment between individual and societal antibiotic costs (19, 51).

By 2050, it is anticipated that the number of drug-resistant infection-related deaths will rise from the current 700,000 to 10 million per year, with a global economic impact of up to 100 trillion US dollars. Therefore, it is possible that the world could soon enter a "post-antibiotic era" in which common infections cannot be cured (52, 53).

Worldwide, the number of deaths could reach 700,000. Furthermore, it is predicted that multidrug-resistant bacteria cause 25,000 fatalities and 1.5 billion euros in additional healthcare costs and lost productivity per year in Europe (54). In the United States (U.S.), the Centers for Disease Control and Prevention (CDC) released the first AR Threats Report in 2013, raising awareness about the danger posed by antimicrobial resistance. The report noted that at least 2 million Americans get an antimicrobial-resistant infection every year, and at least 23,000 of them die as a result. Additionally, AR might cost the US 20 billion USD annually, with extra lost productivity costs reaching up to 35 billion USD annually (55). According to a 2019 report, more than 2.8 million infections with antibiotic resistance take place in the U.S. every year, and as a result, more than 35,000 people die. The U.S. toll of all the risks in the report exceeds 3 million infections and 48,000 deaths when *Clostridioides difficile* is included. This bacterium is not typically resistant, but it can cause fatal diarrhea and is linked to antibiotic use (56).

According to the Antimicrobial Resistance Collaborators' comprehensive assessment of the global burden of AMR in 204 countries and territories in 2019, 495 million deaths were associated with bacterial AMR. At the regional level, they estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa and south Asia and lowest in Australasia. In 2019, a single pathogen-drug combination, meticillin-resistant *S. aureus*, resulted in more than 100, 000 deaths attributable to AMR, while six additional pathogens and drugs each resulted in 50, 000–100, 000 deaths: multidrug-resistant excluding extensively drug-resistant tuberculosis, third-generation cephalosporin-resistant *E. coli*, carbapenem-resistant *A. baumannii*, fluoroquinolone-resistant *E. coli*, carbapenem-resistant *K. pneumoniae*, and third-generation cephalosporin-resistant *K. pneumoniae* (57).

Furthermore, it is predicted that by 2050, cumulative losses in OECD (Organization for Economic Co-operation and Development) countries will cost 2.9 trillion USD and result in 10 million fatalities annually if actions are not taken to reverse present resistance rates. Europe is anticipated to experience 392K deaths out of this total, with Asia and Africa having the largest numbers (4.7M and 4.1M, respectively) (54).

The problem of AMR is aggravated also by the fact that most global pharmaceutical corporations view the development of new antimicrobials as having "little profit." Some people also believe that resistance will ultimately arise to new antimicrobials. As a result, they favor investing in the creation of medications for long-term conditions (such as diabetes and hypertension) as well as those that help people live healthier lives (e.g., Cialis, Viagra, etc.). Therefore, the long-term solution should concentrate on techniques to stop the formation of resistance or the transmission of resistant organisms from one person to another (58).

Accordingly, the WHO's 2015 Global Action Plan on AMR identified several key strategies for minimizing the threat of AMR, including (1) optimizing the use of antibiotics in both human and animal health, (2) reducing infections through efficient sanitation, hygiene, and other infection prevention measures, and (3) making sustainable investments in the development of new antibiotics, diagnostic tools, and other interventions (59).

1.2 Statement of problem

Antimicrobial resistance is a multi-faceted issue that impacts practically all populations, is caused by a number of interconnected variables, and is at an all-time high in all parts of the world. Also, antibiotic use in humans, animals, and agriculture is increasing..

Single solitary attempts or interventions only have a small impact. As a result, as part of an international effort, numerous organizations have established strategies to reduce ambulatory antibiotic consumption (60).

However, the emergence and spread of antimicrobial resistance must be stopped in order to improve the prescribing and use of antibiotics. More coordinated strategies and activities are needed from different stakeholders globally. Governments, agencies, academics, the pharmaceutical industry, healthcare professions, and the community must collaborate in order to achieve this goal via educational, managerial, regulatory, and economic techniques (61).

1.3 Significance of the study

A good number of previous studies related to antibiotics in our country can be found. However, to the best of our knowledge, no previous studies regarding antibiotic utilization and cost in hospitals are available in the West Bank. Overuse and misuse of these medications can lead to antibiotic resistance, more side effects in patients, and extra cost. Therefore, a follow-up study is required to look at current prescribing habits and then assess the financial impact and justification for this prescribing. For practitioners and policymakers, this might be helpful. Based on these findings, training and instructional programs could be created.

1.4 Objectives

This study aimed to assess the prescribing and cost of antibiotics in two major governmental hospitals in the West Bank of Palestine.

1.5 Specific objectives

- To find the most commonly prescribed antibiotics and their classes.
- To evaluate the types of infections for which the antibiotics were prescribed (diagnosis).
- To evaluate and analyze the cost and the economic losses as a result of antibiotic use.
- To find possible associations between some sociodemographic and clinical characteristics with the number of prescribed antibiotics.
- To compare the two hospitals' antibiotic utilization.

Chapter Two

Methods

2.1 Study setting

The majority of Palestinians residing in the West Bank are entitled to governmental healthcare provided by a network of primary healthcare centers and hospitals. Patients are evaluated and treated by a general practitioner or a specialist. All prescription orders are computerized and kept in the Avicenna Health Information System (HIS). The prescription orders have sections that the prescribing physician must completely fill out. These components include the prescription's origin, the prescriber's name, the patient's information, the patient's current diagnosis, a list of prescriptions with directions for the patient and pharmacist, etc.

The target hospitals were two major governmental hospitals; The Palestinian Medical Complex in Ramallah Governorate and Princess Alia Governmental Hospital in Hebron Governorate. These areas have a population of 1,137,400 people, making up 21.7% of the population of Palestine (62).

2.2 Ethical approval

Ethical approval was provided by the Institutional Review Board (IRB) and the Palestinian Ministry of Health before the study; (Appendix A) and (Appendix B).

2.3 Inclusion and exclusion criteria

Only inpatient prescriptions that included antibiotics for any reason were collected from the computerized system (Avicenna HIS) in the included hospitals over a period of four months (1 December 2020–31 March 2021). Convenient sampling was used to collect data.

2.4 Sample size

The estimated sample size using the automated software program, Raosoft sample size program, was 377 prescriptions with 20,000 prescriptions as a population size and 50% as a response distribution to achieve a confidence level of 95% and a margin of error of 5%.
A total of 428 prescriptions containing antibiotics were collected and analyzed retrospectively and systemically.

2.5 Data collection

Considering the importance of data standardization for the internal validity of a study, data collection was standardized by using a Data Collection Form (Appendix C) to gather information from Avicenna HIS.

The collected data included sociodemographic data, reason for admission and diagnosis, medications prescribed during hospitalization and duration of hospitalization. They were assessed for the number of drugs per prescription (NDPP), the number of antibiotics per prescription (NAPP), cost per prescription (CPP), antibiotic cost per prescription (ACPP), the cost of medications was evaluated according to the price list available at the site of the Palestinian Ministry of Health, and presented in new Israel shekels (ILS) (ILS 1= USD 0.29). In addition, main groups of all drugs written on the prescriptions, groups of antibiotics, the most frequently prescribed antibiotics were evaluated.

Antibiotics were grouped by the ATC (Anatomic Therapeutic Chemical) classification. The ATC system is a multi-label classification system developed by the WHO that divides medications into classes based on their properties and therapeutic effects. Each level of this five-level system has a number of classes; the first level alone has 14 major overlapping classes. The ATC classification system takes into account anatomical distribution, therapeutic and pharmacological effects, and chemical characteristics all at once (63).

There are no restrictions on the use of antibiotics; however, the usual pharmacy policy in both hospitals requires that hospital physicians write individual antibiotic prescriptions for patients.

2.6 Statistical analysis

The prescriptions were carefully analyzed and computerized into the Statistical Package for Social Sciences (IBM-SPSS version 21). A 0 or 1 coding system was used to record data. For each variable, a score of 1 was entered when the variable was present and compliant with the standard.

Means ± standard deviations were computed for continuous data. Frequencies and percentages were calculated for categorical variables. Chi-Square and Mann-Whitney tests were used in the statistical analyses. If $p < 0.05$, the comparisons were considered statistically significant.

Chapter Three

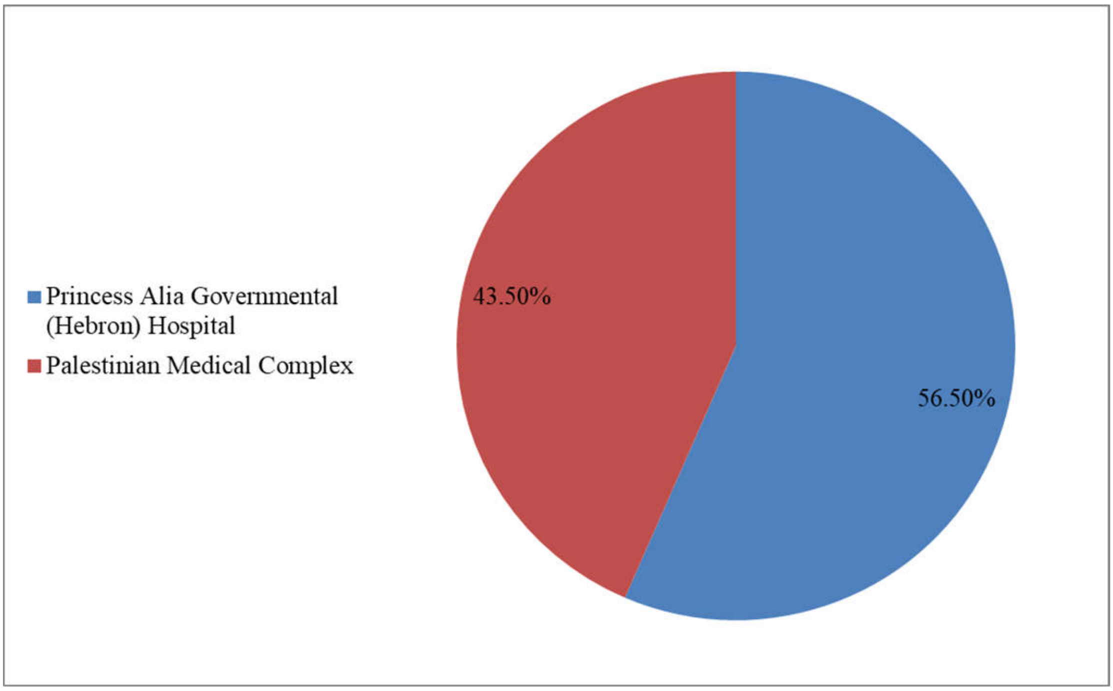
Results

3.1 Sociodemographic Data

In this study, a total of 428 prescriptions were collected; 242 (56.5%) prescriptions from Princess Alia Governmental (Hebron) Hospital and 186 (43.5%) prescriptions from the Palestinian Medical Complex (Figure 1).

