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Antimicrobial Utilizing Pattern in a Governmental Hospital in Palestine Measured Using WHO ATC/DDD Methodology

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Dedication

DETECTED TO MY GREAT FATHER AND AFFECTIONATE MOTHER

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الإقرار

أنا الموقع أدناه موقع الرسالة التي تحمل العنوان:

Antimicrobial Utilizing Pattern in a Governmental Hospital in Palestine Measured Using WHO ATC/DDD Methodology

أقر بأن ما اشتملت عليه الرسالة هو نتاج جهدي الخاص، باستثناء ما تمت الإشارة إليه حيثما ورد، وأن هذه الرسالة ككل، أو أي جزء منها لم يقدم من قبل لنيل أي درجة أو لقب علمي أو بحثي لدى أي مؤسسة تعليمية أو بحثية أخرى.

Declaration

The work provide 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: **اسم الطالب:**

Signature: **التوقيع:**

Date: **التاريخ:**

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LIST OF SYMBOLES AND ABBREVIATIONS

AMR	Antimicrobial Resistance
ARMed project	Antimicrobial Resistance surveillance & control in the Mediterranean region project
ATC	Anatomical Therapeutic Chemical
DDD	Defined Daily Dose
DU90%	Drug Utilization 90%
ESAC	European Surveillance of Antimicrobial Consumption project
ICU	Intensive Care Unit
i.e.	That is
Inh.	Inhabitants
IRB	Institutional Review Board
MOH	Ministry of Health
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
NGOs	Non-Governmental Organizations
PMMS	Palestinian Military Medical Services
SARI	Surveillance of antimicrobial use and antimicrobial resistance in intensive care units
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
UNRWA	United Nations Relief and Work Agency
WHO	World Health Organization

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Abstract

BACKGROUND: Increased consumption of antimicrobial agents is related to a worldwide increased in bacterial resistance, increased costs and dispensable effects of drugs on patients.

OBJECTIVES: To investigate the pattern of antimicrobial consumption data using WHO ATC/DDD methodology in a governmental hospital in Palestine, and to assess the obstacles for implementing rational use of antimicrobial agents in hospital.

METHODS: Antimicrobials consumption in Rafidia hospital was retrieved prospectively. The ATC/ DDD and DU90% methodologies were used. Defined Daily Dose (DDD) per 100 Bed-Days and DDD per 1000 inhabitants per day were calculated for total systemic antimicrobial use and by antimicrobial class.

RESULTS: Antimicrobials were administered to 554 patients (55.4%) out of 1000 who were hospitalized in Rafidia hospital over two months period. The total consumption of antimicrobial agents was 1656.1 DDD that corresponding to 70.55 DDD/100 Bed-Days and 3.31 DDD/1000

Inhabitants/ Day. The most highly used antimicrobial were ceftriaxone followed by cefuroxime and metronidazole. The bulk prescription (DU90%) was made up of 8 out of 22 total antimicrobial agents. And the highest rates of antimicrobial use were found in intensive care unit (ICU) 132.64 DDD/100 Bed-Days and surgical department 98.52 DDD/100 Bed-Days.

CONCLUSIONS: We found that antimicrobial utilization in Rafidia hospital was relatively high, and there were a high tendency for wide-spectrum antimicrobial utilization such as third-generation cephalosporins, carbapenems and aminoglycosides. This study proved that there is an urgent demand for national antimicrobial stewardship and education programs in infection control and prevention in Palestinian hospitals.

Key words: Antibiotic, Consumptions.

CHAPTER ONE

INTRODUCTION

1.1 Background

Occupied Palestinian territories are located in the eastern Mediterranean region and consist of the West Bank and the Gaza Strip. Parts of the territories came under the Palestinian National Authority jurisdiction after Oslo Accords in 1993. Nablus is a city in the northern West Bank, approximately 49 kilometers north of Jerusalem, with a population of 129,132 (1).

The healthcare in Palestine provided by five main health services: Ministry of health (MOH), Palestinian Military Medical Services (PMMS), United Nations Relief and Work Agency (UNRWA), Non-Governmental Organizations (NGOs) and private for profit. The Ministry of health affords the massive burden, because they are in charge.

The hospital services have ameliorated in their facilities, technical and support services through years by giving continuous professional training and adding new departments and diagnostic equipments. There are 81 hospitals in Palestine; 51 in West Bank and 30 in Gaza Strip, with total number of 5,487 beds. Precisely in Nablus city, there are 6 hospitals with a total 525 beds, divided as two hospitals operated by MOH with 270 beds, other two hospitals by NGOs which contains 109 beds and the last two by the privet sector with 146 beds (2). The involved hospital in our study is Rafidia governmental hospital with 215 beds, served the population of Nablus district with surgical and medical services.

Hospitals in Palestine incurred lack of infection control and prevention programs, as well as lack of special guidelines for antimicrobial use (3). To the best of our knowledge, no studies were carried out regarding antimicrobial utilization regarding all the hospital departments in Palestine. However, two studies were carried out in the department level (3-4) and other studies were conducted in the community shows that there is an increase in the antimicrobial use and the antimicrobial resistance (5-8).

To assess and compare drug utilization, a drug classification system is needed to facilitate organizing those data in a uniform way. Most widely used and useful classification system is the Anatomical Therapeutic Chemical (ATC) / Defined Daily Dose (DDD) which is now used by the WHO Collaborating Centre for international drug monitoring in Europe (9). Defined Daily Dose (DDD) which is a unit based on the average daily used for main indication for consumption of certain medication (9). DDD methodology is standardized and allow best comparisons of antimicrobial drug usage between different antimicrobial drugs or between countries, regions and other health care settings, and to examine drug use over time and in different settings (9-10). The average number of DDDs per Bed-Days is used in hospital studies. A 'bed-day' is defined as the number of patients in hospital or each ward per day and is calculated by multiplying the number of admissions by the average length of stay (9). Other indicators for assessing the general quality of drug prescribing habits are the number of drugs accounting for 90% of drug use {the drug utilization

90% (DU90%)} (11). This method allows comparisons over time and between clinics, hospitals and different geographical regions and may serve to identify problem areas where educational intervention is necessary (11).

Antimicrobial resistance has become an important clinical and practical issue in the last two decades (12). The intensity of antimicrobial use in hospitals is known as probably the most substantial factor for antimicrobial resistance (13). Various initiatives encouraged hospitals to constitute an accurate surveillance of antimicrobial usage patterns for clinical and economical issues (13-17). To cope with this problem, many systems have been established to monitor and compare antimicrobial consumption by international professional societies. For instance, the European Surveillance of Antimicrobial Consumption {ESAC} project which collected antimicrobial consumption data from 35 countries and found wide variation in antibiotics consumption in hospitals; with a 3-fold range among countries (18).

The Mediterranean region; applies to both the European and non-European countries, has been classified as a hyper-endemic area for multi bacterial resistance, in particular methicillin-resistant *Staphylococcus aureus* (MRSA) (19-20). The persistent increase in antimicrobial resistance has created concern that we are entering a “post-antibiotic era”, in which some bacterial infections will no longer be treatable (21).

1.2 Objectives

General objectives:

1. To measure antimicrobial consumption using WHO ATC/DDD methodology in Rafidia hospital departments.
2. To assess the obstacles for implementing rational use of antimicrobial agents in hospital.

Specific objectives:

1. To calculate DDD of each prescribed antimicrobial agent at the hospital level.
2. To calculate total DDD for antimicrobial agents prescribed in each departments.
3. To calculate DDD/100 Bed-Day.
4. To calculate DDD/1000 Inhabitants/Day.
5. To calculate DU90%.
6. To compare the usage of antimicrobial agents in Rafidia hospital with other hospital worldwide.
7. To compare the usage of antimicrobial agent with the microorganism susceptibility.

1.3 Significance

Estimation of the antimicrobial consumption using the WHO methodology will help us to compare the status of antimicrobial utilization with neighboring countries at the international level. Furthermore, the study will help drawing and implementing antimicrobial policy inside governmental hospitals through developing protocols for common infectious diseases. The study will introduce the concept of Defended Daily Dose (DDD) into academic and clinical research in Palestine. This study will also be a pilot study for national surveillance studies regarding antimicrobial utilization and resistance which will change the empiric therapy treatment for common diseases. The study will help policy makers pin point cost and money wastage in antimicrobial consumption and will help implement cost-effective policies in governmental hospitals.