Figure 1

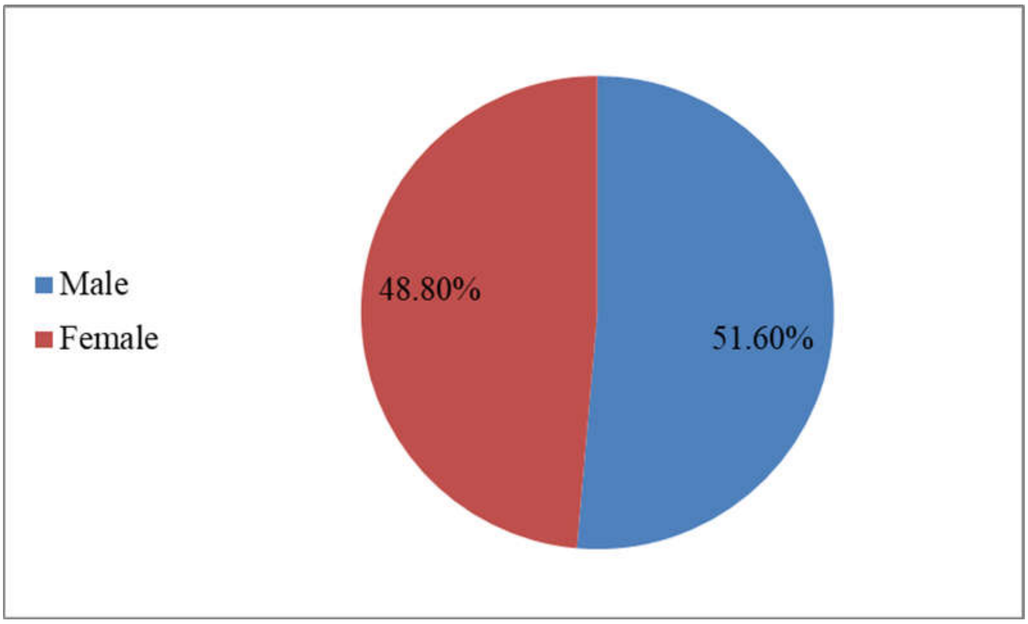
Distribution of the study sample.



The mean age of the patients was 40.45 ± 25.47 years, with 104 years as a maximum and 0.1 years as a minimum, and almost the percentages of gender were equal, male (51.6%) and female (48.8%) (Figure 2).

Figure 2

Patients' gender distribution in the study sample

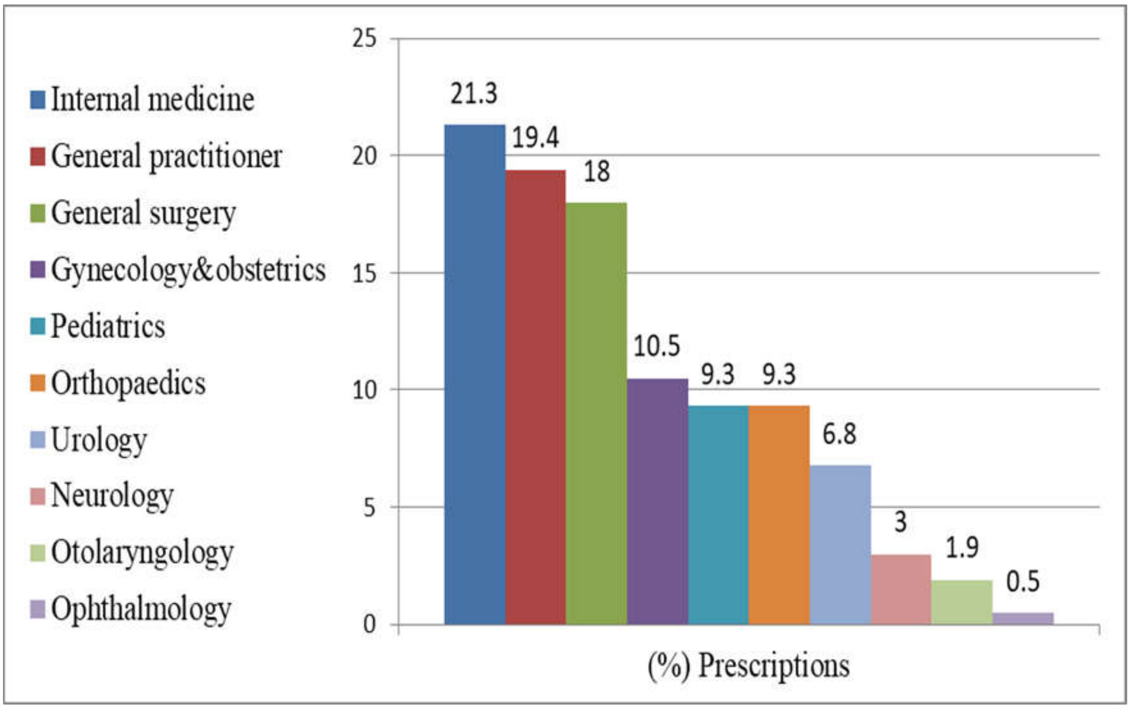


3.2 Hospitalization and Medical Information

The prescriptions were written mostly by specialists in internal medicine (21.3%), followed by general practitioners (GPs) (19.4%), surgical medicine specialists (18.0%), gynecologists (10.5%), and orthopedic and pediatric specialists each provided 9.3% of the prescriptions (Figure 3).

Figure 3

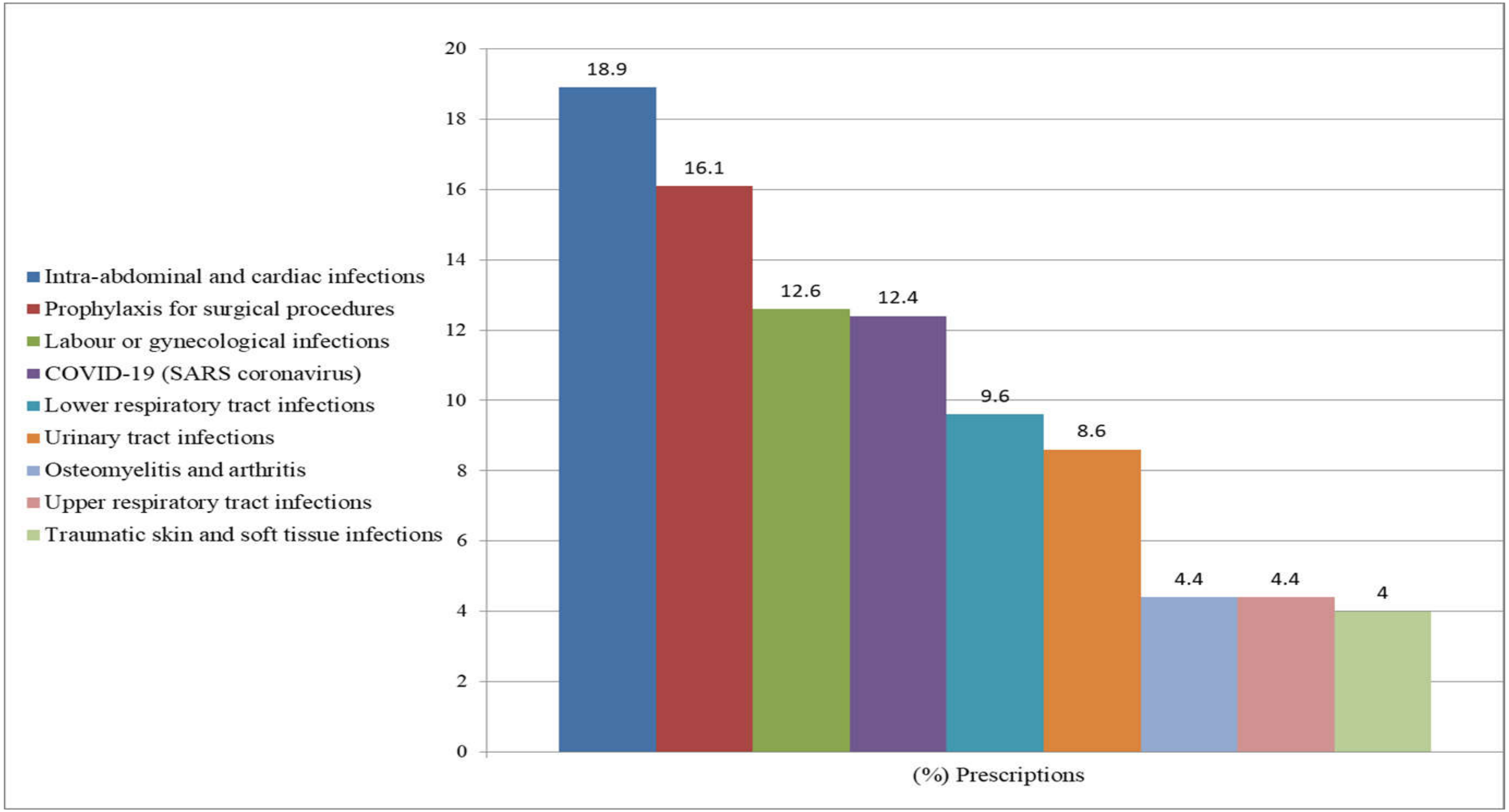
Distribution of the prescriptions by physician specialties.



Antibiotics are used to treat or prevent different types of bacterial infections. Figure 3 indicates the common diagnoses and reasons as written in prescriptions. Intra-abdominal and cardiac infections (18.9%) were the most common, followed by using antibiotics as prophylactic to prevent infections (16.1%), labor or gynecological infections (12.6%), COVID-19 (the SARS coronavirus) (12.4%), and lower respiratory tract infections (9.6%) (Figure 4).

Figure 4

Distribution of the diagnoses on prescriptions.



3.3 Assessment of antibiotic use

A total of 2875 medicines were prescribed. The number of drugs per prescription (NDPP) was 6.72 ± 4.37. Of these medicines, 38.9% were antibiotics. The number of antibiotics per prescription (NAPP) was 2.61 ± 1.54.

The most commonly prescribed antibiotics were ceftriaxone (52.8%), metronidazole (24.8%), vancomycin (21.0%), and amoxicillin/clavulanic acid (16.6%) (Figure 5).

Antimicrobials were classified according to the Anatomic Therapeutic Chemical (ATC) classification developed by the World Health Organization (WHO; https://www.whocc.no/atc_ddd_index/). When the ATC group distributions of all antibiotics were analyzed, "other beta-lactam antibacterials, the cephalosporins" (ATC code: J01D; 42.87%) were the most frequently prescribed antibiotics, followed by "other antibacterials" (J01X; 23.29%), "beta-lactam antibacterials, penicillins" (J01C; 13.36%), and "macrolides, lincosamides and streptogramins" (J01F; 7.76%) (Figure 6).

Figure 5

Distribution of the 15 most commonly prescribed antibiotics.