CHAPTER TWO

LITRATURE REVIEW

Several studies were carried out worldwide regarding antimicrobial utilization in hospitals using Anatomical Therapeutic Chemical classification and Defined Daily Dose (ATC/DDD) methodology. And this is a comprehensive list of published articles since 2000:

1. A study carried out by Sweileh et al., (3) in Palestine about utilization and cost of antibacterial drugs in two general surgery units in Palestine measured using anatomical therapeutic chemical classification and defined daily dose methodology, found that the total consumption of antibacterial agents was 414.1 DDD and 591.5 DDD at Thabet and Rafidia hospitals respectively. These corresponded to 133.6 DDD/100 Bed-Days and 162.2 DDD/100 Bed-Days respectively, figures that were higher than those reported in surgical units in many other countries.

2. A study carried out by Sweileh et al., (4) in Palestine about utilization of anti-infective agents measured in “Defined Daily Dose” (DDD): A study in Palestine, found that the total amount of antibiotic agents prescribed was 38.99 DDD/100 Bed-Days. The most frequently prescribed antibiotics were cefuroxime, ceftriaxone and metronidazole with the percentage of 27.8%, 6.1% and 5.7% respectively. The DDD/patient/day was 0.4 compared to 1 DDD/patient/day as the optimum; therefore optimization of antibiotic therapy is important.

3. A study carried out by Kallel et al., (22) in Tunis about evaluation of the antibiotics consumption in a Tunisian university hospital, found that an

action of good practice should be targeted at the antibio-prophylaxis and should concern especially in prescription was frequently unjustified.

4. A study carried out by Thabet et al., (23) in Tunis about evolution of antibiotic consumption in an intensive care burn department, showed that antibiotic consumption and antibiotic resistance monitoring are important to control antibiotic effectiveness and to put up policies for good use and control of antibiotics.

5. A study carried out by Katakam et al., (24) in Libya about a retrospective study on antibiotic use in different clinical departments of a teaching hospital in Zawiya, Libya, concluded that an overuse of amoxicillin & clavulanic acid in contrast to other antibiotics. High pharmacological effectiveness against most local and systemic infections, low incidence of side effects, and the availability of many suitable dosage forms with different strengths was thought to be the reason that prescribers tended to prefer amoxicillin & clavulanic acid over other antibiotics. This study showed a need for microbiological investigation before treatment of infections. This also helps physicians to have a more precise idea about prescriptive patterns prevalent in the Libyan community.

6. A study carried out by Al-Tawfiq (25) in Saudi Arabia about changes in the pattern of hospital intravenous antimicrobial use in Saudi Arabia, 2006-2008, found that ciprofloxacin was the most frequently used antimicrobial. Therefore, policies are needed to improve prescribing.

7. A study carried out by Bozkurt wt al., (26) in Turkey about assessment of perioperative antimicrobial prophylaxis using ATC/DDD methodology, concluded that the quality of perioperative antimicrobial prophylaxis may be improved through better compliance with healthcare guidelines, close supervision and training activates. Also, surgical site infections and the cost of perioperative antimicrobial prophylaxis may be reduced through more appropriate antibiotic use, thus contributing to the national healthcare budget.

8. A study carried out by Evirgen et al., (27) in Turkey about the intensity of antibiotic usage in the university hospital and investigation of an inappropriate use of antibiotics, concluded that the ratio of an inappropriate antibiotic usage in our hospital is high and parallel to this, the antibiotic consumption ratio is excessive. It is necessary to share microbiology data and provide an adequate education to reduce the antibiotic consumption and enable a better and rational antibiotic consumption.

9. A study carried out by Saba et al., (28) in Turkey about surveillance of antimicrobial use in a Turkish university hospital, emphasized a positive correlation with nosocomial infections densities and the use of broad spectrum antimicrobials in ICUs. To use antimicrobials wisely we must implement a comprehensive education program together with infection control measures. A national program for antimicrobial usage may provide more precise data for inter-hospital comparisons.

10. A study carried out by Akalin et al., (29) in Turkey about application of ATC/DDD methodology to evaluate perioperative antimicrobial prophylaxis, found that the antimicrobial use density in perioperative antimicrobial prophylaxis (PAP) was elevated in the hospital. Antibiotic overuse is obviously observed in the postoperative period.

11. A study carried out by Hosoglu et al., (30) in Turkey about the effect of a restriction policy on the antimicrobial consumption in Turkey, showed that to have a significant reduction in antimicrobial prescribing, a new policy had to be implemented.

12. A study carried out by Arda et al., (31) in Turkey about short-term effect of antibiotic control policy on the usage patterns and cost of antimicrobials, mortality, nosocomial infection rates and bacterial resistance, concluded that antibiotic monitoring is one of the most important and significant trends to decrease expenditures and to prevent antibacterial resistance.

13. A study carried out by Ebrahimzadeh et al., (32) in Iran about utilization pattern of antibiotics in different wards of specialized Sari Emam university hospital in Iran, the study data shown a significant increase in prescribing of antibiotics.

14. A study carried out by Raveh et al., (33) in Israel about longitudinal surveillance of antibiotic use in the hospital, concluded that antibiotic prescribing was essential and increasing. To improve clinical and financial

outcomes and to put a suitable therapy of antibiotics, antimicrobial surveillance needs to be implemented.

15. A study carried out by Kitzes-Cohen et al., (34) in Israel about patterns of systemic antibiotic use in a tertiary hospital in Israel in the years 1999-2000, showed that ATC/DDD methodology represent interpretation of the patterns of antimicrobial use. Although hospital departments use and individual drugs use results were similar with several reports from European hospitals, the overall usage of antimicrobial was higher.

16. A study carried out by Gendel et al., (35) in Israel about antibiotic utilization prevalence: prospective comparison between two medical departments in a tertiary care university hospital, showed that clinical pharmacologist interference in the hospital led to obvious reducing in the antimicrobial use and expenditures. Data showed a significant statistical of the two involved unites in antimicrobial cost analyzes of DDD, DU90% and DC90% indexes.

17. A study carried out by Shalit et al., (36) in Israel about antibiotic use in 26 departments of internal medicine in 6 general hospitals in Israel: variability and contributing factors, found that there is a great diversity in the antibiotic use patterns through the internal medicine departments, that could not demonstrated to objective parameters. The implementation of antibiotic guidelines and further monitoring are needed to adjust antibiotic prescriptions.

18. A study carried out by Weinberger et al., (37) in Israel about correlation between candiduria and departmental antibiotic use; found that the incidence of candiduria in the in-patients was highly correlated to the departmental antibiotics used pattern. This result enhanced the policy of restricting broad-spectrum antibiotics use.

19. A study carried out by Krivoy et al., (38) in Israel, about antibiotic prescription and cost patterns in a general intensive care unit, concluded that to minimize the emergence of bacterial resistance and decrease expenses, an interventional programs should be performed and concentrate on infection control and rational antibiotic prescription.

20. A study carried out by Kritsotakis et al., (39) in Greece about surveillance of monthly antimicrobial consumption rates stratified by patient-care area: a tool for triggering and targeting antibiotic policy changes in hospital, concluded that the substitution of older penicillins and cephalosporins to newer broad-spectrum antibiotics, was observed in all hospital departments. Surveillance of antimicrobial consumption using the ATC/DDD system provided an obvious pattern of antimicrobial use. Stratification of rates allowed areas of interest to be specified and targeted antibiotic policy changes to be initiated.

21. A study carried out by Rafaniello et al., (40) in Italy about hospital consumption of antibiotics at the Policlinico Hospital of the Second University of Naples: results of retrospective data collection, found that

consumption data should be compared with information on prescriptions and costs so as to monitor more closely the consumption of antibiotics and thus rationalize their use with a view to reducing the phenomenon of bacterial resistance. Finally, it would be useful to launch a training program for the proper use of antibiotics in our University Hospital.

22. A study carried out by Malta et al., (41) in Italy about ethical aspects in the management of antibacterial agents utilization, showed that although the cases treated in the hospital have become more complex over the years, the DDD documented in our study are far too high with respect to the actual clinical needs. These findings point to a trend toward the practice of excessively defensive medicine. Greater responsibility among physicians and the promotion of primary and secondary measures of preventive hygiene are fundamental to reduce the prescriptive pressure, a goal that should also have beneficial effects on health-care costs.

23. A study carried out by Vaccheri et al., (42) in Italy about A 3 year survey on the use of antibacterial agents in five Italian hospitals, concluded that there was a significant increase in antibiotic usage and a high tendency for wide-spectrum antibiotics such as penicillins plus β-lactamase inhibitors, fluoroquinolones and third-generation cephalosporins. To rationalize the antibiotic usage in hospital, these outcomes could be the basis for educational initiatives.

24. A study carried out by Port et al., (43) in Italy about comparing neonatal and paediatric antibiotic prescribing between hospitals: a new algorithm to help international benchmarking concluded that this novel method has the potential to be a useful tool to provide antibiotic use comparator data and requires validation in a large prospective point prevalence study.

25. A study carried out by Mondain et al., (44) in France about an antibiotic stewardship program in a French teaching hospital, this program was implemented in the hospital in 1999, and strengthened in 2005, had found that the number of antibiotic prescriptions remained stable since 2005 at around 400 defined daily doses (DDD)/1000 patient-days. And the antibiotic stewardship program is well accepted by physicians and allows controlling antibiotic use in the hospital.

26. A study carried out by Bevilacqua et al., (45) in France about 15 years of antibiotic stewardship policy in the Nancy Teaching Hospital in France, assert that overall yearly cost of antibiotics dropped by 34% and consumption in DDD/1000 patient-day by 10%. This study proved that the implementation of antibiotic stewardship policy led to a considerable decrease in overall antibiotic consumption, modification in prescribing patterns and the use of inexpensive antibiotics.

27. A study carried out by Dumartin et al., (46) in France about antibiotic use in 530 French hospitals: Results from a surveillance network

at hospital and ward levels in 2007, showed that analysis of antibiotic consumption at the department level help hospitals to improve antibiotic usage pattern.

28. A study carried out by PlC et al., (47) in Switzerland about hospital antibiotic consumption in Switzerland: Comparison of a multicultural country with Europe, found that the total consumption of systemic antibiotics increased from 46.1 to 54.0 DDD/ 100 bed-days in the all hospitals between 2004-2008. Several differences' pattern in antimicrobial consumption was observed in European countries and Switzerland.

29. A study carried out by Grau et al., (48) in Spain about antibiotic consumption at 46 VINCat hospitals from 2007 to 2009, stratified by hospital size and clinical services, found that antibiotic consumption was higher in large hospitals than in medium-sized or small hospitals. Catalan hospital recorded an increase of 4.49% from 2007 to 2009, especially due to the rising use of carbapenems, cephalosporins, monobactams and the other antibiotic groups.

30. A study carried out by Meyer et al., (49) in German about surveillance of antimicrobial use and antimicrobial resistance in intensive care units (SARI): Antimicrobial use in German intensive care units, found that the study data serve as a benchmark to promote the quality of antimicrobial drug management and for international differentiation.

31. A study carried out by Meyer et al., (50) in Germany about surveillance of antimicrobial use and antimicrobial resistance in intensive care units (SARI): A summary of the data from 2001 through 2004, found that through a period of 4 years the consumption of antibiotic pattern stayed the same, (the mean were 1,321 DDD/1,000 patients day).

32. A study carried out by Haug et al., (51) in Norway about increased antibiotic use in Norwegian hospitals despite a low antibiotic resistance rate, showed that there was a substantial increase in total antibiotic use, and an even more pronounced increase in the use of broad-spectrum antibiotics, which seems unjustified considering the current low antibiotic resistance.

33. A study carried out by MacKenzie et al., (52) in Europe about relationship between the number of different antibiotics used and the total use of antibiotics in European hospitals, found that in European hospitals the quantitative and qualitative use of antibiotics were relatively high. To assess the restriction policies, whether it could decrease the consumption of antibiotics afterwards decrease the antibiotic resistance, interventional studies should be conducted.

34. A study carried out by Borg et al., (13) in Mediterranean region about antibiotic consumption in southern and eastern Mediterranean hospitals, suggests the necessity of antibiotic stewardship and prescribing approach, that be usable to the entire region.

35. A study carried out by Muraki et al., (53) in Japan about a nationwide surveillance of antimicrobial consumption and resistance to *Pseudomonas aeruginosa* isolates at 203 Japanese hospitals in 2010, concluded that a continuous surveillance program in Japan is necessary in order to evaluate the association among resistance, antimicrobial restriction and consumption. This is the first national surveillance study of antimicrobial consumption in Japan and data were collected 203 Japanese hospitals (a total of 91,147 beds). The total antimicrobial consumption was 15.49 DDDs/100 Bed-Days (median), with consumptions for penicillins, carbapenems, quinolones, and glycopeptides being 4.27, 1.60, 0.41, and 0.49, respectively.

36. A study carried out by Zhou et al., (54) in China about association between antibiotic use density and *Pseudomonas aeruginosa* resistance in surgical intensive care unit, showed that the percentage of the *Pseudomonas aeruginosa* strains resistant to antibiotics increased from 2009 to 2011. These data suggest that the increased consumption of broad spectrum antimicrobial agents is associated with the rising prevalence of antimicrobial resistant *Pseudomonas aeruginosa*.

37. A study carried out by Sharma et al., (55) in India about antibiotic prescribing in two private sector hospitals; one teaching and one non-teaching: A cross-sectional study in Ujjain, India, figured out that both hospitals show extensive antibiotic prescribing. High use of combinations of antibiotics in the non-teaching hospital might indicate pressure from

pharmaceutical companies. There is a need to formulate and implement, based on local prescribing and resistance data, contextually appropriate antibiotic prescribing guidelines and a local antibiotic stewardship program.

38. A study carried out by Pathak et al., (56) in India about surveillance of antibiotic consumption using the "focus of infection" approach in two hospitals in Ujjain, India conclude that the antibiotic consumption in the teaching hospital (95%) was higher than in the nonteaching hospital (90%). therefore, the using of ATC/DDD methodology together with the "focus of infection" approach, seems convenient for recognizing purposes for quality amelioration concerning patterns of antibiotic prescribing.

39. A study carried out by Kavar et al., (57) in India about antibiotic use density in medicine ICU in a tertiary care rural hospital of central India, found that total antibiotic use density was 287.9 DDD/100 patient-days. The high percentage of inappropriate use of antimicrobial raises concerns about the development and spread of drug resistance. Regular auditing of antimicrobial prescription and prescribers' education to improve prescribing patterns to prevent their inappropriate use and unnecessary cost to the patients are required.

40. A study carried out by Liew et al., (58) in Singapore about Surveillance of broad-spectrum antibiotic prescription in Singaporean hospitals: A 5-year longitudinal study, found that there was a considerable

increase, in most antibiotics usage, from an average of 233.12 to 254.38 DDD/1,000 inpatient-days in 2006- 2010. Compare to broad-spectrum consumption in European hospitals, the Singaporean hospital's consumption is much higher. There is an urgent need for a longitudinal surveillance of antibiotic consumption to set policies and interventions.

41. A study carried out by Morales et al., (59) in Chile about an evolution of use of antibiotics of restricted prescription and trend of bacterial susceptibility in Concepcion regional hospital, Chile, showed that a decrease in susceptibility of *Pseudomonas aeruginosa* to imipenem ($p = 0.038$) and *Klebsiella pneumoniae* to ciprofloxacin ($p = 0.021$). The total consumption of restricted antibiotic has significantly increased, especially among complex medical services. A significant decrease in bacterial susceptibility has been observed mainly in gram-negative bacilli. The monitoring of antimicrobial prescribing practices and local susceptibility patterns are essential to promote the rational use of antibiotics.

42. A study carried out by Polk et al., (60) in United State of America about measurement of adult antibacterial drug use in 130 US hospitals: Comparison of defined daily dose and days of therapy, found that DDD methods are useful for benchmarking purposes but cannot be used to conclude the number of “days of therapy” or “relative use” for antibacterial drugs.

43. (60)(60)(60)A study carried out by Rodrigues and Bertoldi (61) in Brazil about the profile of antimicrobial utilization in a private hospital, showed that the high consumption of antimicrobial during the studying period is the result of the absence of a policy for controlling the drugs prescribed in hospital and the lack of protocols of antimicrobial use. In order to control the antimicrobial consumption, the hospitals must assume a surveillance policy on the prescriptions of this drug group.

Other studies concerning the pattern of antimicrobial prescribing in Arab's region, such as;

1. A study carried out by Al-Azzam et al., (62) in Jordan about preoperative antibiotic prophylaxis practice and guideline adherence in Jordan, showed that physicians are aware of the importance of antimicrobial prophylaxis before surgical procedures. However, further efforts are needed to ensure the implementation of the standard surgical antibiotic prophylaxis guidelines in Jordanian hospitals.

2. A study carried out by Al-Momany et al., (63) in Jordan about adherence to international antimicrobial prophylaxis guidelines in cardiac surgery: demonstrates the need for quality improvement, indicated that adherence to international guidelines for antimicrobial prophylaxis is far from optimal in Queen Alia Heart Institute, leading to the inappropriate administration of many antibiotics. Developing local hospital guidelines, as well as giving the clinical pharmacist a central role in the administration,

monitoring, and intervention of antimicrobial prophylaxis may improve the current practice.

3. A study carried out by Azzam et al., (64) in Lebanon about a survey of antimicrobial prophylaxis for surgical procedures in Lebanese hospitals, conclude that antimicrobial prophylaxis in Lebanese hospitals was fairly adequate in terms of respecting indications for selected surgical procedures. Improvement could be made by reducing the duration of prophylaxis and avoiding the use of broad-spectrum antibiotics.