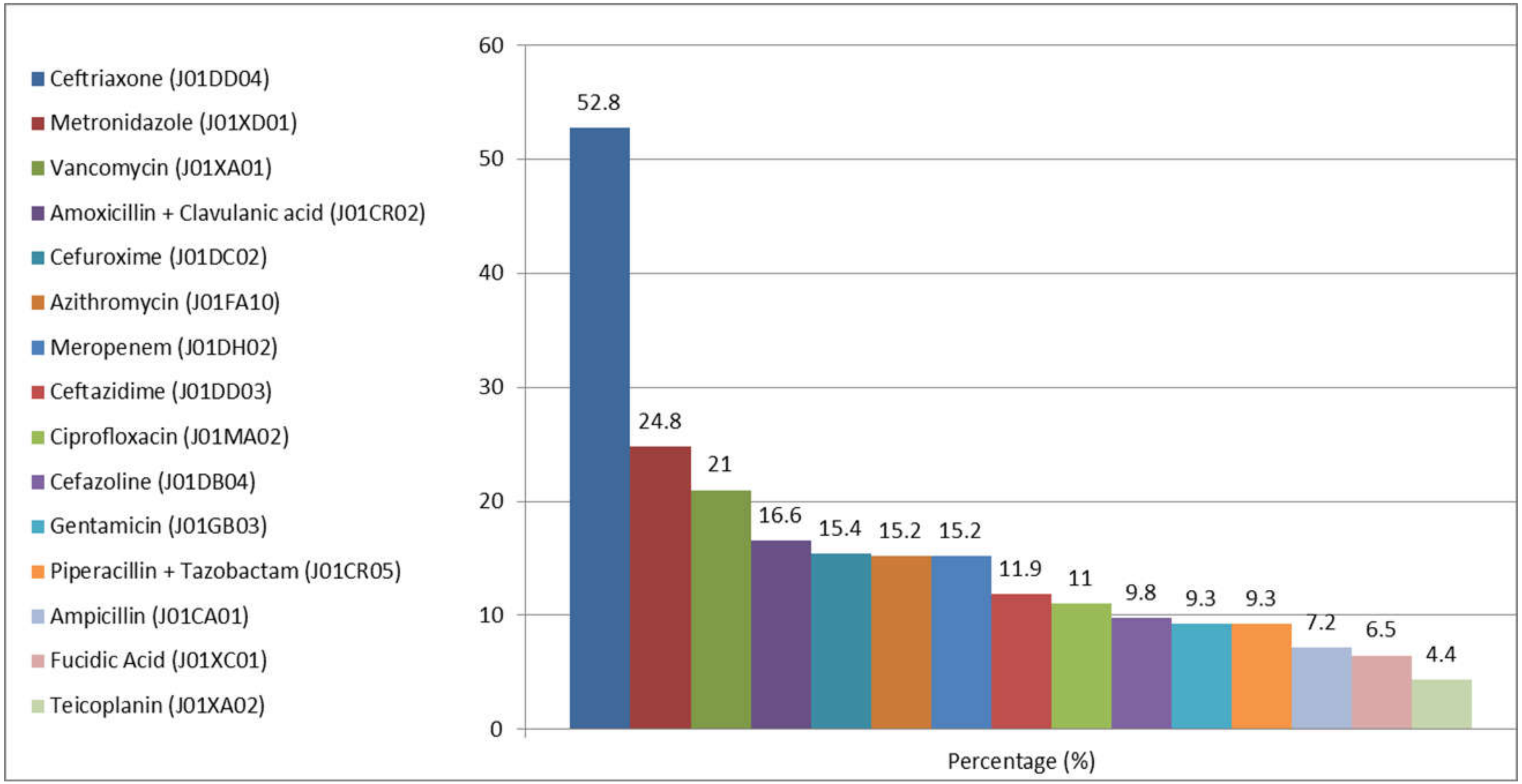
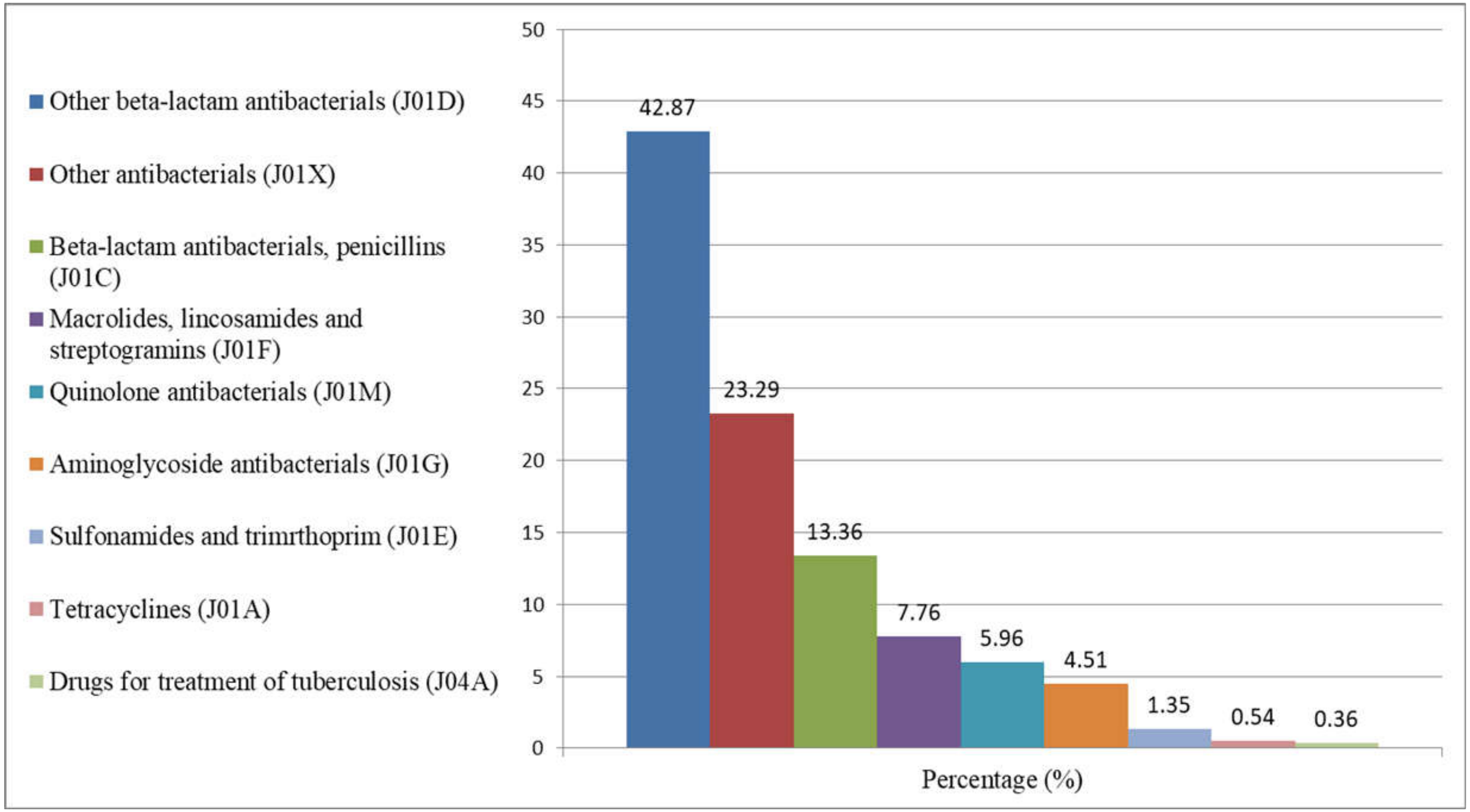


Figure 6

Distribution of the ATC classification of antibiotic groups.



3.4 Cost analysis of medications and antibiotics

The total cost of all prescribed medicines within the four months was 570,918 ILS (167,471 USD). The average cost per prescription (CPP) was 1,333 ± 2,539 ILS (392 ± 744 USD) with a range from 25 to 22,357 ILS. The total cost of all prescribed antibiotics was 402,693 ILS (118,124 USD), which constituted 70.53% of the total cost of all prescribed drugs. The average antibiotic cost per prescription (ACPP) was 940 ± 1,888 ILS (276 ± 553 USD) with a range from 9 to 19,030 ILS, (Table 1).

Table 1

Cost analysis of medications and antibiotics.

The cost		ILS	USD
The total cost of all prescribed medicines		570,918	167,471
CPP	Minimum	25	7.4
	Maximum	22,357	6,575
	Mean	1,333	392
	SD	2,539	744
The total cost of all prescribed antibiotics		402,693	118,124
ACPP	Minimum	9	2.6
	Maximum	19,030	5,597
	Mean	940	276
	SD	1,888	553

CPP: cost per prescription, ACPP: antibiotic cost per prescription

Almost all antibiotics prescribed for inpatients were administered intravenously (IV) 94.63% (n = 405), the second route of administration was orally 5.14% (n = 22) and the last route of administration was topically 0.23% (n = 1).

The average duration of hospitalization and antibiotic use was 7.33 ± 8.19 days, with a maximum duration of 55 days and a minimum duration of one day (Table 2).

Table 2

Rout of administration and duration analysis of medications and antibiotics.

Variables		Frequency (n = 428)	Percentage %
The route of administration	Intravenously	405	94.63%
	Orally	22	5.14%
	Topically	1	0.23%
The duration of hospitalization (day)	Minimum	1	
	Maximum	55	
	Mean	7.33	
	SD	8.19	

3.5 Association between antibiotic number and other variables

All prescriptions written out for inpatients were analyzed in terms of the number of antibiotics and divided into two groups: those with one or two antibiotics (60.9%) and those with three or more antibiotics (39.1%).

Accordingly, the percentage of one or two antibiotics per prescription at Alia Hospital was 60.9%, and 39.1% at the Palestinian Medical Complex. The percentage of three or more antibiotics per prescription at Alia Hospital was 49.7% and 50.3% at the Palestinian Medical Complex. In the comparisons of the NAPP, statistically significant differences were found between the two hospitals (p = 0.022), (Table 3).

Table 3

The number of antibiotics per prescription (NAPP) at the two hospitals.

		Name of Health Facility		
		Alia Hospital	Palestinian Medical Complex	Total
NAPP	One or two antibiotics	60.9% (*n* = 159)	39.1% (*n* = 102)	100% (*n* = 261)
	Three or more antibiotics	49.7% (*n* = 83)	50.3% (*n* = 84)	100% (*n* = 167)
		56.5% (*n* = 242)	43.5% (*n* = 186)	100% (*n* = 428)

When the NAPP was examined in terms of the physicians' specialties, the results were found as illustrated in Table 4. No statistically significant differences were found in the comparisons of the number of antibiotics per prescription with the physicians' specialties ($p = 0.116$).

Table 4

Distribution of the number of antibiotics per prescription (NAPP) with physicians' specialties

		Physicians' specialties									
		Internal medicine	GPs	General surgery	Gynecology	Pediatrics	Orthopedics	Urology	Neurology	ENT	Ophth.
NAPP	One or two antibiotics	17.6% (*n* = 46)	21.1% (*n* = 55)	18.0% (*n* = 47)	11.5% (*n* = 30)	7.3% (*n* = 19)	11.1% (*n* = 29)	8.0% (*n* = 21)	2.7% (*n* = 7)	1.9% (*n* = 5)	0.8% (*n* = 2)
	Three or more antibiotics	26.9% (*n* = 45)	16.8% (*n* = 28)	18.0% (*n* = 30)	9.0% (*n* = 15)	12.6% (*n* = 21)	6.6% (*n* = 11)	4.8% (*n* = 8)	3.6% (*n* = 6)	1.8% (*n* = 3)	0.0% (*n* = 0)
	Total	21.3% (*n* = 91)	19.4% (n = 83)	18.0% (*n* = 77)	10.5% (*n* = 45)	9.3% (*n* = 40)	9.3% (*n* = 40)	6.8% (*n* = 29)	3.0% (*n* = 13)	1.9% (*n* = 8)	0.8% (*n* = 2)

Also, the comparisons of the patients' age and gender with the number of antibiotics per prescription did not give out any statistically significant differences ($p = 0.257$), ($p = 0.522$) respectively (Tables 5,6).

Table 5

Distribution of the number of antibiotics per prescription (NAPP) with patients' age

		Patients' Age (year)			
		18 or less	18-64	65 or more	Total
NAPP	One or two antibiotics	21.8% (*n* = 57)	60.2% (*n* = 157)	18.0% (*n* = 47)	100.0% (*n* = 261)
	Three or more antibiotics	21.0% (*n* = 35)	54.5% (*n* = 91)	24.6% (*n* = 41)	100.0% (*n* = 167)
Total		21.5% (*n* = 92)	57.9% (*n* = 248)	20.6% (*n* = 88)	100.0% (*n* = 428)

Table 6

Distribution of the number of antibiotics per prescription (NAPP) with patients' gender

		Patients' Gender		
		Male	Female	Total
NAPP	One or two antibiotics	52.9% (*n* = 138)	47.1% (*n* = 123)	100.0% (*n* = 261)
	Three or more antibiotics	49.7% (*n* = 83)	50.3% (*n* = 84)	100.0% (*n* = 167)
Total		51.6% (*n* = 221)	48.4% (*n* = 207)	100.0% (*n* = 428)

In comparisons of the diagnosis on prescriptions with the number of antibiotics per prescription (NAPP), statistically significant differences were found ($p = 0.006$), which means the diagnosis affects the NAPP.

Intra-abdominal infections and COVID-19 (SARS coronavirus) had a higher percentage of prescriptions that contained three or more antibiotics, while prophylaxis for surgical procedures and labor and gynecological infections had a higher percentage of prescriptions that contained one or two antibiotics (Table 7).

Table 7

Distribution of the number of antibiotics per prescription (NAPP) with the diagnosis on prescriptions.

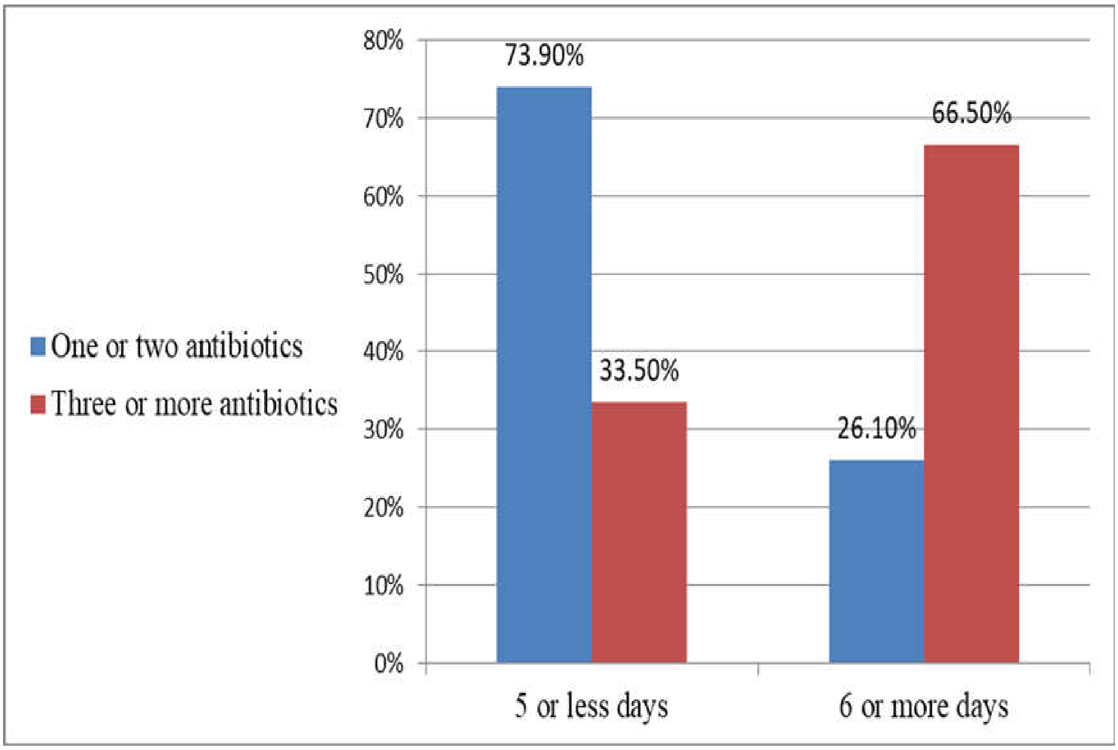
		Diagnosis on Prescriptions									
		Intra-abdominal infections	Prophylaxis for surgical procedures	Labor and gynecological infections	COVID-19 (SARS coronavirus)	Lower respiratory tract infections	Urinary tract infections	Osteomyelitis and arthritis	Upper respiratory tract infections	Traumatic skin and soft tissue infections	Others
NAPP	One or two antibiotics	17.2% (*n* = 45)	19.2% (*n* = 50)	14.2% (*n* = 37)	10.3% (*n* = 27)	8.8% (*n* = 23)	10.0% (*n* = 26)	5.4% (*n* = 14)	5.4% (*n* = 14)	1.5% (*n* = 4)	8.0% (*n* = 21)
	Three or more antibiotics	21.6% (*n* = 36)	11.4% (*n* = 19)	10.2% (*n* = 17)	15.6% (*n* = 26)	10.8% (*n* = 18)	6.6% (*n* = 11)	3.0% (*n* = 5)	3.0% (*n* = 5)	7.8% (*n* = 13)	10.2% (*n* = 17)
Total		18.9% (*n* = 81)	16.1% (*n* = 69)	12.6% (*n* = 54)	10.5% (*n* = 54)	9.6% (*n* = 41)	8.6% (*n* = 37)	4.4% (*n* = 19)	4.4% (*n* = 19)	4.0% (*n* = 17)	8.9% (*n* = 38)

When the durations of antibiotic therapy were analyzed in terms of the number of antibiotics per prescription (NAPP), the results were found as illustrated in Figure 7. A statistically significant difference was found in the comparison of the number of antibiotics per prescription with the durations of antibiotic therapy ($p < 0.001$)

About four-quarters of prescriptions containing one or two antibiotics were written when the hospitalization duration was five days or less. While two-thirds of prescriptions containing three or more antibiotics were written when the hospitalization duration was six days or more, this suggests that more antibiotics were used when patients were hospitalized for longer periods of time.

Figure 7

The relationship between the number of antibiotics prescribed per prescription (NAPP) and antibiotic therapy duration.



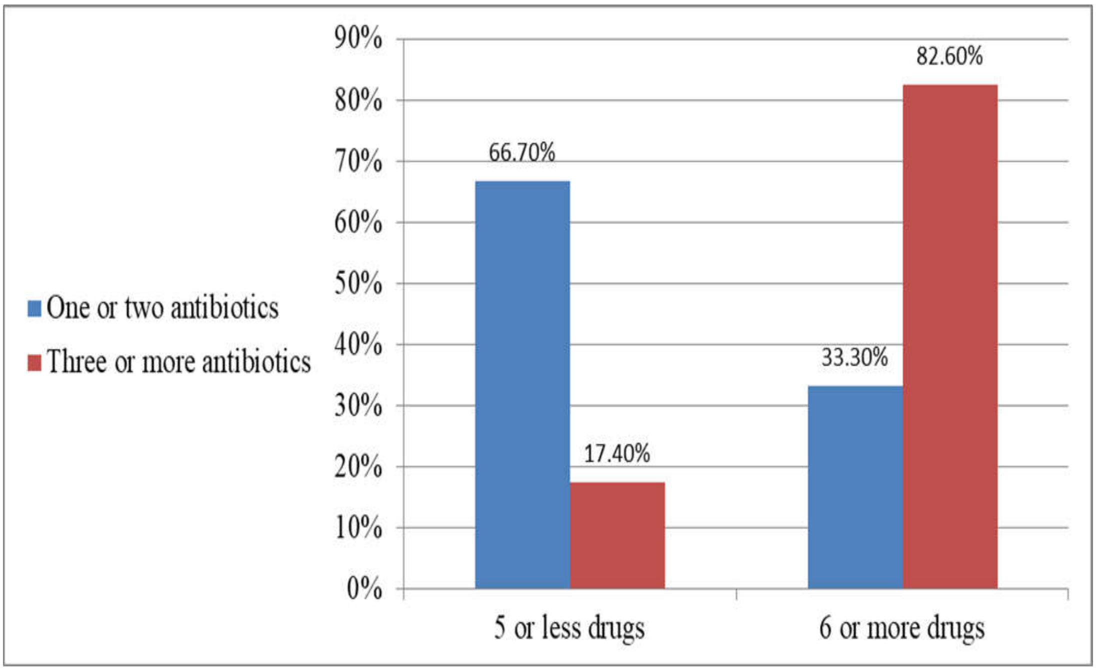
The last comparison was between the number of drugs per prescription (NDPP) and the number of antibiotics per prescription (NAPP). Statistically significant differences were found ($p < 0.001$), which means the NDPP affects the NAPP (Figure 8).

Accordingly, about two-thirds of prescriptions containing one or two antibiotics were written when the number of drugs per prescription (NDPP) was five or less. When the

NDPP prescribed six or more medications, about 83% of prescriptions containing three or more antibiotics were written. This shows that as the number of medications on the prescription increased, more antibiotics were given out.

Figure 8

Distribution of the number of antibiotics per prescription (NAPP) with the number of drugs per prescription (NDPP).



3.6 Comparison of infections and antibiotics use between two hospitals

Previously, in Table 3, we compared the number of antibiotics prescribed per prescription and discovered statistically significant differences (p = 0.022) between the two hospitals. The percentage of one or two antibiotics per prescription at Alia Hospital was 60.9% and 39.1% at the Palestinian Medical Complex. The percentage of three or more antibiotics per prescription at Alia Hospital was 49.7% and 50.3% at the Palestinian Medical Complex.

During the study period, in a comparison of the written diagnoses on prescriptions, we found that the distribution of the infections in the two hospitals was statistically significantly different (p < 0.001), (Table 8). Intra-abdominal and cardiac infections and COVID-19 (the SARS coronavirus) were predominant at the Palestinian Medical Complex, and labor or gynecological infections and using antibiotics for surgical prophylaxis were predominant at Alia Hospital.

Table 8

Distribution of the written infections in the two hospitals.

Diagnosis	Alia Hospital	Palestinian Medical Complex	Total
Intra-abdominal and cardiac infections	7.3%	11.4%	18.9%
Prophylaxis for surgical procedures	9.6%	6.5%	16.1%
Labor or gynecological infections	7.2%	5.4%	12.6%
COVID-19 (SARS coronavirus)	5.8%	6.5%	12.4%
Lower respiratory tract infections	4.7%	4.9%	9.6%
Urinary tract infections	5.6%	3.0%	8.6%
Osteomyelitis and arthritis	3.5%	0.9%	4.4%
Upper respiratory tract infections	3.7%	0.7%	4.4%
Traumatic skin and soft tissue infections	4.0%	0.0%	4.0%
Others	4.9%	4.0%	8.9%

The most frequently prescribed antibiotics were analyzed to compare their use in the two hospitals. Ceftriaxone and metronidazole did not show any statistically significant differences, while the use of vancomycin, amoxicillin/clavulanic acid, and cefuroxime showed statistically significant differences between the hospitals (Table 9).

Table 9

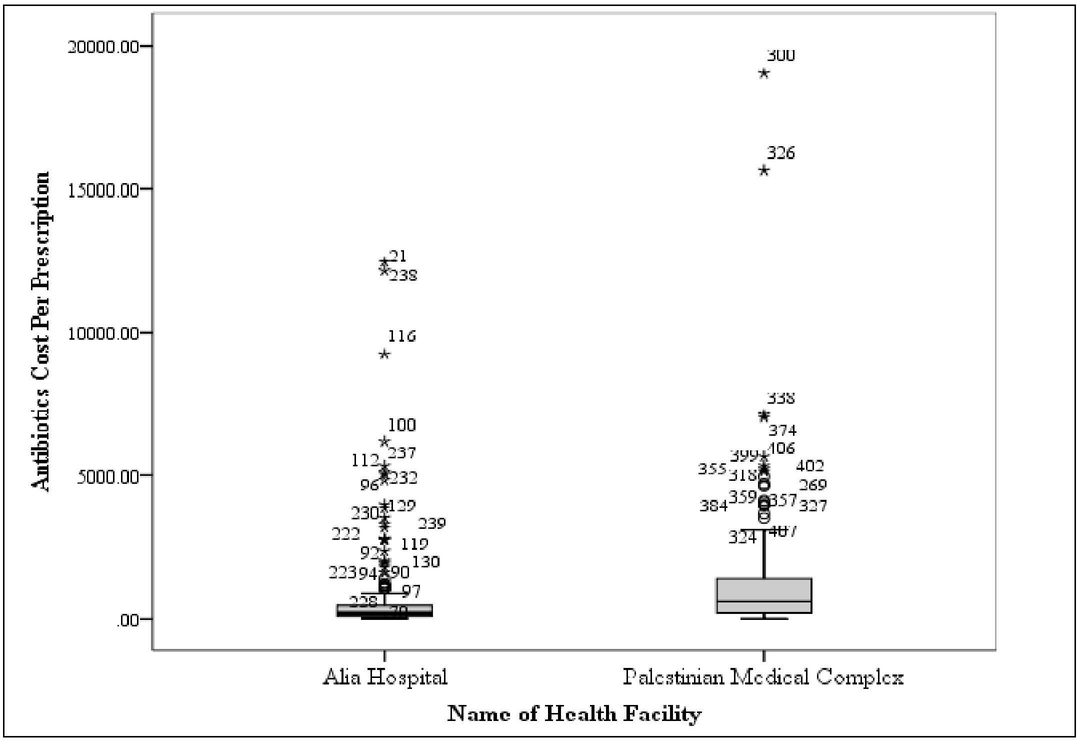
Distribution of the five most commonly prescribed antibiotics in the two hospitals.