4. A study carried out by Saied et al., (65) in Egypt about antimicrobial resistance in pathogens causing nosocomial bloodstream infections in university hospitals, found that there is a high rates of β-lactamase resistance and methicillin-resistant *Staphylococcus aureus* were found in the three Egyptian university hospitals studied. This study highlights the need for strengthening infection prevention and control programs, monitoring antimicrobial resistance (37) at each facility, and developing policies for antibiotic use.

5. A study carried out by Hanssens et al., (66) in Qatar about antibiotic prescribing pattern in a medical intensive care unit, highlights the urgent need for updated empiric and treatment guidelines as well as the monitoring of the antibiotic usage.

6. A study carried out by Abu-Gharbieh and Fahmy, (67) in United Arab Emirates about adherence of surgical site infection guidelines in

cardiac surgery in a tertiary hospital in Dubai, United Arab Emirates, found that adherence to international antimicrobial prophylaxis guidelines for cardiac surgery were found to be suboptimal in the study hospital in Dubai. Various interventions are needed via developing local evidence-based protocols in collaboration with surgeons, and also to strengthen regulations for ensuring adherence to these guidelines.

CHAPTER THREE

METHODOLOGY

3.1 Study design and settings

This study was carried out in Rafidia hospital, a 215-bed governmental-affiliated institution, which serves the general population of Nablus district. The hospital departments that were enrolled for antimicrobial usage reviewing as shown in Table 1 were 8 departments: general surgery, subspecialist surgery (orthognathic surgery, neurological surgery, otorhinolaryngology surgery), urology, gynaecology and obstetrics, intensive care unit, burns department, orthopaedics, paediatric and neonates. Excluded from the study were these departments: emergency department, because the usage of antimicrobial was negligible, and ophthalmology department, because the antimicrobial for systemic use was negligible. The hospital had 10 pharmacists and pharmacy technicians.

The study was cross-sectional and was conducted over two months' period from November to December 2012. Each department was inducted for antimicrobial usage was reviewed for two sequential weeks.

Table 1: Background characteristics of Rafidia hospital.

Hospital characteristics	**No.**
Total beds (no.)	215
Hospital departments (no.)	8
Pharmacists and pharmacy technicians (no.)	10
Departments enrolled in the study	No of beds
Surgical & subspecialist surgery	36
Orthopaedics	20
Urology	25
Paediatrics	34
Neonate	33
Gynaecology & obstetrics	43
Intensive care unit	14
Burn	10

3.2 Data collection form

The researcher, a clinical pharmacist, observed the hospital departments daily and reviewed the patients' drug records. Data that were collected were: age; sex; diagnosis for what the drugs were given; hospital stay; the type of antimicrobial(s) prescribed and any changes in antimicrobial arrangement along with the dose, frequency, duration and route of administration. Antimicrobial therapy was followed from initiation, among potential modification, probable alteration from intravenous to oral therapy, until discontinuation of therapy. Data collection made after written approval from the Institutional Review Board (IRB) and the Ministry of Health to carry out the project.

The obstacles for implementing rational use of antimicrobial agents in the hospital was assessed using a questionnaire, that shown in Table 2, handed out to six physicians [pediatrician, two surgeons, orthopaedician, gynecologist and a burn specialist doctor], three clinical pharmacist and three nurses at Rafidia governmental hospital. A convenient sampling was used for selecting the participants. The questionnaire included questions about antimicrobial prescribing, antimicrobial resistance and what influence in antimicrobial prescribing in the last three years.

Table 2: Questionnaire about antimicrobial's prescribing during the last three years.

No.	Questions
1	During the past 3 years, have your prescribing of antibiotic increased or decreased or remained the same?
2	During the past 3 years, have your prescribing of antibiotics influenced (positively or negatively) by the drug policy of the Ministry of Health?
3	Do you think there is a serious antibiotic resistance problem in the hospital?
4	If there is such resistance, does it influence your antibiotic prescribing?
5	Is your antibiotic prescribing influenced by the demand of the patients' families or the patients' demand themselves?
6	Do you think there is an overuse of antibiotics in the hospital settings?
7	Based on your experience, how much you can decrease in the antibiotic use without affecting the therapeutic outcome?
8	During the past 3 years, have you prescribed "un-necessary antibiotics?
9	Is fear of infection a reason for prescribing "un-necessary" antibiotics?
10	Are the workload and hospital regulations a reason for you to prescribe "un-necessary" antibiotics?
11	Is the patient's sign and symptoms is the only criteria for prescribing antibiotics?

3.3 Indicators

Data were collected as Defined Daily Dose (DDD), according to Anatomic Therapeutic Chemical Classification system (ATC/DDD) (9). The DDD system is described by WHO Collaborating Center for Drug Statistics Methodology. Only antimicrobials for systemic use were included in the subsequent analysis. Other pharmaceutical form such as topical ophthalmological, dermatological or otolaryngological product did not included in the study. For easier comparison, amount of antibiotics (in gram) was converted to unit of Defined Daily Dose (DDD) which is a unit based on the average daily used for main indication for consumption of certain medication (9).

The following indicators were calculated:

1. DDD of each prescribed antimicrobial agent and the total DDD for antimicrobial agents prescribed in each departments. The DDD is assumed average maintenance dose per day for a drug used for its main indication in adults (68).

2. DDD per 100 Bed-Days. A bed-day was defined as the number of patients in the hospital or each ward per day and was calculated by multiplying the number of admission by the average length of stay. Typically, the days of admission and discharge were counted as one single day (9).

$$\text{DDD/100 Bed-Days} = \frac{\text{Total consumption in DDDs}}{\text{Total Hospital Stay}} \times 100$$

3. DDD per 1000 inhabitants per day. It provides a rough estimate of the proportion of the study population within a defined area treated daily with a particular drug or group of drugs (68). The covered inhabitants in Nablus district were 35730 populations in 2012 (1).

$$\text{DDD/1000 Inh./Day} = \frac{\text{Total consumption in DDDs}}{\text{Covered inhabitants x Days of data collection}} \times 1000$$

4. DU90% index was calculated by ranking the antimicrobial by volume of DDD, summing the DDD for these drugs and then determining how many drugs accounted for 90% of drug use (11).

Each drug prescribed was recorded using its generic name and ATC code. Hospital antimicrobial consumption was divided into nine main groups, which are shown in Table 3.

Table 3: ATC code for the antimicrobial agents used in Rafidia hospital during the study period (9).

ATC code	Antimicrobial group
J01C	Penicillins
J01CA	Penicillins with extended spectrum
J01CE	Beta-lactamase sensitive penicillins
J01CF	Beta-lactamase resistant penicillins
J01CR	Combination with Beta-lactamase inhibitors
J01D	Cephalosporins and carbapenems
J01DB	First-generation cephalosporins
J01DC	Second-generation cephalosporins
J01DD	Third-generation cephalosporins
J01X	Others including “glycopeptides & imidazole derivatives”
J01F	Macrolides antibacterial
J01G	Aminglycosides antibacterial
J01M	Quinolone antibacterial
J05A	Antivirals, Direct acting
J02A	Antimycotics
P01A	Antiprotozoals

3.4 Data Analysis

The data collected by the researcher were coded individually, then were entered and analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0 for windows. The continuous variables had been analyzed by descriptive statistics including means and standard deviations, while discrete variables had been analyzed by frequency statistics.

3.5 Ethical approval

All aspects of the study protocol, including access to and use of the patient clinical information, will be authorized by the IRB (Appendix 1) and the local health authorities (Appendix 2) before initiation of this study.

CHAPTER FOUR

RESULTS

4.1 Characteristics of the study sample

During the study period, a total of 1000 patients were admitted to Rafidia hospital and 554 (55.4%) received antimicrobial therapy. Details of characteristics of study sample are shown in Table 4. Further analysis focused only on those who received antimicrobial agents. Two hundred and ninety three (53.2%) were females and 259 (46.8%) were males. The mean (SD) age of the patients was 30.75 ± (21.59) year. The majority (91.3%) of patients were less than 65 years old. A total of 3370 antimicrobial agents had been administered. The total hospital stay of the patients was 2358 days and the mean (SD) length of hospital stay was 2.36 (3.12) days. Admission rate was highest in gynaecology & obstetrics department (29.7%), followed by the surgical department (32.1%). The lowest admission rate was at burn department (1.5%).

Table 4: Characteristics of study sample.

Characteristics of Admissions	
Patients admitted during study period (no.)	1000
Patients receiving antimicrobial agent (no. & %)	554 (55.4%)
Total "Hospital stay" during study period (no.)	2358
Mean (SD) length of hospital stay	2.36 (3.12)
Characteristics of patients received antimicrobial	
Male no. (%)	259 (46.8%)
Female no. (%)	295 (53.2%)
Mean (SD) age (years)	30.75 (21.59)
Type of admissions	**Percentage (%)**
Gynaecology & obstetrics	29.7
Surgical	23.1
Paediatrics	16.1
Subspecialist surgery$^{\infty}$	10.6
Orthopaedics	7.8
Urology	6.1
Neonates	2.5
ICU	2.3
Burns	1.5

ICU: intensive care unit; SD: standard deviation.

$^{\infty}$: orthognathic, neurological & otorhinolaryngology surgery

4.2 Consumption of antimicrobial agents measured by DDD in the studied departments.

As shown in Table 5 and 6, the total consumption of antimicrobial agents at the studied departments at Rafidia hospital was 1656.1 measured as Defined Daily Dose (DDD). This value corresponds to 70.55 DDD/100 Bed-Days and 3.31 DDD/1000 Inhabitants/ Day. The bulk consumption of J01 classes, that is a therapeutic subgroup of the Anatomical Therapeutic Chemical (ATC) system for antimicrobial agents for systemic use, was for cephalosporines & other B-lactamse class 42.11 DDD/100 Bed-Days. While the usage of quinolones and macrolides were slightly low 2.02 and 1.47 DDD/100 Bed-Days respectively. The highest DDD was for ceftriaxone that had 401.27 DDD (i.e. 17.37 DDD/100 Bed-Days), followed by cefuroxime 401.23 DDD (i.e. 17.01 DDD/100 Bed-Days) and metronidazole 326.19 DDD (i.e. 13.83 DDD/100 Bed-Days). While Acyclovir had the lowest 0.13 DDD (i.e. 0.0055 DDD/100 Bed-Days) preceded by vancomycin 0.25 DDD (i.e. 0.011 DDD/100 Bed-Days).

Table 5: Prescribing indices.

Prescribing indices	No.
Total DDD	1656.1
DDD/100 Bed-Days	70.55
DDD/1000 Inhabitants / Day	3.31

DDD: defined daily dose.

Table 6: Defined daily dose (DDD) and anatomical therapeutic chemical (ATC) code of all antimicrobial drugs used in Rafidia hospital.

ATC code	Antimicrobial Drugs	Total DDD no.	DDD/100 Bed –Day	DDD/1000 Inhabitants / Day	% Total DDD
J01DD04	Ceftriaxone	401.27	17.37	0.8022	24.229
J01DC02	Cefuroxime	401.23	17.01	0.8020	24.226
J01XD01	Metronidazole	326.19	13.83	0.6521	19.697
J01GB03	Gentamicin	112.89	4.79	0.2257	6.817
J01DB04	Cefazolin	76.40	3.24	0.1527	4.613
J01CA01	Ampicillin	66.95	2.83	0.1339	4.043
J01DH02	Meropenem	61.50	2.60	0.1229	3.714
J01MA02	Ciprofloxacin	47.60	2.01	0.0951	2.874
J01DD02	Ceftazidime	33.71	1.43	0.0674	2.036
J01FA01	Erythromycin	22.15	0.94	0.0443	1.337
J01CR02	Amoxicillin & Clavulanic acid	18.00	0.76	0.0359	1.087
J01CF02	Cloxacillin	17.25	0.73	0.0345	1.042
J01GB06	Amikacin	15.95	0.68	0.0319	0.963
J01CE01	Benzyl penicillin	15.70	0.67	0.0313	0.948
J01XA02	Teicoplanin	13.00	0.55	0.0259	0.784
J01FA10	Azithromycin	12.49	0.53	0.0249	0.754
J01DD01	Cefotaxime	9.51	0.40	0.0190	0.574
J02AC01	Fluconazole	1.50	0.064	0.0029	0.090
J01DB01	Cefalexin	1.43	0.060	0.0039	0.086
J01CA04	Amoxicillin	1.00	0.042	0.0019	0.060
J01XA01	Vancomycin	0.25	0.011	0.0005	0.015
J05AB01	Acyclovir	0.13	0.0055	0.0003	0.007
Total		**1656.1**	**70.55**	**3.31**	**100%**

ATC: anatomical therapeutic chemical; DDD: defined daily dose

There were 8 drugs in the DU 90% segment out of 22 drugs as shown in Figure 1. The DU90% index placed ceftriaxone in the first place with 401.27 DDD (24.229%). Cefuroxime came in second with 401.23 DDD (24.226%), followed by metronidazole and gentamicin with 326.19 and 112.89 DDD (19.697%, 6.817%) respectively.

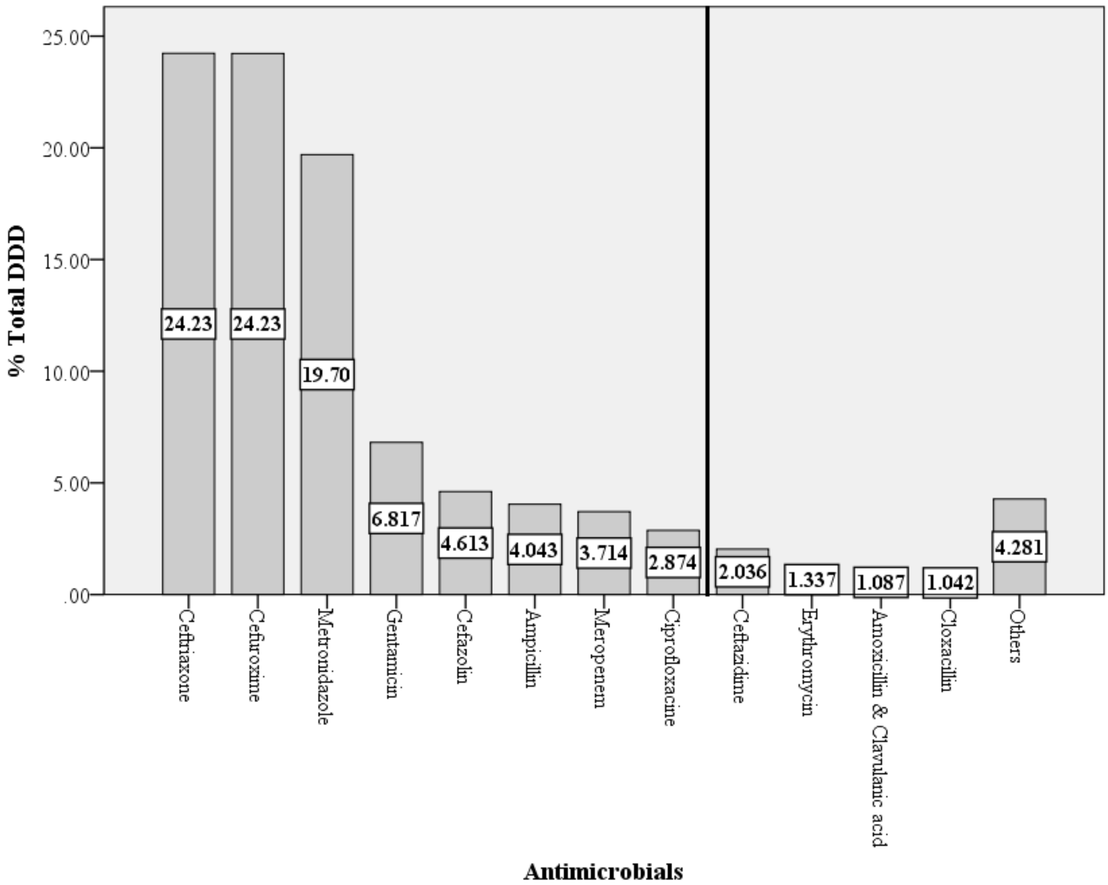

Figure 1: Percentage of total DDD of antimicrobial agents.

Others resemble the antimicrobials agents with less than 1% of total DDD. The reference line in the X-axis shows the DU90%.

4.3 Consumption of antimicrobial agents measured by DDD in each department.

Displays the total DDD of antimicrobial drugs used in every department in Rafidia hospital is shown in Table 8. The highest DDD/100 Bed-Days was for intensive care unit (ICU) with 132.64, followed by surgical department with 98.52 DDD/100 Bed-Days. However, the least antimicrobial used department was neonate department with no DDD/100 Bed-Days and preceded by burn department with 29.74 DDD/100 Bed-Days. Ceftriaxone was the most antimicrobial agent used in most of the departments in Rafidia hospital. Ceftriaxone usage in the urology departments was the highest with 59.64 DDD/100 Bed-Days. Cefuroxime was the second agent mostly used in the hospital and mainly was in the orthopaedics department.

Table 7: Defined daily dose (DDD) of antimicrobial drugs used in hospital's departments.