Antibiotic (ATC Code)	Alia Hospital	Palestinian Medical Complex	*p* values
Ceftriaxone (J01DD04)	57.5%	42.5%	0.662
Metronidazole (J01XD01)	52.8%	47.2%	0.374
Vancomycin (J01XA01)	34.3%	65.6%	< 0.001
Amoxicillin + Clavulanic acid (J01CR02)	69.0%	31.0%	0.020
Cefuroxime (J01DC02)	68.2%	31.8%	0.038

Figure 9 shows that the antibiotics cost per prescription (ACPP) in the two hospitals were not normally distributed. So, we used the Mann-Whitney test to compare the results and found that the cost of antibiotics per prescription was significantly different between the two hospitals ($p < 0.001$); it was much higher in the Palestinian Medical Complex, median ($Q_1 – Q_3$) = 592 (198.8 – 1,409) ILS, while the median ($Q_1 – Q_3$) in Alia Hospital was 187 (94.3 – 452.3) ILS.

Figure 9

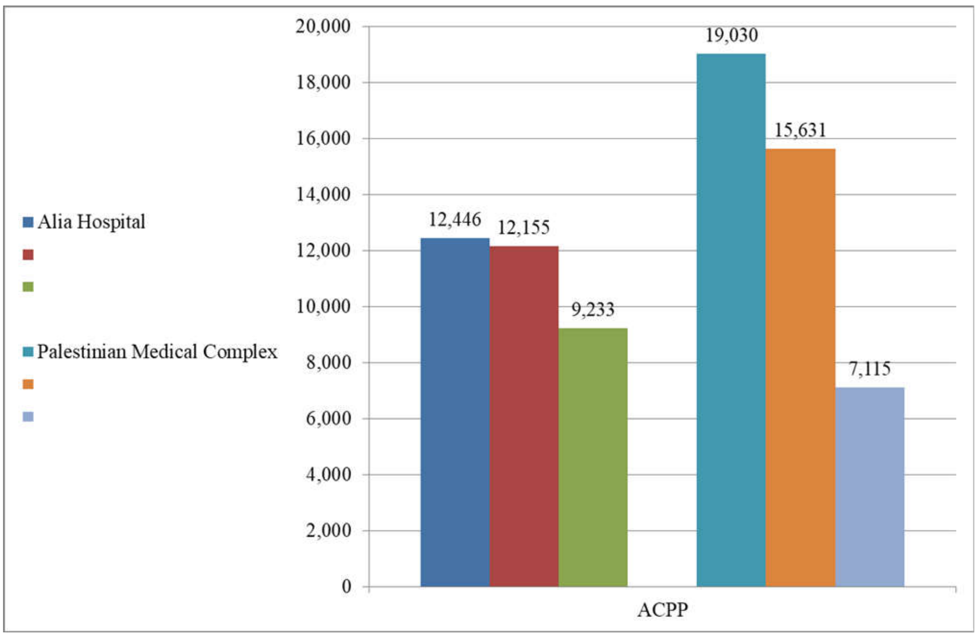
Distibution of antibiotic cost per prescription in the two hospitals.



Furthermore, the Palestinian Medical Complex had the highest antibiotics cost per prescription (19,030 ILS); Figure 10 shows the highest cost values in the two hospitals.

Figure 10

Highest values of antibiotics cost per prescription in the two hospitals.



Chapter Four

Discussions and Conclusions

4.1 Discussion

Evaluation of the prescriptions contributes to conducting effective strategies for the elimination of irrational use of antibiotics-related problems. This is the first study that did an in-depth analysis of the antibiotic utilization by two major governmental hospitals in Palestine. Data for this study (428 prescriptions from these hospitals in the West Bank) was collected and analyzed retrospectively. The mean age of patients identified in this study was 40.45 ± 25.47 years.

The current study revealed that males (51.6%) and females (48.4%) were almost equally likely to receive prescriptions for antibiotics. Other studies suggest that female patients may be receiving more antibiotics than male patients (64).

This study reflects the antibiotic prescribing attitudes of almost all groups of physicians, given the fact that 21.3% of the prescriptions were from internal medicine specialists and general practitioners (GPs) (19.4%), and most of the prescriptions were prescribed for intra-abdominal and cardiac infections (18.9%) and as prophylactic to prevent infections (16.1%). A point prevalence survey of antibiotic use in 18 hospitals in Egypt reported that antibiotics were mostly prescribed for surgical and medical prophylaxis (65), and two studies, one a point prevalence survey of antibiotic use in 26 Saudi hospitals in 2016 and another in Turkey to assess antibiotic prescribing at different hospitals and primary health care facilities, showed that the most frequent indication was respiratory tract infections (66, 67). Most likely, this is affected by the hospital wards included.

The average number of drugs per prescription (NDPP) is one of the drug utilization indicators (68). Our findings suggest that the NDPP was 6.72 ± 4.37, which was higher than the optimal value (1.6–1.8) according to the WHO in collaboration with the International Network of Rational Use of Drugs (INRUD) prescribing indicators. There was considerable over-prescribing of antibiotics, with the number of antibiotics per prescription (NAPP) of 2.61 ± 1.54 and a percentage of 38.9%, while the optimal value is (20.0–26.8%), (Table 10) (69, 70). Moreover, the rate of antibiotic prescribing in Palestine is less than that in some developing countries such as Egypt (59%), Jordan (78.2%), Northern Ireland (46.2%), Iran (68.2%), Latin American countries (54.6%), Kenya (84.8%), Turkey and Tunisia (65, 71-75). This may be connected to doctors' tendency for polypharmacy as well as certain patients' medications being written for many diagnoses. For instance, a widespread practice of prescribing analgesics, respiratory system medications, etc. in addition to antibiotics for infections may also be a contributing factor that affects the percentage of antibiotics prescribed (67). Thus, since the antibiotic prescribing rate is high in the inpatient settings in Palestine, applying interventions to improve that is necessary.

This study also indicates that the NAPP is affected by other variables: the name of healthcare facility ($p = 0.022$), the diagnosis on prescriptions ($p = 0.006$), the duration of antibiotic therapy ($p < 0.001$), and the number of drugs per prescription ($p < 0.001$). The diagnosis is likely to affect number of antibiotics because some infections require more than one antibiotic according to treatment guidelines to cover the likely pathogens. It is logical that an increased duration of hospitalization is associated with a higher number of antibiotics because that means the case is complicated or not responding. Also it is expected that higher numbers of medications are likely to include higher number of antibiotics.

Due to the COVID-19 pandemic, antibiotic prescriptions for both inpatients and outpatients have increased recently; 8% of COVID-19 patients had bacterial or fungal coinfection, according to a study, despite the fact that 72% of COVID-19 patients are getting broad-spectrum antibiotic therapy (76). In our study, 12.4% of antibiotic prescriptions were for the treatment of COVID-19 (the SARS coronavirus). This increase in consumption of antibiotics may cause a disastrous effect on resistance in the future.

However, given that 94.63% of antibiotics prescribed were in injectable form, this value was significantly higher than the optimal value (13.4-24.1%) (Table 10), this is much higher than other studies conducted in Ethiopia (22.39%), Indonesian hospitals (85%) (77, 78), and among children in Asia (88%), Latin America (81%), and Europe (67%) (79). Our findings support the view that physicians, in general, are inclined to prescribe parenteral antibiotics, especially for unconscious cases and in-patients. However, frequent injection use increases the risk of contracting blood-borne infections (68), and injections are always more expensive than a comparable oral formulation (80).

It is highly recommended to prescribe oral antibiotics if the case of the patient allows this or to change parenteral medications to oral when the patient's condition is better. It seems that intervention and educational programs are needed to encourage prescribers to use oral medications and antibiotics for inpatients according to the clinical condition and severity.

Table 10

WHO/INRUD prescribing indicators in Palestinian hospitals.

Indicator	Value	Optimal level
The average number of drugs per prescription	6.72	1.6–1.8
% prescriptions with an antibiotic	38.9%	20.0–26.8%
% prescriptions with an injection	94.63%	13.4–24.1%

The most common antibiotic classes prescribed in inpatient settings were "other beta-lactam antibacterials" (the cephalosporins), "other antibacterials" (glycopeptide antibacterials, polymyxins, imidazole derivatives, etc.) and "beta-lactam antibacterials" (penicillins). Furthermore, the most frequently prescribed antibiotics were ceftriaxone, metronidazole, and vancomycin, while the most commonly prescribed antibiotics in the surgical units of two Palestinian hospitals in 2012 were metronidazole, cefuroxime, and ceftriaxone (81).

In 76 countries between 2000 and 2015, penicillins, cephalosporins, quinolones, and macrolides were the most frequently used antibiotic classes (74). There are some variations in the consumption of different antibiotic classes, despite the fact that broad-spectrum penicillins, carbapenems, and polymyxins consumption has increased in high-, middle-, and low-income countries. For instance, usage of cephalosporins has increased in low-and middle-income countries while declining in high-income countries (74).

Also, in 41 countries in 2012, the most commonly prescribed antibiotics were very broad-spectrum ceftriaxone, cefepime, and meropenem (79).

In Saudi Arabia, the most commonly prescribed antibiotic group was third-generation cephalosporins (66). Similarly, another study conducted in Nigeria reported the same findings that the most frequently used antibiotics include third generation cephalosporins (mainly ceftriaxone) followed by a combination of penicillins (mainly amoxicillin with enzyme inhibitor) and fluoroquinolones (82). In Latin American countries, a study analyzing the use of antibiotics indicated that third-generation cephalosporins were the class of antibiotics most frequently used followed by carbapenems and fluoroquinolones (72). In China, the most prescribed antibiotics groups were cephalosporins, macrolides and fluoroquinolones (83). In Tanzania, the classes of antibiotics commonly prescribed were penicillins (amoxicillin), fluoroquinolones (ciprofloxacin), and nitroimidazoles (metronidazole) in that order (84). In Pakistan, ceftriaxone, metronidazole and cefotaxime were the top most frequently prescribed antimicrobials (85).

The mean duration of the antimicrobial treatment prescription was 7.33 ± 8.19 days, similar to a study conducted in Turkey (7 days) (67) and another one in France (8 days) (86), while the mean duration of antimicrobial treatment prescription in India was 5.24 days (87). According to a survey of American adults, the length of antibiotic therapy should be determined by a validated indicator of clinical stability (resolution of vital sign abnormalities, ability to eat, and normal mentation), and antibiotic therapy should be continued in general for at least 5 days after the patient reaches stability (88). The duration of antibiotic treatment varies according to the severity of the disease and the nature of the drug. Since there is no consensus on the optimal duration of therapy for the majority of infectious diseases, it is better to treat for at least 7-10 days. A short course of treatment may lead to antimicrobial-resistant microbes. At the same time, prolonged exposure increases the risk of adverse drug reactions, antimicrobial resistance, and also unwanted expenditure on antibiotics (87).