Hospital Department	Total DDD no.	DDD/100 Bed-Days	DDD/1000 Inhabitants / Day	Most used Antimicrobial in the Department	DDD/100 Bed-Days for antimicrobial agent
ICU	214.88	132.64	0.429	Ceftriaxone	30.86
Surgical	644.29	98.52	1.288	Cefuroxime Metronidazole	27.65 26.53
Urology	122.71	87.65	0.245	Ceftriaxone	59.64
Subspecialist surgery*	204.97	80.69	0.409	Ceftriaxone	40.55
Orthopaedics	185.03	79.75	0.369	Cefuroxime	35.02
Paediatrics	103.61	40.39	0.207	Ceftriaxone	9..98
Gynaecology & obstetrics	157.09	39.47	0.314	Cefuroxime	13.63
Burns	24.09	29.74	0.048	Ceftriaxone	11.73
Neonates	0.00	0.00	0.00	-----	----

DDD: defined daily dose; ICU: intensive care unit;
*: orthognathic, neurological & otorhinolaryngology surgery.

4.4 Obstacles

A questionnaire about antimicrobial prescribing during the last three years had been handed out to six physicians [pediatrician, two surgeons, orthopaedician, gynecologist and a burn specialist doctor], three clinical pharmacist and three nurses at Rafidia governmental hospital. This questionnaire was pertaining the prescribing, Influence, and resistance problems of the antimicrobial utilization in the hospital. After reviewing and segregation of the results that is shown in Table 9, we noticed that the results are constantly varied between the participants.

1. Two-thirds of physicians reported that the prescribing of antibiotics remained the same. While all clinical pharmacists and two-thirds of nurses reported that the prescribing of antibiotics had been increased.

2. Two-thirds of physicians and two-thirds of clinical pharmacists reported that the prescribing of antibiotics had been influenced positively by the drug policy of the Ministry of Health. While two-thirds of nurses reported that the prescribing had been influenced negatively by the drug policy of the Ministry of Health.

3. Two-thirds of physicians, all the clinical pharmacists and all nurses reported that there was a serious antibiotic resistance problem in the hospital.

4. Five-sixths of physicians, all clinical pharmacists and all nurses reported that the presence of antibiotic resistance problem influence on the prescribing of antibiotics.

5. Two-thirds of physicians, all clinical pharmacists and all nurses reported that the prescribing of antibiotics influenced by the patients' demand themselves.

6. All physicians, all clinical pharmacists and all nurses reported that there was an overuse of the antibiotics at the hospital.

7. Five-sixths of physicians, all clinical pharmacists and all nurses reported that they could decrease the antibiotics use without affecting the therapeutic outcome.

8. Two-thirds of physicians reported that they didn't prescribe un-necessary antibiotics. While all clinical pharmacists and all nurses reported that there were un-necessary antibiotics had been prescribed.

9. Regarding the last three questions, five-sixths of the physicians refused to answer.

10. All clinical pharmacists and all nurses reported that the fear of infection was the reason to prescribe un-necessary antibiotics.

11. All the clinical pharmacists and two-thirds of nurses reported that the workload and the hospital regulations were the reasons to prescribe un-necessary antibiotics.

12. Two-thirds of clinical pharmacists and two-thirds of nurses reported that the patient’s sign and symptoms were the only criteria for prescribing antibiotics.

Table 8: Results of the questionnaire.

Questions	Expected Results	Physicians [6]	Clinical Pharmacists [3]	Nurses [3]
During the past 3 years, have your prescribing of antibiotic increased or decreased or remained the same?	Increased	1	3	2
	Decreased	1	--	--
	Remained the Same	4	--	1
During the past 3 years, have your prescribing of antibiotics influenced (positively or negatively) by the drug policy of the Ministry of Health?	Positively	4	2	1
	Negatively	2	1	2
Do you think there is a serious antibiotic resistance problem in the hospital?	Yes	4	3	3
	No	2	--	--
If there is such resistance, does it influence your antibiotic prescribing?	Yes	5	3	3
	No	1	--	--
Is your antibiotic prescribing influenced by the demand of the patients' families or the patients' demand themselves?	Patients' family	--	--	--
	Patients' demand	4	3	3
	Both	2	--	--
Do you think there is an overuse of antibiotics in the hospital settings?	Yes	6	3	3
	No	--	--	--
Based on your experience, how much you can decrease in the antibiotic use without affecting the therapeutic outcome?	Yes	5	3	3
	No	1	--	--
During the past 3 years, have you prescribed "un-necessary antibiotics?	Yes	2	3	3
	No	4	--	--
Is fear of infection a reason for prescribing "un-necessary" antibiotics?	Yes	1	3	3
	No	--	--	--
Are the workload and hospital regulations a reason for you to prescribe "un-necessary" antibiotics?	Yes	1	1	2
	No	--	2	1
Is the patient's sign and symptoms is the only criteria for prescribing antibiotics?	Yes	1	1	2
	No	--	2	1

CHAPTER FIVE

DISCUSSION

Inappropriate use of antimicrobial agents participates to the emergence of bacterial resistance, therefore the ‘lifespan’ of antimicrobial agents may be minimized and the available treatment choices would be limited. Furthermore, antimicrobial resistance increases morbidity, mortality, health care costs, rate of nosocomial infections and antimicrobial drug toxicity and interactions. Inappropriate prescriptions of antimicrobial agents owing to suspension in the differential diagnosis, lack of experience or training, complex co-morbidities, lack of local epidemiology of antimicrobial resistance knowledge (14, 69-77). MacDougall and Polk (78) shows that the rise of antimicrobial resistance worldwide and the development of few new agents led to the development of antimicrobial stewardship programs that be more important than ever in ensuring the efficacy of available antimicrobials.

To the best of our knowledge; until today, in Palestine, no data were available on consumption of antimicrobial in all the hospitals departments. The only data available were on one department level (3-4). And there is few studies carried out in some of the Arabian countries, such as; Libya (24), Saudi Arabia (25) and Tunis (22-23), and there were some studies from Israel (33-34, 36). Data collected for this research on use of antimicrobials shown that consumption of amoxicllin was very low 0.042 DDD/100 Bed-Days and 0.67 DDD/100 Bed-Days for benzylpencillin, contrary to this, in Italy the first two ranks in antimicrobial consumptions were for amoxicillin and amoxicillin plus enzyme inhibitors (79). In 49

French hospitals, penicillin's were the most frequently prescribed antibiotics (80). Germany shows the same results (81). In our study cephalosporines consumption was 41.77 DDD/100 Bed-Days. This rate of usage is considered relatively high. This agent was used closed to zero in Denmark, less than 0.1 in Norway and 0.3 DDD/100 Bed-Days in Finland (82). While in Italy the third generation of cephalosporines consumption was 10.13 DDD/100 Bed-Days (42) and in Spain was 12.6 DDD/100 Bed-Days in 2009 (48). In this research there were no use of new macrolides (clarithromycin and roxithromycin) and few uses of azithromycin 0.53 DDD/100 Bed-Days, but consumption of erythromycin was reported with 0.94 DDD/100 Bed-Days. In Spain, macrolides (J01F) consumption was 3.66 DDD/100 Bed-Days in 2009 (48), and in Italy the consumption was 5.58 DDD/100 Bed-Days (42). Fluoroquinolones consumption in our study was low 2.02 DDD/100 Bed-Days, contrary to Italy that rank fluoroquinolones of the top five antimicrobial used in their hospitals (42), while in Spain it was the second high antimicrobial agent used in their hospitals with 12.92 DDD/100 Bed-Days in 2009 (48). The consumption of meropenem in our hiospital was relatively high (2.60 DDD/100 Bed-Days), so the use of meropenem should be strictly limited to remain susceptible. The consumption of aminoglycosides was relatively high also (5.46 DDD/100 Bed-Days). 2.72 DDD/100 Bed-Days the consumption in Spain 2009 (48) and 3.65 DDD/100 Bed-Days in Italy (42).

This wide variation in antimicrobial use may refer to the presence of multi-bacterial resistance in Palestine. Also, the Palestinian hospitals depend on the donations from local pharmaceutical companies or European countries that decrease the choices for antimicrobial selection. Another potential reason is that the physicians prefer the usage of wide spectrum antibiotic.

Fluconazole, the only antifungal used in Rafidia hospital, had a low DDD/1000 Inhabitants/ Day (0.0026) compare with other countries, the country with the highest DDD/1000 Inhabitants / Day was Greece (1.120) and the lowest DDD/1000 Inhabitants/ Day was for Malta (0.04) (18). About antiviral, acyclovir, its DDD/1000 Inhabitants/ Day was 0.0003, while the country with the highest DDD/1000 Inhabitants/ Day was France (3.53) and the lowest DDD/1000 Inhabitants/ Day was for Croatia (0.32) (18).

Compare with worldwide hospitals usage of antimicrobial expressed in DDD/1000 Inhabitants/Day from the European Surveillance of Antimicrobial Consumption {ESAC} project (18). The consumption of macrolides (J01F), quinolones (J01M) and penicillin (J01C) in Rafidia hospital were the lowest, while the consumption of other antibiotics (J01X) group (that contains: metronidazole, teicoplanin and vancomycin) and cephalosporines (J01D) were the highest among other hospitals.

The most commonly used agent, according to the DDD and DU90% indexes, were ceftriaxone, followed by cefuroxime and metronidazole. The number of antibacterial agents which accounted for DU90% index was eight. This small number was due limited variety of antimicrobials available in Rafidia hospital during the research period. And this is owing to the dependence of the Palestinian Ministry of Health on donations from local pharmaceutical companies or European countries has led to intensive use of similar kinds of antimicrobial agents for potentially different types of infections or procedures.

Antimicrobial utilization in Rafidia hospital measured using DDD/1000 Inhabitants/Day was 3.31. While in Libya, the total DDD/1000 Inhabitants/ Day was 30.0 in 2008 and increased to 64.2 in 2009 (24). The European Surveillance shows that Cyprus had the highest DDD/1000 Inhabitants/Day with 34.45, while the other involved countries' DDD/1000 Inhabitants/Day range between 3.33- 1.26 (18).

Table 10 shows a comparison of our results of antimicrobial utilization with that reported in similar studies from other countries. A previous study at Rafidia surgical department indicated that utilization of antimicrobial agents reached 162.2 DDD/100 Bed-Days (3). This is higher than reported in the surgical department in our study; this may refer to the presence of a clinical pharmacist in the surgical department after a direct recommendation of the previous researcher. The consumption of antimicrobials agent in our hospital was 70.55 DDD/100 Bed-Days in the studied departments, that is lower than those reported from hospitals in Israel (33, 36) in Turkey (27) and in Iran (32).

ARMed project assessed the antimicrobial use in 25 hospitals from the southern and eastern Mediterranean countries of Cyprus, Egypt, Jordan, Lebanon, Malta, Tunisia and Turkey. The overall antibiotic consumption varied from 45 to 836 DDD/100 Bed-Days with a median of 112 DDD/100 Bed-Days (13). The antimicrobial consumption in Rafidia hospital is within the ARMed project results. And as Borg et al., (13), a member in the ARMed project, concluded that there may not an excessive difference in the total quantity of antibiotic use in the Mediterranean region hospitals from the neighboring countries, and there was an obvious concentration on the use of wide-spectrum agents. This may bring about that reliance on broad-spectrum antibiotics could be a cause of antimicrobial resistance problems.

Table 9: Comparison of antimicrobial utilization with other countries.

Country \ DDD/100 Bed-Days	Year	Burn	Gynecology & Obstetrics	Urology	Orthopedic	ICU	Subspecialist surgery	Pediatric	Surgical	Total
Palestine (Our Study)	2012	29.74	39.47	87.65	79.75	132.64	80.69	40.39	98.52	70.55
Palestine (3)	2010									
Rafidia Hospital									162.2	
Thabeat Hospital									133.6	
Israel (33)	1998 -2000		68±32			232		65	149±39	124
Israel (36) **26 internal medicine**	2003 -2004									Mean±SD 79.9±16.6 Range (49.1-115.1)
Iran (32)	2000		117.4	116.6		178.10			121.67	95.37
	2005		147.2	84.10	131.3	278.99			107.26	124.00
Turkey (27)	2009		5.3	1.9	8.4	17.3	1.8		38.4	81.2
Switzerland (69)	2008									79.8

ARMed Project (13)	2004 -2005									Range: (45-836) Median 112
Italy (42)	2002					149.6		48.2	77.7	64.9
	2003					156.4		50.8	85.2	73.3
	2004					161.5		51.8	88.5	76.7
Spain (48)	2007					155.28			---	74.68
	2008					143.54			70.02	75.13
	2009					147.11			72.13	78.04
India (56) **Teaching Hospital**	2007	216.5	272	82						
Non-Teaching Hospital		127	195	123.5						

ARMed project: antimicrobial resistance surveillance & control in the Mediterranean region project; ICU: intensive care units; SD: standard deviation;.

Comparison of our results with bacterial susceptibility data that are shown in Table 11 and 12 elucidated that antimicrobial with low susceptibility on microorganisms have a higher DDD, for example; ampicillin DDD/100 Bed-Days was 2.83, while the Gram-positive bacteria susceptible to ampicillin around 9%. And it is vice versa with vancomycin, 0.011 DDD/ 100 Bed-Days had 100% susceptibility on Gram-positive bacteria. Ceftriaxone has 17.37 DDD/100 Bed-Days and its susceptibility on *Pseudomonas aeruginosa* was 64%. While amikacin's DDD/100 Bed-Days were 0.68 and its susceptibility on *Pseudomonas aeruginosa was 100%*.

Table 10: Percentage of susceptible Gram-positive bacteria to antibiotics (83).

Organism	Ampicillin	Penicillin	Oxacillin	Erythromycin	Ciprofloxacin	Tetracycline	Vancomycin	Gentamicin	Meropenem	Trimethoprim & Sulfamethoxazole	Chloramphenicol
Staphylococcus aureus (MSSA)(%)	**9**	**9**	**100**	**52**	**72**	**89**	**100**	**--**	**--**	**100**	**100**
Staphylococcus aureus (MRSA)(%)	**0**	**0**	**0**	**73**	**89**	**100**	**100**	**100**	**92**	**--**	**--**
DDD/100 Bed-days	**2.83**	**0.67**	**--**	**0.94**	**2.01**	**--**	**0.011**	**4.79**	**2.6**		

MRSA: Methicillin-Resistant *Staphylococcus aureus*; MSSA: Methicillin-Sensitive *Staphylococcus aureus*.

Table 11: Percentage of susceptible *Pseudomonas aeruginosa* to antibiotics (83).

Organisms	Amikacin	Ceftazidime	Ciprofloxacinn	Gentamicin	Ceftriaxone	Meropenem	Piperacillin	Ticarcillin
Pseudomonas aeruginosa (%)	100	96	94	90	64	96	96	90
DDD/ 100 Bed-Days	0.68	1.43	2.01	4.79	17.37	2.6	--	--

As shown in Table 13, *Escherichia coli* have low susceptibility in the common antibiotics as trimethoprim & sulfamethoxazole, piperacillin, naldixic acid and ampicillin. Abu Taha and Sweileh (5) reported also that the most frequent organism in the studied sample was *Escherichia coli* and had high resistance to first-line antibiotics, therefore meropenem and gentamicin use should be restricted to the most highly resistance bacteria.

Table 12: Percentage of susceptible Gram-negative bacteria to antibiotics (83).

Organsim	Ampicillin	Aztreonam	Ceftazidine	Ciprofloxacin	Naldixic Acid	Gentamicin	Cefotaxime	Cephalothin	Meropenem	Trimethoprim & Sulfamethoxazole	Piperacillin
Escherichia coli	19	67	70	63	36	80	66	0	100	26	27
Klebsiella pneumonia (%)	0	40	53	76	69	31	28	24	100	22	26
Enterobacter species (%)	0	28	35	81	42	54	21	16	100	19	16
DDD/ 100 Bed-Days	2.83	--	1.43	2.01	--	4.79	0.4	--	2.60	--	--

These findings have implications for local antimicrobial policies infection control. Comparison of data collected from Rafidia hospital with other hospitals in other countries showed consumption of antimicrobial was relatively high, and there was a marked preference for wide-spectrum antimicrobial utilization such as third-generation cephalosporins, carbapenems and aminoglycosides. Some of the obstacles for implementing rational use of antimicrobial agents attributed to lack of infection control and prevention programs, also the lack of special guidelines for antimicrobial use in the hospital. Bevilacqua et al., (45) concluded that by implementation of antimicrobial stewardship policy we could decrease in overall consumption of antibiotic significantly, change in prescribing patterns and switch towards the use of inexpensive antimicrobial agents. Another potential reason is that physicians do not depend on the microbiological cultures' results, but instead count on their clinical judgment in concurrence with the use of antimicrobial agents that have a broad spectrum activity. Also, the role of clinical pharmacist is absent in the hospital departments. Gendel et al., (35) showed that a clinical pharmacology specialist intervention in the hospital units was effective in reducing the use of antimicrobial and the cost. Other obstacles could be the personal preferences, local routines, fear of infection, workload and the hospital regulations, patients' family demands and differential patterns of risk-aversion.