The cost of the prescribed medications is another key drug utilization indicator that is relevant and is thus used to evaluate the performance of the physicians' rational drug use (89). However, comparisons of antimicrobial agent utilization costs globally could be misleading because of the huge variations in the pricing of drugs. Our study indicated that the average cost per prescription (CPP) was equivalent to 392 ± 744 USD, and the average antibiotic cost per prescription (ACPP) was equivalent to 276 ± 553 USD, which constituted 70.53% of the total cost of all prescribed drugs. While in the Emergency Department of a tertiary care hospital in Saudi Arabia, the average cost of prescribed antibiotics was equivalent to 17.8 ± 11.6 USD only (90). Another study in the medical intensive care unit (ICU) of a tertiary care teaching hospital in Nepal showed that the average cost of antibiotics per patient was 47.67 ± 63.73 USD (91). A study in India reported that the average cost of antibiotics per patient in the ICU was 32.58 USD (92). In 2012, the total cost of antibiotic use over a one-month period in two Palestinian hospitals' surgical units was about 6,300 USD (81). However, on reviewing data on cost analysis from developed countries, it is found that the ICU antimicrobial agent costs per patient-day varied from 208 USD to 312 USD (93). It is very important to consider the cost of medications and to choose cheaper antibiotics if they cover the suspected microorganism or if results of culture and sensitivity show that they are enough.

In a comparison of the predominant infections between the two hospitals, they were statistically significantly different ($p < 0.001$). Intra-abdominal and cardiac infections and COVID-19 (the SARS coronavirus) were predominant at the Palestinian Medical Complex, and labor or gynecological infections and using antibiotics for surgical prophylaxis were predominant at Alia Hospital. Furthermore, the use of vancomycin, amoxicillin and clavulanic acid, and cefuroxime were statistically significantly different between the hospitals. The final comparison was the cost of antibiotics per prescription, and it was significantly different between the two hospitals ($p < 0.001$); it was much higher in the Palestinian Medical Complex. The differences in prescribing and cost may be explained by the differences in types of infections and reasons of antibiotic use. However, a more detailed review is needed to find the reasons of this high use and cost of antibiotics at the Palestinian Medical Complex.

Different variables, such as a lack of suitable drug use regulations, protocols, recommendations, and formulary books, may be responsible for the antibiotic usage pattern in this study. Inappropriate antibiotic monitoring and evaluation, microbial resistance, a lack of continuing medical education, polypharmacy, and a lack of clinical pharmacologists or clinical pharmacists are some of the other contributing factors that may result in the overuse and abuse of antibiotics in hospitals (94).

4.2 Strengths and limitations of the study

The strength of the study is in the analysis of the cost of medications and antibiotics which is done -to the best of our knowledge- for the first time in our country.

There are some limitations of this study. We explored the antibiotic utilization pattern over a period of 4 months; hence, the influence of seasonal variations on disease patterns and antibiotic utilization could not be considered. Our findings could not be generalized to the whole of Palestine and should not be extrapolated to the international environment. Indeed, antibiotic prescribing can be influenced by many factors, e.g. patient case-mix, prevalence of different types of infections, AMR patterns, and institutional factors. The findings do, however, add to a growing literature, particularly around medicine use and pharmaceutical health systems in developing countries.

4.3 Conclusions and recommendations

This study made a detailed assessment of the prescriptions containing antibiotics prescribed in hospitals in Palestine and gave some interesting findings about antibiotics. It has been concluded that the utilization of antibiotics and their cost in the public hospitals of Palestine are very high and potentially inappropriate. The most commonly prescribed antibiotic classes are the broad-spectrum ones. The most commonly prescribed antibiotic was ceftriaxone, and the most commonly encountered infections in inpatients were intra-abdominal infections. Intra-abdominal and cardiac infections and COVID-19 (the SARS coronavirus) were predominant at the Palestinian Medical Complex, and labor or gynecological infections and using antibiotics for surgical prophylaxis were predominant at Alia Hospital. Furthermore, the use of vancomycin, amoxicillin and clavulanic acid, and cefuroxime were statistically significantly different between the hospitals. The cost of antibiotics per prescription was significantly different between the two hospitals; it was much higher in the Palestinian Medical Complex.

The results of the study support the suggestion that continuous training and education programs for medical professionals about the rational use of antibiotics and injections and their subsequent pharmacoeconomic evaluation be established and monitored in order to make the necessary adjustments in prescribing sustainable. A feedback monitoring system for physicians' antibiotic prescriptions will greatly enhance their prescribing practices. Knowledge and compliance with updated clinical guidelines are also recommended to enhance rational prescribing. Having clinical pharmacists and infectious disease specialists in the wards may help.

Vaccination, hygiene, and sanitation; control of non-human use of antimicrobials; and the availability of routine antimicrobial susceptibility testing to provide information on resistance patterns, including emerging resistance, are essential for routine clinical practice and the development of effective policies against AMR (35, 95).

The inclusion of an antibiotic stewardship program is recommended to improve antibiotic use. One of the cornerstones of any national policy and the basis of a hospital's antimicrobial stewardship program (ASP) to optimize antimicrobial use and patient outcomes is antimicrobial stewardship (AMS), a coherent set of actions that promote the optimal use of antibiotics in ways that ensure sustainable access to effective therapy for everyone in need. In hospitals, ASPs help with infection control, quality improvement, medication, and patient safety (96, 97).

According to a systematic analysis released in 2015, the results of antimicrobial stewardship programs often fell into three categories: antibiotic use, patient outcomes, and economic outcomes. The majority of studies focused solely on antibiotic outcomes, with 68% reporting changes in antibiotic usage. Within the hospital, reductions in the length of stay and mortality were most frequently recorded. Regarding financial results, 62% of studies reported changes in antibiotic spending, and 37% of studies indicated overall cost reductions (98).

It is considered that this study will guide decision-makers to scale-up the rational use of antibiotics and reimbursement systems to provide sustainable services in the country.

There is strong evidence that interventions are successful in increasing compliance with antibiotic policies and shortening the course of antibiotic treatment. Less frequent use of antibiotics most likely does not increase mortality and shortens hospital stays. These findings are unlikely to be altered by additional trials contrasting antibiotic stewardship with no intervention. Instead, future studies should concentrate on selecting the most appropriate course of therapy, examining additional patient safety measurements, evaluating various stewardship interventions, and examining implementation challenges and opportunities (99).

List of Abbreviations

Abbreviation	Meaning
SPSS	Statistical Package for Social Sciences
NDPP	Number of Drugs Per Prescription
NAPP	Number of Antibiotics Per Prescription
CPP	Cost Per Prescription
ACPP	Antibiotics Cost Per Prescription
ABR	Antibacterial Resistance
AMR	Antimicrobial Resistance
WHO	World Health Organization
GPs	General Practitioners
PHCs	Public Health Centers
CDC	The Centers for Disease Control and Prevention
IRB	The Institutional Review Board
HIS	Health Information System
ATC	Anatomic Therapeutic Chemical
ILS	Israeli Shekel
USD	United States Dollar

References

European Parliament Directorate General for Internal Policies of the Union. Antibiotic resistance. Copenhagen,2006 [Available from: https://www.itas.kit.edu/downloads/etag_hoho06a.pdf.

Kislak JW, Razavi LM, Daly AK, Finland M. Susceptibility of pneumococci to nine antibiotics. The American journal of the medical sciences. 1965;250(3):261-8.

Sengupta S, Chattopadhyay MK, Grossart H. The multifaceted roles of antibiotics and antibiotic resistance in nature. Front Microbiol. 2013;4:47-.

Zaman SB, Hussain MA, Nye R, Mehta V, Mamun KT, Hossain N. A Review on Antibiotic Resistance: Alarm Bells are Ringing. Cureus. 2017;9(6):e1403.

Zhu Y, Huang WE, Yang Q. Clinical Perspective of Antimicrobial Resistance in Bacteria. Infection and drug resistance. 2022;15:735-46.

Zinner SH. Antibiotic use: present and future. New Microbiologica. 2007;30(3):321-5.

Coates AR, Halls G, Hu Y. Novel classes of antibiotics or more of the same? British journal of pharmacology. 2011;163(1):184-94.

Cantón R, Morosini MI. Emergence and spread of antibiotic resistance following exposure to antibiotics. FEMS microbiology reviews. 2011;35(5):977-91.

Durão P, Balbontín R, Gordo I. Evolutionary Mechanisms Shaping the Maintenance of Antibiotic Resistance. Trends in microbiology. 2018;26(8):677-91.

Centers for Disease Control and Prevention. Antibiotic-resistant gonorrhea: Centers for Disease Control and Prevention; [Available from: https://www.cdc.gov/std/gonorrhea/arg/default.htm.

Sharma A, Hill A, Kurbatova E, van der Walt M, Kvasnovsky C, Tupasi TE, et al. Estimating the future burden of multidrug-resistant and extensively drug-resistant tuberculosis in India, the Philippines, Russia, and South Africa: a mathematical modelling study. The Lancet Infectious Diseases. 2017;17(7):707-15.

Hoge CW, Gambel JM, Srijan A, Pitarangsi C, Echeverria P. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. Clinical Infectious Diseases. 1998;26(2):341-5.

Jevons MP. “Celbenin” - resistant Staphylococci. The BMJ. 1961;1(5219):124-5.

Lowy FD. Antimicrobial resistance: the example of Staphylococcus aureus. The Journal of clinical investigation. 2003;111(9):1265-73.

Frieri M, Kumar K, Boutin A. Antibiotic resistance. Journal of Infection and Public Health. 2017;10(4):369-78.

Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, et al. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. The Lancet Planetary health. 2021;5(12):e893-e904.

Quick J, Bremer K. Quality control of essential drugs. The Lancet. 1997;350(9084):1106.

Garau J, Xercavins M, Rodríguez-Carballeira M, Gómez-Vera JR, Coll I, Vidal D, et al. Emergence and dissemination of quinolone-resistant Escherichia coli in the community. Antimicrobial agents and chemotherapy. 1999;43(11):2736-41.

World Health Organization. The world medicines situation. World Health Organization; Geneva, Switzerland. 2004 [Available from: https://apps.who.int/iris/handle/10665/68735.

Ayoub SW, Musalam AH, Abu Mahadi AA. Drug utilization in primary healthcare centres in the Gaza Strip. Eastern Mediterranean Health Journal. 2017;23(10):649-56.

Machowska A, Stålsby Lundborg C. Drivers of irrational use of antibiotics in Europe. Int J Environ Res Public Health. 2018;16(1):27.

Worku F, Tewahido D. Retrospective assessment of antibiotics prescribing at public primary healthcare facilities in Addis Ababa, Ethiopia. Interdisciplinary Perspectives on Infectious Diseases. 2018;2018:4323769.

Adeiza SS, Shuaibu AB, Shuaibu GM. Random effects meta-analysis of COVID-19/S. aureus partnership in co-infection. GMS Hygiene Infection Control. 2020;15:Doc29.

Rawson TM, Ming D, Ahmad R, Moore LSP, Holmes AH. Antimicrobial use, drug-resistant infections and COVID-19. Nature Public Health Emergency Collection. 2020;18(8):409-10.

Gonzalez-Gonzalez C, López-Vázquez P, Vázquez-Lago J, Piñeiro-Lamas M, Herdeiro MT, Arzamendi PC, et al. Effect of physicians' attitudes and knowledge on the quality of antibiotic prescription: A Cohort Study. PLoS One. 2015;10(10):e0141820-e.

Md Rezal RS, Hassali MA, Alrasheedy AA, Saleem F, Md Yusof FA, Godman B. Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: a systematic review of the literature. Expert Review of Anti-infective Therapy. 2015;13(5):665-80.

Richards AR, Linder JA. Behavioral economics and ambulatory antibiotic stewardship: A narrative review. Clinical therapeutics. 2021;43(10):1654-67.

Ab Rahman N, Teng CL, Sivasampu S. Antibiotic prescribing in public and private practice: a cross-sectional study in primary care clinics in Malaysia. BMC infectious diseases. 2016;16:208.

Gualano MR, Gili R, Scaioli G, Bert F, Siliquini R. General population's knowledge and attitudes about antibiotics: a systematic review and meta-analysis. Pharmacoepidemiology and drug safety. 2015;24(1):2-10.