CHAPTER SIX

CONCLUSIONS

6.1 Conclusions and perspectives

We found that antimicrobial utilization in Rafidia hospital was relatively high, and there were a high tendency for wide-spectrum antimicrobial utilization such as third-generation cephalosporins, carbapenems and aminoglycosides. This study proved that there is an urgent need for conduction surveillance studies of antimicrobial usage in all the Palestinian hospitals, to encourage the judicious use of antimicrobial for the treatment of infectious conditions, to slow the emergence of bacterial-resistance to drugs and to control expenditures.

However, there is a substantial need to conduct a national antimicrobial stewardship and educational programs in infection control and prevention in the Palestinian hospitals. These programs seek to optimize antimicrobial use in health care settings in order to improve patient care as well as reduce hospital costs and slow the spread of antimicrobial resistance. Many guidelines recommended the presence of a clinical pharmacist in such programs. And there is a clear evidence of the importance of the clinical pharmacist role in the health care settings.

6.2 Strengths and limitations

The main strength of this study is the well controlled and implemented designed ATC/ DDD methodology, which does not affected by patients variables, for example: age, gender and genetic polymorphisms. As well DDDs provide a fixed unit of measurement independent of price, currencies, package size and strength enabling the researcher to assess trends in drugs consumption and to perform comparisons between population groups. In the other hand, drug consumption data prescribed in DDDs only give a rough estimate of consumption and not an exact picture of actual use.

DDD methodology is standardized and allows best comparisons of antimicrobial drug usage between different antimicrobial drugs or between countries, rejoins and other health care settings, and to examine drug use over time and in different settings.

The DDD/100 Bed-Days has been used internationally in the comparison of in-hospital antibiotic use, and such data have been used to compare and throw light on national level of antibiotic use and resistance relationship.

Prescription data presented in DDDs per 1000 inhabitants per day may provide a rough estimate of the proportion of the study population treated daily with a particular drug or group of drugs.

The DU90% is simple method for assessing the quality of drug prescribing in routine health care. This method allows comparisons overtime and between clinics, hospitals and different geographical regions and may serve to identify problem areas where educational intervention is necessary.

The quantitative study shows the obstacles for implementing rational use of antimicrobial agents in the hospital, which will help in the design of the infection control and prevention programs that should be conducted in the Palestinian hospitals.

Overall, this study was subjected to a few limitations. The first limitation that this study was done in one hospital, thus the results might not be generalized to all hospitals in Palestine. In addition, this study was carried out over 2 months period, thus the prescribing pattern of antibiotics might differ among different months in a year.

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Appendix

Appendix(1)

Ministry of Health approval

السلطة الوطنية الفلسطينية
وزارة الصحة- نابلس
الإدارة العامة للتعليم الصحي

Palestinian National Authority
Ministry of Health - Nablus
General Directorate of Higher &
Continuning Education

الرقم: ١٦٥/١٧٩١/٢٠١٦
التاريخ: ١٦/١٠/٢٠١٥

Ref.: ………………
Date:………………

الأخ ق. أ. مديـــر عـــام الادارة العامـــة للمستشفيـــات المحتـــرم،،،

تحيـــة واحتـــرام،،،

<u>الموضـــوع: تسهيل مهمة طلاب – جامعة النجاح الوطنية</u>

تماشياً مع سياسة وزارة الصحة المتعلقة بتعزيز التعاون مـــع الجامعـــات والمؤسســـات الأكاديمية بإتاحة فرص التدريب أمام الطلبة والخريجين والباحثين في المؤسســـات الوطنيـــة وإسهاماً في تنمية قدراتهم.

يرجى تسهيل مهمة **الطالبة مارينا زياد البدا– برنامج ماجستير صيدلة سريرية – كلية الطب وعلوم الصحة/ جامعة النجاح الوطنية** في اجراء بحث بعنوان "نمط استخدام المضادات الحيوية في مستشفى الحكومي في فلسطين بمقياس WHO ATC/DDD" وذلك من بالسماح للطالبة بالاطلاع على ملفات المرضى ومقابلة المرضى والاستفسار عن معلومات تخص البحث وذلك في **مستشفى رفيديا – نابلس.**

مـــع الاحتـــرام،،،

د. أمل أبو عوض
ق. أ. مدير عام التعليم الصحي

Director General of Higher and Continuing Health Education Palestinian M.O.H

/ نسخة مدير دائرة الصيدلة المحترم/ جامعة النجاح الوطنية.

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Appendix(2)

Institutional Review Board (IRB) approval

بسم الله الرحمن الرحيم

An-Najah National University
Faculty of Medicine

جامعة النجاح الوطنية
كلية الطب

IRB Approval letter

Study title:
Antimicrobial Utilizing Pattern in a Governmental Hospital in Palestine Measured using WHO ATC/ DDD Methodology.

Submitted by:
Marina Z. Bada

Date Reviewed:
Sep 27, 2012

Date approved:
Oct 31, 2012

Your study titled " Utilizing Pattern in a Governmental Hospital in Palestine Measured using WHO ATC/ DDD Methodology." Was reviewed by An-Najah National University IRB committee & approved on Oct 31, 2012.

IRB

Samar Musmar,MD, FAAFP

Scm

IRB Committee Chairman,
An-Najah National University

نابلس - ص.ب ٧,٧٠٧ هاتف: ٢٣٤٢٩٠٢/٤/٧/٨/١٤ (٠٩)(٩٧٢)، فاكسميل ٢٣٤٩٧٣٩ (٠٩)(٩٧٢)
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جامعة النجاح الوطنية

كلية الدراسات العليا

نمط استخدام المضادات الحيوية في مستشفى حكومي مقاساً بمقياس (WHO ATC/DDD)

إعداد

مارينا زياد البدا

إشراف

د. أدهم أبو طه

بروفيسور وليد صويلح

قدمت هذه الأطروحة استكمالا لمتطلبات درجة الماجستير لتخصص صيدلة سريرية، بكلية الدراسات العليا في جامعة النجاح الوطنية في نابلس– فلسطين.

2014

نمط استخدام المضادات الحيوية في مستشفى حكومي مقاساً بمقياس
(WHO ATC/DDD)

إعداد
مارينا زياد البدا
إشراف
د. أدهم أبو طه
بروفيسور وليد صويلح

الملخص

الخلفية : يرتبط استهلاك المضادات الحيوية بازدياد مقاومة البكتيريا على امتداد العالم ، شأن ذلك شأن الزيادة في التكاليف والتعرض غير الضروري للمرضى للدواء .
الأهداف : قمنا باختبار بيانات نمط استخدام المضادات الحيوية باستخدام مقياس (WHO ATC/DDD) في مستشفى حكومي في فلسطين وتقييم العقبات لتنفيذ الاستخدام الرشيد للمضادات الحيويية في المستشفى.

الطريقة والإجراءات : تم إسترجاع استهلاك المضادات الحيوية في مستشفى رفيديا مستقبلياً. حيث تم حساب **(**جرعة محددة يومية لكل 100 مريض/ يوم**)** و**(**جرعة محددة يومية لكل 1000 مقيم/ يوم**)** لكل المضادات الحيوية .

النتائج : تم تقديم المضادات الحيوية ل554 مريضاً بنسبة (55.4%) من أصل 1000 مريض تم إدخالهم للمعالجة في مستشفى رفيديا في فترة الدراسة التي تتروح شهرين. وقد بلغ مجموع الاستخدام (16561 جرعة محددة يومية) والتي تطابق ما مقداره (70.23 جرعة محددة يومية لكل 100 مريض/ يوم) و (3.31 جرعة محددة يومية لكل 1000 مقيم). وقد تبين أن أكثر مضاد حيوي أستخدم هو (سفتريكسون) يليه (سيفوركسيم) و(ميترونايدازول). وقد تكونت الوصفة الكبيرة (DU90%) من 8 عوامل من أصل 22 وهو مجموع تلك العوامل. وأن أعلى النسب من استخدام المضادات الحيوية قد تم في في وحدة العناية المكثفة (ICU) وقد بلغت

132.64 جرعة محددة يومية لكل 100 مريض/ يوم ثم في قسم الجراحة حيث بلغت 98.52 جرعة محددة يومية لكل مريض/ يوم .

الخاتمة : وجد أن أستخدام المضادات الحيوية في مستشفى رفيديا مرتفع نسبيا, وهناك تفضيل مميز لاستخدام المضادات الحيوية واسعة_الطيف مثل الجيل الثالث من سيفالوسرين و(كاربابينيمس) و(أمينوجليسوسيد). وقد أثبتت الدراسة وجود حاجة ملحة للقيام بعقد برامج تعليمية تتعلق بالوقاية ومكافحة التلوث في المستشفيات الفلسطينية.

الكلمات الدالة : مضادات حيوية ، استهلاك .

د