Teixeira Rodrigues A, Ferreira M, Piñeiro-Lamas M, Falcão A, Figueiras A, Herdeiro MT. Determinants of physician antibiotic prescribing behavior: a 3 year cohort study in Portugal. Current Medical Research and Opinion. 2016;32(5):949-57.

Cikes M, Vrdoljak L, Buljan I, Mudnic I, Vukojevic K, Medvedec Mikic I, et al. Students' Practices and Knowledge on Antimicrobial Usage and Resistance in Split, Croatia: The Education of Future Prescribers. Microbial Drug Resistance. 2020;26(6):623-9.

Yeika EV, Ingelbeen B, Kemah BL, Wirsiy FS, Fomengia JN, van der Sande MAB. Comparative assessment of the prevalence, practices and factors associated with self-medication with antibiotics in Africa. Tropical medicine & international health : TM & IH. 2021;26(8):862-81.

Alhomoud F, Aljamea Z, Almahasnah R, Alkhalifah K, Basalelah L, Alhomoud FK. Self-medication and self-prescription with antibiotics in the Middle East-do they really happen? A systematic review of the prevalence, possible reasons, and outcomes. International Journal of Infectious Diseases. 2017;57:3-12.

Alsayed AR, Darwish El Hajji F, Al-Najjar MAA, Abazid H, Al-Dulaimi A. Patterns of antibiotic use, knowledge, and perceptions among different population categories: A comprehensive study based in Arabic countries. Saudi Pharmaceutical Journal. 2022;30(3):317-28.

Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrobial Resistance & Infection Control. 2017;6:47.

Getahun H, Balkhy H. Global governance to tackle antimicrobial resistance: the way forward 2019 [Available from: http://resistancecontrol.info/2019-3/armed-conflicts-and-antimicrobial-resistance-a-deadly-convergence.

World Health Organization. Antibiotic resistance: Multi-country public awareness survey. 2015 [Available from:
https://apps.who.int/iris/bitstream/handle/10665/194460/97892415?sequence=1.

Sulis G, Adam P, Nafade V, Gore G, Daniels B, Daftary A, et al. Antibiotic prescription practices in primary care in low- and middle-income countries: A systematic review and meta-analysis. PLoS Med. 2020;17(6):e1003139-e.

Saleh N, Awada S, Awwad R, Jibai S, Arfoul C, Zaiter L, et al. Evaluation of antibiotic prescription in the Lebanese community: a pilot study. Infection ecology & epidemiology. 2015;5:27094.

Talaat M, Zayed B, Tolba S, Abdou E, Gomaa M, Itani D, et al. Increasing Antimicrobial Resistance in World Health Organization Eastern Mediterranean Region, 2017-2019. Emerging infectious diseases. 2022;28(4):717-24.

Sawalha AF, Sweileh WM, Zyoud SH, Al-Jabi SW, Bni Shamseh FF, Odah AA. Analysis of prescriptions dispensed at community pharmacies in Nablus, Palestine. Eastern Mediterranean Health Journal. 2010;16(7):788-92.

Abu-Taha A, Sweileh WM. Antibiotic resistance of bacterial strains isolated from patients with community-acquired urinary tract infections: an exploratory study in Palestine. Current clinical pharmacology. 2011;6(4):304-7.

Tayem YI, Qubaja MM, Shraim RK, Taha OB, Abu Shkheidem IA, Ibrahim MA. Non-steroidal anti-inflammatory drugs and antibiotics prescription trends at a central west bank hospital. Sultan Qaboos University medical journal. 2013;13(4):567-73.

Abu Taha A, Abu-Zaydeh AH, Ardah RA, Al-Jabi SW, Sweileh WM, Awang R, et al. Public knowledge and attitudes regarding the use of antibiotics and resistance: findings from a cross-sectional study among Palestinian adults. Zoonoses and public health. 2016;63(6):449-57.

World Health Organization. Using indicators to measure country pharmaceutical situations: Fact Book on WHO Level I and Level II Monitoring Indicators. 2006 [Available from: https://www.who.int/medicines/publications/WHOTCM2006.2A.pdf.

Belongia EA, Sullivan BJ, Chyou PH, Madagame E, Reed KD, Schwartz B. A community intervention trial to promote judicious antibiotic use and reduce penicillin-resistant Streptococcus pneumoniae carriage in children. Pediatrics. 2001;108(3):575-83.

Martínez-González NA, Coenen S, Plate A, Colliers A, Rosemann T, Senn O, et al. The impact of interventions to improve the quality of prescribing and use of antibiotics in primary care patients with respiratory tract infections: a systematic review protocol. BMJ open. 2017;7(6):e016253.

Broom A, Plage S, Broom J, Kirby E, Adams J. A qualitative study of hospital pharmacists and antibiotic governance: negotiating interprofessional responsibilities, expertise and resource constraints. BMC health services research. 2016;16:43.

Tan EC, Stewart K, Elliott RA, George J. Pharmacist services provided in general practice clinics: a systematic review and meta-analysis. Research in social & administrative pharmacy : RSAP. 2014;10(4):608-22.

Saha SK, Hawes L, Mazza D. Improving antibiotic prescribing by general practitioners: a protocol for a systematic review of interventions involving pharmacists. BMJ open. 2018;8(4):e020583.

Michaelidis CI, Fine MJ, Lin CJ, Linder JA, Nowalk MP, Shields RK, et al. The hidden societal cost of antibiotic resistance per antibiotic prescribed in the United States: an exploratory analysis. BMC Infection Diseases. 2016;16(1):655.

Jasovský D, Littmann J, Zorzet A, Cars O. Antimicrobial resistance-a threat to the world's sustainable development. Ups J Med Sci. 2016;121(3):159-64.

The Review on Antimicrobial Resistance Review on antimicrobial resistance tackling a crisis for the health and wealth of nations. London, United Kingdom; 2014.

European Comission. AMR: A Major Europe and Global Challenge-Factsheet. 2017 [Available from: https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en.

Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States, 2013. Atlanta, GA: U.S. Department of Health and Human Services; 2013 [Available from: https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services; 2019 [Available from: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.

Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022;399(10325):629-55.

Brandenburg K, Schürholz T. Lack of new antiinfective agents: Passing into the pre-antibiotic age? World journal of biological chemistry. 2015;6(3):71-7.

World Health Organization. Antimicrobial resistance: Library of National Action Plans; [Available from: https://www.who.int/teams/surveillance-prevention-control-AMR/national-action-plan-monitoring-evaluation/library-of-national-action-plans.

Steciwko A, Lubieniecka M, Muszyńska A. Antibiotics in primary care. Polski merkuriusz lekarski : organ Polskiego Towarzystwa Lekarskiego. 2011;30(179):323-6.

Dhingra S, Rahman NAA, Peile E, Rahman M, Sartelli M, Hassali MA, et al. Microbial Resistance Movements: An Overview of Global Public Health Threats Posed by Antimicrobial Resistance, and How Best to Counter. Frontiers in public health. 2020;8:535668.

Palestinian Central Bureau of Statistics. Estimated population in Palestine mid-year by governorate, 1997-2021 2021 [Available from: https://www.pcbs.gov.ps/pcbs_search.aspx?q=portals.

Lumini A, Nanni L. Convolutional Neural Networks for ATC Classification. Current pharmaceutical design. 2018;24(34):4007-12.

Schröder W, Sommer H, Gladstone BP, Foschi F, Hellman J, Evengard B, et al. Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis. The Journal of antimicrobial chemotherapy. 2016;71(7):1800-6.

Talaat M, Saied T, Kandeel A, El-Ata GA, El-Kholy A, Hafez S, et al. A point prevalence survey of antibiotic use in 18 hospitals in Egypt. Antibiotics (Basel, Switzerland). 2014;3(3):450-60.

Al Matar M, Enani M, Binsaleh G, Roushdy H, Alokaili D, Al Bannai A, et al. Point prevalence survey of antibiotic use in 26 Saudi hospitals in 2016. Journal of Infection and Public Health. 2019;12(1):77-82.

Mollahaliloglu S, Alkan A, Donertas B, Ozgulcu S, Akici A. Assessment of antibiotic prescribing at different hospitals and primary health care facilities. Saudi Pharmaceutical Journal. 2013;21(3):281-91.

World Health Organization. Promoting rational use of medicines : core components WHO Policy Perspectives on Medicines no5. WHO/EDM/2002.3. 2002 [Available from: https://apps.who.int/iris/handle/10665/67438.

Atif M, Sarwar MR, Azeem M, Umer D, Rauf A, Rasool A, et al. Assessment of WHO/INRUD core drug use indicators in two tertiary care hospitals of Bahawalpur, Punjab, Pakistan. Journal of pharmaceutical policy and practice. 2016;9:27.

Desalegn AA. Assessment of drug use pattern using WHO prescribing indicators at Hawassa University Teaching and Referral Hospital, south Ethiopia: a cross-sectional study. BMC health services research. 2013;13:170.

Elhajji FD, Al-Taani GM, Anani L, Al-Masri S, Abdalaziz H, Qabba'h SH, et al. Comparative point prevalence survey of antimicrobial consumption between a hospital in Northern Ireland and a hospital in Jordan. BMC health services research. 2018;18(1):849.

Levy Hara G, Rojas-Cortés R, Molina León HF, Dreser Mansilla A, Alfonso Orta I, Rizo-Amezquita JN, et al. Point prevalence survey of antibiotic use in hospitals in Latin American countries. Journal of Antimicrobial Chemotherapy. 2022;77(3):807-15.

Nabovati E, TaherZadeh Z, Eslami S, Abu-Hanna A, Abbasi R. Antibiotic prescribing in inpatient and outpatient settings in Iran: a systematic review and meta-analysis study. Antimicrobial resistance and infection control. 2021;10(1):15.

Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proceedings of the National Academy of Sciences of the United States of America. 2018;115(15):E3463-e70.

Nyabuti AO, Okalebo FA, Guantai EM. Examination of WHO/INRUD core drug use indicators at Public Primary Healthcare Centers in Kisii County, Kenya. Advances in pharmacological and pharmaceutical sciences. 2020;2020:3173847.

Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal coinfection in individuals with Coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clinical Infectious Diseases. 2020;71(9):2459-68.

Limato R, Nelwan EJ, Mudia M, de Brabander J, Guterres H, Enty E, et al. A multicentre point prevalence survey of patterns and quality of antibiotic prescribing in Indonesian hospitals. JAC-antimicrobial resistance. 2021;3(2):dlab047.

Mohammed SA, Faris AG. The pattern of medicine use in Ethiopia using the WHO core drug use indicators. BioMed research international. 2021;2021:7041926.

Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. Journal of Antimicrobial Chemotherapy. 2016;71(4):1106-17.

Atif M, Azeem M, Sarwar MR, Shahid S, Javaid S, Ikram H, et al. WHO/INRUD prescribing indicators and prescribing trends of antibiotics in the Accident and Emergency Department of Bahawal Victoria Hospital, Pakistan. SpringerPlus. 2016;5(1):1928.

Sweileh W, Adas S, Sawalha A, AbuTaha A. Utilization and cost of antibacterial drugs in 2 general surgery units in Palestine measured using anatomical therapeutic chemical classification and defined daily dose methodology. Eastern Mediterranean Health Journal. 2012;18(6):641-7.

Fowotade A, Fasuyi T, Aigbovo O, Versporten A, Adekanmbi O, Akinyemi O, et al. Point prevalence survey of antimicrobial prescribing in a Nigerian Hospital: findings and implications on antimicrobial resistance. West African journal of medicine. 2020;37(3):216-20.

Zhao H, Wei L, Li H, Zhang M, Cao B, Bian J, et al. Appropriateness of antibiotic prescriptions in ambulatory care in China: a nationwide descriptive database study. The Lancet Infectious Diseases. 2021;21(6):847-57.

Kilipamwambu A, Bwire GM, Myemba DT, Njiro BJ, Majigo MV. WHO/INRUD core prescribing indicators and antibiotic utilization patterns among primary health care facilities in Ilala district, Tanzania. JAC-antimicrobial resistance. 2021;3(2):dlab049.

Atif M, Azeem M, Saqib A, Scahill S. Investigation of antimicrobial use at a tertiary care hospital in Southern Punjab, Pakistan using WHO methodology. Antimicrobial resistance and infection control. 2017;6:41.

Guillemot D, Carbon C, Vauzelle-Kervroëdan F, Balkau B, Maison P, Bouvenot G, et al. Inappropriateness and variability of antibiotic prescription among French office-based physicians. Journal of clinical epidemiology. 1998;51(1):61-8.

Mugada V, Mahato V, Andhavaram D, Vajhala SM. Evaluation of prescribing patterns of antibiotics using selected indicators for antimicrobial use in hospitals and the Access, Watch, Reserve (AWaRe) classification by the World Health Organization. Turkish journal of pharmaceutical sciences. 2021;18(3):282-8.

Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. American journal of respiratory and critical care medicine. 2019;200(7):e45-e67.

Holloway K., van Dijk L. The World Medicines Situation 2011-Rational use of medicines. Geneva: World Health Organization; 2011 [Available from: http://narst.dmsc.moph.go.th/manuals/The%20World%20Medicines%20Situation%202011%20-%20Rational%20Use%20of%20Medicines.pdf.

Alanazi MQ, Salam M, Alqahtani FY, Ahmed AE, Alenaze AQ, Al-Jeraisy M, et al. An evaluation of antibiotics prescribing patterns in the emergency department of a tertiary care hospital in Saudi Arabia. Infection and drug resistance. 2019;12:3241-7.

Marasine NR, Shrestha S, Sankhi S, Paudel N, Gautam A, Poudel A. Antibiotic utilization, sensitivity, and cost in the medical intensive care unit of a tertiary care teaching hospital in Nepal. SAGE open medicine. 2021;9:20503121211043710.

Anand N, Nagendra Nayak IM, Advaitha MV, Thaikattil NJ, Kantanavar KA, Anand S. Antimicrobial agents' utilization and cost pattern in an Intensive Care Unit of a Teaching Hospital in South India. Indian Journal of Critical Care Medicine. 2016;20(5):274-9.

Weber RJ, Kane SL, Oriolo VA, Saul M, Skledar SJ, Dasta JF. Impact of intensive care unit (ICU) drug use on hospital costs: a descriptive analysis, with recommendations for optimizing ICU pharmacotherapy. Critical care medicine. 2003;31(1 Suppl):S17-24.

Horn E, Jacobi J. The critical care clinical pharmacist: evolution of an essential team member. Critical care medicine. 2006;34(3 Suppl):S46-51.

Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. The Lancet Infectious Diseases. 2005;5(8):481-93.

Dyar OJ, Huttner B, Schouten J, Pulcini C. What is antimicrobial stewardship? Clinical Microbiology and Infection. 2017;23(11):793-8.

Mendelson M, Morris AM, Thursky K, Pulcini C. How to start an antimicrobial stewardship programme in a hospital. Clinical Microbiology and Infection. 2020;26(4):447-53.

Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. Antimicrobial Resistance & Infection Control. 2019;8:35.

Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. The Cochrane database of systematic reviews. 2017;2(2):Cd003543.

Appendices

Appendix A

Ethical Approval of the Institutional Review Board (IRB)

An-Najah
National University
Faculty of medicine Sciences &
Health
Institutional Review Board

جامعة النجاح
الوطنية
كلية الطب وعلوم الصحة
لجنة اخلاقيات البحث
العلمي

Ref: Pharm. Nov. *2020/12*

IRB Approval Letter

Study Title:

"Assessment of Antibiotic Prescribing and Cost in Palestinian Hospitals"

Submitted by:
Rufida D. Manassrah.

Supervisor:
Rowa Al Ramahi

Date Approved:
11th Nov. 2020

Your Study Title **"Assessment of Antibiotic Prescribing and Cost in Palestinian Hospitals"** viewed by An-Najah National University IRB committee and was approved on 1th Nov. 2020

Hasan Fitian, MD

IRB Committee Chairman

An-Najah National University

IRB

نابلس - ص.ب 7 أو 707 || هاتف (970) (09)2342902/4/7/8/14 || فاكسميل (970) (09) 2342910

Nablus - P.O Box :7 or 707 | Tel (970) (09) 2342902/4/7/8/14 | Faximile (970) (09) 2342910 | E-mail : hgs@najah.edu

Appendix B

Ethical Approval of the Palestinian Ministry of Health

State of Palestine
Ministry of Health - Nablus
General Directorate of Education in Health

دولة فلسطين
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Ref.: ....
Date:..................

الرقم: ١٦٦٢/٣٠٥/٢٠٢١
التاريخ: ٩/٣/٢٠٢١

الأخ مدير عام الإدارة العامة للمستشفيات المحتــرم،،،
الأخ مدير مجمع فلسطين الطبي المحترم،،،
تحية واحترام،،،

الموضوع: تسهيل مهمة

يرجى التكرم بتسهيل مهمة الطالبة: رفيده مناصرة/ ماجستير صيدلة سريرية- جامعة النجاح، لعمل بحث التخرج بعنوان:

"**Assessment of Antibiotic Prescribing and cost in Palestine hospitals**"

حيث ستقوم الطالبة بجمع معلومات من خلال مراجعة ملفات المرضى (بوجود مسؤول الملفات)،

مع العلم أن مشرف الدراسة: د. رواء الرمحي.

وذلك في: **مستشفى الوطني - مستشفى عاليه -مجمع فلسطين الطبي**

على أن يتم الالتزام بجميع تعليمات وإجراءات الوقاية الصادرة عن وزارة الصحة بخصوص جائحة كورونا، وتحت طائلة المسؤولية.

على ان يتم تزويدنا بنسخة من نتائج البحث والتعهد بعدم النشر.

مع الاحترام،،،

د. عبد الله القواسمي
مدير التعليم الصحي والبحث العلمي

دولة فلسطين وزارة الصحة
الإدارة العامة للتعليم الصحي

نسخة : معالي وزيرة الصحة حفظها الله
: عميد كلية الطب وعلوم الصحة المحترم/ جامعة النجاح

P.O .Box: 14
Tel.:09-2333901

ص.ب. 14
تلفون: 09-2333901

Appendix C

Data Collection Form

Date:- ___________________

Name of Health Facility:- ___________________

Department:- ___________________

Patient Information

Patient Age:- ___________________

Patient Gender:- Male or Female

Medical Information

Distribution of the prescriptions by physicians' specialties		
General Practitioners (GPs)	Specialists	
		Pediatrics
		Otolaryngology
		Chest Diseases
		Internal Medicine
		Ophthalmology
		Gynecology and Obstetrics
		Urology
		General Surgery
		Emergency Medicine
		Dermatology
		Orthopaedics
		Neurology
		Others

Diagnoses on Prescriptions:- _________________

Number of Drugs on Prescription:- _________________

Number of Antibiotics on Prescription:- _________________

Antibiotics Prescribed

Antibiotics	**Drug Class**	**Dosage form**	**Dose**	**Duration**

Antibiotics Cost per Prescription:- _________________

Cost per prescription:_________________

جامعة النجاح الوطنية

كلية الدراسات العليا

تقييم وصف وتكلفة المضادات الحيوية في المستشفيات الفلسطينية

إعداد

رفيده داود محمود مناصره

إشراف

بروفيسور رواء الرمحي

قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في برنامج الصيدلة السريرية، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2022

تقييم وصف وتكلفة المضادات الحيوية في المستشفيات الفلسطينية

إعداد

رفيده داود محمود مناصره

إشراف

بروفيسور رواء الرمحي

الملخص

الخلفية: واحدة من أكبر المشاكل التي تواجه العالم اليوم هي ارتفاع معدلات الوفيات الهائلة الناجمة عن مقاومة البكتيريا للمضادات الحيوية في الالتهابات البكتيرية. العامل الرئيسي لمقاومة البكتيريا هو الاستخدام غير الرشيد للمضادات الحيوية. هدفت هذه الدراسة إلى تقييم وصف وتكلفة المضادات الحيوية في مستشفيين حكوميين رئيسيين في الضفة الغربية في فلسطين.

الطريقة: تم إجراء دراسة جماعية بأثر رجعي على 428 وصفة طبية للمرضى الداخليين تحتوي على مضادات حيوية من مستشفيين حكوميين رئيسيين في الضفة الغربية في فلسطين، من كانون الأول 2020 إلى آذار 2021، وتم تقييمها من خلال بعض مؤشرات استخدام الأدوية، وتم إجراء الإحصاء الوصفي باستخدام برنامج IBM-SPSS النسخة 21.

النتائج: بلغ عدد الأدوية لكل وصفة 6.72±3.37 , 38.9٪ من بين هذه الأدوية كانت مضادات حيوية. كان عدد المضادات الحيوية لكل وصفة طبية 2.61 ± 1.54. كانت تكلفة الوصفة الطبية 392 ± 744 دولارًا أمريكيًا، وتكلفة المضادات الحيوية لكل وصفة طبية 276 ± 553 دولارًا أمريكيًا. مجموعة المضادات الحيوية الأكثر شيوعًا هي "مضادات الجراثيم بيتا لاكتام الأخرى، السيفالوسبورينات" بنسبة (42.87٪)، بينما كانت المضادات الحيوية الأكثر شيوعًا هي سيفترياكسون (52.8٪) وميترونيدازول (24.8٪) وفانكومايسين (21.0٪). حوالي 19٪ من المضادات الحيوية الموصوفة لالتهابات داخل

البطن والقلب، تليها 16٪ تستخدم كوسيلة للوقاية من الالتهابات. تم إعطاء جميع المضادات الحيوية الموصوفة تقريبًا عن طريق الوريد بنسبة 94.63%، وكانت مدة العلاج بالمضادات الحيوية 7.33 ± 8.19 يوم. كما أشارت الدراسة إلى أن عدد المضادات الحيوية لكل وصفة طبية كان مختلفًا إحصائيًا بين المستشفيات ($p = 0.022$)، كما تأثر بمتغيرات أخرى مثل التشخيص ($p = 0.006$) والمدة الزمنية للعلاج ($p < 0.001$) وعدد الأدوية لكل وصفة طبية ($p < 0.001$). عند مقارنة الإصابات السائدة بين المستشفيين، كانت مختلفة إحصائيا بشكل كبير ($p < 0.001$). كانت التهابات داخل البطن والقلب وكوفيد-19 (فيروس كورونا) سائدًا في مجمع فلسطين الطبي، وكانت السائدة في مستشفى عالية هي الالتهابات النسائية واستخدام المضادات الحيوية للوقاية الجراحية. علاوة على ذلك، كان استخدام الفانكومايسين والأموكسيسيلين وحمض الكلافولانيك والسيفوروكسيم مختلفين إحصائياً بين المستشفيات. وعند مقارنة تكلفة المضادات الحيوية لكل وصفة طبية فقد كانت مختلفة بشكل كبير بين المستشفيين ($p < 0.001$)؛ حيث كانت أعلى بكثير في المجمع الطبي الفلسطيني.

الخلاصة: نمط وصف المضادات الحيوية في المستشفيات العامة في فلسطين يبدو غير مناسب ومكلف جدا ويحتاج إلى تحسين من خلال التعليم، واتباع الإرشادات، والتطعيم السنوي، وبرامج الإشراف. المضاد الحيوي الأكثر وصفًا هو سيفترياكسون، وأكثر أنواع العدوى شيوعًا عند المرضى الداخليين هي التهابات داخل البطن والقلب.

الكلمات المفتاحية: الاستخدام الرشيد للأدوية؛ المضادات الحيوية؛ الوصفات الطبية؛ تحليل التكلفة، مقاومة المضادات الحيوية.